Restricted Nitrogen Inversion in *N*-Methylpolyhalobenz-7-azanorbornadienes. ^{1}H Dynamic NMR Studies and Molecular Conformation Trapping

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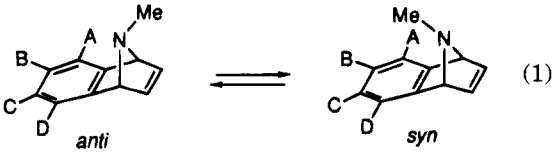
Since early, unsuccessful attempts to resolve simple chiral amines into optical isomers suggested facile inversion at the pyramidal nitrogen, identifying the critical factors that influence the rate of inversion at the pyramidal nitrogen has fascinated chemists.[1] Early studies of *N*-alkylaziridines revealed relatively high inversion barriers due to significant angle strain in the quasitrigonal transition state.[1] At that time, there were no other reported examples of restricted nitrogen inversion in simple tertiary alicyclic amines in which the internal CNC bond angles are constrained by a small ring or by incorporation into a rigid multicyclic molecular system. In 1970, one of us reported the first example of significantly restricted inversion in *N*-methylnaphthalen-1,4-imine systems including *N*-methyl-7-azatetrafluorobenzonorbornadiene (eq 1; A = B = C = D = F) and



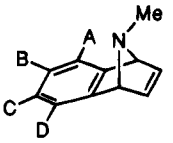
(1)

N-methyl-7-azatetrachlorobenzonorbornadiene.[2,3] The ^{1}H NMR spectrum of each compound decoalesced into two subspectra showing the presence of *syn* and *anti* conformations (eq 1). We observed that the equilibrium constant associated with eq 1 is not unity and that the free energy of activation for inversion is about 14 kcal/mol. This work showed that the invertomer ratio in eq 1 is larger for the tetrafluoro analogue (83:17) than for the tetrachloro compound (75:25). On the basis of a presumed attractive lone pair/benzene ring interaction, we suggested that the *anti* conformer is preferred. Since our report, several groups have corroborated our experimental results and extended our original study.[4–9] Recently, Malpass and co-workers have reported detailed studies of nitrogen inversion in a series of 7-azabenzonorbornadienes and 7-azadibenzonorbornadienes.[9] A MNDO calculation for 7-azanorbornadiene gives a barrier to inversion of 12.3 kcal/mol.[10]

While it is now generally believed that the *syn* conformation is the preferred invertomer in eq 1,[6,8–13] and not the *anti* as we originally suggested,[2] direct, irrefutable evidence for this preference has not been forthcoming. In this paper, we utilize molecular conformation trapping at low temperatures to provide an unequivocal assignment of conformational preference in a series of five *N*-methylpolyhalobenz-7-azanorbornadienes.[14] In addition, there have been no reports of the measurement of activation parameters for nitrogen inversion in these systems using complete dynamic NMR (DNMR) line shape simulation methods. In this paper, we report activation parameters for nitrogen inversion in five *N*-methylpolyhalobenz-7-azanorbornadienes determined by complete ^{1}H DNMR line shape simulation.

Results and Discussion

The compounds of interest in this study (**1**–**5**) are all known compounds that were synthesized by a Diels–Alder cycloaddition reaction between *N*-methylpyrrole and the appropriate polyhalobenzyne.[15]



1 A = C = Cl; B = D = H
2 A = B = D = Cl; C = H
3 A = B = C = D = Cl
4 A = C = F; B = D = H
5 A = B = C = D = F

The ^{1}H NMR spectrum (250 MHz) of **1** in $CDCl_3$ at 325 K shows differentially broadened signals due to the aromatic protons (δ 7.09; δ 6.94), the alkenyl protons (δ 6.88), the bridgehead protons (δ 4.71; δ 4.53), and the *N*-methyl group (δ 2.19). The broadening is due to the onset of slowing inversion at the pyramidal nitrogen.[2] At temperatures below 325 K, all resonances decoalesce. DNMR spectra of the *N*-methyl protons are shown in Figure 1. At slow exchange (see 240 K spectrum in Figure 1), the *N*-methyl group shows two differentially populated singlets at δ 2.34 (28%) and δ 2.15 (72%) clearly indicating the presence of two diastereomeric conformations. In one conformation, the methyl group resides over the aromatic ring (*syn* invertomer; eq 1) and,

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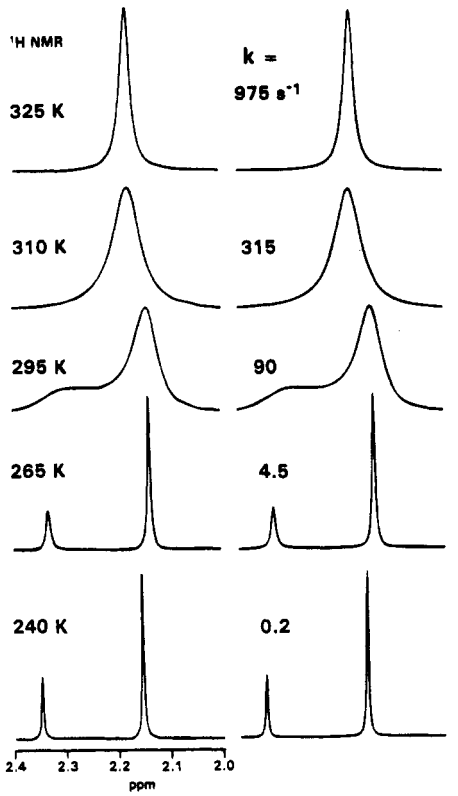

Figure 1. ^{1}H DNMR spectra (250 MHz) of the *N*-methyl group of compound **1** in $CDCl_3$. Experimental spectra are shown in the left column and theoretical simulations in the right column. The rate constant is associated with conversion of the minor (*anti*) to major (*syn*) conformation.

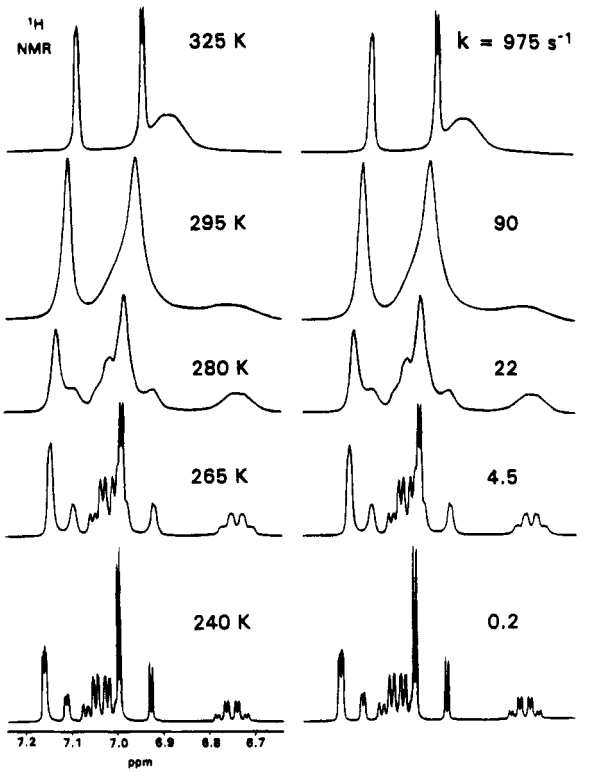

Figure 2. ^{1}H DNMR spectra (250 MHz) of the aromatic and alkenyl protons of compound **1** in $CDCl_3$. Experimental spectra are shown in the left column and theoretical simulations in the right column. The rate constant is associated with conversion of the minor (*anti*) to major (*syn*) conformation.

in the other conformation, over the alkenyl double bond (*anti* invertomer). DNMR spectra of the aromatic and alkenyl protons are shown in Figure 2. At 240 K, the NMR spectrum due to the aromatic, alkenyl, and bridgehead protons is simulated accurately by the superposition of two subspectra.[16] In the minor subspectrum (28%), there are aromatic proton chemical shifts at δ_B 7.11 and δ_F 6.92, alkenyl proton signals at δ_L 6.77 and δ_M 6.73, and bridgehead proton resonances at δ_W 4.84 and δ_X 4.70 (J_{BF} = 1.7 Hz, $J_{BL} = J_{BM} = J_{FL} = J_{FM} = J_{FW} = J_{FX} = 0$, J_{BW} = 0.7, J_{BX} = 0.3, J_{LM} = 5.0, J_{LW} = 1.9, J_{LX} = 0.3, J_{MW} = 0.3, J_{MX} = 1.9, J_{WX} = 1.6). The calculated subspectrum due to the aromatic and alkenyl protons in the minor conformation is shown in Figure 3. In the major subspectrum (72%), there are aromatic proton chemical shifts at δ_A 7.16 and δ_E 6.99, alkenyl proton signals at δ_C 7.06 and δ_D 7.01, and bridgehead proton resonances at δ_Y 4.72 and δ_Z 4.56 ($J_{AC} = J_{AD} = J_{CE} = J_{DE} = J_{EY} = J_{EZ} = 0$ Hz, J_{AE} =1.7, J_{AY} = 0.8, J_{AZ} = 0.3, J_{CD} = 5.7, J_{CY} = 2.8, J_{CZ} = 0.6, J_{DY} = 0.6, J_{DZ} = 2.8, J_{YZ} = 2.0). The calculated subspectrum due to the aromatic and alkenyl protons in the major conformation is also shown in Figure 3. Superposition of the two, properly weighted subspectra gives an accurate fit of the experimental spectrum at 240 K (Figures 2 and 3).

In the interest of obtaining accurate rates of pyramidal inversion, simulations of the complete DNMR spectra of **1** were performed.[17] Accurate simulations of the DNMR spectra of the aromatic, alkenyl, and bridgehead protons

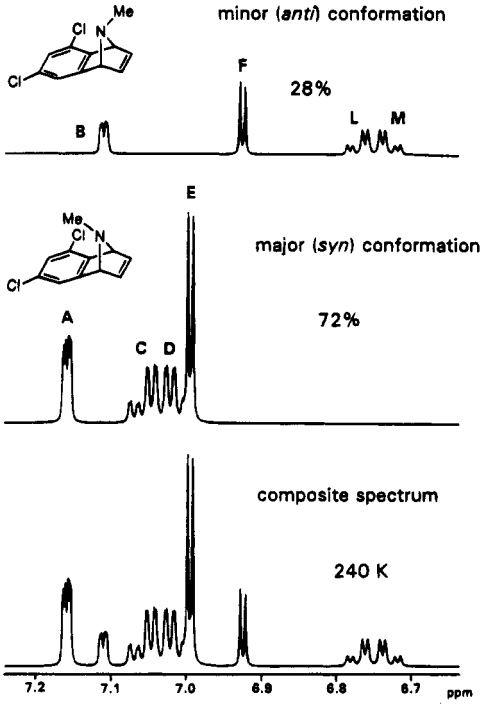

Figure 3. Decomposition of the theoretical simulation of the aromatic and alkenyl protons NMR spectrum of **1** at 240 K. Superposition of the subspectra due to the minor (*anti*) and major (*syn*) conformations produces the composite spectrum that fits the experimental spectrum at 240 K.

were achieved by using a BFLMWX (minor conformation) to AECDYZ (major conformation) exchange of magnetization (Figures 2 and 3). The DNMR spectra of the *N*-methyl group were simulated by using a simple two-

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Table 1. Activation Parameters for Conversion of the Minor (*Anti*) to Major (*Syn*) Conformation in Compounds 1–5[a]

compd	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol-K	$\Delta G^{\ddagger}$,[b] kcal/mol
1	14.9 ± 0.3	1 ± 1	14.6 ± 0.1
2	13.9 ± 0.3	−1 ± 1	14.3 ± 0.1
3	13.6 ± 0.3	−2 ± 1	14.0 ± 0.1
4	14.8 ± 0.3	0 ± 1	14.9 ± 0.1
5	13.0 ± 0.3	−4 ± 2	14.1 ± 0.1

[a] Solvent is $CDCl_3$. [b] At 280 K.

Table 2. Selected NMR and Thermodynamic Parameters for the Conformational Equilibrium in Compounds 1–5

	^{1}H chemical shift of methyl, ppm			
compd	minor conf	major conf	K_{eq}[a]	ΔG°,[b] kcal/mol
1	2.35	2.16	2.8	−0.45 ± 0.02
2	2.36	2.20	2.9	−0.47 ± 0.02
3	2.35	2.22	3.8	−0.58 ± 0.02
4	2.34	2.13	3.0	−0.48 ± 0.02
5	2.34	2.16	5.2	−0.72 ± 0.03

[a] See eq 1; solvent is $CDCl_3$. [b] At 220 K.

site exchange (Figure 1). In Figures 1 and 2, the rate constant is associated with conversion of the minor to the major conformation. Activation parameters for conversion of the minor to the major species in **1** are compiled in Table 1.

The ^{1}H DNMR spectra of the *N*-methyl group of compounds **2**–**5** are highly analogous to those for **1**. Activation parameters for conversion of the minor to major conformation in **2**–**5** were obtained by simulating the ^{1}H DNMR spectra of the *N*-methyl group (Table 1). For **2**–**5** at slow exchange, the *N*-methyl group shows a minor singlet at higher frequency (lower field) and a major singlet at lower frequency (higher field). *N*-Methyl chemical shifts, equilibrium constants, and free energy differences at 220 K are compiled in Table 2. The *N*-methyl ^{1}H NMR chemical shifts of the minor species are essentially identical in all five compounds (Table 2). The chemical shifts of the major conformation show more variation but still occur in a very narrow range. Malpass has observed similar chemical shift behavior.[9]

While there is strong consistency in the respective *N*-methyl chemical shifts of the minor and major conformations of compounds **1**–**5** (Table 2), there is nothing about the NMR spectra that allows unequivocal conformational assignments. Therefore, we turned to molecular conformation trapping to make the assignments.[14,18]

X-ray crystallography shows that the crystalline tetrafluoro compound **5** is homogeneous as the *syn* conformation (Figure 4).[19] By using the activation parameters in Table 1, it can be calculated that the half-life of either the *syn* or *anti* conformation (eq 1) is about 160 days at 150 K. At 150 K, the two conformations are essentially separate compounds that have lifetimes long enough to allow isolation on the laboratory time scale. A 10-mm NMR tube was placed in a silvered and vacuum-jacketed glass cooling chamber equipped with a viewing window. The tube was cooled to 200 K. A 1 mL sample of CD_2Cl_2 was added, and 3 mL of CHF_2Cl was condensed into the tube. The tube was cooled to 150 K and allowed to equilibrate for about 0.5 h. A 2 mg sample of **5** containing many different crystals was added to the solvent and the mixture stirred until *all* the crystals dissolved. The NMR tube was quickly transferred to a 10-mm broadband probe at 150 K and the ^{1}H NMR spectrum observed through the proton decoupling channel. The spectrum at 150 K showed one *N*-methyl singlet at δ 2.07 consistent with the conformational purity of the crystals (see spectrum a in Figure 5). This resonance must be assigned to the *syn* conformation that is present exclusively in the crystal. At 190 K, a minor singlet due to the *anti* form appears at δ 2.29 and builds up with time (see asterisked peak in Figure 5). At 200 K, the two signal intensities equilibrate rapidly (Figure 5). Therefore, the major conformation of **5** must be assigned to the *syn* conformer and the minor form to the *anti*. In the major species, the methyl group resides over the aromatic ring in agreement with previous conclusions.[9,12,13] In light of the respective essentially identical *N*-methyl chemical shifts of the major and minor conformations of compounds **1**–**5**, it is reasonable to conclude that the *syn* conformation is the major species in all five cases.

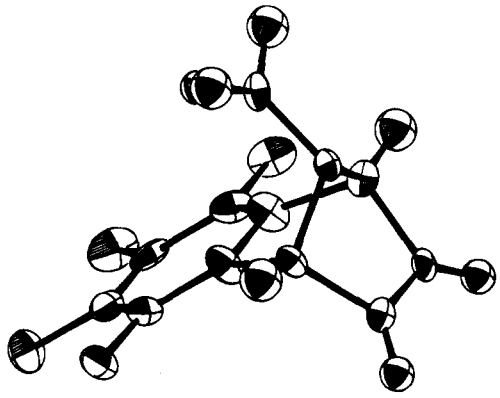

Figure 4. Molecular crystal structure of *syn*-**5**.[19]

A perusal of Table 1 shows activation parameters for conversion of the *anti* to the *syn* conformer in **1**–**5** that are similar in magnitude. At 280 K, free energies of activation for conversion of the minor to major species vary from 14.0 to 14.9 kcal/mol. There is a perceptible decrease in the enthalpy and entropy of activation with increasing halogenation of the aromatic ring. With regard to conformational preference (Table 2), increasing halogenation increases the population of the *syn* conformation. However, the differences in free energy are small and preclude any identificaton of the factors important in determining the conformational preference.

Although unusually high nitrogen inversion barriers in 7-azanorbornyl systems have been known for 25 years, there is no universal agreement about the origin of this "bicyclic effect".[1b,8,9] We believe that the extreme rigidity of the benzo-7-azanorbornadiene framework prevents the highly strained internal C–N–C bond angle (96°)[19] from opening in the quasitrigonal transition state and leads to relatively high 14–15 kcal/mol inversion barriers. Indeed, the C–C(O)–C bond angle in 7-norbornanone is also 96°,[20] the same as the corresponding bond angle in norbornane,[21] reflecting the fact that essentially no internal bond angle opening can occur for an sp^3 to sp^2 rehybridization at the 7-atom. This absence of *any* relief in the transition state for nitrogen inversion in the

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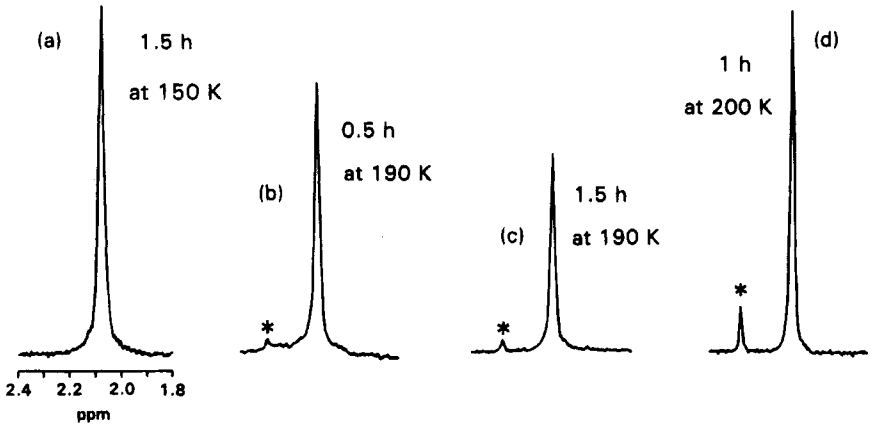

Figure 5. ^{1}H NMR spectra of the *N*-methyl group of **5** illustrating the isolation of pure *syn* conformation at 150 K and equilibration of the *syn* and *anti* (asterisk) conformations at higher temperatures.

7-azanorbornyl systems accounts for the unusually high nitrogen inversion barriers. Also consistent with this argument is the observation that the solvolysis of 7-norbornyl tosylate (sp^3 to sp^2) is 10^7 *times slower* than that for cyclohexyl and 2-propyl tosylate[22,23] and 700 000 times slower than 2-adamantyl tosylate.[23] Moreover, the solvolysis of 7-norbornyl tosylate gives *retention* of configuration, unlike normal secondary tosylates.[24] This demonstrates a tremendous hindrance to forming a carbocation at C7 of the norbornyl system. Conversely, any sp^2 to sp^3 rehybridization at C7 of the norbornyl framework is unusually facile. The sodium borohydride reduction of 7-norbornanone is, respectively, 1000 and 55 times faster than that for acetone and cyclobutanone.[25]

Barriers to nitrogen inversion in the four-membered azetidine ring system (~10 kcal/mol)[26] are significantly lower than those in compounds **1**–**5** despite the fact that the internal C–N–C bond angle in azetidines (90°–95°) is very small.[1b,19] However, the azetidine ring is inherently more flexible than the 7-azanorbornyl system and can better accommodate the quasitrigonal transition state for nitrogen inversion. Similarly, nitrogen inversion barriers are much lower for less rigid azabicyclic systems including 2-azabicyclo[2.2.2]octanes (6.6, 8.4 kcal/mol),[27,28] 6-azabicyclo[3.2.1]octane (9.2 kcal/mol),[29] 3-azabicyclo-[3.2.2]nonane (8.8 kcal/mol),[28] and 9-azabicyclo[3.3.1]-nonane (9.5 kcal/mol).[1b]

Thus, while ground state (and/or transition state) electronic stabilization (destabilization) from lone pair, σ framework mixing (repulsion) may play a role in nitrogen inversion,[1b,9] we believe that simple ring strain is the major cause of the unusually high nitrogen inversion barriers in the 7-azanorbornyl and related sytems.

Experimental Section

The NMR spectra were recorded by using a Bruker WM-250 NMR system. 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 NMR tubes. All spectra are referenced to tetramethylsilane at 0 ppm.

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