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THE "SIZE" OF THE LONE PAIR ON NITROGEN

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During the last few years there has been a flurry of activity directed at determining the relative size of the lone pair on nitrogen with respect to other nitrogen substituents[1]. During the ensuing melee, there has been a considerable tendency to lose sight of the connection between the expression "size of the lone pair on nitrogen", and the physical measurements reported. Since in the last year or two the confusion has tended to become compounded, it seemed desirable to point out that in fact such diametrically opposed statements as "the lone pair is larger than a hydrogen attached to nitrogen[2]" and "the lone pair is smaller than a hydrogen attached to nitrogen[3]" may both be perfectly correct, but only when each is applied to certain definite (and different) types of experimental systems.

It is not our present intent to report here experimental work with regards to this problem. Large numbers of well conceived and executed experiments already exist, and the problem is one of their proper interpretation. This paper is concerned with an analysis of what factors will tend to make a group "smaller" or "larger" than a lone pair, a summary of the results of experiments which have led to these conclusions, and an understanding of these experiments in terms of the above interactions. Finally, we wish to report the outcome of some semi-empirical calculations of the Westheimer-Hendrickson-Wiberg type, which offer support for the interpretations to be given. Since the number of papers concerned with the size of the lone pair on nitrogen is quite large, and the number of experiments described in those papers is even larger, a step by step discussion of the literature would constitute a sizeable review, well beyond the scope of this paper. We will therefore simply state here that the bulk of the data in the literature can be explained on the basis to be presented, but we wish to point out that there are some experiments which cannot be so explained. It is our belief that most of the latter type of experiments suffer from inadequate interpretation or actual experimental error, and it is intended to report on some of these discrepancies in the near future.

There are three different types of physical systems which we must consider at the outset, as most of the experiments which have been carried out are involved with either one of these systems themselves, or more complicated systems of which the present ones represent the basic features. The first case to examine is piperidine itself, where there is a hydrogen on nitrogen, and no other substitutents are present in the ring to complicate matters. The second system is the N-methylpiperidine system, again where there is just a methyl on nitrogen, and no additional substituents. Finally, we wish to examine the methyl-axial conformation of 3-methylpiperidine. This system can be considered the parent which is related to various reduced quinoline and isoquinoline examples which have been studied.

Beginning with piperidine, if the hydrogen on nitrogen is in the axial position, it does not suffer any unfavorable interactions with the syn-axial hydrogens, because the distances are so great relative to the van der Waals radius of the hydrogen. In our view, there is no need to consider the lone pair explicitly at all. One simply needs to consider the nitrogen atom and its substituents, since the lone pair is adequately accounted for as just a part of the nitrogen atom. Now, ordinarily we think of a substituent as being more favorably located when it is equatorial, but this is because of the syn-axial repulsions. This is not the case if all the syn-axial substituents are hydrogen, as with piperidine. There is nothing whatever unfavorable about the hydrogen being axial, in fact the syn-axial hydrogens exert a small attractive force on one another. On the other hand, this axial hydrogen on nitrogen is unfavorably located with respect to the equatorial hydrogens on carbons 2 and 6. Just as a hydrogen in ethane exerts a repulsion on a gauche vicinal hydrogen, so there is a repulsion of the axial hydrogen with the two equatorial neighbors. If the hydrogen is in the equatorial position, the hydrogens axial at C - 3 and C - 5 still exert a small attractive effect; however, the equatorial hydrogen on nitrogen now lies between the equatorial and axial hydrogens on carbons 2 and 6, and hence there are four repulsions, whereas in the axial isomer there were but two. Consequently, it would seem a priori that the hydrogen on nitrogen should prefer an axial position, although the degree of preference might be small.

Next, consider what happens when there is a methyl group located on the nitrogen as in N-methylpiperidine. When the methyl group is axial, there exist the usual repulsions between the methyl and the syn-axial hydrogens. Similarly, the axial N-methyl has two repulsions from the gauche hydrogens on the neighboring carbons, and there are four of the latter repulsions if the methyl is equatorial. Hence the sign of the conformational energy of the methyl cannot be specified a priori, since it depends on whether the repulsion between the methyl and a hydrogen at C - 2 is smaller or larger than the repulsion between the axial methyl and the axial hydrogen at C - 3. We believe, however, that the repulsion between the methyl group and the syn-axial hydrogen is the larger, as will be developed below, and hence the methyl prefers to be in an equatorial position, but this preference is not as great as it is when the methyl is attached to a cyclohexane ring.[4, 5]

Finally, we would like to consider the hydrogen attached to nitrogen when there is a methyl group (or its steric equivalent) located in the axial position at C - 3. The energy of the equatorial proton on nitrogen in this case is the same as if the methyl were absent, but the axial proton on nitrogen now suffers a repulsion from the methyl at C - 3. Hence, while a hydrogen on nitrogen should prefer to be axial when there is no syn-axial substituent, the presence of such a substituent will diminish the tendency, and may well force the hydrogen to prefer an equatorial position.

If we examine the literature with these interpretations in mind, we note that there are very few cases reported which are in disagreement with the above. (Most of the exceptions in fact come from our own laboratory, and these will be discussed in a subsequent publication.)

In order to support the above qualitative interpretations, we have carried out calculations of the Westheimer-Hendrickson-Wiberg type, following methods similar to those outlined in our previous paper.[6] The various parameters which go into the calculations and the calculations themselves, were discussed earlier, in so far as the hydrocarbon portions of the molecules are concerned. The exact numerical values used in the current work are an improved set,[7] derived for hydrocarbons by refinements of the methods previously discussed. For the nitrogen portion of the molecule, the various natural lengths, angles, etc., were chosen so as to reproduce the known structures of methylamine, dimethylamine, and trimethylamine. These results are given in Table I. For various piperidine systems in question, then, there were no adjustable parameters. The calculations were completely straightforward, and the results which were obtained are shown in Table II.

Our qualitative conclusions given above were nicely born out by these calculations. The predicted energy favoring the axial hydrogen in piperidine itself is seen to be 0.6 kcal/mole. This value appears to be in satisfactory agreement with the NMR data.[2]

TABLE I[*]

	Calculated	Experimental	Reference
Methylamine			8
r(C-N)	1.468	1.474 ± 0.005 A	
r(N-H)	1.014	1.014 A	
θ(C-N-H)	111.96	112.05 ± 1.0°	
θ(H-N-H)	105.88	105.71 ± 1.0°	
Rotational Barrier	1.95	1.958	
Dimethylamine			9
r(C-N)	1.469	1.463 A	
r(N-H)	1.017	1.01 A	
θ(C-N-C)	111.52	112.08°	
θ(C-N-H)	109.64	109.5°	
Rotational Barrier	3.56	3.564	
Trimethylamine[a]			10
r(C-N)	1.469	1.472 ± 0.008 A	
θ(C-N-C)	110.436	108.7° ± 1.0°	
Rotational Barrier	5.16	-	

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[*] All calculations are for the compound in the gas phase at 25°C.

[a] The ground state is calculated as a completely staggered conformation, and the rotational barrier is for rotation of one methyl group to an eclipsed conformation.

which in our opinion is the most definitive because it was carried out on piperidine itself, and does not involve problems concerned with substituents.

For N-methylpiperidine, it is noted that the calculated value places the methyl group in the equatorial position by 0.8 kcal/mole. Again, this value is in agreement with the NMR data[2]. Finally, when there exists a methyl group axial at C - 3, it was calculated that the hydrogen will still prefer to be axial, but only by 0.1 kcal/mole. In different actual systems there are usually various other substituents also present, and there are

TABLE II*

	Piperidine		N-Methylpiperidine		3-Axial-Methylpiperidine	
	AX-H	EQ-H	AX-Me	EQ-Me	AX-H	EQ-H
r(C-C)	1.523-5	1.523-5	1.525-6	1.523-6	1.524-9	1.525-8
r(C-N)	1.463	1.466	1.466	1.468	1.463	1.465
r(N-H)	1.016	1.016	-	-	1.013	1.016
r(Me-N)	-	-	1.469	1.471	-	-
θ(C-C-C)	110.6-7	110.3-1.5	111.3-7.8	110.2-2.8	106.5-17.6	107.0-14.5
θ(C-N-C)	110.8	110.5	108.0	109.1	109.8	109.9
θ(C-N-H)	109.7	110.6	-	-	110.8-11.2	109.6-11.0
θ(C-N-Me)	-	-	111.62	111.40	-	-
Conf. Energy	0	0.6	0.8	0	0	0.1

*All calculations are for the compound in the gas phase at 25°C.

small or large deformations of the ring, which might shift the equilibrium in either direction. Thus it would seem that this type of system might have the hydrogen located preferentially one way or the other, which would have to be determined for the individual case (e.g., reference 3).

We believe that the concept of a "size" for the lone pair on nitrogen has proven to be an extremely unfortunate one, and we believe that the above discussion illustrates just how misleading the concept can become when taken from its original context. So far, there is no evidence of which we are aware which requires the "size" of the lone pair be given explicit consideration. Until such time as it is established that such explicit consideration is required, we do not feel that it should be used as a convenient explanation for recalcitrant experimental facts.

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REFERENCES

1. Because of the very large number of papers which have appeared in recent years concerning this subject, only leading references will be given here.
2. (a) J.B. Lambert and R.G. Keski, J. Am. Chem. Soc., 88, 620 (1966).
   (b) J.B. Lambert, in press.
3. H. Booth and A.H. Bostock, Chem. Commun., 177 (1967).
4. N.L. Allinger, J.G.D. Carpenter and F.M. Karkowski, J. Am. Chem. Soc., 87, 1232 (1965).
5. R.J. Bishop, L.E. Sutton, D. Dineen, R.A.Y. Jones and A. R. Katritzky, Proc. Chem. Soc., 257 (1964).
6. N.L.Allinger, M.A. Miller, F.A. Van-Catledge and J.A. Hirsch, J. Am. Chem. Soc., 89, in press (1967).
7. M.A. Miller and J.A. Hirsch, unpublished results.
8. D.R. Lide, Jr., J. Chem. Phys., 27, 343 (1957); T. Nishikawa, T. Itoh, and K. Shimoda, J. Chem. Phys., 23, 1735 (1955).
9. J. Wollrab and V. Laurie, personal communication.
10. D.R. Lide, Jr., and D.E. Mann, J. Chem. Phys., 28, 572 (1958).