

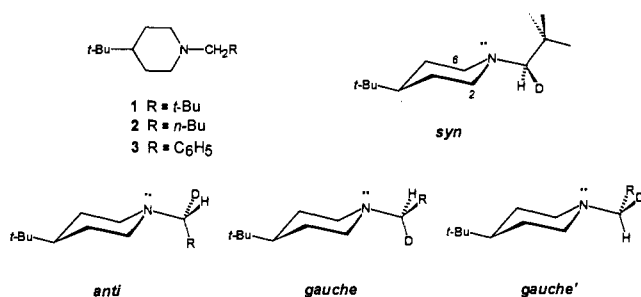
## NMR Detection of Unusual Eclipsed Structure Establishes the Origin of Large Specific Rotations in Chirally Deuterated Amines

David A. Forsyth\* and Suzanne M. Johnson

Department of Chemistry  
Northeastern University  
Boston, Massachusetts 02115

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Compounds which are optically active by virtue of chiral deuterium labeling are widely used in studies of the stereochemistry and mechanisms of organic reactions. In one such study of the  $S_N2'$  mechanism, Magid and Fruchey observed specific rotations of tertiary amines that were unusually large for saturated chiral deuterium compounds and suggested that the large rotations could be rationalized on the basis of unequal populations of conformations having opposite-sign rotatory powers.<sup>1</sup> In seeking to substantiate their rationale through conformational analysis via NMR isotope shifts, we have found evidence for an unusual, eclipsed, syn geometry for the side chain in *N*-neopentyl-4-*tert*-butylpiperidine (**1**). Comparison of the specific rotation and NMR isotope shifts for **1** with those for *N*-amyl-4-*tert*-butylpiperidine (**2**) and *N*-benzyl-4-*tert*-butylpiperidine (**3**) provides strong support for conformational equilibrium isotope effects as the origin of high optical rotations in chirally labeled tertiary amines.



Complete conformational analysis of acyclic tertiary amines can be quite challenging because of multiple low barriers for rotation and inversion.<sup>2</sup> Staggered conformations are preferred, thus an alkyl group attached to nitrogen by a methylene group generally is found in either of two gauche alignments or an anti alignment with respect to the amine lone pair. We chose to study *N*-alkyl-4-*tert*-butylpiperidines so as to eliminate any conformational equilibria other than those involving the single *N*-alkyl side chain. We have previously demonstrated for several *N*-alkylpiperidines at low temperatures that both gauche and anti forms are populated and rapidly equilibrating.<sup>3</sup> The *N*-neopentyl group was included in the present study with the intention of eliminating the anti form due to steric crowding.

Introduction of a single deuterium at C1' of the *N*-alkyl side chain could cause a gauche  $\rightleftharpoons$  gauche equilibrium to be nondegenerate<sup>3,4</sup> and result in the temperature-dependent separation of signals for C2 and C6 in <sup>13</sup>C NMR spectra that would

Table I. NMR Isotope Shifts<sup>a</sup> for C2 and C6 in C1'-Deuterated *N*-Alkyl-*tert*-butylpiperidines

compd	T, K	$\delta_{eq}$ , <sup>b</sup> ppm	$^3\Delta C(d_2)$ , <sup>c</sup> ppm	
1	292	0.032 <sup>d</sup>	0.078 <sup>d</sup>	
	216	0.027	0.074	
	235	0.028	0.073	
	255	0.029	0.071	
	271	0.028	0.072	
	293	0.030	0.071	
	304	0.028	0.069	
	324	0.030	0.070	
	2	216	0.242	0.071
235		0.216	0.072	
255		0.193	0.071	
271		0.175		
293		0.160	0.069	
304		0.153	0.072	
324		0.141	0.072	
3		216	0.140	0.106
		235	0.120	0.101
	255	0.107	0.096	
	271	0.095	0.092	
	293	0.089	0.088	
	304	0.084	0.086	
	324	0.078	0.077	

<sup>a</sup> Measured from <sup>13</sup>C spectra (CDCl<sub>3</sub>) at 75 MHz;  $\pm 0.005$  ppm. <sup>b</sup> Separation between C2 and C6 signals in 1'-*d* isotopomers. <sup>c</sup> Chemical shift difference in position of C2,6 signal between 1',1'-*d*<sub>2</sub> and unlabeled isotopomers. All are upfield isotope shifts. The average  $^3\Delta C(d)$  for C2 and C6 in each 1'-*d* isotopomer was one-half that of the 1',1'-*d*<sub>2</sub> isotopomer, within experimental error. <sup>d</sup> Measured from <sup>13</sup>C spectra at 125 MHz;  $\pm 0.002$  ppm.

be characteristic of an equilibrium NMR isotope shift.<sup>5</sup> Separate C2 and C6 signals are indeed found for 1-1'-*d*, 2-1'-*d*, and 3-1'-*d*, as shown in Table I. However, the shift separation,  $\delta_{eq}$ , between C2 and C6 is small and shows no temperature dependence for 1-1'-*d*, in contrast to the 2-1'-*d* and 3-1'-*d* data. The magnitude may be evaluated by comparing the 1'-*d* isotope shifts to those for the 1',1'-*d*<sub>2</sub> isotopomers in which any gauche  $\rightleftharpoons$  gauche equilibria must remain degenerate. The  $\delta_{eq}$  between C2 and C6 in 1-1'-*d* is smaller than the ordinary, three-bond intrinsic isotope shift,<sup>6</sup>  $^3\Delta C(d_2)$ , while  $\delta_{eq}$  is comparable or larger than  $^3\Delta C(d_2)$  for **2** and **3**. The small size and lack of temperature dependence are strong indicators that only intrinsic isotope shifts, associated with a single structure, are being observed for **1**, rather than equilibrium isotope shifts arising from isotopic perturbation of equilibria between two or more structures, as seen for **2** and **3**.<sup>7</sup> Conversion of 1-1'-*d* to the *N*-oxide (oxygen axial) resulted in a  $\delta_{eq}$  that was larger and temperature dependent (from 0.065 ppm at 324 K to 0.080 ppm at 255 K), thus indicating that the preference for an eclipsed structure is lost.

The C2 and C6 signals in **1** also show an easily discernible difference in the  $^3J(C-N-C-D)$  coupling to the deuterium at C1':  $^3J(C2-N-C-D) = 1.1$  Hz;  $^3J(C6-N-C-D) \leq 0.3$  Hz (not resolved). Only small differences in line widths for the apparent singlets for C2 and C6 are seen for **2**, **3**, and previously examined piperidines.<sup>3</sup> While a Karplus-type relation for vicinal C-N-C-D (or H) coupling has not been established, the  $^3J(C2-N-C-D)$  in 1-1'-*d* is precisely the magnitude expected for the 0° dihedral angle of the syn structure from the Karplus relation for C-C-C-H coupling (predicted  $^3J_{CCCD} = 1.2$  Hz).<sup>8</sup> In **2** and **3**, where couplings to C2 and C6 are weighted averages from the

(1) Magid, R. M.; Fruchey, O. S. *J. Am. Chem. Soc.* 1979, 101, 2107.

(2) For a recent review, see: Bushweller, C. H. In *Acyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH Publishers: New York, 1992; Chapter 1.

(3) Forsyth, D. A.; Prapansiri, V. *J. Am. Chem. Soc.* 1989, 111, 4548.

(4) For other isotope effects on amine conformations, see: (a) Tamagake, K.; Tsuboi, M. *Bull. Chem. Soc. Jpn.* 1974, 47, 73. (b) Anet, F. A. L.; Kopelevich, M. *J. Chem. Soc., Chem. Commun.* 1987, 595. (c) Forsyth, D. A.; Hanley, J. A. *J. Am. Chem. Soc.* 1987, 109, 7930. (d) Forsyth, D. A.; Prapansiri, V. *Tetrahedron Lett.* 1988, 29, 3551. (e) Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* 1989, 111, 3429. (f) Forsyth, D. A.; Zhang, W.-Y. *J. Org. Chem.* 1991, 56, 3928.

(5) (a) Saunders, M.; Telkowski, L.; Kates, M. R. *J. Am. Chem. Soc.* 1977, 99, 8070. (b) Saunders, M.; Kates, M. R. *J. Am. Chem. Soc.* 1977, 99, 8071.

(6) (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.

(7) There is some temperature dependence of  $^3\Delta C(d_2)$  for **3**, attributable to changing relative populations of gauche and anti forms toward the favored anti structure.<sup>3</sup>

(8) Aydin, R.; Günther, H. *Magn. Reson. Chem.* 1990, 28, 448.

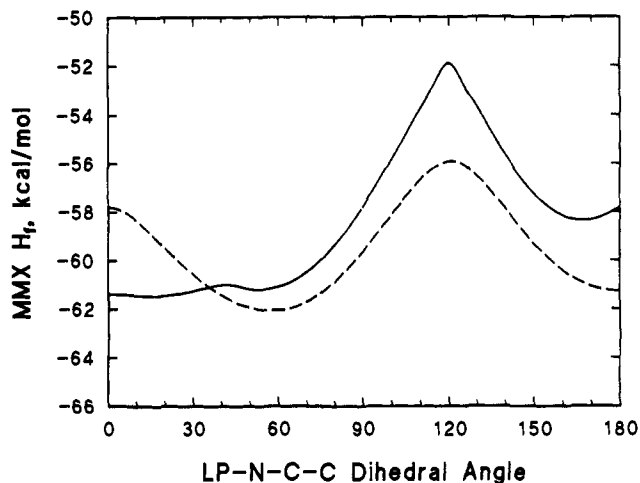


Figure 1. Plot of MMX heat of formation vs lone pair-N-C1'-C2' dihedral angle. The solid line is for **1**; the dashed is for **2**. Curves are splined fits to points at 5° intervals.

anti, gauche, and gauche' structures, the difference in coupling to C2 and C6 is expected to be much smaller.<sup>9</sup>

While the evidence for a single structure for **1** is strong, it does not unequivocally establish the structure as syn, as opposed to anti. However, molecular mechanics calculations (MMX; Allinger MM2 parameters for amines<sup>10</sup>) predict a 3.5 kcal/mol preference for the syn form. Although the syn structure<sup>11</sup> is the central point on a predicted shallow energy surface (Figure 1) in the vicinity of the syn and gauche structures, the <sup>3</sup>J<sub>CNCD</sub> data are much more consistent with a true syn minimum rather than libration over a shallow syn-gauche surface. The isomeric **2** is predicted to have distinct minima of comparable energy at gauche and anti.

(9) If all three conformers were equally populated, the Karplus relation would predict identical coupling constants.

(10) (a) PCMODEL program from Serena Software. (b) Profeta, S., Jr.; Allinger, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 1907. (c) Conformations with N-alkyl groups axial were less stable than equatorial conformations by at least 2 kcal/mol in all cases.

(11) All other alignments in the molecule are staggered, including the *tert*-butyl group relative to the CH<sub>2</sub>N segment.

The specific rotation,  $[\alpha]^{20}_D$ , of  $0.46 \pm .03^\circ$  (ether) for (*R*)-**1-1'-d** is distinctly smaller than those found for (*R*)-**2-1'-d** and (*R*)-**3-1'-d** at  $3.10 \pm 0.25^\circ$  and  $2.75 \pm 0.25^\circ$ , respectively.<sup>12,13</sup> Thus, it can be concluded that optical activity for **2** and **3** is enhanced by isotopic perturbation of an equilibrium between two gauche conformers that are enantiomeric in the absence of labeling. The result from chiral labeling of **1**, which appears to be in an unusual, achiral, eclipsed conformation, suggests that the inherent optical rotation due to chiral labeling with deuterium in tertiary amines is small and typical ( $<|1^\circ$ ) of saturated compounds.<sup>14</sup>

The current results are also directly relevant to the recent studies of Anderson et al. regarding eclipsed conformations.<sup>15,16</sup> He postulated that the central bond in any molecular fragment R<sup>1</sup>X-YR<sup>2</sup>R<sup>3</sup> (involving tetrahedral atoms X = CH<sub>2</sub>, NH, O, etc., Y = CH, N, etc.) with groups R demanding of space would tend to be eclipsed. Several hydrocarbons and ethers were cited as examples supporting the postulate. It was suggested that a rich source of eclipsed conformations would be molecules with three adjacent equatorial substituents on a six-membered ring, the middle one being -X-R, where the flanking groups would push the central bond conformation toward eclipsing of the X-R bond with the ring-H bond<sup>16</sup> (e.g., 1-neopentyl-2,6-dimethylcyclohexane<sup>15</sup>). We conclude that **1**, which has no flanking substituents but does have the combination of the sterically demanding neopentyl group (R<sup>1</sup>X) and the sterically undemanding lone pair of piperidine (YR<sup>2</sup>R<sup>3</sup>), may represent a lower limit on the steric crowding needed to achieve a nearly eclipsed structure.

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(12) Amines were prepared by direct displacement by 4-*tert*-butylpyridine of tosylate from the *p*-toluenesulfonates of the known (*S*)-alcohols, followed by catalytic hydrogenation of the *tert*-butylpyridinium salts.

(13) Specific rotations are corrected for percent deuteration and enantiomeric excess (ee). Ee values were determined from <sup>1</sup>H spectra of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol complexes with amines, N-oxides, and/or precursor *tert*-butylpyridinium tosylates.

(14) Verbit, L. *Prog. Phys. Org. Chem.* **1970**, *7*, 51.

(15) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 299.

(16) Anderson, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1517.