Tetrahedron Letters,Vol.29,No.29,pp 3551-3554,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CONFORMATIONAL EQUILIBRIUM ISOTOPE EFFECTS IN 3-AZABICYCLO[3.2.2]NONANES

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Summary: Conformational equilibrium isotope effects are reported for 3-azabicyclo[3.2.2]nonane-2-d_1 and the N-methyl analog. Conformations with deuterium in a gauche rather than anti alignment with the lone pair are favored.

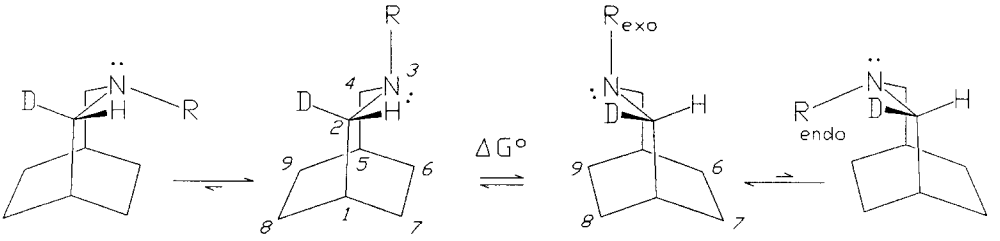
We recently reported a conformational equilibrium isotope effect (CEIE) in N-methylpiperidine-2-d_1 in which equatorial placement of deuterium at C-2 is favored over the axially deuteriated conformer by 61 ± 4 cal/mol. Anet reported similar preferences for equatorial deuterium in N,N,5,5-tetramethylhexahydropyrimidine-2-d_1 and other heterocycles.[2,3] The primary source of these effects was attributed to n-σ^* negative hyperconjugation which weakens the stretching force constant for equatorial C-H(D) bonds situated anti to a lone electron pair.

We now present CEIE data for the more conformationally restricted N-methyl-3-azabicyclo[3.2.2]nonane, **1**, and the less restricted 3-azabicyclo[3.2.2]nonane, **2**. These data not only strengthen the previous conclusion of an isotope effect of hyperconjugative origin, but also provide the basis for using CEIEs as a probe of conformation in other amines. The 3-azabicyclo[3.2.2]nonane system was chosen for the current study because it is similar in structure to piperidine in the alignment of atoms around the nitrogen, but differs importantly in steric restriction of possible conformations. An N-alkyl substituent should be heavily favored in the exo position. because in an endo position it would find strong steric interactions with the methylenes of a two-carbon bridge.

Molecular mechanics calculations using Allinger's MM2 method and parameters for amines[4] indicate that in **1** an exo N-methyl is preferred over an endo N-methyl by 8.2 kcal mol^{-1}.[5] Thus, the endo N-methyl conformation should not be populated at equilibrium. In contrast, MM2 calculations are parameterized to show only a 2.5 kcal mol^{-1} preference for an equatorial vs. axial N-methyl in N-methylpiperidine.[4] Since the extent of the contribution of an axial N-methyl group to conformational equilibria in N-methylpiperidine has been controversial,[4,6] and since NMR methods used to determine CEIEs detect only populational differences in the axial vs. equatorial location of the deuterium label and not location of the N-substituent, we thought it essential to measure the CEIE in **1**. On the other hand, in the secondary amine **2** the endo N-H conformation is expected to contribute to the equilibrium mixture, because it is predicted in MM2 calculations to be only 0.5 kcal mol^{-1} less stable than the exo N-H conformation.

That the N-methyl in **1** does prefer the *exo* position is apparent in ^{1}H NMR spectra. At -120 °C in $CFCl_3$, two $C_{2,4}$ ^{1}H resonances are found at δ_H 2.91 and 2.02 ppm, a separation of 0.89 ppm. These values are characteristic of tertiary amines in which an axial methylene hydrogen anti to the lone pair appears upfield and an equatorial hydrogen gauche to the lone pair appears downfield.[7] If the N-methyl were *endo*, all $C_{2,4}$ protons would be gauche to the lone pair and would have chemical shifts analogous to quinuclidine, δ_H = 2.95.

The results of MM2 calculations on the *exo*-*endo* equilibria as well as the isotope effects on the ring reversal equilibria are summarized in the Scheme below. No mechanism of interconversion of the *exo* conformations is implied, i.e., neither ring flip followed by N-inversion nor simultaneous ring flip and inversion.



1 R = CH_3 MM2 $\Delta E_{exo\text{-}endo}$ = 8.2 kcal mol^{-1} $\Delta G^o(2\text{-}d_1)$ = -63 cal mol^{-1}

2 R = H MM2 $\Delta E_{exo\text{-}endo}$ = 0.5 kcal mol^{-1} $\Delta G^o(2\text{-}d_1)$ = -24 cal mol^{-1}

The chair-chair (*exo*) equilibrium is degenerate and rapid in **1** at room temperature, as shown by a degenerate signal for C_6, C_7, C_8, and C_9, appearing as a singlet in a ^{1}H-decoupled ^{13}C NMR spectrum. However, the degeneracy is lifted and the equilibrium is perturbed in 1-*2*-d_1, so that each of the methylene carbons in the two-carbon bridges gives a separate signal.

Figure 1 shows the ^{1}H-decoupled 75.43 MHz ^{13}C NMR spectrum of a 1:1 mixture of **1** and 1-*2*-d_1 at 17.5 °C in $CFCl_3$. The averaged signal for $C_{6,7,8,9}$ in **1** appears at 26.37 ppm and serves as a reference. The signals for C_6 and C_9 in 1-*2*-d_1 are split symmetrically about the reference position, with a separation of 0.225 ± 0.003 ppm. This separation is temperature dependent (see Table 1), and this fact, along with the symmetrical character of the splitting, clearly indicates that it arises from a perturbed equilibrium. The C_7 and C_8 signals are also separated by 0.225 ppm, but these are shifted upfield of the C_6 and C_9 signals by a three-bond intrinsic isotope shift, $^3\Delta C(D)$, of 0.031 ppm. The C_8 and C_9 signals are upfield of the reference and C_6 and C_7 signals are downfield. These signal assignments are made possible because the C_7 signal is broadened by coupling to deuterium, $^3J_{C\text{-}D}$. The coupling from the deuterium to C_7 is expected[8] to be larger than to C_8 because C_7 is at skewed but near anti alignments (dihedral angles of 150° and 161° by MM2 calculation) to deuterium in both conformers, while C_8 would experience the average of a more skewed (35°) and a nearly perpendicular (84°) alignment. Values of $^3J_{C\text{-}D}$ = 1.1 Hz for C_7 and 0.3 Hz for C_8 may be estimated from the MM2 angles and the Karplus curve derived for $^3J_{C\text{-}H}$ by Günther.[8a]

Since C_8 and C_9 are shifted upfield by the equilibrium isotope effect, it is clear that the equilibrium is shifted to favor the conformation with the nitrogen closer to C_8 and C_9 than C_6 and C_7. The γ-substituent effect of the nitrogen will shield the closer methylenes relative to the more distant ones. The low-temperature (-123 °C), slow-exchange ^{13}C NMR spectrum of 1 shows a separation of 4.166 ± 0.003 ppm between $C_{6,7}$ and $C_{8,9}$ signals.[9] The equilibrium constant can be calculated from the 0.225 ppm equilibrium isotope shift and 4.166 ppm maximum peak separation by using Saunders' equation.[10] At 17.5 °C, K = 1.114 ± 0.002, corresponding to ΔG° = -62 ± 1 cal mol^{-1}. From the data in Table 1 and a plot of ln K vs. 1/T, analysis yields ΔH = -69 ± 2 cal mol^{-1} and ΔS = -0.023 ± 0.007 eu.

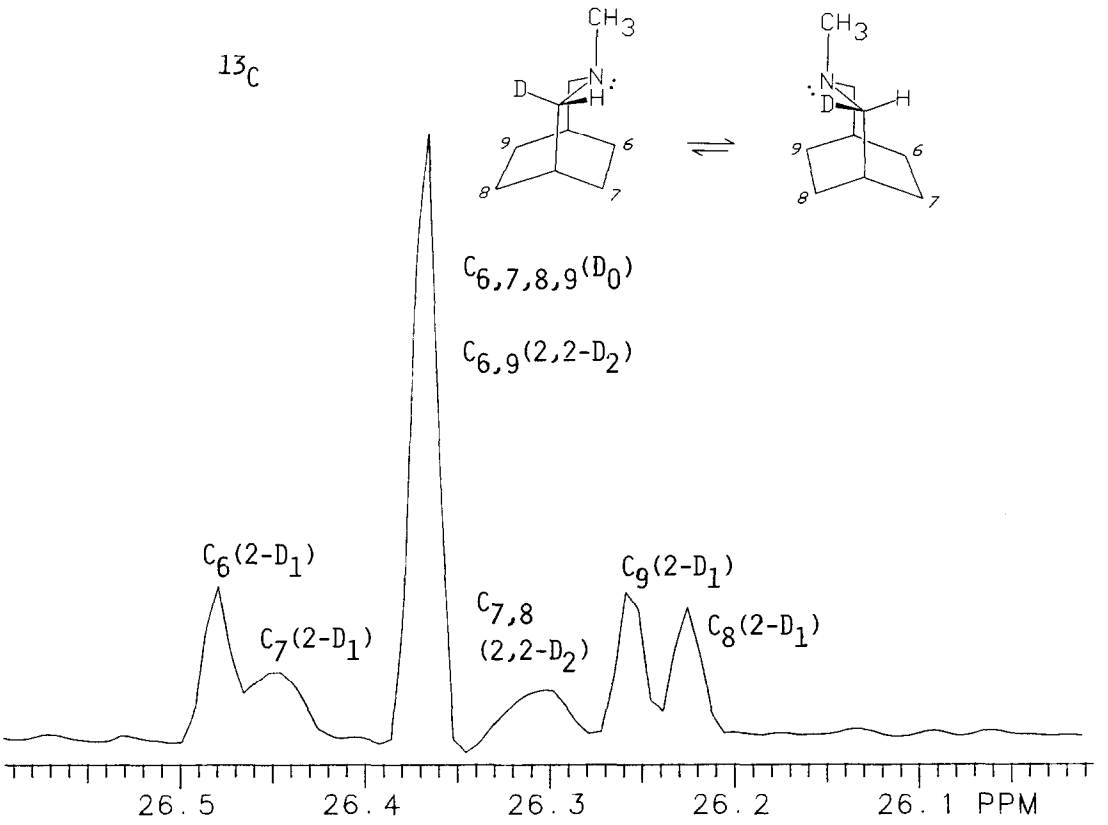


Figure 1. The $C_{6,7,8,9}$ region of a 75.43 MHz $^{13}C\{^1H\}$ NMR spectrum of a mixture of the $\underline{d}_0$, $\underline{2\text{-}d}_1$, and $\underline{2,2\text{-}d}_2$ isotopomers of 1 at 17.5 °C in $CFCl_3$.

Qualitatively similar results are found for the deuterated secondary amine, 2-$\underline{2\text{-}d}_1$. The equilibrium isotope shift between C_7 and C_8 and between C_6 and C_9 is 0.099 ± 0.003 ppm at 19.4 °C. The upfield intrinsic shift, $^3\Delta C(D)$, is 0.030 ppm at C_7 and C_8. The low-temperature (-148 °C) peak separation between $C_{6,7}$ and $C_{8,9}$ is 4.746 ± 0.003 ppm.[11] At 19.4 °C, K = 1.043 ± 0.002, corresponding to ΔG° = -24 ± 1 cal mol^{-1}. Analysis of data in Table 1

gives $\Delta H = -15 \pm 1$ cal mol^{-1} and $\Delta S = 0.032 \pm 0.006$ eu.

Table 1. Temperature Dependence of Isotope Shifts

	1-2-d_1			2-2-d_1*			2-2-d_1*	
δ, ppm	K_{eq}	temp, °C	δ	K	temp	δ	K	temp
0.225	1.114	17.5	0.099	1.042	20.2	0.098	1.042	19.4
0.236	1.120	3.5	0.101	1.044	12.5	0.106	1.046	-16.7
0.258	1.132	-17.1	0.108	1.050	-16.8	0.113	1.049	-36.8
0.282	1.145	-37.1	0.119	1.051	-47.5	0.120	1.052	-57.7
						0.130	1.056	-77.3

*From two separate experiments

The isotope effects in **1** and **2** favor the conformation with the C-D in a gauche rather than anti alignment with the lone pair. This is consistent with the placement of deuterium in the more stiffly bound position, since the anti C-H(D) bond is expected to be weakened by negative hyperconjugation.[1-3] The 62 ± 1 cal mol^{-1} effect in 1-2-d_1 is essentially identical to the 61 ± 4 cal mol^{-1} effect in N-methylpiperidine-2-d_1,[1] confirming this value as properly representing the isotope effect on the anti-gauche fractionation of a methylene deuterium interacting with the lone pair of a tertiary amine. Thus, the value of 62 cal mol^{-1} could be used as a standard to deduce conformations in other amines on the basis of the magnitude of the isotope effect.

We attribute the much smaller isotope effect of 24 cal mol^{-1} for the secondary amine to a significant contribution of N-H_{endo} structures in the conformational equilibria. In both of the N-H_{endo} structures, the C-D bond is gauche to the lone pair, so that any isotope effect on the equilibrium between endo conformers should be very small. Therefore, to the extent that N-H_{endo} structures are present, the apparent isotope effect on the ring-reversal equilibrium will be reduced. There could also be a substituent effect on the lone pair interaction with C-H(D) bonds in N-H_{exo} structures. We are currently examining the substituent dependence of this type of isotope effect through a combination of experimental and theoretical approaches.

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(Received in USA 11 March 1988)