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STERIC MANIPULATION OF THE LONE PAIR IN PIPERIDINE

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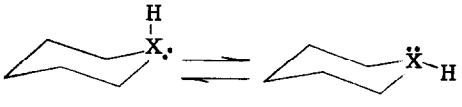
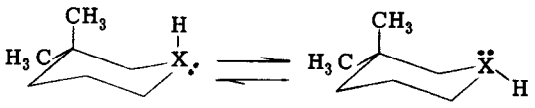
The remarkable preference of single-atom substituents for the axial position in certain molecules of the structure I[1,2] was first satisfactorily explained by Allinger, et al.[3] Their



Ia Ie



IIa IIe

analysis showed that the interactions in Ia between the axial proton on X and the 3,5-axial protons are attractive, and that Ia possesses two fewer gauche H-H interactions than Ie. Such an explanation obviates the unpleasant necessity of attributing the equatorial lone-pair preference to steric bulk. Although several examples of such a preference have now been recorded,[1,2] the causative factors have not been the subject of direct, experimental tests. This paper describes experiments that offer conclusive evidence that the axial-proton-equatorial-lone-pair situation is favored by net attractive N-proton interactions rather than by repulsive lone-pair interactions.

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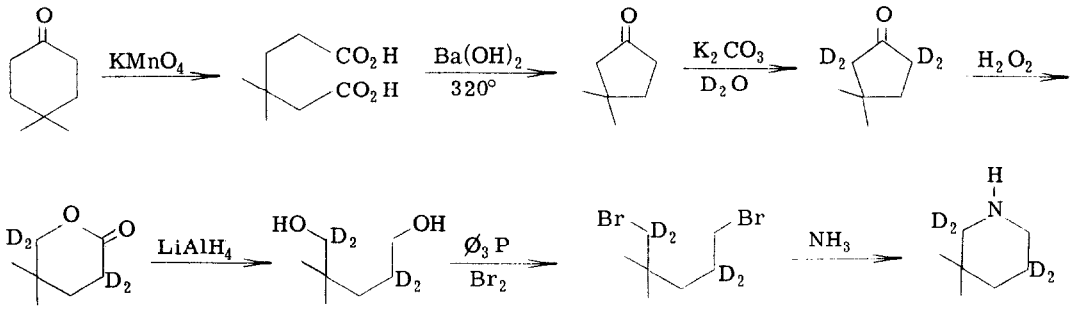
If a methyl group is placed in the 3-axial position of piperidine (II, X: N), the explanation of Allinger[3] predicts an increased proportion of the equatorial isomer (IIe). The axial form would be less favored because an attractive 1,3 H-H interaction in Ia has been replaced by a repulsive 1,3 CH_3-H interaction in IIa. On the other hand, if the large percentage of axial N-proton in piperidine were due to repulsive interactions between an axial lone pair and the 3,5-axial protons, i.e., "lone pair sterically bulky," the added axial methyl group in II should increase these repulsions and enhance the percentage of axial proton. Determination of whether the methyl group in II increases or decreases the amount of axial N-proton therefore offers a choice between the two explanations.

Geminal methyls are required in order to insure that there is always a 3-axial methyl group in this conformationally mobile system. To determine the location of the N-proton in II, the chemical-shift difference between the axial and equatorial 6 protons [$\delta_{ae}(6)$] was measured below the coalescence temperature for ring reversal.[4] In piperidine, $\delta_{ae}(6)$ is about 0.43 ppm. Any increase in the proportion of the axial-lone-pair isomer will preferentially shield the 6-axial proton and enhance the magnitude of $\delta_{ae}(6)$.[4] To remove the coupling between the 6 and the 5 protons and to eliminate the 2 protons, whose chemical shift is close to that of the 6 protons but affected by the adjacent methyl groups,[5] 3,3-dimethylpiperidine-2,2,5,5-d_4 was synthesized by the following route.[6] The magnitude of $\delta_{ae}(6)$ was determined at -80° from the

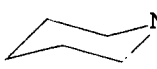
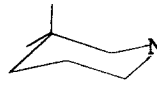
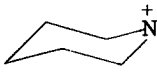
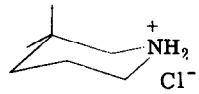
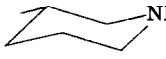
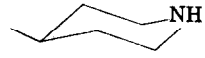
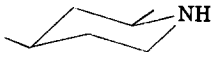
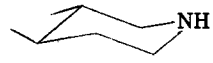


60- and the 90-MHz proton spectra.[7] The pertinent data, together with those for model systems, are recorded in Table I.

If one or two methyl groups are placed in the 2-, 3-, or 4-equatorial positions, there is little or no effect on $\delta_{ae}(6)$, in comparison with that of piperidine. The only compound that possesses a value of $\delta_{ae}(6)$ that is appreciably enhanced by substitution is II, in which an increase of almost 0.2 ppm with respect to I is observed. The proportion of axial lone pair

TABLE I

NMR Spectral Parameters for Piperidine Systems

Compound	Solvent	$\delta_{ae}(6)$, ppm	Compound	Solvent	$\delta_{ae}(6)$, ppm
	CH_2Cl_2[a] CD_3OD[a]	0.48 0.43		CH_2Cl_2[b] CD_3OD[b]	0.66[e] 0.62[e]
	CD_3OD[a]	0.40		CD_3OD[b]	0.43[f]
	$CDCl_3$[c]	0.48			
				$CDCl_3$[c]	0.49
	$CDCl_3$[d] C_6D_6	0.43 0.43			
				$CDCl_3$[d] C_6D_6[d]	0.37 0.37
	$CDCl_3$-D_2O[d]	0.43			

[a]Ref. 4. [b]This work. [c]Ref. 8. [d]Ref. 9. [e]Centered at δ 2.80. [f]Centered at δ 3.18.

must therefore be larger in II than in I. That this increase is not due to a direct shielding by the methyl group[5] or to a deformation of the ring may be proved by examination of the protonated piperidines. There is little change in $\delta_{ae}(6)$ between I (0.43 ppm in CD_3OD) and I-H^+ (0.40), but the change is substantial between II (0.62) and II-H^+ (0.43). The latter decrease must be caused by removal through protonation of the shielding due to an axial lone pair in II.

A substantially larger chemical-shift difference in II than in I indicates that the 3-axial methyl group decreases the proportion of axial N-proton. Two conclusions may be derived from this observation. First, it is the proton on nitrogen and not the lone pair that is removed from the region of steric congestion. Thus, the large proportion of equatorial lone pair in piperidine is not in contradiction with the extensive literature[10] that indicates that the lone pair is generally placed in more crowded regions. As suggested by Allinger,[3] it must be the net attractive interactions of the N-proton that produce the piperidine result, and the lone pair need not be directly considered. Second, the magnitude of $\delta_{ae}(6)$ is found to be a valid probe

for an adjacent axial lone pair on nitrogen. It has been suggested that the enhanced value of δ_{ae}(6) in N-methylpiperidine is due entirely to the adjacent equatorial methyl group.[5] Although the methyl effect has proved to be too small to explain this enhancement,[5] molecule II comprises the first example of an enhanced chemical-shift difference for a methylene group adjacent to nitrogen in the absence of an N-alkyl substituent. The decrease on protonation also points to the lone pair as the cause of the enhancement. It may very well be that the proton on nitrogen in II is not entirely equatorial.[3] The present experiments only indicate that there is more equatorial N-proton in II than in I.

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4. J. B. Lambert and R. G. Keske, J. Amer. Chem. Soc., 88, 620 (1966).

5. J. B. Lambert and R. G. Keske, Tetrahedron Lett., 2023 (1969); M. J. T. Robinson, ibid., 1153 (1968); J. B. Lambert and Y. Takeuchi, Org. Magnetic Resonance, 1, 0000 (1969); H. Booth and J. H. Little, Tetrahedron, 23, 291 (1967); H. Booth, ibid., 22, 615 (1966).

6. This procedure produces a mixture of the 3,3- and 4,4-dimethylpiperidines, which were separated by preparative gas chromatography and compared with known samples.

7. The kinetics of ring reversal have been determined for this series of compounds and will be reported elsewhere.

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10. See, for example, P. J. Brignell, A. R. Katritzky, and P. L. Russell, J. Chem. Soc. (B), 1459 (1968).