714 *J. Org. Chem.* **1993**, *58*, 714–717

# Conformational Studies by Dynamic NMR. 49.[1] The High Rotation Barrier and Lower Nitrogen Inversion/Rotation Barrier in *N,N*-Diisobutyl-2,4-dimethyl-3-pentylamine[†]

Daniele Casarini and Lodovico Lunazzi*

*Department of Organic Chemistry "A. Mangini", the University, Risorgimento 4, Bologna 40136, Italy*

J. Edgar Anderson*

*Chemistry Department, University College, Gower Street, London WC1E 6BT, U.K.*

*Received February 21, 1992*

The temperature dependence of the $^{13}$C and $^{1}$H NMR spectra of the title compound is reported and discussed in terms of a rotation about the dimethylpentyl to nitrogen bond, with a barrier of 9.4 kcal mol$^{-1}$ and a lower barrier of 7.9 kcal mol$^{-1}$ to nitrogen inversion/rotation.

## Introduction

The stereodynamics of a wide range of trialkylamines has been studied over the last few years[2–16] largely by observing the temperature dependence of NMR spectra. While it is helpful to talk of the interconversion of specific (often enantiomeric) conformations, it has to be remembered that this interconversion involves a combination of inversion of the configuration at the nitrogen center and rotation about the carbon–nitrogen bonds. In favorable conditions the NMR method may allow a separate study of both these processes and a measurement of two (or more than two) distinct barriers.

The NMR spectrum changes imply that to interconvert minimum energy conformations both of these processes also involve reorientations about carbon–carbon bonds which are usually so fast as to have no effect on NMR spectra. With suitably complex alkyl groups, however, the barrier to such carbon–carbon bond rotation may be high enough for a dynamic NMR study,[3,4,10,12,14] in which case the role of nitrogen inversion and carbon–nitrogen bond rotation in such a process has to be considered.

The transition state for nitrogen/inversion rotation is quite structure dependent: comparisons along a series of analogous compounds suggest that certain substituents make the inversion of the nitrogen configuration less energetically demanding than the accompanying rotation about the various bonds in the molecule. In these cases the process has changed from being inversion-dominated to being rotation-dominated.

For several amines more than one set of changes in the NMR spectra have been observed, allowing a determination of both carbon–nitrogen rotation and nitrogen inversion/rotation barriers. Up to now, however, in all the cases where both barriers could be measured[2,6,9,14,15] the rotation has been found to be smaller than the inversion barrier. A few molecules are reported[10,12] where a C–N rotational barrier has been measured but the inversion/rotation barrier was too low to be measured at the lowest practically accessible temperatures. We now report an example, *N,N*-diisobutyl-2,4-dimethyl-3-pentylamine 1, in which both barriers have been measured and the rotation barrier was found to be the higher.

## Experimental Section

Compound 1 was commercially available and distilled before use. Samples for low-temperature measurements were prepared by condensing gaseous $CHF_2Cl$ into NMR tubes (containing the compound and some $C_6D_6$ or $CD_2Cl_2$ as lock) connected to a vacuum line. The tubes were then sealed in vacuo and allowed to reach room temperature before being introduced in the precooled probe of the spectrometers (75.5 MHz for $^{13}$C and 600 MHz for $^{1}$H). The temperature was measured by replacing the sample with one containing acetone-$d_6$ and $CHF_2Cl$, the separation of the CO and $CHF_2Cl$ chemical shift having been previously calibrated as function of the temperature.[17]

Line-shape analysis was carried out at a temperature (−65 °C) close to the coalescence point of the $NCH_2$ signals for the determination of the higher barrier and at −100 °C (near to the coalescence of the methyl signals of the dimethylpentyl moiety) for the determination of the lower barrier. A two sites computer program based on the Bloch equations was employed for the simulation[18] and the best fit judged by superimposing the plotted traces with the $^{13}$C experimental spectra. The assignment of the 11-Hz separation to a *J* coupling constant (rather than to a chemical shift difference) in the eight-line spectrum at −115 °C

---

[†] Dedicated to Professor Antonino Fava on the occasion of his 70th birthday.

(1) Part 48. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1363.

(2) Bushweller, C. H.; Fleischmann, S. H.; Grady, G. L.; McGoff, P.; Rithner, C. D.; Whalon, M. R.; Brennan, J. G.; Marcantonio, R. P.; Domingue, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 6224.

(3) Bushweller, C. H.; Anderson, W. G.; Stevenson, P. E.; Burkey, D. L.; O'Neil, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 3892.

(4) Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. *J. Am. Chem. Soc.* **1971**, *93*, 542.

(5) Reny, J.; Wang, C. Y.; Bushweller, C. H.; Anderson, W. G. *Tetrahedron lett.* **1975**, 503.

(6) Bushweller, C. H.; Wang, C. Y.; Reny, J.; Lourandos, M. Z. *J. Am. Chem. Soc.* **1977**, *99*, 3938.

(7) Fleischmann, S. H.; Whalon, M. R.; Rithner, C. D.; Grady, G. L.; Bushweller, C. H. *Tetrahedron Lett.* **1982**, *23*, 4233.

(8) Bushweller, C. H.; O'Neil, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 2159.

(9) Danehey, C. T., Jr.; Grady, G. L.; Bonneau, P. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7269.

(10) Lunazzi, L.; Macciantelli, D.; Grossi, D. *Tetrahedron* **1982**, *39*, 305.

(11) Casarini, D.; Davalli, S.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1989**, *54*, 4616.

(12) Berger, P. A.; Hobbs, C. A. *Tetrahedron Lett.* **1978**, 1905.

(13) Bushweller, C. H.; Anderson, W. G.; Stevenson, P. E.; O'Neil, J. W. *J. Am. Chem. Soc.* **1975**, *97*, 4338.

(14) Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731.

(15) Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1791.

(16) Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1431.

(17) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1986**, *51*, 517.

(18) Sandstroem, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.

0022-3263/93/1958-0714$04.00/0

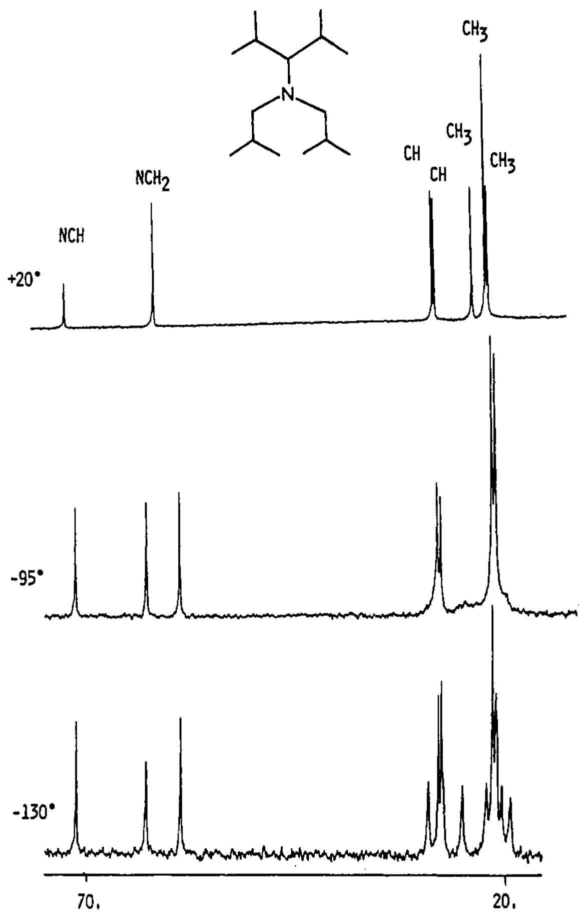


**Figure 1.** $^{13}C$ spectrum (75.5 MHz) of 1 in $CHF_2Cl$ at room temperature (top) and at lower temperatures showing the splittings due to slow C–N rotation (–95 °C) and to nitrogen inversion/rotation (–130 °C).

(see Figure 3) is the result of the invariance of this splitting in the low-temperature proton spectra taken at 300 and 600 MHz.

## Results

The $^{13}C$ (75.5 MHz) spectrum of 1 in $CHF_2Cl$ at three different temperatures is shown in Figure 1. The assignment to CH, $CH_2$, $CH_3$ carbons (see Table I) was obtained by means of a DEPT sequence. At +20 °C the four methyl groups of the dimethylpentyl moiety display two lines (each corresponding to two carbons) owing to the diastereotopicity due to the nearby prochiral NCH carbon. On the other hand the methyl groups of the two isobutyl moieties are enantiotopic on the NMR time scale (thus isochronous), and the corresponding single line (four carbons) lies between the pair of the dimethylpentyl methyl signals. Of the two methine carbon signals, the one at lower field was assigned to the dimethylpentyl and that at higher field to the isobutyl moiety as a result of a 2D heterocorrelated (HETCOR) experiment. The low-field C-13 methine line is in fact correlated to the low field H-1 methine multiplet: the latter belongs to the dimethylpentyl group as it is coupled (COSY experiment) to the diastereotopic methyl groups. Conversely the C-13 upfield methine line is correlated (HETCOR) to the upfield H-1 methine multiplet which belongs to the isobutyl groups, being coupled (COSY) to the $NCH_2$ doublet and to the four enantiotopic methyl groups.

On lowering the temperature the three signals (one CH, two $CH_3$) of the dimethylpentyl moiety broaden to the point of being, eventually, invisible, so that at –95 °C only the lines of the isobutyl moiety can be detected. By this temperature each of the three isobutyl lines observed at +20 °C has broadened and then split into pairs, the spectrum thus displays six lines for the $NCH_2$, CH, and $CH_3$ carbons of the isobutyl group.

On further lowering the temperature to –130 °C the lines of the dimethylpentyl group sharpen again and each of the three lines observed at +20 °C is split into two, so that six lines are eventually observed for the CH and $CH_3$ carbons of the dimethylpentyl moiety. Only the NCH carbon signal does not split at low temperature (Table I).

Line-shape analysis indicates that the motion responsible for the splitting of the isobutyl lines has a free energy of activation ($\Delta G^*$) of 9.4 kcal $mol^{-1}$, and the motion responsible for the splitting of the dimethylpentyl lines has a $\Delta G^*$ equal to 7.9 kcal $mol^{-1}$.

## Discussion

One major simplifying assumption is made in discussing these results, viz. that the rotation about all carbon–carbon bonds has a barrier lower than the lesser of the two reported barriers (i.e., 7.9 kcal $mol^{-1}$) in this paper. The necessary adjustments in the C–C bond conformation, which accompany the high barrier C–N bond rotation and nitrogen inversion, are thus assumed to take place readily.

The $^{13}C$ spectral changes accompanying the process with the 9.4 kcal $mol^{-1}$ barrier indicate that the isobutyl groups are anisochronous and thus diastereotopic: this process cannot be explained by the inversion of nitrogen and must be attributed to the rotation about a nitrogen–carbon bond, putatively the dimethylpentyl-to-nitrogen bond. Nitrogen inversion is not yet locked on the NMR time scale and the arrangement around the N-atom appears as if planar on the average, with the two isobutyl groups located as in the conformation **1a** of Scheme I (isobutyl = B). No change is expected, however, in the isopropyl signals of the dimethylpentyl moiety since, even as rotation slows, they remain symmetrically placed with respect to the dynamic plane of symmetry due to N-inversion.

At lower temperatures, where nitrogen inversion becomes even slower on the NMR time scale, discrete structures represented by the enantiomers **1b**, **1b′** in Scheme I become NMR visible. Thus, we have four isopropyl methyl signals (Table I) and we should also expect four isobutyl methyl signals: the latter, however, only yield two lines of double intensity owing to accidental isochronicity (the isobutyl methyl groups are in fact farther away than isopropyl methyl groups from any prochiral center). It is evident that only gauche conformers such as **1b**, **1b′** (where the angle between the C–H bond and the direction of the nitrogen lone pair is close, but not necessarily equal, to 60° in the Newman projection) agree with the experiment. A conformation anti (i.e., a conformation where the angle between the C–H bond and the direction of the nitrogen lone pair is about 180° in the Newman projection) would yield, in fact, two enantiotopic isopropyl CH groups within the dimethylpentyl moiety as well as two enantiotopic $CH_2$ groups, in contrast with the –130 °C spectrum.

It might appear surprising that the apparently more congested gauche form is the only propulated conformer

---

(19) Hounshell, W. D.; Dougherty, P. A.; Mislow, K. J. *J. Am. Chem. Soc.* **1978**, *100*, 3149.

(20) Ruchardt, C.; Beckhaus, H.-D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 529.

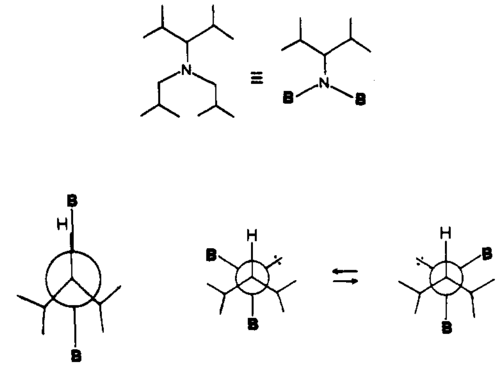
(21) Anderson, J. E.; Bettles, B. R.; Hoffmann, H. M. R.; Pauluth, D.; Hellmann, S.; Beckaus, H.-D.; Ruchardt, C. *Tetrahedron* **1988**, *44*, 3701.

**Table I. Chemical Shifts (ppm from TMS) of the Carbon Signals of 1 in $CHF_2Cl$ at Temperatures (°C) where Fast Exchange Still Occurs (−45 °C) and at Temperatures where the First (−95 °C) and the Second Motion (−130 °C) Are Slow**[a]

| temp | $NCH_2$ | CH(*i*-Pr) | CH(*i*-Bu) | $CH_3$(*i*-Pr) | | $CH_3$(*i*-Bu) |
|---|---|---|---|---|---|---|
| −45 | 61.1 | 28.0 | 27.8 | 22.8 | 21.0 | 21.2 |
| −95 | 62.9; 58.9 | | 28.0; 27.6 | | | 21.6; 21.1 |
| −130 | 63.0; 58.8 | 29.3; 27.4 | 28.0; 27.6 | 25.0; 20.5 | 22.3; 19.3 | 21.6; 21.1 |

[a] The NCH signal remains a singlet (71.4 ppm) at every temperature.

**Scheme I**



1a 1b 1b′

of 1. There are, however, well-documented examples[9,19–21] showing that bulky alkyl substituents can make a gauche conformation, albeit quite distorted, more stable than the anti.

Molecular mechanics calculations were carried out to have some theoretical indication for the relative stability of these conformers and to gain an insight into the overall structure of conformer **1b**. The title compound has three carbon–nitrogen and four carbon–carbon bonds about which conformational isomerism might take place, implying three possible staggered conformations. Although this large number might be diminished a little by degeneracy and enantiomerism, a detailed investigation of all these possibilities is beyond the aim of the present work. Amongst the "reasonable" structures that were calculated, we found that the gauche conformer shown in Figure 2 actually has a lower energy than that of the anti conformer by 3.9 kcal mol$^{-1}$. We were unable to find any anti structure having an energy lower than that of the gauche form of Figure 2. This indicates that the amount of the anti conformer is indeed too low to detect experimentally.

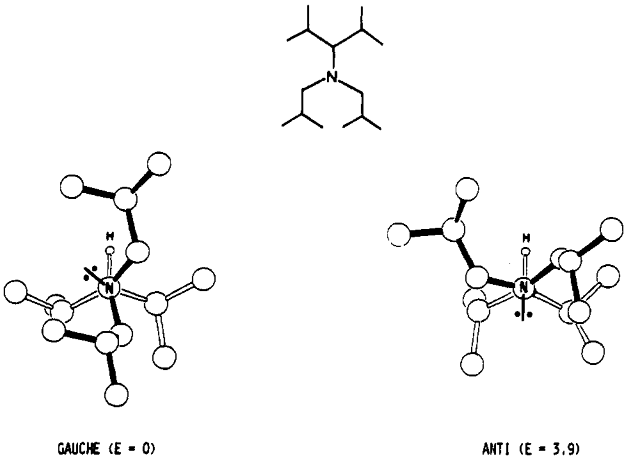
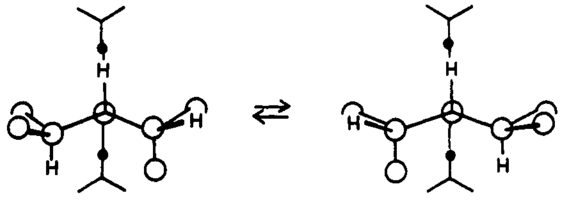


**Figure 2.** Pictures of the gauche (left) and anti (right) conformations of 1 as obtained from MM calculations: the hydrogen atoms (with the exception of that of the NCH group) have been omitted for the sake of clarity. The difference between the calculated total energies (*E* in kcal mol$^{-1}$) reported underneath confirms that the gauche is the more stable conformer, as experimentally observed.

**Scheme II**



1c 1c′

It has to be pointed out that there is another interpretation of the second low-temperature process in compound 1 in terms of carbon–carbon bond rotation which merits discussion, although the bulk of the evidence favors nitrogen inversion/rotation. If the latter process is assumed to be fast on the NMR time scale over the temperature range studied, the changes in the spectrum of the dimethylpentyl group could be alternatively explained by a rotation process **1c** ⇌ **1c′** (Scheme II) becoming slow on the NMR time scale with a barrier of 7.9 kcal mol$^{-1}$. Rotation about isopropyl-CH bonds usually has a lower barrier than the one we observed, dimethylbutane (4.5 kcal mol$^{-1}$)[22] and triisopropylmethane (6.6 kcal mol$^{-1}$)[23] serving as examples. Nitrogen inversion barriers for trialkylamines with two primary and a secondary alkyl group agree better with that found for 1: e.g., *i*-PrNMeEt (7.5 kcal mol$^{-1}$),[6] *s*-BuNMeEt (7.3 kcal mol$^{-1}$),[9] and $(PhCH_2)_2NPr$-*i* (7.0 kcal mol$^{-1}$)[5].

Almost planar nitrogen, and thus negligible N-inversion barrier, has been suggested for two trialkylamines: triisopropylamine (2)[24] and 3-(dimethylamino)-2,2,4,4-tetramethylpentane (3),[12] but molecular mechanics calculations show that it is unlikely that compound 1 has a planar nitrogen. Such calculations show in fact that in the case of 2 the C–N–C angle is 118° and the sum of the three C–N–C angles is thus 354°: a value which is close to the 360° sum expected for perfect planarity. On the other hand a perfectly tetrahedral nitrogen should have the sum of C–N–C angles equal to 328.5° and trimethylamine (C–N–C = 111°, sum = 333°)[24] approaches this ideal. We have calculated that the corresponding sum in 3 is 352.3°, so molecular mechanics confortably verifies both planar and tetrahedral nitrogen conformations. Furthermore, the crystal structure of a trialkylamine with two primary and a tertiary alkyl group has been determined and is matched well by calculations. Thus for neopentylbenzyladamantylamine (4) (which has a nitrogen inversion/rotation barrier[14] of 9.2 kcal mol$^{-1}$) X-ray diffraction[14] shows a $CH_2$–N–$CH_2$ angle of 110.7° and a sum of the C–N–C angles equal to 338.8°. The molecular mechanics calculated values (110.0° and 337.4°, respectively) match these values quite well.[14]

---

(22) Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 4573.

(23) Anderson, J. E.; Koon, K. H.; Parkin, J. E. *Tetrahedron* **1985**, *41*, 561.

(24) Bock, H.; Goebel, I.; Havlas, Z.; Liedle, S.; Oberhammer, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 187.

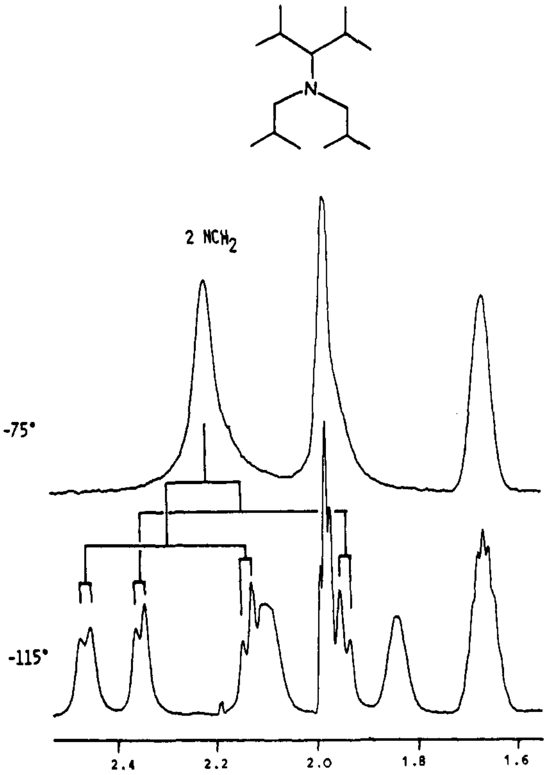


**Figure 3.** Methylene and methine region of the 600-MHz proton spectrum of 1 at two different temperatures in $CHF_2Cl$. The 2.22 ppm signal corresponding to the four hydrogens of the two $NCH_2$ groups (a singlet at −75 °C as the 7-Hz coupling with the vicinal CH hydrogen is obscured by line broadening) is split into eight lines (i.e., two AB quartets with geminal couplings of −11 Hz) at −115 °C. The smallest chemical shift difference (0.15 ppm) arises from the presence of two diastereotopic methylene groups, and the two larger separations (0.32 and 0.41 ppm) are due to hydrogens diastereotopic *within* each methylene group due to slow N-inversion/rotation.

For 1, molecular mechanics calculations yield 110.8° for the $CH_2$–N–$CH_2$ angle and 340.1° for the sum of the three C–N–C angles: these values are quite different from those expected for a planar nitrogen and suggest a slightly flattened tetrahedral conformation. As a consequence it is reasonable to expect an inversion barrier not too different from that reported for compound 4.

An investigation of the proton NMR spectrum of 1 (recorded at 600 MHz to reduce signal overlap) sheds further light on these possibilities. At −115 °C the four methylene hydrogens yield an eight-line spectrum, actually two AB quartets with a geminal coupling of −11 Hz (Figure 3). The vicinal coupling with the adjacent CH groups, which yields a doublet ($J$ = 7 Hz) at room temperature, becomes undetectable at −115 °C, owing to the lower resolution occurring at that temperature (line width ≃ 10 Hz at −115 °C). From the eight-line spectrum we conclude that the two hydrogens within each methylene group are diastereotopic (and geminally coupled) with relative shifts of 0.32 and 0.41 ppm, respectively, and the two methylene groups are themselves diastereotopic, so that the two AB quartets have a relative shift of 0.15 ppm.[25]

While the conformational enantiomers **1b** and **1b′** of Scheme I or **1c** and **1c′** of Scheme II might, in principle, account equally well for an eight-line spectrum for the methylene hydrogens, the observed chemical shift differences agree better with other separations observed for $NCH_2$ hydrogens made anisochronous by a slow nitrogen/inversion/rotation.[26] This relatively large separation, in fact, suggests a source of asymmetry (a prochiral pyramidal nitrogen) close to the methylene hydrogens involved, as in Scheme I. In Scheme II, in contrast, the methylene groups are quite distant from the putative source of the asymmetry, i.e., the isopropyl group conformation in the dimethylpentyl group.

The barriers measured in 1 are worth comparing with those for *N,N*-diethylisopropylamine **5**, which has similarly two primary alkyl and one secondary alkyl substituent.[5] The nitrogen inversion barrier in **5** is 5.9 kcal $mol^{-1}$, and any rotational barrier in this compound is too low for detection by the dynamic NMR technique. Both processes observed in 1 have therefore markedly higher barriers than in **5**, and in the case of the carbon–nitrogen bond rotation this may well reflect not only increased substitution (isopropyl for methyl) at the carbon end of the bond, but also more hindered rotations about other bonds which have to take place to complete the process. A comparably substituted compound with a similar rotational barrier of 9.2 kcal $mol^{-1}$ is *N,N*-diisopropyl-3-pentylamine (**6**).[10]

The increase in the nitrogen inversion barrier in 1 compared with **5** (2 kcal $mol^{-1}$) is not a direct consequence of the substituent effect, for increasing bulk leads to reduced inversion barriers.[10,27–30] It seems more likely that rotation about carbon–nitrogen and carbon–carbon bonds (which has to accompany nitrogen inversion to complete the interconversion of enantiomeric structures) is more difficult in 1 than in **5**, thus causing an increase of the measured N-inversion barrier in the former compound. An analogous behavior is found for the nitrogen inversion barrier of compounds of general formula $(i\text{-Pr})_2NCH_2R$: namely 6–6.95, 6.5, 7.8, and 8.9 kcal $mol^{-1}$ when R = H,[5,10] $CH_3$,[5,10] *i*-Pr,[15] and *t*-Bu,[15] respectively.

## Conclusion

This investigation clearly shows that, owing to the particular gauche structure of 1, two motions (C–N rotation and N-inversion/rotation) are amenable to NMR measurements and, for the first time, evidence has been obtained of two such measurable barriers where rotation is the larger one.

**Acknowledgments.** D.C. and L.L. acknowledge the financial support of MURST and CNR, Rome. Thanks are due to the Magnetic Resonance Laboratory of the University of Florence for the low-temperature 600-MHz spectra and to Mr. M. Lucci for skillful assistance. The international collaboration was made possible by a NATO research grant (RG86/0200).

---

[25] Since the calculated preferred gauche conformation of Figure 2 has both the $CH_2$ groups similarly oriented with respect to the nitrogen lone pair, the AB chemical shift differences are taken to be 0.32 and 0.41 ppm rather than 0.21 and 0.52 ppm. The relative line intensities of each AB group do not allow the possibility that the relative shifts *within* the AB quartets are 0.11 or 0.19 ppm.

[26] E.g.: 0.42 ppm in *t*-BuN(Cl)Et (ref 13); 0.38 ppm in $Et_2NMe$ (ref 2); 0.28 ppm in $(PhCH_2)_2NMe$ (Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. *Tetrahedron* **1972**, *28*, 2697).

[27] Lehn, J.-M.; Wagner, J. *J. Chem. Soc., Chem. Commun.* **1968**, 1298.

[28] Cowley, A. H.; Dewar, M. J. S.; Jackson, W. R. *J. Am. Chem. Soc.* **1968**, *90*, 4185.

[29] Raban, M.; Kost, D. *J. Org. Chem.* **1972**, *37*, 499; **1976**, *41*, 1748.

[30] Riddell, F. G.; Turner, E. S. *J. Chem. Soc., Perkin Trans. 2* **1978**, 707.