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Nonempirical Calculation of Structural, Electric and Spectral Characteristics of Diprazine

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Abstract—Calculations of IR spectra, dipole moments, atomic charges, and structural characteristics of three forms of diprazine (molecular, cation and dication) were carried out. Changes in the studied characteristics in going from one form to another were analyzed.

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Diprazine [10-(2-dimethylaminopropyl)phenothiazine hydrochloride] belongs to the strongest antigystamine and sedative preparations [1] that are the objects of study by criminalistic medicine. In aqueous solution diprazine can exist in three forms: molecular, single-charged cation, and double-charged cation. We found no publications on the changes in the diprazine properties in dependence on the medium pH. There are several procedures for determination of diprazine in solutions, including biological fluids, based on various methods (electrochemical, chromatographic, and spectral) [2–8]. The method of IR spectroscopy is one the most widely used for the identification of strongly acting drugs [9, 10]. Since recently, for the complete interpretation of experimental data the methods of quantum chemistry with computer programs often were used [11]. In this work for the analysis of the IR spectra of various ionic forms of diprazine aimed at the elucidation of the features that could promote identification of certain forms in a real sample, we carried out quantum-chemical calculations of the respective systems. In addition, we used the computer experiment for the calculation of structural (bond lengths and angles) and electrical (atomic charges, dipole moments) characteristics of the studied structures for revealing the most probable alternative of the two possible diprazine cationic forms.

Optimal configurations of molecular and ionic forms of diprazine were elucidated using GAUSSIAN03 program [12] by the Hartree–Fock method with 6-31G(d,p) basis, and calculation of their structural, spectral, and electrical characteristics was performed.

Ionic forms of diprazine. Structure of diprazine molecule is depicted in Fig. 1. Depending on the medium acidity, one of the two possible cationic forms of diprazine can dominate in solution. The cationic forms correspond to addition of protons H^+ to the nitrogen atoms of the molecule ($pK_1 = 4.0$; $pK_2 = 9.1$) (Fig. 2).

Below are considered the possible routes of formation of diprazine cation. The diprazine molecule (Fig. 1) has three electronegative centers including two nitrogen atoms, of which the first (N^1) is in the structure of phenothiazine ring and the second (N^2) in the isopropyl substituent, and sulfur atom. As shown further, in optimized structures the sulfur atom bears positive charge, nitrogen atoms are negatively charged, therefore diprazine cation is formed by adding proton to either N^1, or N^2 atom. By calculation of total energy

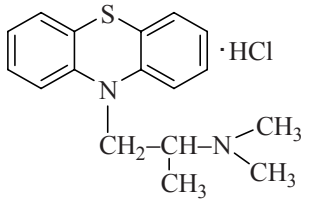

Fig. 1. 10-(2-Dimethylaminopropyl)phenothiazine hydrochloride.

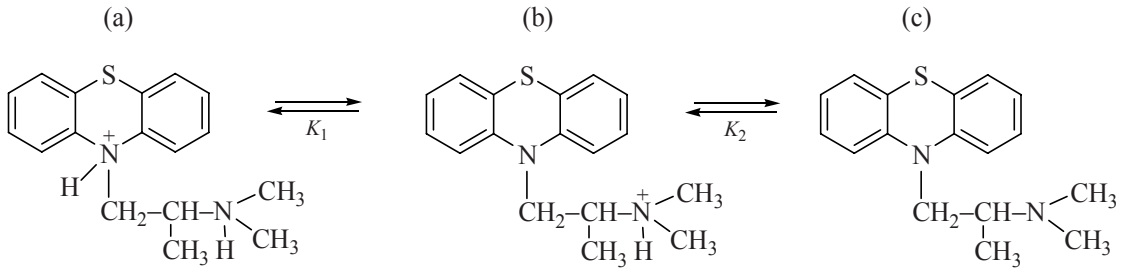

Fig. 2. Equilibrium forms of diprazine in aqueous solution: (a) dication, (b) cation, (c) molecular form.

of each structure the most probable structure of cation was established. The calculation gives the values of total energy for the cations with the proton at the nitrogen atom N^2 of aminopropyl group $E_{HF}(N^2)$ = –1162.2320596 au, for structure protonated at the atom N^1 of phenothiazine ring $E_{HF}(N^1)$ = –1162.1951649 au. From these data follows that the first structure is characterized by lower energy, hence by higher stability. This is a consequence of steric hindrances to approach by a hydrogen ion to the nitrogen atom of phenothiazine ring as compared with aminopropyl nitrogen atom. Therefore further we consider only the diprazine cation protonated at the N^2 nitrogen atom in the aminopropyl substituent.

Comparative analysis of structural characteristics of the diprazine ionic forms. The optimal structures are depicted in Figs. 3–5. The C–C, C–H, and C–S bond lengths in the phenotiazine ring remain practically the same in all structures: the average C–H bond length is 1.075 Å; the average C–C bond length in the molecule and in cation is 1.387 Å, in the dication, 1.386 Å. The calculated C–C and C–H bond lengths as well as the bond angles in the benzene rings conjugated with the heterocycle are consistent with the published data on the bond length in benzene and other aromatic systems [13]. The C–S bonds are found longer than in some phenothiazine cation-radicals (on the average by 0.062 Å) [11]. The angle $C^1N^1C^2$ in the phenothiazine ring is

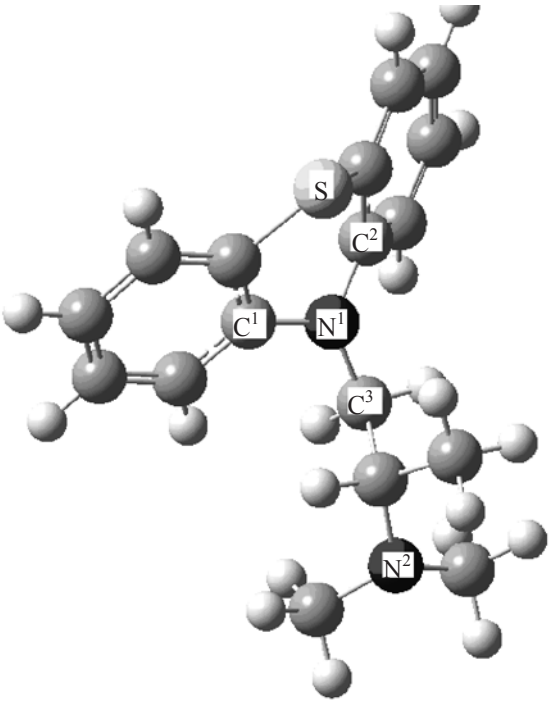

Fig. 3. Optimized structure of diprazine molecule.

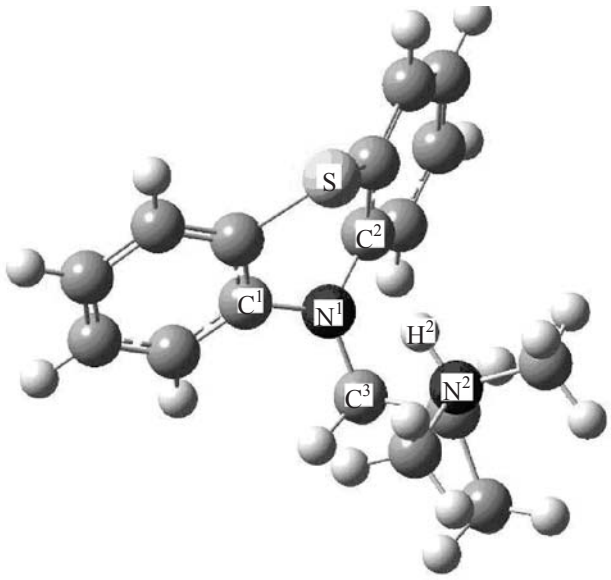

Fig. 4. Optimized structure of diprazine cation.

~116º in all the considered forms of diprazine; the CSC angle equals to 97.6º, 97.7º, and 99.1º in the molecule, cation, and dication, respectively. In [11] the calculated values of this type in similar systems were somewhat higher (102.2º, 102.7º). The C–N bond lengths in phenothiazine ring and in the substituent increase in going from molecular form to the dicationic form that suggests their weakening on the protonation. The average length l_{C-N^1} in the diprazine molecule, cation and dication is respectively 1.412, 1.422, and 1.486 Å. In aminopropyl radical this tendency retains for $H_3C–N^2$ bond in going from the molecule to the dication (1.446, 1.489, 1502 Å).

Analysis of the data obtained shows that the bond $C–N^1$ in phenothiazine ring suffers the maximal weakening in going from cationic form to dicationic one while in the radical the bond $H_3C–N^2$ is weakening maximally in going from the molecular form to the cationic form**.**

The bond lengths C–C and C–H in the aminopropyl group undergo little changes in going from one form of diprazine to another. The bond angles and dihedral angles characterizing the change in the structure of the aminopropyl group in going from the molecular form to the dication also change little (by 1º– 4º). Hence directions of chemical bonds in the substituent depend insignificantly on the state of diprazine.

The dihedral angles characterizing the position of aminopropyl radical relatively to the phenothiazine ring undergo changes: the $C^1N^1C^2C^3$ angle in the molecule, cation, and dication equals 158.80º, 163.80º, and 136.99º, respectively. Two first values are close while the third differs considerably. This is defined by the fact that in the molecular form and cationic form the $N^1–C^3$ bond between the ring nitrogen atom and the substituent is directed to provide maximal overlap of electron clouds of the atoms N^1 and C^3. In the dication the proton attached to the ring N^1 atom

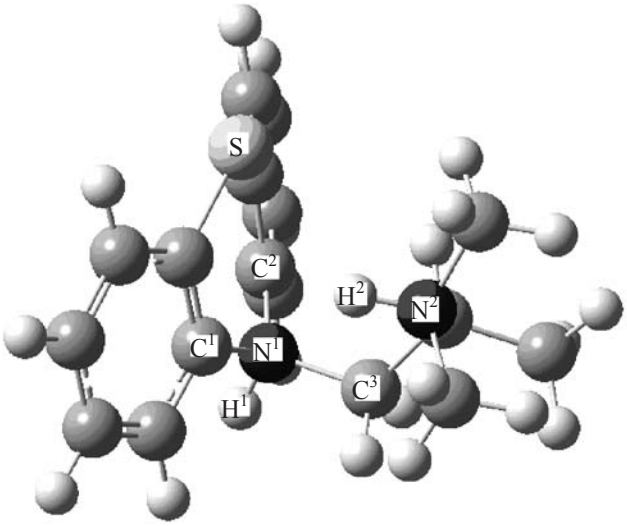

Fig. 5. Optimized structure of diprazine dication.

introduces steric hindrances to the formation of $N^1–C^3$ bond in this direction leading to the change in the value of $C^1N^1C^2C^3$ angle. The increase in C–N bond length in the thiazine ring and in the substituent (Table 1) indicating the weakening of the bonds on protonation shows that the added protons hinder also the formation of these bonds.

Thus, the analysis of structural changes allows to conclude that the proton attached to the N^2 atom of substituent little affects directions of chemical bonds in diprazine. This characteristic depends stronger on the presence of hydrogen atom at the N^1 nitrogen atom of the heterocycle. However both in the first and the second cases changes occur in the length of the chemical bonds formed by the atoms N^1 and N^2 with neighboring carbon atoms that attests change in electron density in going from one form of diprazine to another.

The bond length of the $N^1–C^3$ bond connecting phenothiazine ring with the substituent undergoes non-

Table 1. Frequencies and assignment of vibrations in the calculated IR spectra of three forms of diprazine

Vibration assignment	Strongest absorption bands, ν_{max}, cm^{-1}		
	Molecule	Cation	Dication
Out-of-plane bending C–H vibrations in phenathiazine ring	766	782	786
Stretching C–N bond vibrations in aminopropyl group	1204	1155	942
Stretching C–N vibrations in thiazine ring	1251	1333	few intensive
Skeleton vibrations of phenothiazine ring	1466, 1618	1467, 1601	1442, 1584
Stretching N–H bond vibrations	–	3211	3313, 3332

Table 2. Calculated properties of systems

Form	Internal energy of system E_{HF}, au	Dipole moment, μ, D
Molecule	–1161.82129044	2.4147
Cation	–1162.23205958	8.8363
Dication	–1162.47469423	7.8493

monotonic variations: 1.456 Å, 1.442 Å, and 1.524 Å in the series of molecule–cation–dication. This bond is the strongest in the cationic form of diprazine. This is also explainable by low steric hindrances at the formation of cation and by ion–dipole interaction in the subsystems of RH^+ and phenothiazine.

IR spectra of diprazine. The features of IR spectra of the three forms of diprazine can be elucidated by the analysis of the calculated frequencies. Their values and assignments are given in Table 1.

The band assignment in the theoretical IR spectra was carried out by the analysis of the forms of vibrations with the GaussView 3.07 program [14] (supplement to GAUSSIAN03) taking into account the published data [15–17]. In [8] are given the principal characteristic bands in the diprazine IR spectra: 1259, 1287 cm^{-1} are stretching vibrations of C–N bond, 1229 cm^{-1} are stretching vibrations of C–S bond, 758 cm^{-1} are bending vibrations of C–H bonds. The results of our calculations show that these frequencies correspond to the molecular form of diprazine.

The quantum-chemical calculation allows elucidation of the changes in the IR spectra in going from one form of diprazine to another. In the series: molecular form–cationic form–dicationic form of diprazine, the following features are revealed: (1) The characteristic diprazine band near 750 cm^{-1} undergoes a shift to lower frequencies while halfwidth of this band in the spectrum of dication increases considerably. (2) Intensities of characteristic bands in the region of 1200–1300 cm^{-1} fall considerably, and in the spectrum of dication these bands are absent. (3) The bands in the spectrum of diprazine dication are much broader than the related bands in the spectra of molecular and cationic forms. (4) In the spectra of diprazine cation and dication appears a strong absorption in the region > 3500 due to the stretching vibrations of N–H bond.

The spectra of ionic forms differ from that of molecular form not only by the appearance of additional bands (>3500 cm^{-1}, stretching vibrations of N–H bond), but also by the shift and splitting of the bands (700–1500 cm^{-1}) corresponding to certain types of vibrations in passing from one form to another. This last feature is defined by the redistribution of the electron density in the considered systems at the consecutive protonation.

Analysis of electric characteristics of the studied forms of diprazine. Calculated dipole moments (Table 2) and atomic charges by Mulliken (Table 3) of the studied structures allow the following conclusions. Electron density redistribution is attested by the changes in dipole moments μ of the forms (Table 2). The dipole moment is not changed monotonically. In passing from the molecule to cation occurs a sharp jump in the dipole moment value due to the shift of the center of positive charge of the system and the electron density redistribution at the appearance of an additional proton in the structure of the molecule. In the dication the dipole moment somewhat decreases. In this case the change in μ value is not so significant as in the preceding instant, hence it is presumable that the change in the electron density in going from the cation to the dication is less significant than in passing from the molecular form to the cation.

In this work we studied the changes in the atomic charges on the atoms in these three systems (Table 3). Changes in atomic charges (Δq) indicate the following character of redistribution of electron density in going from one form to another. In going from the molecule to the cation the electron density increased on all the carbon atoms of phenothiazine ring, and also on nitrogen N^1, sulfur atom S, carbon atoms in the CH_3 groups of aminopropyl substituent, on the nitrogen atom N^2, carbon atom of CH group, and maximal increase in electron density occurs at the attached proton. The increase in electron density is a result of its decrease on the hydrogen atoms of the phenothiazine ring, hydrogen atoms in aminopropyl substituent and on the carbon atom of CH_2 group. The total maximal decrease in the electron density occurs on the hydrogen atoms of aminopropyl group.

The going from the cation to the dication leads to the increase in the electron density on the carbon atoms of phenothiazine ring, carbon atoms of CH_3 groups, carbon atom of CH group, carbon atom of CH_2 group, and atom H^2 (Table 3). The total increase in the electron density on these atoms is compensated by the decrease in the electron density on the hydrogen atoms of phenothiazine ring, S atom, N^1 atom, hydrogen atoms in the substituent, and N^2 atom. Two bottom

Table 3. Atomic charges in the studied systems

Structural element	Atomic charges[a]	Molecule	Cation	Δq_1	Dication	Δq_2
		q_1	q_2	q_1-q_2	q_3	q_3-q_2
Phenothiazine ring	$\Sigma q\,(H)_{ring}$	+1.256	+1.454	+0.198	+1.792	+0.338
	$q(S)$	+0.255	+0.231	–0.024	+0.330	+0.099
	$\Sigma q(C)_{ring}$	–0.990	–1.033	–0.043	–1.143	–0.110
	$q(N^1)_{ring}$	–0.805	–0.851	–0.046	–0.741	+0.110
Aminopropyl group	$\Sigma q(C)_{CH}$	–0.574	–0.736	–0.162	–0.781	–0.045
	$\Sigma q(H)_R$	+1.386	+2.114	+0.728	+2.431	+0.317
	$q(N^2)_R$	–0.593	–0.619	–0.026	–0.616	+0.003
	$q(C)_{CH}$	+0.062	–0.001	–0.063	–0.005	–0.004
	$q(C)_{CH}$	+0.001	+0.014	+0.013	–0.056	–0.070
Additional protons	$q(C)_{CH}$	–	+0.425	–0.575[b]	+0.387	–0.038
	$q(H^1)$	–	–	–	+0.400	–0.600[b]
Positive terms totally				+0.939		+0.867
Negative terms, totally				–0.939		–0.867

[a] $\Sigma q(A)$, A = H,C is sum of charges on all the hydrogen (carbon) atoms, subscribed index in second column indicates the structural element to which the sum of charges or atomic charge relate [ring, substituent (R), methyl groups in the substituent (CH_3), methylene group in the substituent (CH_2)]. [b] Calculated with the formula $\Delta q_{1,2} = q_{2,2} - 1$, here 1 is the charge of the entered proton.

lines in Table 3 show that the total transfer of positive charge equals by the absolute value to the transferred negative charge. The total charge transfer in going from the molecule to the cation (0.939) is greater that in going from the cation to the dication (0.867). This is consistent with the larger change in the dipole moment of the system in going from the molecular form to cationic form than in going from cation to the dication.

Thus, the appearance in the system of the first proton (cation) and further adding of the second proton (dication) not only leads to the change of the charge of whole system but also results in redistribution of the electron density in the system.

The calculation allows to conclude that changes in the IR spectra and in the structure of diprazine in going from one form to another are defined by redistribution of the electron density in the system at adding the protons.

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