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ELECTRONIC AND SPATIAL STRUCTURE OF PIPERIDINE AND ITS SUBSTITUTED DERIVATIVES FROM THE RESULTS OF *ab initio* CALCULATIONS

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The results of non empirical quantum-chemical calculations using the RHF/6-31G(d) and MP2/6-31G(d) methods do not agree with proposals for the axial position of the H atom on the N atom in the piperidine molecule. According to RHF/6-31G(d) calculations for the N-methylpiperidine molecule and its chloro-substituted derivatives an equatorially placed methyl group is energetically more favored than an axial. The axial C–Cl and C–H bonds in these molecules are longer than the equatorial. The ^{35}Cl NQR frequencies for the axial Cl atoms are lower than the equatorial. The ^{35}Cl NQR frequency of the axial chlorine atom in 2-chloro-1-methylpiperidine is anomalously low. This is chiefly due to the high population density of its p_σ-orbital and this is a result of the polarization of the C–Cl bond via the N atom unshared electron pair directly through the field. The effect of a similar unshared electron pair on the parameters of the C–Cl bond in the $ClCH_2NH_2$ molecule has been studied by the RHF/6-31(g) method for different angles of rotation of the $ClCH_2$ group around the C–N bond.

Keywords: N-methylpiperidine and its chloro-substituted derivatives, piperidine, axial and equatorial atoms, quantum-chemical calculations, ^{35}Cl NQR frequencies.

As a rule, substituted piperidines exist in a chair form (e.g. see [1]). There is conflicting data regarding the relative orientation of a substituent on the nitrogen atom and in the ring. NMR Data is considered to be (e.g. see [1]) the most reliable for the case of R = H and this points to an axial position for the hydrogen atom (Form **1**). For R = alkyl all available data indicates an equatorial position for an alkyl group (Form **2**).

For a substituent in the ring of substituted piperidines as well as in substituted cyclohexanes the generally more favored orientation is an equatorial position. However, in 2-substituted piperidines, as in 2-substituted tetrahydropyrans, 1,4-dioxanes, cyclohexanones, etc, an electron-acceptor substituent usually occupies an axial position (e.g. see [1]). The distribution of the electron density in these 2-substituted oxygen containing compounds are significantly different and have a character reverse to that observed for the axial and equatorial atoms found in other ring positions (e.g. see [2-6]).

The aim of our work is to examine by nonempirical, quantum-chemical methods the conformational features of substituted piperidines, the effect of the nitrogen atom on the electron densities of the Cl and H atoms in variously substituted chloro N-methylpiperidines, and also to study the ^{35}Cl NQR parameters in the latter. For this task we carried out quantum-chemical calculations of the molecular forms **1-10** *via* full optimization of their geometry by the Hartree-Fock method on a 6-31G(d) split valence basis using the Gaussian 94W program [7].

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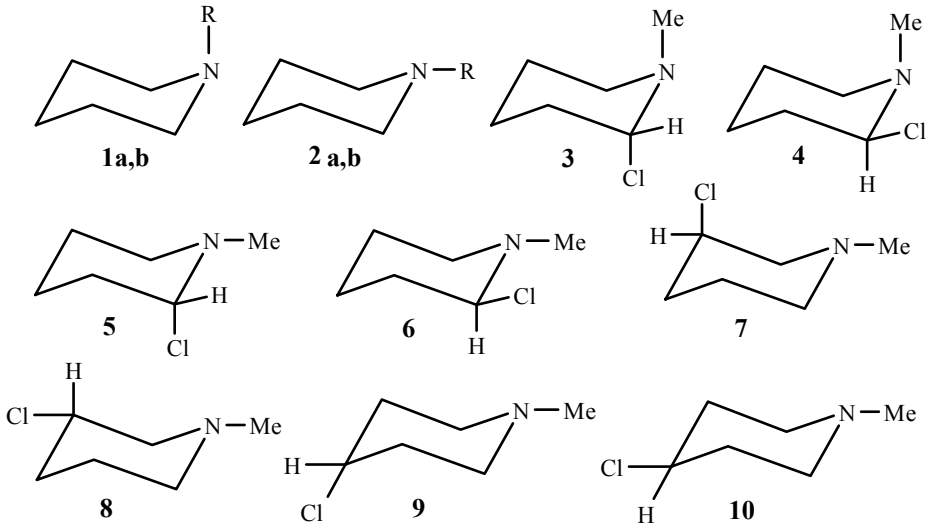
In the quantum-chemical calculations of the chloro-substituted N-methylpiperidines the initial coordinate location was always placed at the Cl atom. The *z*-axis then coincided with the axis of symmetry of the p_σ-orbital of the Cl atom and the *x*- and *y*-axes with the axes of symmetry of the orbital of its unshared electron pairs. Base points on the potential energy surfaces of all the molecules studied were found as a result of these calculations. In all cases, virtual valence vibrational frequencies were absent and the stable states of these molecules were found.



1, 2 a R = H, **b** R = Me

According to the calculations for the unsubstituted piperidine carried out by the RHF/6-31G(d) method the form **2a** is energetically more favored (Table 1). However, the difference between the total energy of form **1a** and **2a** (3.4 kJ/mol) is comparatively small. When calculating the zero point vibrations this difference is even smaller (3.0 kJ/mol).

This data is not in agreement with the conclusions concerning the axial position of the H atom on the N atom in the piperidine molecule (see above) hence we carried out calculations of these two forms using the MP2/6-31G(d) electron correlation method. The relationship of the total energy of forms **1a** and **2a** is the same as before. However, the difference in their total energy is less (2.3 kJ/mol). When calculated from zero point energies form **2a** is favored over **1a** by 2.1 kJ/mol.

The rather small difference in energy for the forms **1a** and **2a** as calculated by the two quantum-chemical methods does not allow us to confirm that the conclusions based on the NMR data (see above) is wrong. It is possibly true for piperidine in solution.

The results of the calculations of forms **1b** and **2b** (Table 1) agree with the previously obtained data (see above) pointing to an equatorial position of the methyl group on the N atom (form **2b**). The difference in total energies of these forms is 15.1 kJ/mol.

In the 2-chloro-1-methylpiperidine molecule an equatorial position for the methyl group is also more favored than an axial. The total energies for forms **5** and **6** are markedly lower than **3** and **4** (Table 1). The Cl atom in the molecule **5** occupies an axial position, the total energy of form **5** being 26.5 kJ/mol lower than that of **6**.

Bearing in mind that, in substituted N-methylpiperidines, the equatorial position is more favored than an axial for a methyl group the 3- and 4-chloro-substituted N-methylpiperidines were calculated only with such a position for this group. The results of the calculations show that the Cl atom in 3-chloro-N-methylpiperidine

TABLE 1. RHF/6-31G(d) Calculations of the Total Energies of Structures **1-10** (E), C–Cl Bond Lengths, $C_{(2)}$-H and $C_{(6)}$-H Axial and Equatorial Bond Lengths (*d*), and Charges (*q*) on the Cl and H Atoms Involved in Bond Formations

Structure	-*E*, a. e.	*d*, Å			*q*, e		
		(C–Cl)	(C(2)–H_{ax}) (C(6)–H_{ax})	(C(2)–H_{eq}) (C(6)–H_{eq})	Cl	H_{ax}	H_{eq}
1a	250.187411	—	1.088	1.085	—	0.160	0.168
2a	250.188712	—	1.096	1.085	—	0.129	0.166
1b	289.213593	—	1.088	1.085	—	0.162	0.166
2b	289.219330	—	1.097	1.085	—	0.127	0.165
3	748.118328	1.831	—	1.077	-0.126	—	0.233
			1.085	1.083		0.195	0.173
4	748.116042	1.806	1.080	—	-0.095	0.220	—
			1.087	1.083		0.172	0.182
5	748.131194	1.902	—	1.076	-0.230	—	0.229
			1.090	1.084		0.173	0.174
6	748.121107	1.815	1.088	—	-0.106	0.190	—
			1.096	1.083		0.137	0.181
7	748.121965	1.811	1.098	1.082	-0.112	0.142	0.194
			1.097	1.084		0.128	0.174
8	748.125373	1.807	1.094	1.083	-0.109	0.155	0.191
			1.096	1.084		0.136	0.173
9	748.124057	1.820	1.093	1.084	-0.131	0.160	0.172
			1.093	1.085		0.160	0.172
10	748.125380	1.808	1.097	1.084	-0.106	0.136	0.179
			1.097	1.084		0.136	0.179

molecule occupies an equatorial position, as in substituted cyclohexanes. The total energy of form **8** is 8.9 kJ/mol less than in **7** with an axial Cl atom. The equatorial position of the Cl atom is evidently more favored in the 4-chloro-N-methylpiperidine molecule. The total energy of form **10** is 3.5 kJ/mol less than in **9**.

Upon going from R = H to R = Me the N–$C_{(2)}$ and N–$C_{(6)}$ bond lengths in forms **1** and **2** are virtually the same (1.452-1.455 Å). However, significant changes of the charge of the N atom occur. Hence with the change from **1a** to **1b** the charge on the N atom changes from -0.680 to -0.555 and from **2a** to **2b** from -0.701 to -0.565, i.e. the electron donor methyl group unexpectedly lowers the negative charge on the N atom. The length of the equatorial C–H bonds geminally related to this atom in forms **1** and **2** are the same for R = H and R = Me and somewhat less than the axial (Table 1). The axial C–Cl bonds in all of the chloro containing structures are longer than the equatorial and the negative charges on the axial Cl atoms are higher than the equatorial. A greater length of the axial C–Cl bond and higher negative charge on the Cl atom is observed in compound **5**.

In all of the molecules studied the axial C–H bonds situated in a geminal position with relation to the N atom are somewhat longer than the equatorial and the positive charge on the axial H atoms taking part in the formation of these bonds is lower than in the equatorial. An exception is the charge on the axial and equatorial H atoms in form **3** at position 6 in the piperidine ring (Table 1). The axial C–H bonds in other ring positions for all of these structures are also generally longer than the equatorial.

We have previously studied features of the electronic distribution in α-chloro ethers including the cyclic tetrahydropyran [2] and 1,4-dioxane [3-5]. It was found that the O atom markedly increases the p_σ-electron density of the axial Cl atom situated geminally to it. A similar anomalous increase in the p_σ-electron density of the Cl atom (not related to the electronegativity of the M atom and the inductive effect of its substituent) is observed in other non linear triatomic Cl–C–M groupings with an electron acceptor M atom (e.g. see [3, 5]). This is explained by the polarization of the C–Cl bond through the action of the M atom directly through the

field (e.g. see [3-6]). 2-Chloro-N-methylpiperidine does not prove an exception. The density of the $p_z(p_\sigma)$-orbital of the axial Cl atom in the energetically more favored form of this molecule (**5**) is significantly higher than the equatorial in **6** and also higher than in the 3- and 4-chloro-substituted N-methylpiperidines (Table 2).

The trend in the change of p_σ-electron density for the Cl atom in the non linear triatomic Cl–C–M groupings does not relate to the electronegativity of the M atom and the inductive effect of its substituent as was shown by a study of the ^{35}Cl NQR spectra of organic and organoelemental compounds containing such a group (e.g. see [3-6]). For these compounds it was shown that an increase in the electronegativity or negative charge on the M atom lowers the ^{35}Cl NQR frequency (increasing the p_σ-electron density of the Cl atom) and, conversely, a lowering of the electronegativity or an increase in the positive charge on the M atom increases the ^{35}Cl NQR frequency (lowering the p_σ-electron density of the Cl atom) (e.g. see [3]). The lower ^{35}Cl NQR frequency for the axial Cl atom than the equatorial in cyclic α-chloro ethers is explained by the different polarization of the axial and equatorial C–Cl bonds under the influence of the charge on the O atom directly through the field. The degree of polarization of the C–Cl bond caused by the charge on the O atom depends on the orientation of the unshared pair of electrons relative to this bond [3, 4].

Experimental ^{35}Cl NQR frequencies for chloro-substituted piperidines are not available. However, they can be determined using equation 1 (e.g. [3, 8]) and the density of the 3*p*-component of the valence *p*-orbitals of the Cl atoms for the corresponding molecules (Table 2) calculated using the RHF/6-31G(d) method (e.g. [3-6]).

$$\nu = (e^2Qq_{at}/2h)[(N_x + N_y)/2 - N_z](1 + \eta^2/3)^{1/2} \qquad (1)$$

where: e^2Qq_{at} is the quadrupolar interaction atomic constant, h is Planck's constant, N the population density of the corresponding atomic orbital, and η is the asymmetry gradient parameter of the electric field at the

TABLE 2. Population Densities of the Cl Atomic *p*-Orbitals (Σ*Np*) and their 3*p*- and 4*p*-Components in the Structures **3-10** as Calculated by the RHF/6-31G(d) Method and ^{35}Cl NQR Frequencies ν_Q) Calculated from the Densities of the 3*p*-Components

Structure	Orbital	Np_x	Np_y	Np_z	ν_Q, MHz
3	3*p*	1.298	1.297	0.969	30.582
	4*p*	0.674	0.679	0.262	
	Σ*Np*	1.972	1.976	1.231	
4	3*p*	1.302	1.303	0.962	31.633
	4*p*	0.667	0.674	0.240	
	Σ*Np*	1.969	1.977	1.202	
5	3*p*	1.279	1.283	0.998	26.322
	4*p*	0.693	0.695	0.333	
	Σ*Np*	1.972	1.978	1.331	
6	3*p*	1.300	1.303	0.963	31.570
	4*p*	0.669	0.674	0.247	
	Σ*Np*	1.969	1.977	1.210	
7	3*p*	1.302	1.301	0.959	31.897
	4*p*	0.673	0.674	0.254	
	Σ*Np*	1.975	1.975	1.213	
8	3*p*	1.299	1.300	0.965	31.153
	4*p*	0.674	0.675	0.248	
	Σ*Np*	1.973	1.975	1.213	
9	3*p*	1.298	1.298	0.967	30.797
	4*p*	0.677	0.676	0.264	
	Σ*Np*	1.975	1.974	1.231	
10	3*p*	1.300	1.299	0.963	31.291
	4*p*	0.675	0.675	0.246	
	Σ*Np*	1.975	1.974	1.209	

resonating nucleus. In this case the value of e^2Qq_{at} (93.093 MHz) was obtained from the density of the 3*p*-valence component of the *p*-orbitals of the Cl atoms in the molecule Cl_2 calculated by the RHF/6-31G(d) method. The ^{35}Cl NQR frequencies for the chloro substituted N-methylpiperidines calculated by this method are given in Table 2.

As might have been expected, the calculated ^{35}Cl NQR frequency of form **5** with an axial Cl atom in a geminal position with respect to the N atom is markedly lower than form **6** with an equatorial Cl atom and also structures **7-10** with axial or equatorial Cl atoms in other positions in the piperidine ring. As in cyclic α-chloro ethers, the very low ^{35}Cl NQR frequency of the axial Cl atom in form **5** is basically due to the very high density of the 3*p*-component of its valence p_z-orbital. Some contribution to this lowering of the NQR frequency is also introduced by the very low average orbital density of its unshared pair of electrons (Table 2).

The relationship of the NQR frequencies for forms **3** and **4** and the densities of the 3*p*-components of its Cl atoms is similar to that for the forms **5** and **6**. However, the difference for the first pair of structures is comparatively small. For form **3**, which differs from **5** only in the position of the methyl group on the N atom, the calculated NQR frequency is significantly less than for form **5**.

The negative charge on the N atom in form **5** (-0.557) is somewhat larger than in form **3** (-0.546). The matches up with the ratio of the NQR frequencies for these molecules and the previously mentioned dependence of the change in NQR frequencies with variation of the charge on the M atom in molecules containing a Cl–C–M group. However, the difference in charges on the N atom in **3** and **5** seems insufficiently large to bring about a large change in the ^{35}Cl NQR frequencies for these molecules. Evidently the latter is due also to the varied orientation of the unshared electron pair orbital of the N atom relative to the axial and equatorial C–Cl bond in these structures. Only in form **5** is this unshared pair of electrons orientated in such a relationship to the C–Cl bond as to increase significantly the p_σ-electron density of its Cl atom.

The dependence of the electron density of the Cl atom on the orientation of the unshared electron pair orbital of the N atom can track the rotation of the $ClCH_2$ group around the C–N bond in the $ClCH_2NH_2$ molecule. We have carried out quantum-chemical calculations using the RHF/6-31G(d) method for this molecule with total optimization of its geometry and also for different angles of rotation ϕ for the $ClCH_2$ group around the C–N bond and optimization of its geometric parameters. With the total optimization of the molecular geometry we have located a fixed point on the potential energy surface with a dihedral angle ϕ = 61.8° (ClCNH) (virtual valence vibrational frequencies are absent at this point).

At this angle the C–Cl bond is found in a trans position relative the orbital of the unshared pair of electrons of the N atom and is most efficiently polarized by the action of the latter. Approximately the same is realized in structure **5** in which the ClCNC dihedral angle is 66.0°. The dependence of the relative total energy of the $ClCH_2NH_2$ molecule on the angle ϕ is given in Fig. 1. For ϕ = 0, 20, 120, and 140° the fixed points are absent (in each of these the point is located at one virtual frequency of the valence vibrations).

From equation (1) and the population densities of the 3*p*-components of the valence *p*-orbitals of the Cl atom the ^{35}Cl NQR frequencies were calculated for $ClCH_2NH_2$ with different angles ϕ (Fig. 2, curve 1). Changing these frequencies by variation of ϕ is similar to a change of the average density of the 3*p*-component valence p_x- and p_y-orbitals of the Cl atom and opposes the change in the density of the 3*p*-components of its valence p_z-orbital (Fig. 2, curves 2 and 3), which might have been expected according to equation (1). However, the absolute change in the average density of the 3*p*-components of the valence p_x- and p_y-orbitals of the Cl atom are approximately three times less than in the case of the 3*p*-component of its valence p_z-orbital. Hence the change in orientation of the orbital of the unshared electron pair of the N atom relative to the C–Cl bond in this molecule has the greatest effect on the p_σ-electron density for its Cl atom.

In the energetically more favored form of the $ClCH_2NH_2$ molecule the ^{35}Cl NQR frequency is a minimum as is the average content of the 3*p*-valence components of the p_x- and p_y-orbitals of the Cl atom while the population of the 3*p*-components of the valence p_z-orbital is a maximum (Fig. 2). In this form an overlap of the orbital of the unshared N electron pair with the bonding or antibonding orbital of the C–Cl bond is not possible. Polarization of the latter by the unshared N electron pair occurs only *via* the field.

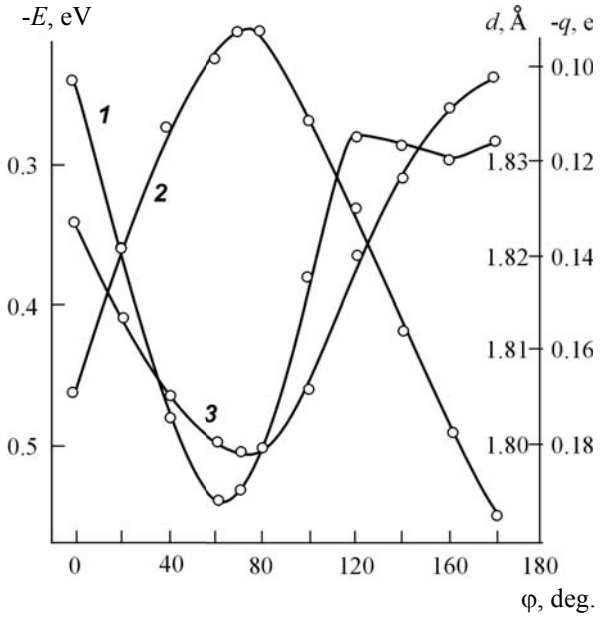


Fig. 1. RHF/6-31G(d) Calculations of the dependence on the angle ϕ of 1: the relative energy (-*E*) of the $ClCH_2NH_2$ molecule; 2: the lengths (*d*) of the C–Cl bond; and 3: the charge (-*q*) on the Cl atom.

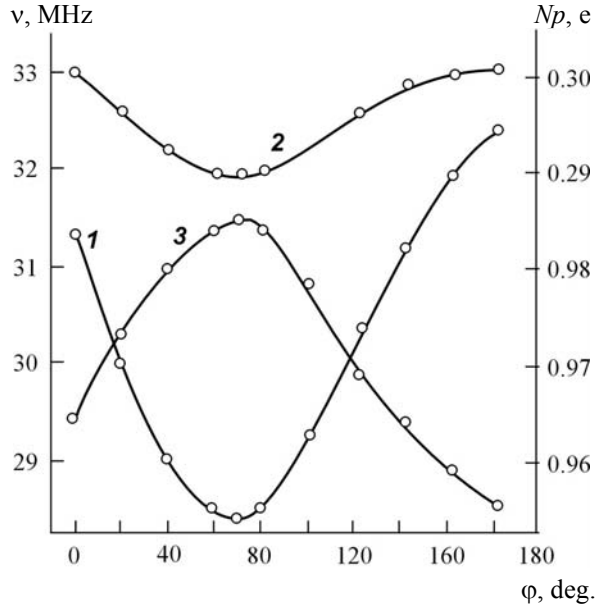


Fig. 2. Dependence on the angle ϕ of 1: the ^{35}Cl NQR frequency (ν_Q) of the $ClCH_2NH_2$ molecule; 2: The calculated densities of the 3*p*-components of the Cl atom valence *p*-orbitals, the population average (N) of the p_x- and p_y-valence orbitals; and 3: the populations of the 3*p*-components of the p_z-valence orbitals.

With a variation of the angle ϕ the ^{35}Cl NQR frequency decreases (Fig. 2) as the negative charge on the Cl atom increases (Fig. 1) and the length of the C–Cl bond increases (Fig. 1). These results correlate with the data for the chloro substituted N-methylpiperidines (see above).

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