Restricted Nitrogen Inversion in 9,10-Diazatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecanes. Dynamic NMR Studies

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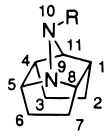
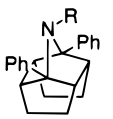
Introduction

Barriers to pyramidal inversion at nitrogen in hydrazines are consistently higher by 2−10 kcal/mol than inversion barriers in analogous amines.[1−2] The higher inversion barriers in hydrazines have been ascribed to a combination of lone-pair−lone-pair repulsions in the transition state and the effect of electronegativity of one nitrogen atom on the other.[3−5] For example, *N*-aminoaziridines,[6] diaziridines,[7] acyclic hydrazines,[8] cyclic hydrazines,[9] and bicyclic hydrazines[10] all exhibit higher barriers to nitrogen inversion than their amine counterparts. While care must be taken in assigning dynamic NMR (DNMR) behavior, especially in acyclic hydrazines, to nitrogen inversion or N−N bond rotation,[1] there have been only two cases for which it appears that the barrier-raising effect is due to lone-pair−lone-pair repulsions in the transition state rather than electronegativity.[10b,d] Electronegativity effects are important in raising the inversion barrier at phosphorus and arsenic in heteroatom-substituted phosphines and arsines.[11]

To address further the roles of electronegativity and electron-pair repulsions in determining nitrogen inversion barriers in hydrazines, we measured inversion barriers in the series of 10-alkyl-9,10-diazatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecanes below (**1**−**3**). In these systems, the nitrogen atoms are constrained in a rigid multicyclic system. The only internal motion involving the N−N bond is inversion at N10. Rotation about the N−N bond cannot occur. In the transition state for inversion in **1**−**3**, lone pairs are constrained to be orthogonal and lone-pair−lone-pair repulsions are minimized. This study complements our recent study of nitrogen inversion and isolated phenyl rotation in the related 10-methyl-9,11-diphenyl-10-azatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecane (**4**) and 10-benzyl-9,11-diphenyl-10-azatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecane (**5**).[12]



1, R = Me
2, R = Bn
3, R = *t*-Bu



4, R = Me
5, R = Bn

DNMR Studies

The ^{1}H NMR spectrum (250 MHz) of **1** (3% v/v in toluene-d_8) at 320 K shows the C11 bridgehead proton triplet at δ 3.32 ($^3J_{HH}$ = 4.3 Hz), a multiplet due to the C5 and C8 methine protons at δ 3.31 (2H), a multiplet due to the C1 and C4 methine protons at δ 2.08 (2H), the methyl singlet at δ 2.39, and complex resonances due the methylene protons at δ 1.65 (2H) and δ1.44−1.29 (6H). At temperatures below 300 K, all resonances decoalesce except those due to the C11 bridgehead proton and the methyl protons revealing the slowing of inversion at N10.[12] DNMR spectra over the chemical shift range from 2.2 to 1.0 ppm are illustrated in Figure 1. The most clearcut decoalescence is shown by the C1 and C4 methine protons that give the signal at δ 2.08 in the 320 K spectrum. This resonance is decoalesced at 200 K into two well-separated multiplets at δ_M 2.07 and δ_N 1.85 (Figure 1). A completely rigorous theoretical simulation of the DNMR spectra of the aliphatic protons in Figure 1 requires exchange of magnetization between two 13-spin spectra. This is well beyond the capability of current DNMR line-shape computer programs. However, as shown in Figure 1, acceptable theoretical fits of the DNMR spectra due to the C1 and C4 methine protons were obtained by employing a simplified spin system exchange that involves exchange of magnetization between the M and N resonances of MABX (δ_M 2.07, δ_A 3.30, δ_B 3.32, δ_X 1.40, J_{MA} = 9 Hz, J_{MB} = 5, J_{MX} = 5, J_{AB} = 0, J_{AX} = 1, J_{BX} = 1) and NBDY (δ_N 1.85, δ_B 3.30, δ_D 3.32, δ_Y 1.40, J_{BN} = 9 Hz, J_{DN} = 4, J_{NY} = 4, J_{BD} = 0, J_{BY} = 1, J_{DY} = 1) spin systems.[13] This simplified DNMR exchange model (vide supra) suggests that each of the M and N protons are coupled strongly to one vicinal proton and weakly to two others, i.e., the essential line shape of each multiplet at 200 K is a doublet of triplets. The resonance at δ_M 2.07 is assigned to the C1 or C4 proton in **1**; the resonance at δ_N 1.85 is also assigned to the C1 or C4

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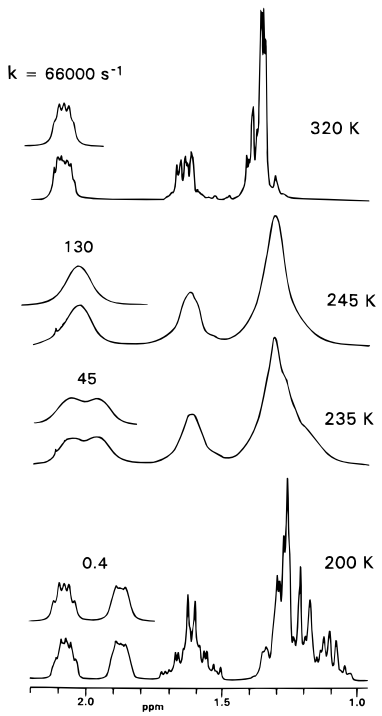

Figure 1. The ^{1}H DNMR spectra (250 MHz) of methine and methylene protons of 10-methyl-9,10-diazatetracyclo-[6.3.0.0.^{4,11}0.^{5,9}]undecane (**1**; 3% v/v in toluene-d_8) and theoretical simulations. The rate constant is associated with nitrogen inversion.

Table 1. Activation Parameters for Nitrogen Inversion

compd[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol K	$\Delta G^{\ddagger}$, kcal/mol (T (K))
1	12.2 ± 0.3	1.6 ± 2	11.9 ± 0.1 (235)
2	11.7 ± 0.4	1.7 ± 2	11.3 ± 0.1 (240)
3[b]	8.8 ± 0.4	0 ± 2	8.8 ± 0.3 (180)
4[c]	12.4 ± 0.4	0.8 ± 2	12.2 ± 0.1 (250)
5[c]	11.6 ± 0.4	4.6 ± 2	10.6 ± 0.1 (215)

[a] For all compounds except **3**, the solvent is toluene-d_8. For **3**, the solvent is 50% $CHFCl_2$/50% CHF_2Cl. [b] $\Delta G^{\ddagger}$ (*t*-Bu rotation) = 5.3 ± 0.5 kcal/mol at 115 K. [c] Reference 12.

proton in **1**. The spectrum at 200 K does not allow an unequivocal assignment of either resonance. On the basis of the Karplus relationship for vicinal coupling constants, the large J_{MA} value is assigned to coupling between C1 and C8 protons or to coupling between the C4 and C5 protons; the large J_{BN} value is also assigned to coupling between C1 and C8 protons or the C4 and C5 protons. The smaller coupling constants are consistent with the dihedral angles between the C1 and C11 protons, C4 and C11 protons, the C1 proton and the exo proton on C2, and the C4 proton and the exo proton on C3.

The activation parameters for nitrogen inversion are $\Delta H^{\ddagger} = 12.2 \pm 0.3$ kcal/mol, $\Delta S^{\ddagger} = 1.6 \pm 2$ cal/mol K, $\Delta G^{\ddagger} = 11.9 \pm 0.1$ kcal/mol at 235 K. Activation parameters for nitrogen inversion in **1** and other compounds are listed in Table 1.

The ^{1}H NMR spectrum (250 MHz) of **2** (3 wt/v in toluene-d_8) at 325 K shows aromatic proton multiplets at δ 7.43 (ortho protons), δ 7.20 (meta protons), and δ 7.11 (para proton), the benzylic methylene singlet at δ 3.69, the C11 bridgehead proton triplet at δ 3.41, a multiplet due to the C5 and C8 methine protons at δ 3.36 (2H), a multiplet due to the C1 and C4 methine protons at δ 2.09 (2H), and complex resonances due to the cage methylene protons at δ 1.64 (2H) and δ 1.44−1.29 (6H).

In a stable equilibrium invertomer of **2**, the benzylic methylene protons are diastereotopic. The only rate process that will effect a complete and mutual exchange of the molecular environments of the benzylic methylene protons, and coalescence of the NMR signal into a singlet, is pyramidal inversion at N10 with concerted or accompanying rotation about the *N*-benzyl bond.[2] The benzylic methylene protons signal can be used as a probe of pyramidal inversion at N10.

As shown in Figure 2S in the Supporting Information, the benzylic methylene protons show a sharp singlet at 325 K consistent with rapid inversion−rotation on the NMR chemical exchange scale. At lower temperatures, this resonance decoalesces and, at 190 K, shows an AX spectrum (δ_A 4.16, δ_X 3.22, $^2J_{AX} = -12.5$ Hz). At 190 K, the X resonance overlaps the C11 bridgehead proton triplet. The observation of a single AX spectrum at 190 K is consistent with slow inversion−rotation at N10 and fast isolated rotation about the *N*-benzyl bond.[2] The DNMR spectra of the methylene protons were simulated by invoking exchange between AX and XA spin systems.[13] The activation parameters for nitrogen inversion are $\Delta H^{\ddagger} = 11.7 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = 1.7 \pm 2$ cal/mol K, $\Delta G^{\ddagger} = 11.3 \pm 0.1$ kcal/mol at 240 K.

It is interesting to note that the chemical shift difference between the A and X benzylic methylene protons at 190 K is 0.94 ppm. In acyclic trialkylamines, this chemical shift difference is typical of methylene protons that are oriented gauche and anti to the vicinal lone pair.[2,14] While the diamagnetic anisotropy in the region of the N−N bond is different from that in a trialkylamine, this large chemical shift difference suggests a strong conformational preference for the benzyl group. Two reasonable equilibrium conformations have the phenyl group either gauche or anti to N9. The preferred conformer may be that with phenyl gauche to N9 in which the phenyl group experiences reduced nonbonded repulsions with the N9 lone pair as compared to repulsions with H11 in the anti form.

The ^{1}H NMR spectrum (250 MHz) of **3** (1 wt/v in 50% $CHFCl_2$/50% CHF_2Cl) at 200 K shows the C11 bridgehead proton triplet at δ 3.93 ($^3J_{HH} = 4.1$ Hz), a multiplet due to the C5 and C8 methine protons at δ 3.30 (2H), a multiplet due to the C1 and C4 methine protons at δ 2.07 (2H), complex overlapping resonances due to the methylene protons at δ 1.88−1.48 (8H), and the *tert*-butyl singlet at δ 1.19 (9H). The spectrum at 200 K is consistent with inversion-rotation at N10 still being rapid on the NMR chemical exchange time scale. At temperatures down to 130 K, all resonances except those due to the bridgehead proton and the *tert*-butyl group decoalesce. The most clearcut DNMR behavior is due to the C1, C4, C5, and C8 methine protons. At 130 K, the signal due to the C5 and C8 protons is decoalesced into two resonances at δ_A 3.43 and δ_B 3.21 (Figure 3S in the Supporting Information). The signal due to the C1 and C4 protons is separated into two multiplets at δ 2.36 and 2.23 at 130 K. These decoalescence phenomena are due to slowing inversion at N10 and reveal an inversion barrier that is significantly lower than that in **1** and **2**.

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The DNMR spectra due to the C5 and C8 methine proton resonance were simulated accurately by using an exchange of magnetization between the A and B nuclei of AXMY (at 130 K: δ_A 3.43, δ_X 1.60, δ_M 2.40, δ_Y 1.80, J_{AX} = 9 Hz, J_{AM} = 3, J_{AY} = 4, J_{MX} = 0, J_{XY} = 1, J_{MY} = 1) and BXMY (at 130 K: δ_B 3.21, δ_X 1.60, δ_M 2.40, δ_Y 1.80, J_{BX} = 9 Hz, J_{BM} = 3, J_{BY} = 4, J_{MX} = 0, J_{XY} = 1, J_{MY} = 1) spin systems.[13] The activation parameters for nitrogen inversion are $\Delta H^{\ddagger} = 8.8 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = 0 \pm 2$ cal/mol K, $\Delta G^{\ddagger} = 8.8 \pm 0.2$ kcal/mol at 180 K.

At temperatures below 130 K, the *tert*-butyl signal for **3** shows significant differential broadening consistent with slowing isolated *tert*-butyl rotation. At 115 K, the height of the *tert*-butyl signal is comparable to that for the methylene protons. Unfortunately, transverse relaxation is very efficient at these low temperatures, and the resultant broad lines preclude a well-defined decoalesced spectrum. The free energy of activation for *tert*-butyl rotation is estimated to be 5.3 ± 0.5 kcal/mol at 115 K. The barrier to nitrogen inversion in **3** is significantly higher than that for isolated *tert*-butyl rotation.

Discussion

Pyramidal inversion (or inversion−rotation) at the nitrogen atom of a sterically unencumbered acyclic trialkylamine is facile.[2] The inversion barrier ($\Delta G^{\ddagger}$) in diethylmethylamine is 7.9 kcal/mol at 160 K.[14] The inversion barrier in dibenzylmethylamine is 6.6 kcal/mol at 132 K.[15] Nitrogen inversion is also facile in acyclic tetraalkylhydrazines.[1] The free energy of activation for nitrogen inversion in tetrabenzylhydrazine is 8.2 kcal/mol at 168 K.[1,16] For $(i\text{-Pr})_2NNMe_2$, the inversion barrier at NMe_2 is 7.5 kcal/mol at 161 K and 5.1 kcal/mol at 113 K for inversion at $(i\text{-Pr})_2N$.[17] It is apparent that the sterically larger isopropyl group decreases the pyramidality at nitrogen resulting in a lower barrier to inversion at $(i\text{-Pr})_2N$. For *N*-alkyl substituents of comparable steric size, the barriers to inversion in trialkylamines and tetraalkylhydrazines are similar but consistently higher in the hydrazine systems, e.g., compare inversion barriers in tetrabenzylhydrazine (8.2 kcal/mol) and dibenzylmethylamine (6.6 kcal/mol). Barrier differentials can be higher in other systems.[1−10]

Incorporation of the nitrogen atom into a rigid multicyclic framework that constrains a CNC bond angle in the transition state for inversion to some value much less than 120° generates significant angle strain in the transition state and a significant increase in the barrier to inversion.[1−5,12,18] The inversion barrier in 7-methyl-7-azanorbornane is 13.8 kcal/mol[19] and 14.4 kcal/mol in 7-methyl-1,7-diazanorbornane.[19,20] In 2-methyl-1,2-diazabicyclo[2.2.2]octane, angle strain is reduced and the nitrogen inversion barrier is lowered to 7.9 kcal/mol.[10b]

The barriers to inversion in **1** and **2** are consistent with substantial N−N−C angle strain in the transition state for inversion (Table 1). The inversion barriers are 1−2 kcal/mol lower than those in 7-methyl-7-azanorbornane and 7-methyl-1,7-diazanorbornane, suggesting less angle strain in **1** and **2**. It is reasonable to assume that the multicyclic systems associated with **1** and **2** and **4** and **5** constrain the central bond angle, including the inverting nitrogen, to essentially the same degree. A respective comparison of the inversion barriers in **4** (12.2 kcal/mol)[12] and **5** (10.6 kcal/mol)[12] with those in **1** (11.9 kcal/mol) and **2** (11.3 kcal/mol) shows that the second nitrogen atom in the hydrazines does not appreciably affect the rate of inversion. In **1** and **2**, neither nitrogen lone-pair−lone-pair repulsions nor electronegativity effects seem to be major factors in determining the rate of inversion−rotation. With regard to lone-pair−lone-pair repulsions, this is not surprising because, in the transition state for inversion in **1** and **2**, the lone pairs are constrained to be orthogonal and repulsions are minimized.

In **3**, the inversion barrier is about 3 kcal/mol lower than that in the methyl and benzyl analogues (Table 1). Steric repulsions associated with the bulky *tert*-butyl group decrease the pyramidality at nitrogen, thereby decreasing the inversion barrier.[1−5] As stated above, the barrier to nitrogen inversion in **3** is significantly higher than that for isolated *tert*-butyl rotation. This contrasts with a series of *tert*-butyldialkylamines in which the barrier to isolated *tert*-butyl rotation is higher than the inversion barrier and the lowest barrier pathway for exchange of the *tert*-butyl methyl groups among different molecular environments is via a concerted inversion−rotation pathway.[21]

Experimental Section

The DNMR spectra were recorded by using a Bruker WM-250 NMR system at the University of Vermont. The NMR sample temperature was varied by using a custom-built nitrogen gas delivery system used in conjunction with a Bruker BVT-1000 temperature-control unit. Temperature measurement is accurate to ±1 K. NMR samples were prepared in precision 5-mm tubes. All spectra are referenced to tetramethylsilane at 0 ppm.

The three compounds of interest in this report were synthesized as described previously.[22]

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Supporting Information Available: Figure 2S (The ^{1}H DNMR spectra of the bridgehead, methine, and benzylic methylene protons of 10-benzyl-9,10-diazatetracyclo-[6.3.0.0.^{4,11}0.^{5,9}]undecane (**2**, 3% v/v in toluene-d_8) and theoretical simulations of the DNMR spectra due to the benzylic methylene protons). Figure 3S (The ^{1}H DNMR spectra (250 MHz) of the bridgehead proton triplet and methine protons of 10-*tert*-butyl-9,10-diazatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecane (**3**; 1 wt/v in 50% $CHFCl_2$/50% CHF_2Cl) and theoretical simulations (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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