alternative mechanisms, one can gain deeper insights into how to construct better oscillatory mechanisms. The negative feedback scheme suggested in this work is only one of many possible patterns that are sufficient to generate oscillation when coupled to a similar positive feedback loop. Other types will be discussed elsewhere.

The proposed mechanism gives good agreement with the major observations on the rich dynamics of this exceedingly complex system. The remaining discrepancies with the experiments clearly call for further refinement or revision. Though the intermediates suggested must still be considered hypothetical, the calculations presented here suggest new approaches to the extremely difficult problem of mechanistic oxysulfur chemistry.

Acknowledgment. This work was supported by Grant CHE-8800169 from the National Science Foundation and by a U. S.-Hungarian cooperative grant from the NSF (INT-8613532) and the Hungarian Academy of Sciences.

Registry No. H_2O_2, 7722-84-1; SCN^-, 302-04-5; Cu, 7440-50-8.

Conformational Analysis via NMR Isotope Shifts. Side-Chain Equilibria in *N*-Alkylpiperidines

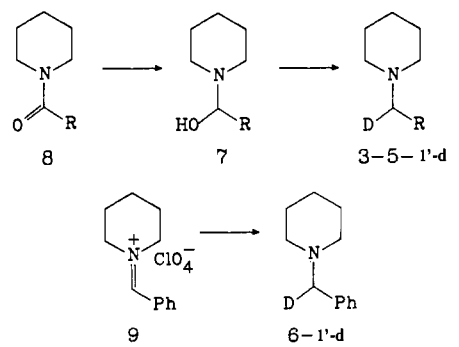
David A. Forsyth* and Vichukorn Prapansiri

Contribution from the Department of Chemistry, Northeastern University, Boston, Massachusetts 02115. *Received October 5, 1988*

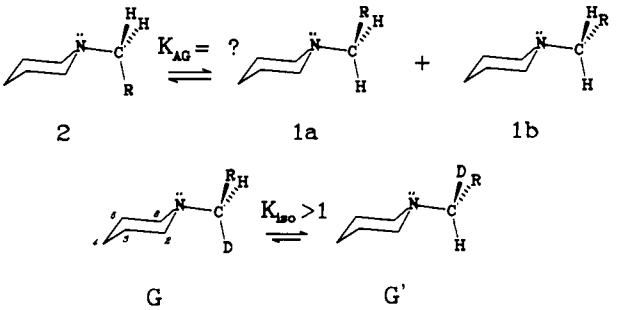
Abstract: Conformational equilibria involving the *N*-alkyl side chain of *N*-alkylpiperidines were detected via NMR isotope shifts. Introduction of a single deuterium at C1′ of the side chain causes a gauche ⇄ gauche equilibrium to be nondegenerate and observable by the separation of signals for C2 and C6 in ^{13}C NMR spectra at low temperature. The separation is temperature dependent, as expected for an equilibrium isotope effect. Actual K_{iso} and $\Delta G°_{iso}$ for the isotopically perturbed equilibrium cannot be directly calculated by the application of Saunders' equation because the equilibration process is too rapid to obtain the maximum chemical shift difference between C2 and C6 at the slow exchange limit. Nonetheless, some useful estimates of these values can be made. The observations can be accounted for by the presence of both gauche and anti conformers in the equilibrium. MM2 calculations using Allinger's parameters for amines also support the conclusion that both gauche and anti conformers are present, with the proportion of gauche conformers declining in the sequence *N*-ethylpiperidine > *N*-propylpiperidine, *N*-butylpiperidine > *N*-benzylpiperidine.

Isotope effects on NMR chemical shifts can be used to differentiate equilibrating systems from static structures.[1] The technique is particularly well suited to detect degenerate equilibria, which have low energy barriers and are thus too rapid to be accessible by other NMR techniques. Bushweller et al. have demonstrated that some conformational equilibria occurring via C–N bond rotations in amines occur too rapidly to be detectable by ordinary dynamic NMR techniques.[2] For example, even at the temperature of 99 K where nitrogen inversion and one C–N bond rotation process were slow on the NMR time scale, it was still not possible to determine with certainty whether the major conformer of diethylmethylamine actually had C_s symmetry or simply time-averaged symmetry due to very rapid C–N bond rotations.[2] In this paper we explore the application of the isotopic perturbation method to conformational analysis of acyclic alkyl chains of tertiary amines, with the specific example of *N*-alkylpiperidines. It has recently been reported that substantial conformational equilibrium isotope effects (CEIE)[3] are associated with deuteriation adjacent to the nitrogen in cyclic amines.[4-6] If this type of effect accompanies deuteriation of acyclic alkyl groups, it could be used to advantage in conformational analysis.

Scheme I



N-(*n*-Alkyl)piperidines can be assumed to have gauche **1** and/or anti **2** conformations, defined by the alignment of alkyl substituents relative to the nitrogen lone pair. In the case of the gauche conformation, there would be two isoenergetic enantiomeric structures, **1a** and **1b**. Interconversion among these three possible



(1) (a) Saunders, M.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8071. (b) Saunders, M.; Kates, M. R.; Wiberg, K. B.; Pratt, W. *J. Am. Chem. Soc.* **1977**, *99*, 8072. (c) For a recent review, see: Siehl, H. U. *Adv. Phys. Org. Chem.* **1987**, *23*, 63.

(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) Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663.

(4) Anet, F. A. L.; Kopelevich, M. *J. Chem. Soc., Chem. Commun.* **1987**, 595.

(5) Forsyth, D. A.; Hanley, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 7930.

(6) Forsyth, D. A.; Prapansiri, V. *Tetrahedron Lett.* **1988**, *29*, 3551.

0002-7863/89/1511-4548$01.50/0

Table I. ^{13}C Chemical Shifts[a] of **3–6** at 195 K in CF_2Cl_2

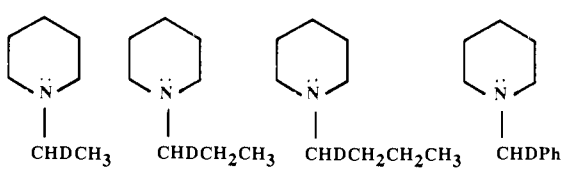
compd	C2,6	C3,5	C4	C1′	C3′	C4′	C5′
3	54.86	26.43	25.37	53.71	12.64		
4	55.38	26.57	25.42	62.33	20.80	12.38	
5	55.41	26.60	25.45	60.21	30.16	21.67	14.74
6	55.29	26.63	25.22	64.74	139.67[b]	129.77[b]	128.82[b] 127.58[b]

[a] ppm from internal standard TMS. [b] Aromatic carbons.

conformers should be a rapid process with an energy barrier low enough (<5 kcal/mol) to be under the limit of detection by the usual dynamic NMR methods.[7] Even at a temperature low enough to slow the ring reversal and nitrogen inversion on the NMR time scale, the conformational preference of the side chain is still undetectable in ordinary NMR spectra (vide infra). However, the degeneracy of the possible gauche ⇄ gauche (**1a** ⇄ **1b**) equilibrium could be removed by substituting a single deuterium label into the side chain at C1′. With the equilibrium between labeled gauche conformers G and G′ being nondegenerate, the time-averaged equivalence of C2 and C6 in the piperidine ring is removed, at least in principle. Thus, the observation in ^{13}C spectra of the labeled compound of a temperature-dependent separation of C2 and C6 signals arising from the isotopically perturbed equilibrium would provide evidence that the gauche conformation is populated. The introduction of a single deuterium makes C2 and C6 diastereotopic and hence formally chemical shift nonequivalent even without a perturbed equilibrium. However, such nonequivalence could only be observed if the intrinsic isotope shifts were measurably different at C2 and C6. Such intrinsic shifts would not be expected to be temperature dependent.

Results and Discussion

Detection of Gauche Conformers. Four *N*-alkylpiperidines labeled with a single deuterium at C1′ of the side chain were prepared for this investigation: *N*-ethylpiperidine-*1′-d*$_1$ (**3**-*1′-d*$_1$), *N*-propylpiperidine-*1′-d*$_1$ (**4**-*1′-d*$_1$), *N*-butylpiperidine-*1′-d*$_1$ (**5**-*1′-d*$_1$), and *N*-benzylpiperidine-*1′-d*$_1$ (**6**-*1′-d*$_1$). Compounds **3**-



3-1′-d_1 **4**-1′-d_1 **5**-1′-d_1 **6**-1′-d_1

5-*1′-d*$_1$ were prepared, as shown in Scheme I, by in situ reduction of aminols **7** with lithium aluminum deuteride (LAD). The aminols were obtained by partial reduction of the amides **8** with lithium triethoxyaluminum hydride ($LiAl(OEt)_3H$) by a modified method of Brown.[8] Compound **6**-*1′-d*$_1$ was prepared by reduction of the perchlorate salt **9** by LAD in anhydrous ether solution.[9] Unlabeled **3–6** were prepared in LAH reductions of the amides **8**, and **3**-*1′,1′-d*$_2$ was prepared by LAD reduction of the corresponding amide.

At room temperature the 75.43-MHz ^{13}C NMR spectra of compounds **3–6**-*1′-d*$_1$ show degenerate signals of C2 and C6 ring carbons due to a rapid ring reversal (E_a = 14.6 kcal mol^{-1} for *N*-methylpiperidine) and nitrogen inversion (low barrier).[10] However, at temperatures low enough that ring reversal becomes slow on the NMR time scale (215 K), a split signal of C2 and C6 is seen. These signals are degenerate in the unlabeled compounds. For example, Figure 1 shows ^{13}C NMR spectra of the C2 and C6 region of a 1:1 mixture of **3** and **3**-*1′-d*$_1$ at room temperature in $CFCl_3$ and at 195 K in CF_2Cl_2. At room temperature (293 K), two signals for C2 and C6 are seen in the ^{13}C NMR spectrum (Figure 1a). The upfield signal corresponds to C2,6 of the **3**-*1′-d*$_1$ isotopomer, which is shifted upfield by 0.032 ± 0.010 ppm from the unlabeled **3** by the intrinsic isotope shift over three bonds, $^3\Delta C(D)$.[11] However, three signals are seen at lower temperature (195 K; Figure 1b). The middle, taller peak belongs to the C2,6 signal of unlabeled **3** while the C2 and C6 signals of **3**-*1′-d*$_1$ are separated by 0.335 ± 0.010 ppm, and the average position is 0.034 ± 0.010 ppm upfield of the signal for unlabeled compound. This average upfield shift is the same average $^3\Delta C(D)$ intrinsic isotope effect seen for the C2,6 signal at room temperature. The chemical shift separation of the C2 and C6 signals of **3**-*1′-d*$_1$ is 1 order of magnitude larger than the average intrinsic shift and will be considered as the equilibrium NMR isotope shift, δ_{eq}.[12]

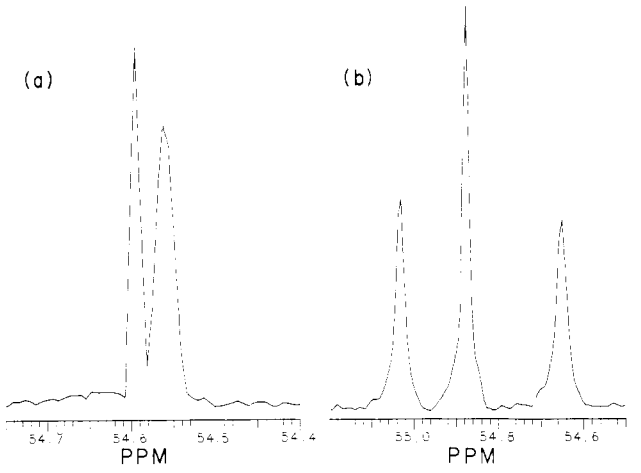


Figure 1. C2,6 region of a 75.43-MHz $^{13}C\{^1H\}$ NMR spectra of a mixture of **3** and the **3**-*1′-d*$_1$ isotopomer (a) at 293 K in $CFCl_3$ and (b) 195 K in CF_2Cl_2. Resolution-enhancing weighting functions were applied.

Similar results were found for the *N*-propyl-, *N*-butyl-, and *N*-benzylpiperidines, **4–6**. The ^{13}C chemical shifts for unlabeled **3–6** are listed in Table I for solutions in CF_2Cl_2 at 195 K. Table II summarizes the average intrinsic isotope shifts, $^3\Delta C(D)$, and the equilibrium isotope shifts, δ_{eq}, observed at different temperatures for C2 and C6 of **3–6** due to the substitution of a single deuterium at C1′.

The temperature-dependent separation of signals that are equivalent in the absence of labeling is diagnostic of isotopic perturbation of a degenerate equilibrium.[1] In **3–6**-*1′-d*$_1$, the isotope effect on the equilibrium results in one of the C2,6 signals moving upfield and the other moving downfield by an equal amount. Clearly, this is strong evidence that the gauche conformation is populated. Unequal weighting of the two gauche conformers G and G′ due to the isotope effect provides slightly different time-

(7) (a) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982. (b) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH Publishers: Weinheim, FRG, 1985.
(8) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.
(9) (a) Cervinka, O. *Collect. Czech. Chem. Commun.* **1961**, *26*, 673; **1965**, *30*, 2403. (b) Leonard, N. J.; Pankstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.
(10) (a) Lambert, J. R.; Oliver, W. L., Jr.; Packard, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 933. (b) The conformation with the *N*-alkyl group in the axial position can be safely ignored since such conformations are insignificantly populated in *N*-alkylpiperidines. See: Crabb, T. A.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 1, and references therein.
(11) For leading references on three-bond intrinsic isotope shifts, see: (a) Majerski, Z.; Zuanic, M.; Metelko, B. *J. Am. Chem. Soc.* **1985**, *107*, 1721. (b) Aydin, R.; Frankmölle, W.; Schmalz, D.; Günther, H. *Magn. Reson. Chem.* **1988**, *26*, 408.
(12) In principle, the chemical shift separation between C2 and C6 is not precisely δ_{eq}, because C2 and C6 may have different intrinsic shifts in a single gauche conformation. In practice, both will experience nearly the same average intrinsic shift because the isotope effect on the equilibrium is small. Any correction to δ_{eq} will also be minor since it is 1 order of magnitude larger than the intrinsic shifts.

Table II. Equilibrium and Average Intrinsic Isotope Shifts at C2,6 of 3–6-*1′-d* in CF_2Cl_2

compd	temp, K	δ_{eq}, ppm	$^3\Delta C(D)^a$
3-*1′*-d_1	215.7	0.323	0.041
	194.9	0.376	0.037
	174.9	0.432	0.035
	154.8	0.504	0.033
	134.8	0.614	0.027
	124.4	0.714	0.019
4-*1′*-d_1	195.0	0.314	0.040
	174.9	0.360	0.037
	154.9	0.417	0.038
	134.7	0.473	0.036
	124.7	0.544	0.021
5-*1′*-d_1	214.9	0.267	0.033
	194.9	0.322	0.035
	174.8	0.356	0.037
	154.9	0.409	0.042
	134.7	0.469	0.044
6-*1′*-d_1	195.0	0.143	*b*
	174.8	0.168	*b*
	154.7	0.189	*b*
	134.7	0.210	*b*

[a] Upfield shift in ppm of average position of C2 and C6 signals. [b] Not measured; δ_{eq} values were determined without unlabeled **6** in solution.

averaged environments for C2 and C6.

Although in this particular case there is no independent evidence of the direction in which the G,G′ equilibrium is perturbed, it is expected that the equilibrium will favor placement of the deuterium gauche to the lone pair.[4-6] In the numbering scheme shown for G and G′, C2 would then move downfield and C6 upfield, because C6 would experience more of the shielding effect of the *gauche*-alkyl chain.

Qualitatively, simple observation of the δ_{eq} for C2,6 indicates that the gauche conformers exist, but it does not indicate the relative gauche, anti populations. Both the populations of the two types of conformers and the magnitude of the isotope effect could be determined if it were possible to obtain separate signals for each conformer by slowing down the C1′–N bond rotation to the slow exchange limit. However, we were unable to freeze out the low barrier process of C–N bond rotation or even see any exchange-broadened lines at 125 K. Thus, quantitation of the gauche and anti populations can only be tackled through the less direct means of using model compounds to estimate the chemical shift difference between C2 and C6 in the frozen-out gauche conformer and by making assumptions about the magnitude of the isotope effect.

It may also be noted in Table II that the average intrinsic isotope shifts, $^3\Delta C(D)$, display a dependence on temperature. Intrinsic isotope shifts usually show little temperature dependence. For comparison, we have also determined $^3\Delta C(D)$ for the dideuteriated 3-*1′,1′*-d_2 in CF_2Cl_2 at various temperatures [temp (K), $^3\Delta C(D)$ (ppm)]: 293.4, 0.069 (in $CFCl_3$); 215.0, 0.065; 194.9, 0.068; 174.8, 0.069; 154.7, 0.066. Clearly, the $^3\Delta C(D)$ do not change significantly with temperature for this isotopomer in which the ratio of the two gauche conformers will remain at 1:1. However, in the 3-*1′*-d_1 isotopomer, the two gauche conformers G and G′ have different alignments of the C–D bond with respect to C2 and C6. The changing ratio of the two conformers should produce some variation in the $^3\Delta C(D)$ values because $^3\Delta C(D)$ is known to depend upon the dihedral angle.[11]

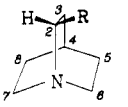
Magnitude of Isotope Effect and Gauche vs Anti Populations. The equilibrium constant, K_{iso}, for an isotopically perturbed degenerate equilibrium can be calculated from an observed δ_{eq} value by applying Saunders' equation[13] (eq 1) where Δ represents the

$$K_{iso} = (\Delta + \delta_{eq})/(\Delta - \delta_{eq}) \quad (1)$$

maximum possible signal separation, determined at the slow exchange limit. In the present study, δ_{eq} is the isotopically induced separation of signals for C2 and C6, and Δ is the chemical shift difference between C2 and C6 in a frozen-out gauche conformer. However, there are two problems preventing direct application of Saunders' equation: (i) the Δ values are unknown in **3–6**; (ii) to the extent that the anti conformation is populated, the apparent free energy change, $\Delta G°_{iso}$, associated with the isotope effect will be proportionately reduced below the true value (the extreme case of 100% anti would show no δ_{eq} and thus apparent values of $K_{iso} = 1$ and $\Delta G°_{iso} = 0$).

A starting point for analysis is to assume that only gauche conformers are present. The magnitude of the apparent isotope effect obtained from eq 1 at different temperatures may then be compared with other indicators of the likely magnitude of the isotope effect. An approximate determination of anti population can then be achieved by attributing any reduction below the expected magnitude to the presence of the anti conformer.

Since the Δ values are unknown, they must be estimated from suitable model compounds. We propose 2-alkylquinuclidines **10** as suitable models for the *gauche-N*-alkylpiperidine conformers in regard to structural features around the nitrogen atom. They are analogous in that the substituent R in **10** is gauche to C6 and anti to C7, much as the alkyl chain is gauche to C2 and anti to C6 in the G conformation of piperidines. Therefore, the chemical shift differences between C6 and C7 in series **10** will be used to represent the C2–C6 shift differences at frozen-out equilibrium in the related *N*-alkylpiperidines.

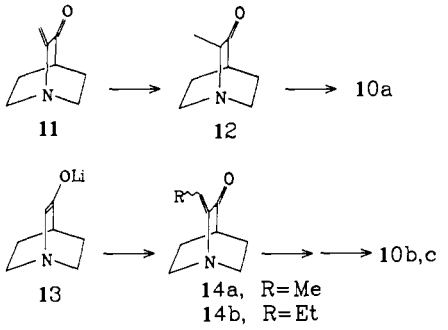


10a, R = Me
b, R = Et
c, R = Pr
d, R = Ph

Scheme II shows the preparative outline of compounds **10**. Compound **10a** was prepared in two steps from 2-methylene-3-quinuclidinone (**11**) by catalytic hydrogenation[14] to **12**, followed by Huang–Minlon reduction.[15] Compounds **10b** and **10c** were obtained by a modification of Stotter's method.[16] Reaction between the lithium enolate of 3-quinuclidinone (**13**) and appropriate aldehydes led to the 2-alkylidene-3-quinuclidones **14** after workup. Catalytic hydrogenation followed by Huang–Minlon reduction ultimately gave the desired **10b** and **10c**. This approach is not applicable to the synthesis of **10d**.

^{13}C chemical shifts of compounds **10a–10c** are listed in Table III. From the shift differences between C6 and C7 in Table III, estimated Δ values between C2 and C6 for use in eq 1 are 8.818 ppm for **3**, 8.746 ppm for **4**, and 8.447 ppm for **5**. An arbitrarily selected Δ value of 8.000 ppm will be used for **6**.

Scheme II



(13) Saunders, M.; Telkowski, L.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8070.

(14) Augustine, R. L. *J. Org. Chem.* **1958**, *23*, 1853.

(15) Morgan, T. K., Jr.; Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 2259.

(16) Stotter, P. L.; Friedman, M. D.; Minter, D. E. *J. Org. Chem.* **1985**, *50*, 29.

Table III. ^{13}C NMR Chemical Shifts[a] of Compounds **10a–c** in $CDCl_3$

compd	C2	C3	C4	C5	C6	C7	C8	C1′	C2′	C3′
10a	51.054	35.107	22.109	26.868	40.847	49.692	25.378	20.991		
10b	57.627	33.608	21.755	26.673	41.232	49.641	25.589	28.301	10.998	
10c	55.487	34.007	21.821	26.814	41.274	49.729	25.680	37.831	19.622	14.039

[a] Referenced to $CDCl_3$ (77.00 ppm); ±0.007 ppm. Assignments are based on the chemical shifts for quinuclidine (Wenkert, E., Bindra, J. S.; Chang, C. J.; Cochram, D. W.; Schell, F. M. *Acc. Chem. Res.* **1974**, *7*, 46) and expected γ- and δ-substituent effects (Duddeck, H. *Top. Stereochem.* **1986**, *16*, 219).

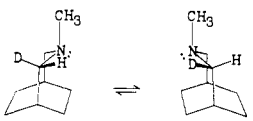
Table IV. Apparent Equilibrium Constants, K_{iso}, from Equation 1 and Derived Thermodynamic Values for the Isotopically Perturbed G ⇄ G′ Process

compd	temp, K	K_{iso}	$-\Delta G°_{iso}$, cal/mol	$-\Delta H°_{iso}$,[a] cal/mol	$\Delta S°_{iso}$,[a] eu
3-*1′*-d_1	215.7	1.076	31.3	50 ± 2	−0.09 ± 0.01
	194.9	1.089	33.0		
	174.9	1.103	34.1		
	154.8	1.121	35.2		
	134.8	1.149	37.2		
	124.4	1.176	40.1		
4-*1′*-d_1	195.0	1.074	27.7	35 ± 2	−0.04 ± 0.02
	174.9	1.086	28.7		
	154.9	1.100	29.3		
	134.7	1.114	28.9		
	124.7	1.133	30.9		
5-*1′*-d_1	214.9	1.065	26.9	34 ± 2	−0.03 ± 0.01
	194.9	1.079	29.4		
	174.8	1.088	29.3		
	154.9	1.102	29.9		
	134.7	1.118	29.8		
6-*1′*-d_1	195.0	1.038	14.4	13 ± 1	0.001 ± 0.003
	174.8	1.043	14.6		
	154.7	1.048	14.4		
	134.7	1.054	14.1		

[a] Errors given are 1 standard deviation in these values from a simple linear regression, not including probable systematic error from neglect of anti isomer in the equilibrium (see text).

Use of the estimated Δ and observed δ_{eq} values in eq 1 gives the apparent equilibrium constants K_{iso}, which are listed in Table IV, for the isotopically perturbed G ⇄ G′ equilibria for **3–6**-*1′*-d_1. It is important to note that the K_{iso} are minimum values, calculated with the assumption that only the gauche conformations are populated. The associated $\Delta G°_{iso}$ are also listed in Table IV, as are the derived $\Delta H°_{iso}$ and $\Delta S°_{iso}$. Two features of these data suggest that the anti conformers also contribute. First, the $\Delta G°_{iso}$ are smaller than anticipated from comparison with stretching frequencies of the C–D bonds. Second, the pattern of variation in $\Delta G°_{iso}$ with temperature differs notably between **3**-*1′*-d_1, where $\Delta G°_{iso}$ increases in magnitude from −32 cal/mol at 215 K to −40 cal/mol at 124 K, and **6**-*1′*-d_1, where $\Delta G°_{iso}$ is nearly constant.

Previous studies of conformational equilibrium isotope effects in heterocycles have demonstrated that CEIEs associated with deuteriation adjacent to a heteroatom can be accounted for largely by zero-point energy contributions associated with C–H stretching frequencies.[4-6] The stretching motions of C–H bonds anti to a lone pair occur at lower frequency (Bohlmann bonds in amines[17]) than those of gauche C–H bonds, probably because of n–σ* (negative) hyperconjugation. For example, the conformational equilibrium for *N*-methyl-3-azabicyclo[3.2.2]nonane-*2*-d_1 (**15**)



15

exchanges C–H and C–D bonds of the C2 methylene between gauche and anti positions with respect to the lone pair. We found a CEIE for **15** of $\Delta G°_{iso}$ = 62 cal/mol at 291 K.[6] We now report that **15** shows C–D stretching bands in the IR at 2149 and 2033 cm^{-1}. A predicted isotope effect of 58 cal/mol may be calculated from the C–D stretching frequencies, by assuming that ν_{CH}/ν_{CD} is about 1.35[18] and by finding the difference in the sum of C–H and C–D stretching frequencies for the two conformers.

The G ⇄ G′ equilibria also exchange C–H and C–D bonds between gauche and anti alignments with respect to the lone pair. Thus, an estimate of the expected isotope effect on the relative energy content of the G and G′ conformers may be found from the difference between the sums of C–H and C–D stretching frequencies for each conformer. In IR spectra of **3–6**-*1′*-d_1, C–D stretching bands are found in the regions around 2050 and 2150 cm^{-1}, which we assign to the C–D(anti) and C–D(gauche) bonds, respectively. Specific differences between the positions of these two bands for each isotopomer are the following: **3**-*1′*-d_1, 98 cm^{-1}; **4**-*1′*-d_1, 104 cm^{-1}; **5**-*1′*-d_1, 104 cm^{-1}; **6**-*1′*-d_1, 96 cm^{-1}.[19] The frequency differences correspond to predicted isotope effects of 49, 52, 52, and 48 cal/mol for the *1′*-d_1 isotopomers of **3–6**, respectively.

We expect that the entropy component of the true $\Delta G°_{iso}$ should be small since the gauche conformers are enantiomeric in the absence of the label. For **15**, which interconverts only between two forms, a previous study found $\Delta S°_{iso}$ = −0.023 eu.[6] Similarly, $\Delta S°_{iso}$ is −0.003 eu for *N*-methyl-2-azabicyclo[2.2.2]octane-*3*-d_1.[20]

If we make the simplifying approximation that $\Delta S°_{iso}$ is zero, then the magnitude and temperature variation of the apparent $\Delta G°_{iso}$ in Table IV could be attributed to changes in the gauche–anti ratio. Each apparent $\Delta G°_{iso}$ can only be a fraction of the true $\Delta G°_{iso}$, with the fraction corresponding to the proportion of the amine existing in the gauche form. The apparent $\Delta G°_{iso}$ would be zero if the gauche conformation were unpopulated and could approximate the true value only if there were no anti conformer present. For example, when the $\Delta G°_{iso}$'s at 195 K in Table IV are compared to the predicted energy differences predicted from the C–D stretching frequencies, the proportion of gauche is calculated to be 67% for **3**, 53% for **4**, 56% for **5**, and 30% for **6**. These percentages are of course sensitive both to the Δ values that were used to derive the K_{iso} values and to the predicted isotope effects from the infrared stretching frequencies. Thus, rather than use these percentages directly, we will take a more conservative approach and only use the trends that are not sensitive to the possible errors in these values. Specifically, the magnitudes of the apparent $\Delta G°_{iso}$ and the percentages of gauche conformer occur in the sequence **3** > **4**,**5** > **6**. Further, the magnitude of $\Delta G°_{iso}$ increases with decreasing temperature for **3**, increases slightly for **4** and **5**, and is constant or slightly declines for **6**.

There are two gauche forms and only one anti, so the gauche conformation is statistically favored, i.e., favored with respect to entropy by $R(\ln 2)$. If this were the only (or dominant) contribution to entropy and if the anti ⇄ gauche equilibrium were thermoneutral ($\Delta H°_{AG}$ = 0), the proportion of gauche would be 67% at all temperatures. If $\Delta H°_{AG}$ is negative, favoring the

(17) (a) Bohlmann, F. *Ber. Dtsch. Chem. Ges.* **1958**, *91*, 2157. (b) Hamlow, H. P.; Okuda, S.; Nakagawa, N. *Tetrahedron Lett.* **1964**, 2553. (c) Krueger, P. J.; Jan, J. *Can. J. Chem.* **1970**, *48*, 3229. (d) McKean, D. C. *Chem. Soc. Rev.* **1978**, *7*, 399.

(18) Krueger, P. J.; Jan, J. *Can. J. Chem.* **1970**, *48*, 3236.

(19) These are the differences between the positions of the most intense absorptions. Since the anti conformer is also thought to be present in each case, its C–D bands must overlap and hence could skew the observed difference. In the case of **6**-*1′*-d_1, two bands of nearly equal intensity are observed at 2160 and 2141 cm^{-1}; the reported difference is between a 2054-cm^{-1} band and the average position of 2150 cm^{-1}.

(20) Unpublished results.

gauche form, the proportion of gauche will be above 67% and will increase with decreasing temperature. If $\Delta H°_{AG}$ is positive, the proportion of gauche will decrease with decreasing temperature. On the basis that the changing proportion of gauche vs anti forms should be reflected in the $\Delta G°_{iso}$ values, the increase in magnitude of $\Delta G°_{iso}$ for **3** as the temperature decreases suggests that the gauche form is enthalpically favored. The $\Delta G°_{iso}$'s for **4** and **5** show a lesser increase and thus a less favorable enthalpy for the gauche form. For **6**, $\Delta G°_{iso}$ is constant or possibly decreases slightly with lower temperature, indicating either thermoneutrality or enthalpy slightly favoring the anti form.

For comparison with the above analysis, we have performed molecular mechanics calculations with the MM2 method and parameters of Allinger.[21] The MM2 calculations predict that the gauche conformation is energetically favored in all four cases but by less than 1 kcal/mol. The predicted energy differences (not including the statistical entropy component) for the anti $\rightleftarrows$ gauche equilibrium are the following: **3**, −0.88 kcal/mol; **4**, −0.85 kcal/mol; **5**, −0.82 kcal/mol; **6**; −0.69 kcal/mol. The MM2 results are in excellent qualitative agreement with our conclusions that the anti conformers are present and that the gauche–anti ratios occur in the order **3** > **4**,**5** > **6**. However, our analysis suggests energy differences nearer thermoneutrality between the anti and gauche conformers.

Conclusions

The isotopic perturbation method has obvious utility for detection of conformers that may interconvert too rapidly to be distinguished from a symmetrical conformer. However, if it is necessary to use this tool because the equilibration is very rapid, then the information gained will of necessity be qualitative, because accurate chemical shifts at the slow exchange limit can not be measured. In the present case of the *N*-alkylpiperidines, the presence of the gauche conformers is demonstrated, but many approximations, assumptions, and sources of error are involved in attempting to extract quantitative information about the gauche–anti ratio from the observed equilibrium NMR isotope shifts. The two major sources of uncertainty in deriving such ratios are the chemical shift differences (Δ values) from model compounds and the predicted isotope effects from C–D stretching frequencies. Nevertheless, we are convinced that the attempt does lead to useful conclusions, albeit not very precise. Namely, we conclude that both the anti and gauche conformers are present to an appreciable extent in **3**–**6** and that the proportion of the gauche conformers declines in the sequence **3** > **4**,**5** > **6**. The gauche conformers are favored over the anti conformer on statistical grounds, and it is likely that the enthalpy difference also favors the gauche conformer in **3** but favors the anti conformer in **6**.

Experimental Section

Spectral Measurements. ^{13}C NMR spectra were acquired at 75.43 MHz on a Varian Model XL-300 spectrometer with a broad-band tunable probe and low-power Waltz-16 decoupling. The spectra were acquired within 192–256 scans by using a 50–60° pulse, 2.0-s repetition time, and 64K data points and 16 500-Hz spectral window for digital resolution of 0.007 ppm. ^{2}H NMR spectra were acquired at 46.04 MHz. Spectra were run unlocked in CF_2Cl_2 or $CFCl_3$ solution when determining isotope shifts or at low temperatures. Chemical shifts were referenced to internal standard TMS (0 ppm) or to $CDCl_3$ (77.00 ppm) solvent signal in routine spectra. Temperatures were read directly from the calibrated (CH_3OH) thermocouple monitor and varied less than 1° during each acquisition.

Routine IR spectra were obtained on a Perkin-Elmer 1310 IR spectrophotometer. More precise determinations of the separation of C–D stretching bands were carried out on a Perkin-Elmer IR-727 (neat, 64 scans).

Materials. The *N*-(1′-oxoalkyl)piperidines (**8**) were prepared by following Cope.[22] The 3-quinuclidone hydrochloride and 2-methylene-3-quinuclidinone hydrochloride dihydrate were supplied by Aldrich.

General Procedure for Preparation of *N*-Alkylpiperidines-*1′-d*$_1$. The procedure[8] for partial reduction of tertiary amides by lithium triethoxyaluminum hydride ($LiAl(OEt)_3H$) was modified. Lithium aluminum hydride (LAH) (2.28 g, 60 mmol) was added to ether (60 mL) at 0 °C. Ethyl acetate (8.78 mL, 90 mmol) was injected into the stirred slurry under N_2 gas, and stirring was continued at 0 °C for 10 min. An appropriate amide **8** (25 mmol) in ether (30 mL) was added via syringe. The reaction mixture was stirred at 0 °C for an additional 10 min and then without cooling for 2 h. After cooling back down to 0 °C, lithium aluminum deuteride (LAD) (0.525 g, 12.5 mmol) was introduced. The mixture was brought to reflux and refluxed for 12 h. After cooling, the excess of hydride was destroyed by adding water (0.5 mL) dropwise, followed by 20% sodium hydroxide (0.5 mL). The ether layer was filtered and dried (Na_2SO_4), and ether was removed by distillation. The residual liquid was distilled at atmospheric pressure. Analysis by NMR revealed about 50–60% deuteration at C1′.

***N*-Ethylpiperidine-*1′-d*$_1$ (**3**-*1′-d*$_1$)**: colorless liquid, bp 129–130 °C, 69% yield. ^{13}C NMR ($CDCl_3$): δ 54.01 (C2,6), 52.50 (t, J_{CD} = 20.2 Hz, C1′), 25.88 (C3,5), 24.42 (C4), 11.78 (Me). IR (neat): 2056, 2154 cm^{-1}.

***N*-Propylpiperidine-*1′-d*$_1$ (**4**-*1′-d*$_1$)**: colorless liquid, bp 148–149.5 °C, 58% yield. ^{13}C NMR ($CDCl_3$): δ 61.14 (t, J_{CD} = 20.3 Hz, C1′), 54.54 (C2,6), 25.95 (C3,5), 24.46 (C4), 19.90 (C2′), 11.99 (Me). IR (neat): 2052, 2156 cm^{-1}.

***N*-Butylpiperidine-*1′-d*$_1$ (**5**-*1′-d*$_1$)**: colorless liquid, bp 170–172 °C, 57% yield. ^{13}C NMR ($CDCl_3$): δ 58.88 (t, J_{CD} = 20 Hz, C1′), 54.54 (C2,6), 28.96 (C2′), 25.94 (C3,5), 24.41 (C4), 20.86 (C3′), 13.96 (Me). IR (neat): 2049, 2153 cm^{-1}.

***N*-Benzylpiperidine-*1′-d*$_1$ (**6**-*1′-d*$_1$).** LAD reduction of *N*-benzylidenepiperidinium perchlorate **9**, prepared by following Leonard's procedure,[9b] in ether solution following Cervinka's procedure[9a] gave **6**-*1′-d*$_1$ in 83% yield as a pale yellow oil. NMR analysis showed more than 99% monodeuteration at C1′. ^{13}C NMR ($CDCl_3$): δ 138.51, 129.12, 127.99, 126.73 (aromatic carbons), 63.44 (t, J_{CD} = 20.3 Hz, C1′), 54.39 (C2,6), 25.94 (C3,5), 24.35 (C4). IR (neat): 2054, 2141, 2160 cm^{-1}.

2-Methylquinuclidine (10a). 2-Methylquinuclidinone (**12**) was obtained in two steps from 2-methylene-3-quinuclidinone hydrochloride dihydrate as described by Nielsen.[23] Treatment[15] of **12** (1.86 g, 13.4 mmol) with hydrazine hydrate (1.79 g, 55.9 mmol) and KOH (1.8 g, 32.1 mmol) in triethyleneglycol (15 mL) at 150–170 °C for 2 h gave **10a** as a colorless liquid after distillation: 0.94 g, 7.5 mmol, 56% yield, bp 98–99 °C (98 mm) [lit.[24] bp 162–164 °C (748 mm)]. ^{1}H NMR ($CDCl_3$): δ 3.10–2.82 (m, 4 H), 2.73–2.52 (m, 1 H), 1.8–1.6 (m, 2 H), 1.51–1.38 (m, 4 H), 1.14 (d, 3 H), 1.1–1.0 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 51.05 (C2), 49.69 (C7), 40.88 (C6), 35.11 (C3), 26.87 (C8), 25.38 (C5), 22.11 (C4), 20.99 (Me).

2-Ethylquinuclidine (10b). 2-Ethylidene-3-quinuclidinone (**14a**) was prepared by a modified Stotter's method.[16] Hydrogenation[14] of **14a** (2.60 g, 17.2 mmol) at 3–4 atm over 250 mg of 5% Pd/C in 100 mL of methanol for 2 h gave 2-ethylquinuclidinone (2.50 g, 16.3 mmol). Huang-Minlon reduction[15] as described above for the synthesis of **10a** led to **10b** (1.14 g, 8.2 mmol, 50%) as a pale yellow liquid after filtration and evaporation of solvent. ^{1}H and ^{13}C NMR indicated about 95% purity of the crude product. The impurity appears to be 2-ethyl-3-hydroxyquinuclidine from over reduction of **14a**. Further purification was not attempted. ^{1}H NMR ($CDCl_3$): δ 3.10–2.82 (m, 3 H), 2.75–2.57 (m, 2 H), 1.80–1.67 (m, 2 H), 1.55–1.36 (m, 6 H), 1.12–1.00 (m, 1 H), 0.92 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 57.63 (C2), 49.64 (C7), 41.23 (C6), 33.61 (C3), 28.30 (C1′), 26.67 (C8), 25.59 (C5), 21.76 (C4), 10.99 (Me).

2-Propylquinuclidine (10c). Preparation as for **10b** from 2-propylidene-3-quinuclidinone gave **10c** in 54% yield as a colorless liquid, bp 105–106 °C (28 mm). ^{1}H NMR ($CDCl_3$): δ 3.05–2.80 (m, 3 H), 2.73–2.55 (m, 2 H), 1.80–1.65 (m, 2 H), 1.60–1.25 (m, 8 H), 1.10–1.00 (m, 1 H), 0.92 (t, 3 H). ^{13}C NMR ($CDCl_3$): δ 55.49 (C2), 49.73 (C6), 41.27 (C6), 37.83 (C3), 34.01 (C1′), 26.81 (C8), 25.68 (C5), 21.82 (C4), 19.62 (C2′), 14.04 (Me).

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

(21) (a) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907. (b) Calculations were performed with the MMX86 program from Serena Software.

(22) Cope, A. C.; Ciganek, E. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 339.

(23) Nielsen, A. T. *J. Org. Chem.* **1966**, *31*, 1053.

(24) Lukes, R.; Palecek, I. *Collect. Czech. Chem. Commun.* **1964**, *29*, 1582.