Revealing "NMR-Invisible" Conformational Processes in Amines through NMR Isotope Shifts

David A. Forsyth* and Suzanne M. Johnson

Contribution from the Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

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Abstract: Symmetry and the ordering of the inversion and isolated rotation barriers can render inversion "NMR-invisible" in many simple amines, such as all dimethylamino compounds. NMR-invisible processes in $RCH_2NR'R'$ amines can be revealed through NMR isotope shifts if the methylene is monodeuteriated to create a chiral center that makes the R′ groups diastereotopic. A $\Delta G^{\ddagger}$ of 8.2 kcal mol^{-1} for inversion in *N,N*-dimethylpentanamine-*1*-d_1 was found through complete DNMR line-shape analysis of the *N*-methyl signals in 75 MHz $^{13}C\{^1H\}$ spectra. A barrier of 9.5 kcal mol^{-1} for the exchange process in *N,N*-diethyl-2,2-dimethylpropanamine, **3**, was found from both ^1H spectra of **3** and ^{13}C spectra of **3**-d_1. The barrier for **3** is higher than expected for inversion and can be explained by inversion of a conformation that has a nearly eclipsing neopentyl group to a conformation that has a high barrier for a rotation to complete the exchange process.

Introduction

Dynamic NMR (DNMR) studies have provided extensive information on inversions and rotations in organonitrogen compounds.[1] In a trialkylamine of the type $RCH_2NR'R''$, the *N*-methylene protons are diastereotopic in any nonplanar conformer but undergo exchange via inversion and accompanying rotation.[2] NMR line-shape analysis of the ^1H NMR spectra at several temperatures can provide the inversion barrier when it is higher than rotational barriers. However, symmetry and the ordering of the inversion and isolated rotation barriers can render inversion "NMR-invisible" in many simple cases such as triethylamine[3] and all dimethylamino compounds.[4] In these cases, slowing inversion produces no change in ^1H NMR line shapes.

The present paper describes how NMR-invisible conformational processes in amines of the type $RCH_2NR'R'$ can be revealed through NMR isotope shifts. Monodeuteriation of the methylene carbon creates a chiral center, making the R′ groups formally diastereotopic. In principle, the chemical shift nonequivalence of the R′ groups could then be detected in either ^1H or ^{13}C NMR upon slowing inversion, and line-shape analysis could be applied. In practice, the chemical shift differences for the R′ groups are likely to be readily detectable only when there is a favorable combination of four circumstances: (i) The gauche conformers (R gauche to the lone pair) should be substantially populated. A gauche conformer has different environments for the R′ groups, while the anti conformer has enantiotopic R′ groups. Monodeuteriation makes the R′ groups diastereotopic even in the anti conformer, but only a small, stereochemically dependent,[5] intrinsic NMR isotope shift would contribute to a chemical shift difference between the R′ groups in the anti conformer. (ii) The chemical shift difference between

the R′ groups in a gauche conformer must be substantial. (iii) A conformational equilibrium isotope effect (CEIE) on the rotational equilibrium between gauche conformers must be of sufficient magnitude to create detectably different time-averaged environments for the two R′ groups.[6] In the unlabeled amine, a rapid C−N bond rotation between enantiomeric gauche conformers would average the R′ environments to equivalence. The resulting equilibrium NMR isotope shifts[7] are expected to be temperature dependent and larger than the separation between signals induced by different intrinsic isotope shifts.[8] (iv) The line-shape changes caused by slowing inversion must not be obscured by changes associated with other processes.

Results and Discussion

N,N-Dimethylpentanamine, **1**, has a ^1H and ^{13}C NMR-invisible inversion barrier. However, the substitution of a deuterium for a protium at C1 in **1**-d_1 allows the detection of the inversion in ^{13}C spectra. In 75 MHz $^{13}C\{^1H\}$ spectra, the *N*-methyl signals appear as a singlet at higher temperatures that decoalesces to two singlets below 170 K. The $^{13}C\{^1H\}$ spectra for several temperatures between 157 and 180 K are shown in Figure 1. The separation between the two signals increases as the temperature is lowered because the shift difference depends upon the position of the gauche−gauche rotational equilibrium that is perturbed by a CEIE. The separation is linearly dependent on temperature over a reasonable temperature range,

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(2) Bushweller, C. H., ref 1a, Chapter 1.

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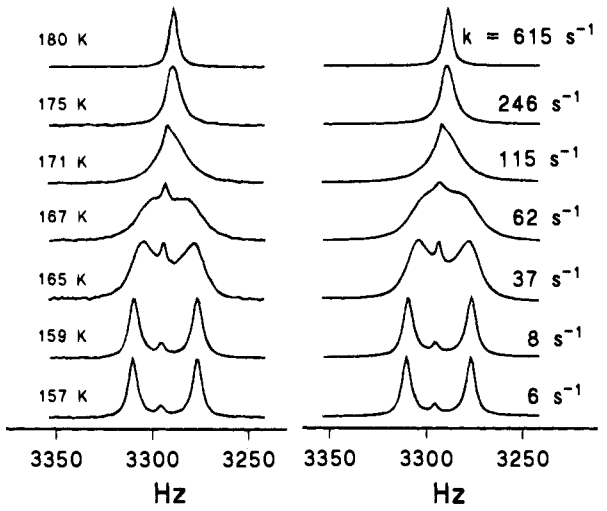


Figure 1. Experimental 75.43 MHz $^{13}C\{^1H\}$ NMR spectra of the *N*-methyl region of **1**-d_1 (CF_3Br) in the left column and DNMR5 theoretical simulations in the right column. The small central signal is the singlet for the *N*-methyls of unlabeled **1** (5%).

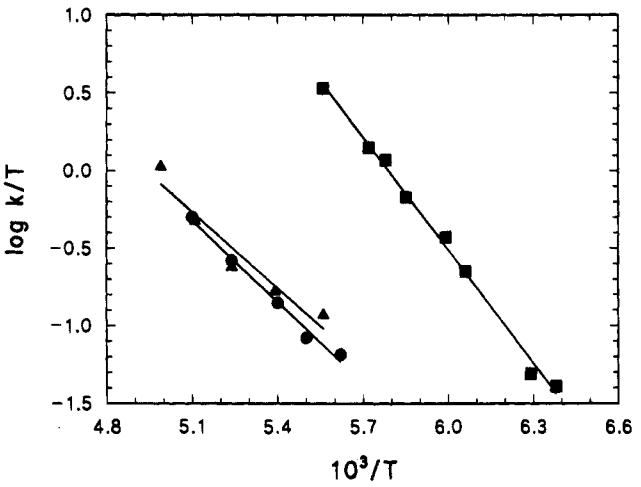
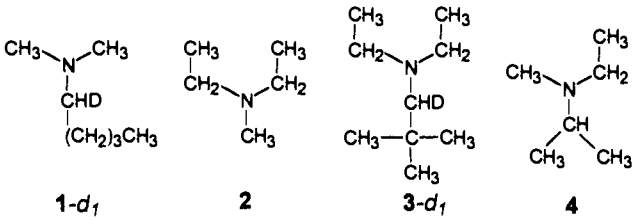


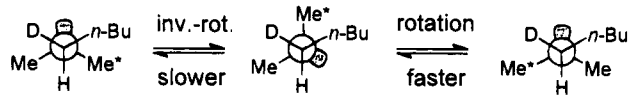
Figure 2. Eyring plots of DNMR kinetic data from complete line-shape analysis of ^{13}C spectra for **1**-d_1 (■), ^1H spectra for **3** (▲), and ^{13}C spectra for **3**-d_1 (●).

so that it could easily be extrapolated to all temperatures needed for the complete line-shape analysis. Line-shape analysis with the DNMR5 program[9] gave the matching theoretical spectra for different exchange rates that are also shown in Figure 1. The $\Delta G^{\ddagger}$ is 8.2 (±0.2) kcal mol^{-1} at 170 K; the Eyring plot of log *k*/*T* *vs* 1/*T* is shown in Figure 2.[10]



The methyl exchange barrier of 8.2 kcal mol^{-1} for **1**-d_1 constitutes a determination of the inversion barrier on the least sterically crowded, acyclic, tertiary amine that has been directly measured by NMR methods. This barrier is clearly appropriate for inversion when compared with the DNMR-derived inversion barrier of 7.9 kcal mol^{-1} for diethylmethylamine, **2**,[3] and the inversion barrier of 8.3 kcal mol^{-1} found for the prototypical trimethylamine from fluorescence and absorption spectra.[11]

Scheme 1



Another possible approach to the problem of measuring inversion in an amine with enantiotopic R′ groups is to measure the inversion in a chiral environment. Lunazzi et al. measured the inversion barrier of dimethylethylamine in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE), finding $\Delta G^{\ddagger}$ = 10.4 ± 0.3 kcal mol^{-1}.[12] This is clearly too high for an inversion barrier for the free amine, so the barrier was corrected for the influence of H-bonding to the amine from the chiral alcohol. A correction of −1.8 kcal mol^{-1} was applied, based on data from a chiral amine in the presence and absence of TFAE, giving an estimated $\Delta G^{\ddagger}$ of 8.6 kcal mol^{-1} for dimethylethylamine. This estimate may be slightly high in light of our results on **1**-d_1 that has similar steric bulk surrounding the nitrogen.

As noted by Bushweller,[2] the inversion process that gives NMR exchange is really an inversion−rotation phenomenon. Pure inversion, without rotation, of a conformation that is all-staggered about C−N bonds would lead to an unstable, all-eclipsed conformation. Thus, in many amines, inversion is apparently coupled with a rotation of about 60° around each C−N bond to end at an all-staggered conformer.[11,13,14] For a RCHDNR′R′ compound such as **1**-d_1, the exchange of R′ groups after inversion−rotation at nitrogen is formally complete only after another ~120° rotation about the *N*-methylene bond, as shown in Scheme 1. The 120° rotation is simply the rapid gauche−gauche equilibrium (MMX[15] predicted barrier in **1** of 4.4 kcal mol^{-1}). Thus, the observed barrier is essentially that for inversion because the necessary rotations are lower energy processes.

The success of chiral deuteriation in revealing the inversion process in **1**-d_1 can be explained in terms of the four circumstances stated earlier. (i) The gauche conformers should be substantially populated as MMX calculations predict that a gauche conformer of **1** is favored over the anti conformer by 0.87 kcal mol^{-1}. (ii) The ^{13}C chemical shift difference between the two *N*-methyl groups in a frozen-out gauche conformer of **1** is unknown but should be relatively large. As seen in Scheme 1, the *n*-butyl portion of the chain is gauche to one methyl and

(9) A modified version of the D. S. Stephenson and G. Binsch DNMR5 program was used, which was further adapted by LeMaster, C. B.; LeMaster, C. L.; True, N. S.: Program No. QCMP059, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN 47405.

(10) The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are 11.1 kcal mol^{-1} and 17.2 cal deg^{-1} mol^{-1}, respectively. These values are expected to have much greater errors than the $\Delta G^{\ddagger}$ value, especially considering the narrow temperature range. (a) Binsch, G. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; Chapter 3. (b) Anet, F. A. L.; Anet, R., ref 10a, Chapter 14.

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(15) Molecular mechanics implemented in PCMODEL program from Serena Software; nitrogen parameters from MM2 force field. Profeta, S., Jr.; Allinger, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 1907.

anti to the other. The familiar γ-substituent effect[16] leads to the expectation of a several ppm shielding of the gauche methyl relative to the anti methyl. In related *N*-alkylpiperidines, the C2−C6 shift difference was estimated at more than 8 ppm on the basis of model compounds.[6b] (iii) Several previous studies have found CEIEs of about 50−60 cal mol^{-1} favoring a C−D bond in a position gauche to the lone pair over an anti alignment in a tertiary amine.[6b,17] In the IR spectrum of **1**-d_1, bands are found in the C−D stretching region at 2155 and 2050 cm^{-1}, assigned to the gauche and anti C−D bonds, respectively. The difference of 105 cm^{-1} leads to a predicted CEIE of 52 cal mol^{-1} due to zero point energy differences for C−H(D) stretching vibrations.[6b] This isotope effect is an order of magnitude larger than expected for an analogous hydrocarbon such as 2-methylheptane-*3*-d_1.[18] (iv) The only other conformational process that could be frozen-out on the NMR time scale is rotation about the C−N bond that would interconvert gauche and anti conformers. This is expected at lower temperatures[2] and would be evident in several other ^{13}C signals as well.

The validity of the isotopic perturbation approach to revealing hidden conformational processes in amines was verified by a DNMR study of *N*,*N*-diethyl-2,2-dimethylpropanamine (or diethylneopentylamine), **3**, and **3**-d_1. Inversion−rotation in **3** is ^{1}H NMR-visible because **3** has diastereotopic protons in the methylene of each ethyl group, while it is ^{13}C NMR-invisible because the methylene carbons are not diastereotopic. On the other hand, inversion−rotation in **3**-d_1 is ^{13}C NMR-visible in the signals for the methylene carbons of the ethyl group, as described above for **1**-d_1. Thus, the kinetic data from the two NMR sources can be compared. In the 300 MHz ^{1}H spectrum of **3**, irradiation of the methyl protons of the ethyl groups results in a simple AB pattern for the diastereotopic methylene protons at 180 K that coalesces to a singlet above 195 K. Complete line-shape analyses of the 300 MHz ^{1}H spectrum of **3** and the 75 MHz ^{13}C{^{1}H} spectrum of **3**-d_1 at various temperatures as shown in Figures 3 and 4 lead to the Eyring plots in Figure 2. Clearly, equivalent rate data are obtained from the two sources, both giving a $\Delta G^{\ddagger}$ of 9.5 (±0.2) kcal mol^{-1} at 191 K.[19]

In contrast to the observation for **1**, the exchange barrier of 9.5 kcal mol^{-1} for **3** is too large to be an inversion barrier. In simple saturated tertiary amines with no ring constraints or strong electronic effects, the steric bulk of the nitrogen substituents governs the magnitude of the inversion barrier, with lower barriers associated with bulkier substituents.[2,20] For example, the inversion barrier in *N*-ethyl-*N*-methyl-2-aminopropane, **4**, is 7.5 kcal mol^{-1} ($\Delta G^{\ddagger}$),[2,21] and it is further lowered to 7.3 kcal mol^{-1} in *N*-ethyl-*N*-methyl-2-aminobutane.[22] The inversion barrier for **3** should certainly be lower than the 7.9 kcal mol^{-1} for **2**. We have recently demonstrated that the steric bulk of the neopentyl group actually results in a syn conformation in an *N*-neopentylpiperidine, wherein the *tert*-butyl group eclipses the nitrogen lone pair.[6b] We suggest that the high exchange barrier for **3** occurs because the lowest energy conformers have a nearly eclipsing neopentyl group rather than a gauche, staggered alignment. MMX calculations support this suggestion, predicting the two lowest energy conformers to be **3a** (MMX $E_{rel} \equiv 0.0$), with a LP−N−C−C(*t*-Bu) dihedral angle of 15°, and **3b** (MMX E_{rel} = 0.1 kcal mol^{-1}), with a dihedral angle of 8°.

Upon inversion, a nearly eclipsed conformation for **3** would give a staggered conformation for the neopentyl group, with the *tert*-butyl portion anti to the lone pair. A crowded anti conformer, e.g., **3c** (MMX E_{rel} = 2.8 kcal mol^{-1}), would not be populated enough to be observed. In order to complete the exchange process with an ~180° rotation, the *tert*-butyl group must pass by an ethyl group in a high-energy eclipsed rotamer (MMX E_{rel} = 10.3 kcal mol^{-1}). Thus, we suggest that the height of the barrier for the exchange process in **3** is determined by

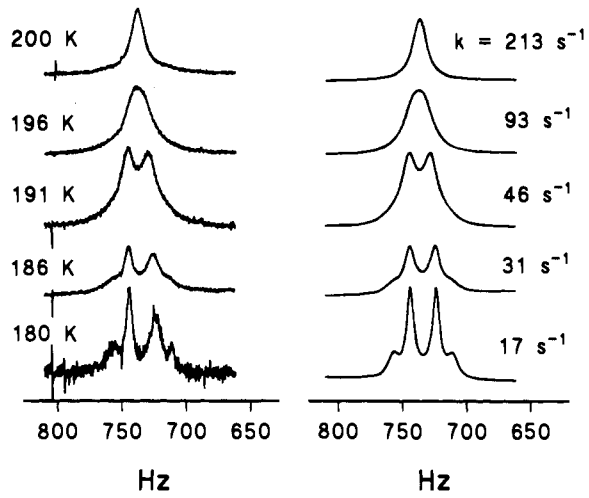

Figure 3. In left column, experimental 300 MHz ^{1}H NMR spectra (acetone-d_6) of *N*-methylene signals of the ethyl groups of **3**, with irradiation of the methyl signals of the ethyl groups for decoupling. Incomplete decoupling or some broadening due to the slowing of another conformational process may be responsible for the asymmetry in the experimental spectrum at low temperature. In the right column, DNMR5 theoretical simulations.

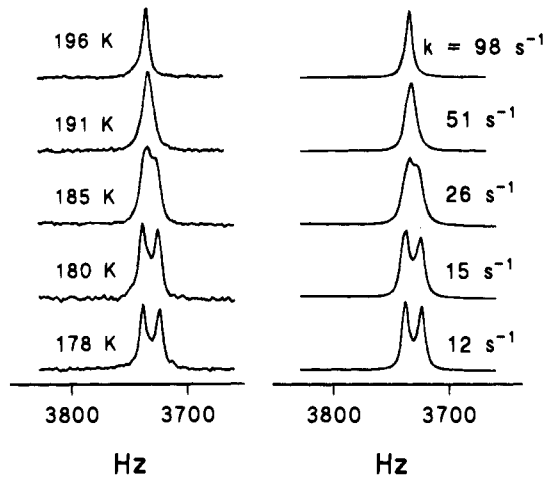

Figure 4. Experimental 75.43 MHz ^{13}C{^{1}H} NMR spectra (acetone-d_6) of the *N*-methylene carbons of **3**-d_1 in the left column and DNMR5 simulations in the right column. The asymmetry of the peaks is due to 3.5% of the unlabeled **3** that gives a signal at slightly higher frequency than the center position.

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(19) From ^{1}H data: $\Delta H^{\ddagger}$ = 7.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −10.2 eu. From ^{13}C data: $\Delta H^{\ddagger}$ = 8.0 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −7.8 eu.

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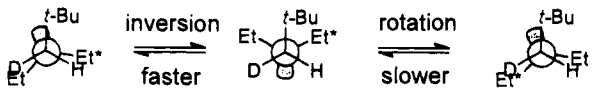
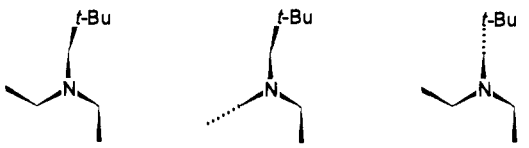
Scheme 2



the height of the rotational barrier, as shown in the simplified itinerary for exchange shown in Scheme 2. For simplicity, the necessary rotations of the ethyl groups have been omitted, as well as the details of the rotamer families with various ethyl group alignments, but these rotations are predicted to be lower energy processes.



3a **3b** **3c**

The proposed stereodynamics of a sequential inversion–rotation process for **3** differs from the mechanism proposed for some other trialkylamines having large rotational barriers, such as $(t\text{-}C_4H_9)_2CHN(CH_3)_2$, that are so sterically encumbered that the nitrogen is close to being or is actually trigonal planar;[23] in these cases inversion is irrelevant because the inversion barrier is either absent or extremely small. The inversion–rotation processes for some other tertiary neopentylamines have also been considered as rotation-dominated,[12,24] although they are somewhat less obvious examples since the reported barriers are lower than found here for **3**.

Experimental Section

***N,N*-Dimethylpentanamine (1-*d*$_1$).** 1-Pentanol-*1*-d_1 was available from reduction of valeraldehyde with sodium borodeuteride in methanol. Conversion to 1-pentyl-*1*-d_1 *p*-toluenesulfonate followed the method of Edgell.[25] Dimethylamine (100 mL) and 1-pentyl-*1*-d_1 tosylate (2.42 g, 970 mmol) were combined in a pressure bottle and allowed to react until monitoring by TLC indicated that the tosylate was consumed. The mixture was combined with 1.5 N KOH and extracted three times with pentane. The pentane fractions were combined and washed with saturated NaCl solution. Fractional distillation removed the solvent and further distillation under reduced pressure gave 0.82 g (9.3 mmol, 96%) of **1**-d_1: bp 45 °C (42 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.7 Hz, 3 H), 1.30 (m, 4 H), 1.45 (m, 2 H), 2.21 (m, 7 H); ^{13}C NMR ($CDCl_3$) 13.6 (C5), 22.1 (C4), 23.2 (C2), 28.4 (C3), 57.6 (NCH_3), 70.7 (t, J = 20.8 Hz, CHD); IR (neat) 2155, 2050 cm^{-1}.

***(R)*-*N,N*-Diethyl-2,2-dimethylpropanamine-*1*-d_1 (3-d_1)** was prepared by combining (*R*)-*N*-neopentylamine-*1*-d_1[26] (2.87 g, 32.6 mmol) with $NaHCO_3$ (8.22 g, 97.8 mmol) and iodoethane (7.88 mL, 15.2 g, 97.7 mmol) in 30 mL of methanol and refluxing for 17 h. The mixture was filtered and the filtrate was added to water. The aqueous mixture was extracted 3 times with pentane. The organic extract was extracted three times with 1 N H_2SO_4. The aqueous extract was made basic with 15% KOH and extracted three times with pentane. The combined organic extracts were dried ($MgSO_4$), pentane was removed by distillation, and further distillation under reduced pressure gave 3.80 g (81%) of **3**-d_1: bp 62–64 °C (36 mmHg); 96.5 mol % D; $[\alpha]^{20}_D$ 2.85 ± 0.14° (ether, not corrected for ee or deuterium content); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 9 H), 0.99 (t, J = 7.2 Hz, 6 H), 2.08 (t, J = 2.1 Hz, CHD), 2.51 (q, J = 7.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_2CH_3), 28.1 (CCH_3), 32.8 (CCH_3), 49.4 (CH_2), 66.0 (t, J = 19.7 Hz, CHD); IR (neat) 2068, 2095, 2124, 2141 cm^{-1}.

NMR spectra were run on a Varian XL-300 FT NMR spectrometer operating at a frequency of 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. A Waltz-16 decoupler was used for ^{13}C spectra, which were typically obtained with a spectral window of 16 501 Hz, 30 016 data points, a 1.0 s acquisition time, and 2 s delay. The variable temperature device was calibrated with a standard methanol sample. The temperature varied no more than ±0.5 K during acquisition, and temperatures are estimated to be accurate to ±2.5 K (used in error determination). The DNMR data were obtained in acetone-d_6 for **3**-*1*-d_1 and in CF_3Br (unlocked) for **1**-*1*-d_1.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

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