Tetrahedron Letters No.25, pp. 2023-2026, 1969. Pergamon Press. Printed in Great Britain.

FACTORS CONTRIBUTING TO THE CHEMICAL SHIFT OF PROTONS ADJACENT TO NITROGEN IN PIPERIDINES

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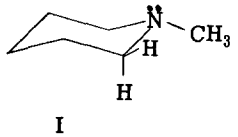
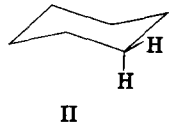
(Received in USA 21 March 1969; received in UK for publication 29 April 1969)

The shielding of an axial proton by an adjacent, axial lone pair on nitrogen was first recognized by Hamlow, Okuda, and Nakagawa in quinolizidines.[1] During the intervening five years, a number of applications of this effect have been reported in structurally dissimilar molecules.[2] Recently,[3] the view has been expressed that the axial-proton shielding is caused not by the lone pair, but rather by the equatorial alkyl substituent on nitrogen. In this paper we assess the relative importance of the two sources and conclude that the lone pair is the dominant, though not the exclusive contributor.

At the focus of this discussion will be N-methylpiperidine (I). Because the α-axial proton in I is shifted upfield, the chemical-shift difference between the α protons, $\delta_{ae}(\alpha)$, is considerably larger[2b] than the value in cyclohexane.[4] The structural source of this enhancement may be the axial lone pair, the equatorial substituent, or both. Model compounds have been examined in order to isolate and assess the lone-pair effect, on the one hand, and the alkyl effect, on the other.



I



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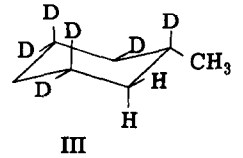

III

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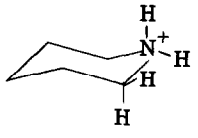
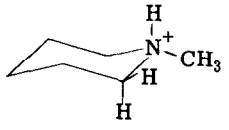
If all bond angles were tetrahedral and all bond lengths equal in a six-membered ring, introduction of an equatorial methyl group would not affect $\delta_{ae}(\alpha)$. Since cyclohexane and piperidine are slightly flattened, a differential effect is to be expected. The appropriate choice of models must remain within the same family of chair distortions; otherwise, the effect of the distortion on δ_{ae} might be greater than the lone-pair and alkyl effects to be assessed. For this reason, puckered sulfur and selenium heterocycles[5a,b] and substantially flattened cyclohexanones[5a,c] and polycyclic compounds must be rejected as worthwhile models for chemical-shift differences in piperidines.[6] According to the R-value criterion,[5] cyclohexane and piperidine rings are very similarly shaped.[7] We will therefore restrict our models to compounds from these two series. Furthermore, the model compounds should ideally be only one or two structural modifications removed from N-methylpiperidine.

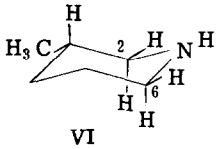
We have examined one carbocyclic and two heterocyclic systems in order to assess the influence of a methyl group on $\delta_{ae}(\alpha)$. The procedure involves comparing the chemical-shift difference for compounds that differ only in the presence or absence of a methyl group (Table I). For cyclohexane (II), δ_{ae} has been reported to be about 29 Hz.[4] Methylcyclohexane-1,2,3,3,5,5-d_6 (III) was synthesized and found to have a $\delta_{ae}(6)$ of 45 Hz.[8] The enhancement by the equatorial methyl group is seen to be about 16 Hz in this carbocyclic system. For the protonated piperidines, $\delta_{ae}(\alpha)$ is about 22 Hz (CD_3OD) or 28 Hz (FSO_3H-SO_2) for the unmethylated form (IV), and



IV



V



VI

27 Hz (CD_3OD) or 36 Hz (FSO_3H-SO_2) for the methylated form (V). The methyl effect for this pair of compounds is thus only 5-8 Hz in a given solvent system. Molecule VI contains methylene groups both with (C-2) and without (C-6) an adjacent methyl, so that an internal comparison is possible. The effect of the methyl group is seen in this case to be about 18 Hz. If the example with the methyl on nitrogen (V) is deemed the only acceptable model for N-methylpiperidine, the equatorial alkyl effect is indeed small (< 10 Hz). If the C-methyl systems are accepted as well, a range of 5 to 18 Hz has been observed.

The procedure to assess the effect of the lone pair on $\delta_{ae}(\alpha)$ is to compare systems known to have an axial lone pair with their protonated analogues. Protonation of N-methyl-

piperidine (I⟶V) is seen to decrease $\delta_{ae}(\alpha)$ by 30 Hz in CD_3OD (Table I). It should be recognized that both systems (I and V) contain the equatorial methyl group and that the positively charged nitrogen in V should inductively affect H_a and H_e in an equivalent manner. The observed difference can therefore be attributed to the lone pair. Similar observations have been made with N-t-butylpiperidine,[2b] although the unassessed influence of the t-butyl group makes the data somewhat less reliable. Since $\delta_{ae}(\alpha)$ is solvent dependent for both I and V, the lone-pair effect might be as low as 21 Hz or as high as 39 Hz, if the extremes from the table are used.

For a methylene group that lacks an adjacent lone pair or alkyl substituent but resides in a chair undistorted from the shape of cyclohexane, δ_{ae} is about 29 Hz.[2b,4] The value of $\delta_{ae}(\alpha)$ in N-methylpiperidine (57-66 Hz) thus represents an enhancement of 28-37 Hz. The alkyl effect observed in the protonated piperidines (<10 Hz) is wholly inadequate to explain this increase. Even the maximum alkyl effect, which is only about 18 Hz, cannot by itself cause the enhancement in III. The minimum lone-pair effect (21 Hz) likewise cannot explain the entire change, although the maximum value (39 Hz) is sufficient. In summary, the lone pair must give rise to a significant portion of the shielding effect observed by Hamlow, et al.,[1] and it can be the entire cause. The present data do not permit a more precise division. A dual cause of the enhanced chemical-shift difference has previously been suggested by Booth and Little.[10]

TABLE I

Geminal Chemical-Shift Differences in Six-Membered Rings

Compound	Solvent	Position	δ_{ae}, Hz (At 60 MHz)	References
I	CD_3OD	2	57	2b
	CH_2Cl_2	2	61	2b
	Cyclopropane	2	64	2b
	Toluene-d_8	2	66	2b
II	CS_2	All	29	4
III	CCl_4	6	45	8
IV-Cl^-	CD_3OD	2	>22	2b
IV-FSO_3^-	FSO_3H-SO_2	2	28	2b
V-Cl^-	CD_3OD	2	27	2b
V-FSO_3^-	FSO_3H-SO_2	2	36	2b
VI	$CDCl_3$	2	29	9
	$CDCl_3$	6	47	9

Acknowledgments. The authors are grateful to the National Science Foundation (GP-6611 and GP-9257) and to the donors of the Petroleum Research Fund, administered by the American Chemical Society (487-G1 and 2970-A4, 5), for financial support of this research.

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6. Thus, we have found that the cyclic sulfides, sulfoxides, sulfones, and sulfonium salts have chemical shifts that fit into no previous pattern; J. B. Lambert and R. G. Keske, unpublished results.

7. For piperidine, R = 2.09;[2b] for cyclohexane, R = 2.16, cf., E. W. Garbisch, Jr., and M. G. Griffith, J. Am. Chem. Soc., 90, 6543 (1968).

8. The synthesis and analysis will be described in the full paper. We thank Mr. Y. Takeuchi for assisting us in the deuteration procedure and Dr. E. W. Garbisch, Jr., of the University of Minnesota, for obtaining the decoupled spectrum of III for us.

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