

# THE CONFORMATION OF THE PIPERIDINE RING SYSTEM FROM X-RAY STUDIES

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## ABSTRACT

X-ray crystal structure data of twenty-one compounds are analysed in order to bring out the salient features of the piperidine ring system in terms of bond lengths, bond angles and torsion angles. It is found that, in all the cases, the ring system exists in the chair conformation. The compounds are analysed in terms of five major groups depending on the substitution at the hetero nitrogen which predominantly exists (in 15 of the twenty-one structures) in the quaternary charged state in the crystal structures. Any single substitution at N prefers the equatorial position than the axial. A comparative study is made among the five major groups. It is observed that there are significant differences in C—N bond lengths and in torsion angles about various bonds of piperidine between structures with nitrogen in the charged and uncharged states. The piperidine ring is in general seen to be more puckered than the cyclohexane ring.

## INTRODUCTION

THE piperidine ring is closely related to cyclohexane with the replacement of one methylene group of cyclohexane by an NH group. For cyclohexane, two main conformations of the ring are possible, *i.e.*, the energetically stable chair and the less favoured boat conformation. The boat form is found to have a greater energy than the favoured chair conformation by about 6.9 kcal/mole. The chair conformation is preferred in piperidine also, with the boat form having 4.7 kcal/mole greater energy than the chair form<sup>1</sup>. The piperidine ring is of additional conformational interest because of the controversy over whether the hydrogen of N is 'axial' or 'equatorial' with respect to the ring. For instance, it is found from theoretical calculations and other reasoning that the hydrogen of N in the axial position (with the lone pair equatorial) is conformationally more favoured<sup>2</sup> by 0.6 kcal/mole. However, more recent work<sup>3,4</sup> claims that the N-H equatorial conformation of piperidine is preferred to axial by 0.4 kcal/mole.

Crystal structure data of 21 piperidine compounds are available for comparison of the conformational aspects of piperidine and it is found that the piperidine structures predominantly have nitrogen in the charged quaternary form (15 of the 21 structures). The six structures in which nitrogen is uncharged have a carbon atom (of methylene, ethylene, aromatic groups, etc.) bonded to it instead of a hydrogen. The 21 structures are listed in Table I with references<sup>5-20</sup> and the accuracy of the structure analysis (R-factor). Figure 1 gives the structural formulae of these compounds. They are broadly subdivided into five categories depending on the substitution at N and whether these are axial or equatorial as given in Table II. Fig. 2

gives the numbering of atoms in the piperidine ring and the equivalent bond lengths and torsion angles represented as  $p$ ,  $q$  and  $r$  while equivalent bond angles are numbered as 1, 2, 3 and 4 for convenience in further discussion.

## ANALYSIS OF THE DATA AND DISCUSSION

The R-factor reported for each structure is a measure of its accuracy and in general all the structures have reasonable accuracy except the structures 21 (with two molecules in the asymmetric unit) which has a relatively large R-factor (17%) and hence discussion on this structure may not be as reliable as the other structures. There are three structures in group I (having two hydrogens at N). They are piperidine-2-carboxylic acid 4H<sub>2</sub>O(1), piperidine-3-carboxylic acid (2) and piperidine HCl (3). Bond lengths, bond angles and torsion angles\* show that structure 3 has marked differences compared to the other two. The reason for this difference is not clear. Hence structures 1 and 2 are individually classified (for further discussion) as group I<sub>1</sub> and structure 3 as I<sub>2</sub>. The weighted mean C—C bond length ( $\bar{r}$ ) of 1.55 (1) Å and the weighted mean C—C—C bond angle of 107.2 (11)° and the mean angles {3} and {4} of group I<sub>2</sub> have significantly different values compared to structures reported in II to IV. The weighted mean torsion angle ( $\phi_m'$ ) of structure 3 of 64 (1)° is large and compares only with the large value of 63 (3)° observed for group V.

The weighted mean C—C bond lengths of individual structures are found to be, in general, less than the standard C—C single bond distance of 1.54 Å. The weighted mean value of 1.523 (18) Å of all the struc-

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\* Tables of bond lengths, bond angles and torsion angles of all the 21 structures are available with the authors. Those in need of it may please write.

TABLE I  
List of piperidine structures

Code No.	Group	Compound Name	Space Group	R-factor	Reference
1.	I <sub>1</sub>	Piperidine-2-carboxylic acid 4H <sub>2</sub> O	P2 <sub>1</sub> /c	7.9%	5
2.		Piperidine-3-carboxylic acid	Pna2 <sub>1</sub>	3.3%	6
3.	I <sub>2</sub>	Piperidine hydrochloride	Pbcm	9.4%	7
4.	II	(-)[(-)-1-Methyl-3-ethyl-3-benzoylpiperidine R : R-(+)-bitartrate]	P2 <sub>1</sub>	4.1%	8
5.		1-(1-Phenyl-cyclohexyl) piperidine hydrochloride	P2 <sub>1</sub> /c	11.0%	9
6.		$\beta$ -DL-1,3-Dimethyl-4-phenylpropionoxypiperidine hydrochloride	P2 <sub>1</sub> /c	9.0%	10
7.		(+)-1-Benzyl-4(2,6-dioxo-3-phenyl-3-piperidyl) piperidine hydrobromide hemihydrate	P1	4.6%	11
8.		(+)-[(-)-1-methyl-3-benzoylpiperidine R : R-(+)-bitartrate] monohydrate	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	4.0%	12
9.		(+)-(1-methyl-3-benzoyl-3-bromoacetoxypiperidine) hydrobromide	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	5.0%	13
10.		1,2-Dimethyl-4-hydroxy-4-phenylpiperidine hydrochloride	C2/c	6.4%	14
11.		1e, 2a, 6e-Trimethyl-4e-phenyl-4a-acetoxypiperidine hydrobromide	P2 <sub>1</sub> /c	5.6%	15
12.		DL- $\alpha$ -1 : 3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride	P2 <sub>1</sub> /c	15.0%	16
13.		DL-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrobromide	Pbca	10.0%	17
14.	III	(+)-(1,3-dimethyl-3-benzoylpiperidine methiodide)	P2 <sub>1</sub>	7.1%	18
15.		(-)-[1-Methyl-3-methoxy-3-benzoylpiperidine methiodide] chloroform	P2 <sub>1</sub>	5.5%	19
16.	IV	1-Benzyl-4(2,6-dioxo-3-phenyl-3-piperidyl) piperidine	C2	5.0%	20
17.		( $\pm$ )- $\gamma$ -1,2,5-trimethyl-4-phenylpiperidin-4-ol	P2 <sub>1</sub> /c	4.8%	21
18.		( $\pm$ )- $\beta$ -1,2,5-trimethyl-4-phenylpiperidin-4-ol	P2 <sub>1</sub> /n	5.4%	22
19.		( $\pm$ )- $\alpha$ -1,2 $\alpha$ -5e-trimethyl-4e-phenylpiperidin-4a-ol	P2 <sub>1</sub> /c	4.9%	23
20.		4-( <i>p</i> -chlorophenyl)-4-hydroxy-N,N, $\gamma$ -trimethyl- $\alpha$ <sub>1</sub> , $\alpha$ -diphenyl-1-piperidinebutyramide	P2 <sub>1</sub> /c	9.0%	24
21.	V	N-tripropylacetyl piperidine	Pbca	17.0%	25

tures (excluding 3 and 21 for obvious reasons) compares well with the value of 1.533 Å of Bartell and Kohl<sup>26</sup> observed for *n* alkanes. Also, the weighted mean C—C—C bond angle of 111.0 (23)° is slightly less than the theoretically expected value of 111.5° of the cyclohexane chair conformation<sup>27</sup>. The weighted mean

C—C bond length and the mean C—C—C bond angle compare well with the values of 1.520 Å for bond length and 111.05° for bond angle observed in the electron diffraction study of gaseous cyclohexane<sup>28</sup>. However, this is found to be larger than the tetrahedral angle of 109° 28'. The weighted mean C—N—C



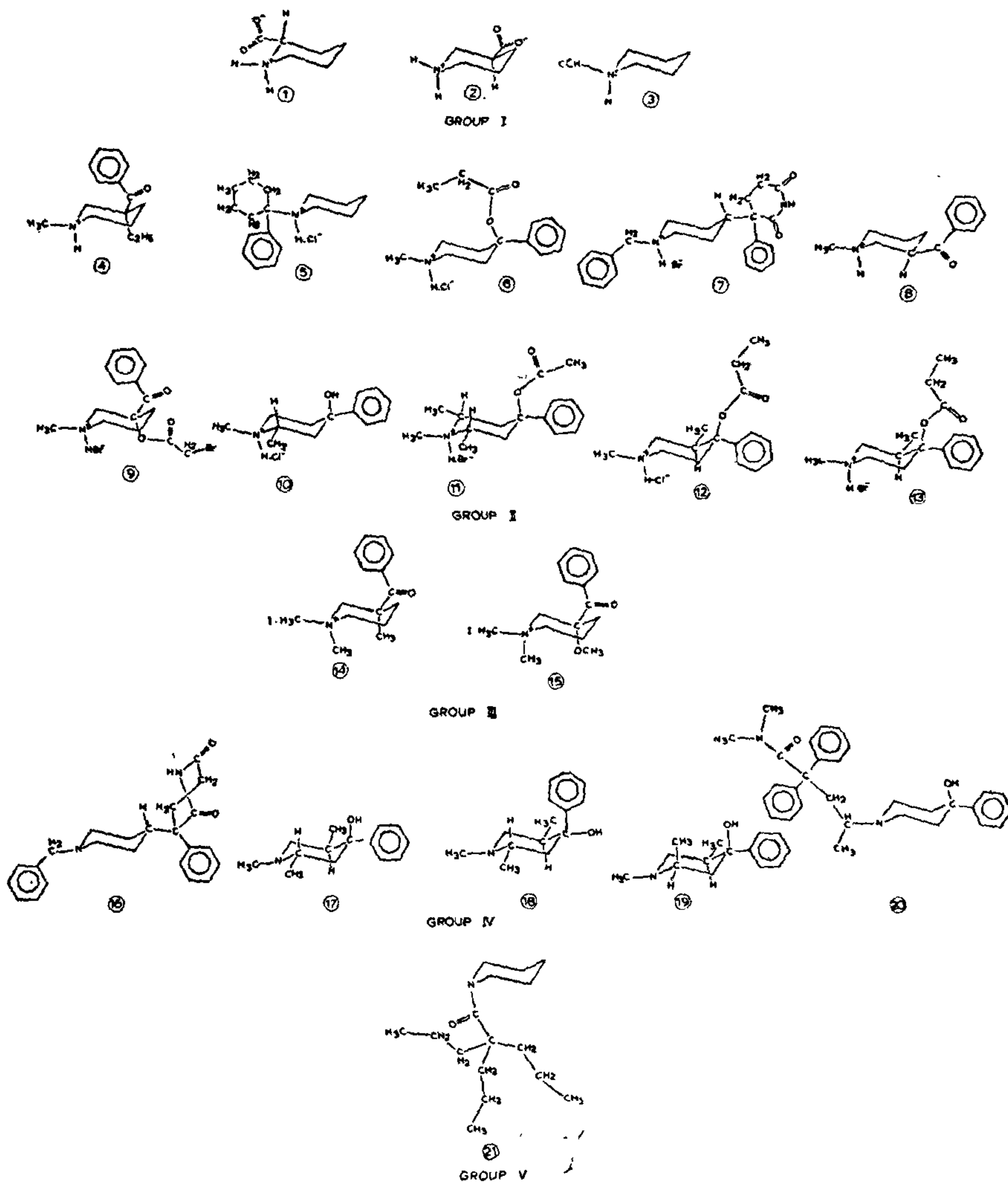


FIG. 1

bond angle of  $111.0(14)^\circ$  is also found to be larger than tetrahedral. Torsion angles of the structures show that all the structures exist in the energetically favoured chair conformation. The weighted mean  $\phi_{av}$  value of the structures of  $56(3)^\circ$  shows that, in general, the value is greater than  $\pm 54.7^\circ$  of cyclohexane<sup>27</sup> and we may conclude that piperidine, in general, is more puckered than cyclohexane.

Comparison among individual groups is possible with the aid of the weighted mean values of equivalent bond lengths, bond angles and torsion angles which are given in Table III. The C—N bond lengths for groups I to III, in which N exists in the quaternary state, have ascending values showing that the C—N bond length increases with bulkier substituents at N (Table IIIa). However, for group IV in which N exists

TABLE II  
Disposition of the nitrogen atom

Group	Whether nitrogen exists in the quaternary state	Atom equatorially bonded to nitrogen	Atom axially bonded to nitrogen
I	Yes	H	H
II	Yes	C (methyl, aromatic, etc.)	H
III	Yes	C (methyl)	C (methyl)
IV	No	C (methyl, methylene, etc.)	Nil
V	No	Nil	C (carbonyl)

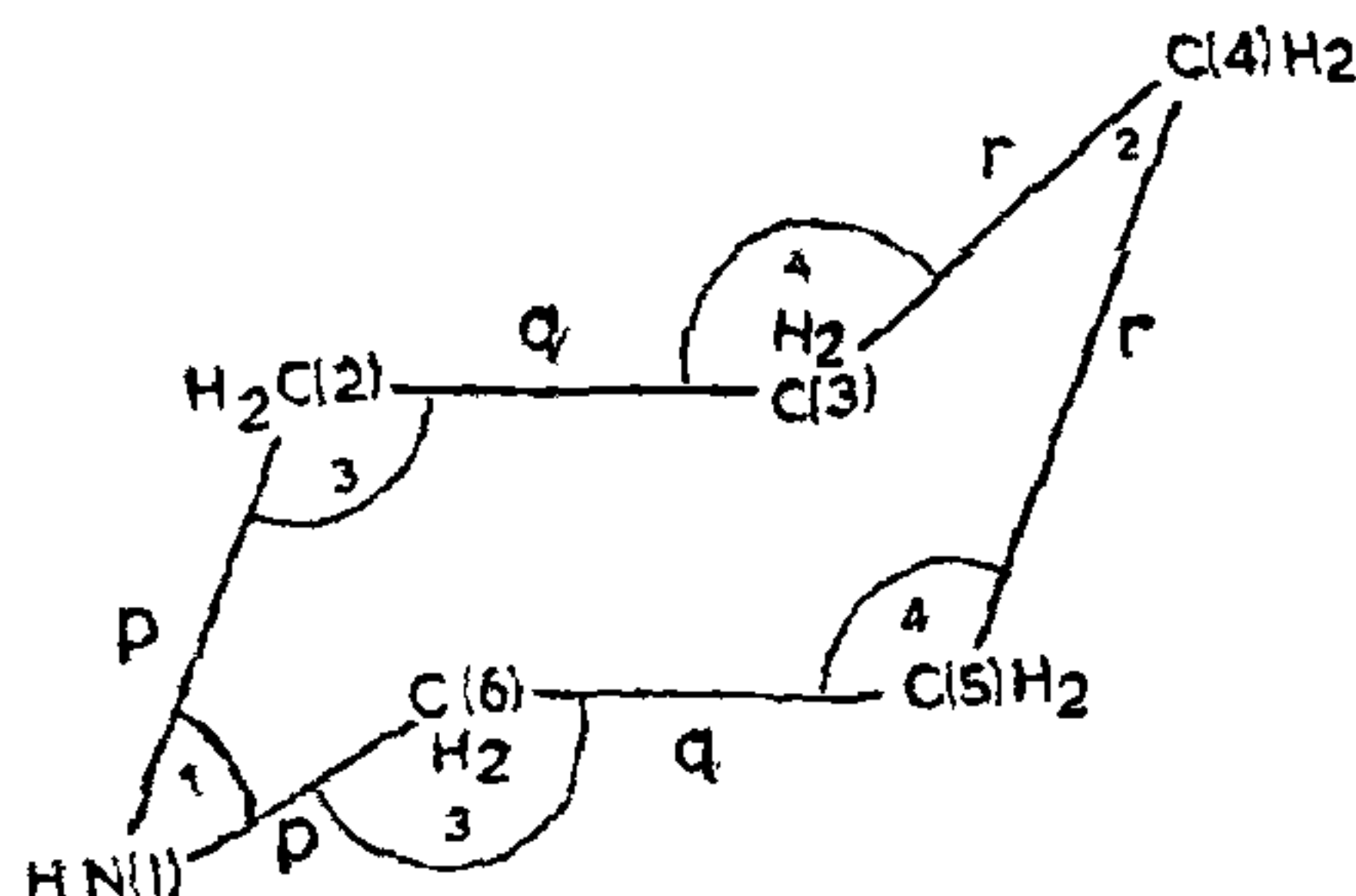


FIG. 2. The piperidine ring with the equivalent bond lengths and angles indicated.

in the unionised state the C—N value is found to be significantly smaller. Table IIIa shows that the C—C bonds which are close to N (bond *q*) have weighted mean values which are systematically less, for all the groups (except group III where they are found to have equal values), compared to the farthest C—C bonds (bond *r*). The weighted  $\langle \text{C—N—C} \rangle$  values of individual groups (Table IIIb) are larger than tetrahedral with structure 3 (*i.e.*, I<sub>2</sub>) having the largest angle of 116.6 (9)°. The geometrically opposite C—C—C angle of N (*i.e.*, angle 2) has values, in general, above and below the tetrahedral value with a minimum of 107 (3)° for group V and a maximum of 112.1 (11)° for I<sub>2</sub>. Also, the weighted mean C—C—N bond angle ( $\langle 3 \rangle$ ) shows larger variations from the tetrahedral value with a minimum of 104 (2)° for V and 111 (2)° for groups II and III. Comparing torsion angles for the

structures (Table IIIc) it is found that in structure I<sub>2</sub> all the values are large with a maximum of 68 (1)° for  $\langle p \rangle$  and a minimum of 59 (1)° for  $\langle q \rangle$ . Table IIIc shows that for all the groups (except group III) the weighted mean torsion angle  $\langle p \rangle$  is found to be the largest compared to the mean torsion angles  $\langle q \rangle$  and  $\langle r \rangle$ . Although the standard deviations of mean values are fairly large for some of the groups, it is possible to make the observations that in general the piperidine ring is more puckered at the N atom end of the ring. The variation is more pronounced when N is in an uncharged state as in group IV with the substituent at N in the equatorial position. The overall weighted mean torsion angle in group V, the only structure with the substituent at N in the axial position, is 63 (3)° and this is much larger than the other groups (except I<sub>2</sub>) and it shows a maximum of 67 (3)° for  $\langle p \rangle$  with  $\langle q \rangle$  and  $\langle r \rangle$  having the same value of 61 (3)°. The overall weighted mean torsion angle for the structures in all the groups is found to be larger than the theoretical value of 54.7° of the cyclohexane chair conformation<sup>27</sup> and from this, one may conclude that the piperidine ring is in general more puckered than the cyclohexane chair conformation.

As already mentioned, it is observed that all the structures reported exist in the chair form. It is also observed that whenever N has a bulky substituent as in group II structures, the substituent favours the equatorial position with the hydrogen axial to the piperidine ring system. When N is uncharged, the only substituent at N predominantly exists in the equatorial position as is observed for all the structures in group IV with the only exception of one structure in group V. In group V which has an axial substituent, the piperidine ring appears to be more puckered than when there is an equatorial substituent as in group IV. Apart from substituents at N, bulky substitutions like the phenyl group, the methyl group, etc., are seen in quite a few of the piperidine structures reported (see Fig. 1) attached to other positions of the piperidine ring. It is seen that in such cases the bulkier substituents generally favour the equatorial position, which is energetically more favoured than the axial position, as is generally observed in cyclohexane structures. Even though none of the structures reported has only one hydrogen attached to N, as in the case of pure piperidine (where there is a controversy as to whether the energetically favourable position of H is axial or equatorial), our observations seem to indicate (based on the preponderance of equatorial substituents observed for piperidine structures in the uncharged state) that the preference may be more for the equatorial position of H (than the axial) with the lone pair existing in the axial position which is probably the energetically favoured conformation of piperidine. Comparing the structures with cyclohexane we see that the piperidine ring is, in general, more puckered than the cyclohexane ring.

TABLE IIIa

Weighted Average Bond lengths	Group→	I <sub>1</sub>	I <sub>2</sub>	II	III	IV	V
$\langle p \rangle$ or $\langle \text{C-N} \rangle$		1.493 (3)	1.48 (1)	1.50 (4)	1.50 (3)	1.466 (4)	1.49 (4)
$\langle q \rangle$		1.519 (4)	1.53 (1)	1.53 (6)	1.52 (3)	1.524 (4)	1.56 (5)
$\langle r \rangle$		1.527 (4)	1.57 (1)	1.53 (4)	1.55 (2)	1.536 (4)	1.59 (5)
$\langle \text{C-C} \rangle$		1.523 (4)	1.55 (1)	1.53 (5)	1.53 (2)	1.529 (4)	1.56 (5)

TABLE IIIb

Weighted Average Bond angle	Group→	I <sub>1</sub>	I <sub>2</sub>	II	III	IV	V
$\langle 1 \rangle$ or $\langle \text{C-N-C} \rangle$		112.2 (2)	116.6 (9)	111.5 (10)	111 (2)	110.0 (2)	115 (2)
$\langle 2 \rangle$		110.7 (3)	112.1 (11)	110 (2)	109 (2)	108.4 (2)	107 (3)
$\langle 3 \rangle$ or $\langle \text{C-C-N} \rangle$		110.3 (3)	105.0 (10)	111 (2)	111 (2)	110.6 (2)	104 (2)
$\langle 4 \rangle$		110.4 (3)	105.0 (10)	112 (3)	112 (2)	112.6 (2)	109 (2)
$\langle \text{C-C-C} \rangle$		110.5 (3)	107.2 (11)	111 (2)	111 (2)	111.1 (2)	109 (2)

TABLE IIIc

Weighted Average Torsion angle	Group→	I <sub>1</sub>	I <sub>2</sub>	II	III	IV	V
$\langle p \rangle$		57.8 (3)	68 (1)	57 (1)	59 (2)	60.6 (3)	67 (3)
$\langle q \rangle$		56.3 (3)	59 (1)	56 (1)	57 (2)	57.3 (3)	61 (3)
$\langle r \rangle$		56.4 (3)	63 (1)	54 (3)	54 (2)	52.1 (3)	61 (3)
Weighted mean Torsion angle ( $\phi_{av}$ )		56.7 (3)	64 (1)	55 (3)	57 (2)	56.8 (3)	63 (3)

Note: The weight used for the averages is  $1/\sigma^2$  where  $\sigma$  is the standard deviation of each parameter. The r.m.s. value of the standard deviation is given in parentheses.

The puckering in piperidine is found in general to be more pronounced near the N atom of the ring.

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## MAGNETIC AND SPECTRAL STUDIES OF COPPER(II) COMPLEXES WITH SCHIFF BASES DERIVED FROM *o*-AMINO-BENZOYL HYDRAZIDE

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### INTRODUCTION

THE transition metal complexes with hydrazones have been investigated during the past few years<sup>1</sup>. However, there is not much work on the complexes of transition metals with bis(salicylidene)-*o*-amino-benzoylhydrazones<sup>2</sup>. In this communication we wish to report the synthesis and spectral properties of a few copper(II) complexes with the Schiff bases derived from *o*-aminobenzoylhydrazide. Following aldehydes were used for the preparation of hydrazones.

1. Salicylaldehyde, 2. 5-Methyl salicylaldehyde, 3. 2-Hydroxynaphthaldehyde and 4. Acetylacetone.

### EXPERIMENTAL

Methyl anthranilate and hydrazine hydrate used were of reagent grade. Substituted aldehydes were prepared by Duff's method<sup>3</sup>. *o*-Amino-benzoylhydrazide was prepared by the standard method<sup>4</sup>. The respective hydrazones were prepared following known methods<sup>5</sup>.

Copper acetate and hydrazones in 1 : 1 molar ratio were refluxed in ethanol medium for about five hours. The separated copper complexes were filtered, washed with ethanol and soxhleted using ethanol. They were then dried in vacuum over fused calcium chloride,

The metal and nitrogen content in these complexes, were analysed and are indicated in Table I.

TABLE I

*Elemental analysis, magnetic data and electronic spectra of copper(II) complexes with hydrazones of salicylidene methyl anthranilate*

Sl. No.	Empirical formula of complexes	% Cu	% N	$\mu_{\text{eff}}$ (B.M.)	$\lambda_{\text{max}}$ (nm)
1.	(C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ) Cu	14.91 (15.10)	10.07 (9.99)	1.81	650 350
2.	(C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> ) Cu	14.00 (14.16)	9.52 (9.36)	1.80	630 375
3.	(C <sub>29</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> ) Cu	12.31 (12.11)	7.82 (8.01)	1.89	675 412
4.	(C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> ) Cu	16.55 (16.78)	11.00 (11.09)	1.99	660 380

Note : (i) The values in the parenthesis are the calculated values.

(ii) Electronic spectra of the complexes are taken in Nujol Mull.