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5-Fluorouracyl. Molecular Structure in the Gas Phase

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Abstract—By means of gas electronography studies combined with nonempirical calculations (BLYP/6-31G*) data on the structure of 5-fluorouracyl corresponding to the theoretical calculations were obtained. Some propeties of 5-fluorouracyl as compared to its isomer, 6-fluorouracyl, were studied. Main geometrical parameters of 5-fluorouracyl molecule are as follows: interatomic distances (r_α, Å) N^1–C^1 1.396(1), N^3–C^4 1.412(1), C^4–C^5 1.452(1), C^3=C^6 1.452, C^6–C^1 1.349, C–F 1.337(2); bond angles, deg: $N^1C^2N^3$ 113.6(2), $C^2N^3C^4$ 128.9(5), $N^3C^4C^5$ 113.0(2), $C^4C^5C^6$ 120.2(3), $C^5C^6N^1$ 121.1(4), $C^6N^1C^2$ 123.3(4), FC^5C^6 120.3. Pyrimidine cycle was regarded as planar according to the quantum chemical calculations. Comparative analysis of difference in 5- and 6-fluorouracyl + H_2O systems was carried out.

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5-Fluorouracyl (5-Fu) was for the first time synthesized in 1957 [1]. It is widely used in medical practice for treatment of some forms of cancer like malignant tumors of esophagus, ventricle, pancreas, liver, and some other organs [2–4]. 5-Fluorouracyl is the structural analog of pyrimidine. Mechanism of its action is based on its metabolic transformation to 5-fluorodeoxyuridine monophosphate, the competing inhibitor of timidinesynthetase ferment. It leads to blocking of DNA synthesis and to suppression of RNA synthesis by includsion of 5-fluorodeoxyuridine monophosphate in its structure and hence to suppression of cell fission.

Structure of 5-fluorouracyl was for the first time studied in crystal by means of X-ray analysis in 1973 using photomethod [form (1)] [5]. It was shown that the asymmetric part of the triclinic elementary cell (space group $P\bar{1}$) contains four independent molecules bound by means of hydrogen bonds in the endless layers. Complete structural analysis of 5-fluorouracyl including localization of hydrogen atoms using modern methods was carried out recently [6]. In this work conclusions of Fallon [5] were completely confirmed and the monoclinic polymorphic form (2) of 5-fluorouracyl was found. In this crystal one independent molecule is present and hydrogen bonds join molecules in endless chains. Note that anticancer effect of 5-fluorouracyl appears in water medium at the intravenous injection. It may be suggested that the structure of the 5-fluorouracyl molecule in water solutions is to some extent similar to that of a "free" molecule. That is why it seemed expident to obtain data on its molecular structure in the gas phase by electronographic method and to study 5-fluorouracyl + H_2O system. This work deals with the problem.

Analysis of electronographic experiment. Preliminary theoretical calculation of molecular structure and vibrational frequencies was carried out by means of B3LYP/6-31G* method using Gaussian software [7]. For the calculation of theoretical mean square amplitudes u_{ij} necessary for the structural analysis an original program created by M.A. Tafipol'skii on the basis of algorithm offered by V.A. Sipachev [8] was used. In Table 1 results of quantum-chemical calculation of molecular structure of 5-fluorouracyl are presented. Numbering of atoms is shown in Fig. 1.

Interpretation of electronograms was carried out proceeding from the $sM(s)$ curves obtained in the range 3.1–14.9 and 4.8–24.0 s. In Fig. 2 "joined" experimental $sM(s)$ function is presented, and in Fig. 3 its Fourier transformation is shown. It is seen that C–N,

† Deceased.

Table 1. Geometrical parameters of 5-fluorouracyl according to gas electronography (r_a), X-ray analysis, and ab initio calculations

5-Fluorouracyl				6-Fluorouracyl
parameter	B3LYP/6-31G*	experiment, gas, r_a	experiment, crystal	B3LYP/6-31G*
		Bond length, Å		
N^1–C^2	1.391	1.394	1.362(1)	1.402
C^2–N^3	1.392	1.394 (2)	1.378(1)	1.382
N^3–C^4	1.407	1.410	1.374(1)	1.418
C^4–C^5	1.465	1.464(2)	1.435(1)	1.457
C^5=C^6	1.346	1.355	1.332(1)	1.346
C–F	1.338	1.342 (2)	1.348(1)	1.331
C^6–C^1	1.381	1.343	1.367(1)	1.368
C=O	1.216	1.217(1)	1.223(1)	1.214
N^1–H^{10}	1.010	1.014	0.881(17)	1.112
N^3–H^{11}	1.014	1.014	0.882(17)	1.014
C^6–H^{12}	1.083	1.083	1.006(17)	–
		Bond angles, deg		
$N^1C^2N^3$	112.7	112.4		112.5
$C^2N^3C^4$	128.9	128.6 (1)		128.4
$N^3C^4C^5$	112.1	111.8		113.9
$C^4C^5C^6$	121.6	121.3		118.6
$C^5C^6N^1$	120.6	121.8(3)		123.7
$C^6N^1C^2$	124.0	124.0(2)		122.9
$O^7C^2N^1$	123.3	125.8		122.3
$O^8C^4C^5$	125.8	128.7		126.1
$O^8C^4N^3$	122.1	119.5		120.1
FC^5C^6	123.4	122.8(5)		123.3 (FC^6C^5)
FC^5C^4	117.0	115.9		112.9 (FC^6N^1)
$C^2N^1H^{10}$	115.2	115.2		116.8
$C^2N^3H^{11}$	115.3	115.3		115.7
$C^5C^6H^{12}$	122.3	122.3		–
R-factor, %		4.04		

C–C, C=C, C–F, and C=O bonds are located in the narrow range 1.2–1.4 Å (the first peak at 1.36 Å). It follows also from the results of theoretical calculation (Table 1).

Second peak on the radial distribution curve (2.34 Å) contains information concerning bond angles of the $X_1 \cdots Y_3$ type. Third peak (2.7 Å) characterizes the diagonal C···N and C···C distances in the heteroring.

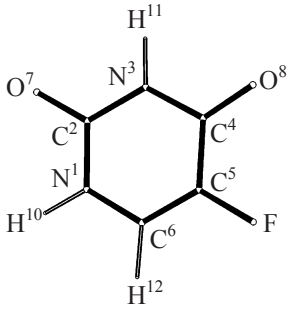

Fig. 1. Geometry of 5-fluorouracyl molecule and numbering of atoms.

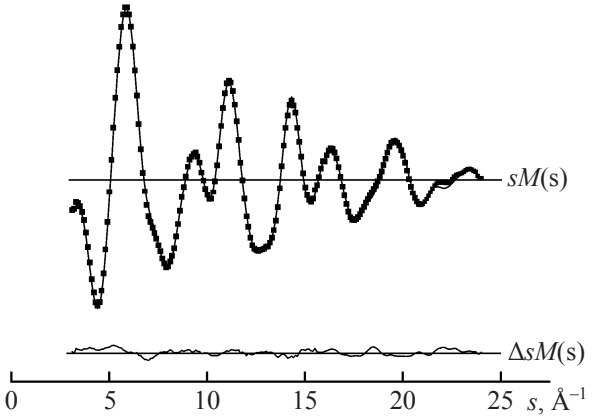

Fig. 2. Experimental $sM(s)$ function.

Results of simultaneous refining of bond distances and endocyclic angles in the pyrimidine ring proved to be unreliable though good agreement was achieved between the experimental and the theoretical $sM(s)$ functions (R-factor 4.04%) because of high correlation (up to |0.94|) between the refined parameters. Some of endocyclic angles differed by ~3° from the corresponding experimental values in uracyl [9] and 6-methyluracyl [10]. That is why MOCED method [11] based on the use of theoretical differences between the bond distances and bond angles was used.

Refining of the mean square vibrational amplitudes u_{ij} was carried out on the basis of theoretical calculations using the group method. All amplitudes for the interatomic distances close in value were subdivided in groups (Table 2).

Table 2. Main mean-square vibrational amplitudes for 5-fluorouracyl, Å

Parameter	r_{ij}	u_{ij} (exp.)		u_{ij} (theor.)	Parameter	r_{ij}	u_{ij} (exp.)		u_{ij} (theor.)
N^1–C^2	1.396	0.046		0.048	N^1C^5	2.355	0.064		0.056
C^2–N^3	1.396	0.046		0.048	N^1O^7	2.333	0.065	0.002[b]	0.057
N^3–C^4	1.412	0.048		0.050	C^6F^9	2.365	0.069		0.061
C^4–C^5	1.452	0.049		0.051	N^1C^4	2.817	0.059		0.065
C^5=C^6	1.345	0.041	0.002[a]	0.043	C^2C^5	2.836	0.057	0.002[c]	0.063
C^6–N^1	1.349	0.044		0.046	N^3C^6	2.683	0.061		0.067
C–F^9	1.337	0.042		0.046	O^8F^9	2.800	0.103		0.109
C=O	1.217	0.036		0.038	N^1F	3.596	0.070		0.061
N^1N^3	2.321	0.065		0.057	C^2O^8	3.592	0.073	0.003[d]	0.063
N^1C^5	2.382	0.063		0.056	N^3F^9	3.582	0.076		0.066
C^2C^4	2.531	0.068		0.060	C^4O^7	3.614	0.075		0.065
C^2C^6	2.419	0.066	0.002[b]	0.059	N^1O^8	4.030	0.076		0.066
N^3C^5	2.373	0.068		0.060	C^2F^9	4.173	0.076	0.001[e]	0.066
N^3O^7	2.279	0.075		0.057	C^5O^7	4.053	0.075		0.065
C^4C^6	2.440	0.058		0.058	O^7O^8	4.571	0.075		0.075
C^4F^9	2.355	0.075		0.068					

[a–e] Signs of grouped refining.

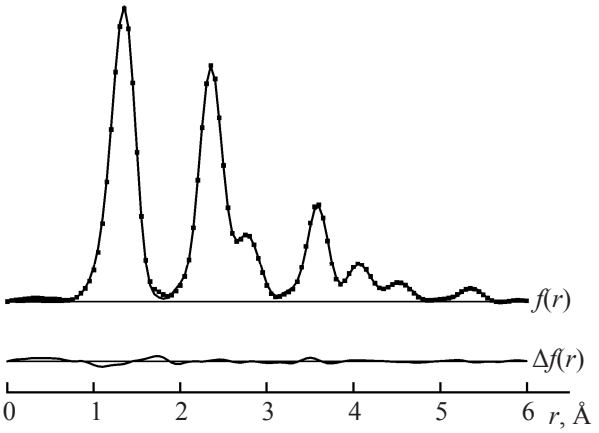

Fig. 3. Fourier transformation of the experimental *sM*(*s*) function.

Such approach permits to obtain more reliable experimental geometrical parameters for the free molecule (Table 1). Geometrical parameters of 5-fluorouracyl in crystalline phase are presented in this Table for comparison [12]. The radial distribution curve *f*(*r*) showed the range of internuclear distances where additional refining of amplitudes must be carried out. But complete removal of strong correlations was not achieved [see the correlational matrix of 5-fluorouracyl (U^1–U^5 is cluster of mean square amplitudes, Table 2). It is seen from Table 1 that good agreement between the experimental and theoretical molecular parameters is achieved. Note that molecular parameters of free molecule and that in the crystal to some extent differ because of the difference in physical meaning of parameters evaluated by means of electronography and the X-ray diffraction analysis.

In Table 3 results of normal coordinate calculation of 5-fluorouracyl are presented. Scale factor equal 0.95 was used for all frequencies (only for νH it was underestimated according to recommendations in [3] for this theoretical approximation).

The agreement between the theoretical and the experimental frequencies is quite satisfactory. Hence, it may be believed that the force constants for 5-fluorouracyl are reliable (see Table 4). Attention must be attracted by the absorption frequency ν(C–F) 1254 cm^{-1}, its PED reaches 50%.

To some extent this vibration may be regarded as characteristic. In the IR spectrum of crystalline sample of 5-fluorouracyl very strong absorption is observed at 1246 cm^{-1} which can be attributed to ν(C–F). Small absorption looking like a shoulder is marked at 1223 cm^{-1}. We attributed it to ν(C^6–N) (PED 16%).

A question appears naturally why 5-fluorouracyl is a biologically active compound while its 6-isomer exhibits no such properties. The corresponding properties are determined finally by the electronic density distribution ρ(*r*) in the molecule. Usually ρ(*r*) calculations are carried out on the theoretical non-

Parameter	r^1	r^2	r^3	r^4	α^1	α^2	α^3	U^1	U^2	U^3	U^4	U^5
$r^1(C^1N^2)$	100											
$r^2(C^4C^5)$	–56	100										
r^3(C=C)	27	–81	100									
r^4(C=O)	5	–52	30	100								
$\alpha^1(N^1C^2N^3)$	–70	51	–65	11	100							
$\alpha^2(O{=}C^2N^1)$	50	–29	13	19	–31	100						
$\alpha^3(FC^5C^4)$	10	–56	58	18	–28	–41	100					
U^1	–1	–75	76	56	13	0	54	100				
U^2	54	–81	67	29	–53	–11	72	60	100			
U^3	–51	48	–31	–19	39	–18	–33	–19	–49	100		
U^4	4	5	–19	6	13	2	–9	–8	–3	–1	100	
U^5	–36	42	–40	–14	43	–2	–34	–19	–42	30	4	100

Table 3. Resuls of normal-coordinate analysis of 5-fluorouracyl[a]

5-Fluorouracyl					6-Fluorouracyl
Run no.	ν, cm^{-1}	I_{IR}	PED, %	ν, cm^{-1} (exp.)	ν, cm^{-1} (theor.)
1	114	0.9	$36\gamma N^1H + 17\tau C^2N^3 + 16\tau C^4C^5 + 13\tau C^2N^1$	109	132
2	148	0.3	$45\gamma N^3H + 20\tau C^4C^5 + 15\tau C^4N^3$	167	160
3	292	1.1	$28\alpha C^4C^5F + 21\alpha C^6C^5F + 17\alpha C^5C^4O^8$		200
4	336	11.1	$33\gamma C^5F + 15\gamma C^6H + 28\gamma N^1H$	331	339
5	367	11.6	$49\gamma C^5F + 14\gamma C^4O^8 + 11\gamma N^1H + 11\tau C^5C^6$	365	372
6	378	18.6	$22\alpha N^1C^2O^7 + 16\alpha N^3C^2O^7 + 11\nu CF$	365	467
7	444	0	$16\alpha C^4C^5C^6 + 11\alpha N^3C^4C^5 + 11\alpha N^3C^2O^7 + 11\alpha N^1C^2N^3$	464	481
8	523	6.6	$14\alpha C^2N^3C^4 + 12\alpha N^1C^6C^5$		503
9	532	66.0	$35\gamma N^1H + 31\tau N^1C^6 + 27\tau C^2N^1$	545	589
10	612	2.3	$18\alpha C^5C^6O^8 + 14\alpha N^1C^2O^7 + 14\alpha N^3C^2O^7 + 11\alpha C^4C^5F$	633	615
11	661	63.2	$30\gamma N^3H + 22\tau N^3C^4 + 19\tau C^2N^3$	638	621
12	723	93.3	$40\gamma C^2O^7 + 31\gamma C^4O^8 + 16\gamma N^3H$	735	664
13	727	8.5	$40\nu C^4C^5$		702
14	729	1.7	$44\gamma C^2O^7 + 41\gamma C^4O^8$	757	722
15	793	30.3	$19\nu CF + 11\alpha N^1C^2N^3$	757c	780
16	865	30.8	$78\gamma C^6H$	895	930
17	948	12.9	$31\nu N^1C^2 + 10\nu C^2N^3$	949	962
18	1135	12.0	$27\nu N^1C^6 + 21\nu C^4N^3$		1028
19	1161	77.2	$25\nu N^3C^4 + 25\nu C^2N^3 + 10\alpha N^1C^6H^{12}$	1182	1173
20	1254	232.5	$48\nu CF + 16\nu C^6N^1$	1224	1178
21	1326	18.0	$21\alpha N^1C^6H^{12} + 20\alpha C^5C^6H^{12} + 11\nu C^5C^6$		1289
22	1372	14.7	$35\alpha C^2N^3H^{11} + 28\alpha C^4N^3H^{11}$	1349	1366
23	1397	60.5	$13\nu C^2N^3 + 12\nu C^4C^5$	1386	1370
24	1470	44.5	$18\nu C^6N^1 + 17\alpha C^6N^1H^{10} + 13\alpha C^2N^1H^{10} + 10\gamma C^2O^7$	1477	1493
25	1690	36.1	$57\nu C^5C^6$	1685	1679
26	1743	565.0	$76\nu C^4O^8$	1742	1742
27	1761	525.0	$72\nu C^2O^7$	1754	1771
28	3085	2.5	$99\nu C^6H^{12}$	3067	3201
29	3416	66.1	$99\nu N^3H^{11}$	3416	3422
30	3456	101.0	$99\nu N^1H^{10}$	3468	3448

[a] (ν) are bond vibrations; (α) are flat vibrations, deflection of atoms from the plane; (τ) are torsional vibrations .

Table 4. Comparison of force constants of 5-fluoro- and 6-fluorouracyls for bonds (din $Å^{-1}$) and bond angles (din Å)

Bond or angle	5-Fluorouracyl	6-Fluorouracyl	Bond or angle	5-Fluorouracyl	6-Fluorouracyl
$N^1–C^2$	4.58	4.24	$C^2–O^7$	13.03	13.15
$C^2–N^3$	4.60	4.87	$N^1C^2N^3$	0.75	0.74
$N^3–C^4$	4.17	3.90	$C^2N^3C^4$	0.70	0.72
$C^4–C^5$	3.88	4.03	$N^3C^4C^5$	0.68	0.69
$C^5–C^6$	6.75	6.71	$C^4C^5C^6$	0.71	0.67
$N^1–C^6$	5.10	5.27	$C^6C^5N^1$	0.66	0.71
C–F	7.02	7.04	FC=C	0.62	0.66
$C^4–O^8$	13.07	12.95			

empirical base. Nowadays X-ray studies permit to obtain experimental data characterizing such distribution (for example, see [14]). In Fig. 4 charges on atoms in fluorouracyls according to Mulliken are presented. The calculations were carried out by means of AM1 and B3LYP/6-31G* methods. Their results show that the largest charge difference is observed on C^5 and C^6 atoms leading to different polarity of C–F bonds, and hence to different properties of molecules particularly in relation to water.

It must be marked specially because the biological effect of 5-fluorouracyl in organism is exhibited in a water medium. In Fig. 5 5-fluorouracyl + H_2O and 6-fluorouracyl + H_2O systems are shown.

We have considered only the system where one molecule of water is H-bonded with the fluorine atom. According to AM1 calculations one molecule of water is bound with 5-fluorouracyl by a system of the bifurcate H-bonds $O^8\cdots H^{15}$, $O^8\cdots H^{13}$, and $F\cdots H^{13}$, while for the 6-fluorouracyl+H_2O system only one H-bond is possible. At the same time its F···H-OH angle is close to 180°. We presume that difference in the H-bond systems for the isomeric fluorouracyl+H_2O mixtures determines different stability of these isomers in water medium. Contrary to the case of 6-fluorouracyl, the molecule of its 5-isomer is bound with water not only by means of H..F bond, but also by the system of hydrogen bonds with O^8 what determines the stability of 5-fluorouracyl in water medium.

As known, 6-fluorouracyl is decomposed by water to form barbituric acid [15]. This fact agrees with our theoretical calculations. Oxo-form of barbituric acid is more stable as compared to its oxy-form (the difference being 11.4 kcal mol^{-1}) in conformity to analogous equilibria for uracyl [16]. In Table 3 theoretical absorption frequencies (B3LYP/6-31G*) are included for comparison, and in Table 1 the main geometrical parameters of this isomer are presented.

EXPERIMENTAL

Electronograms of 5-fluorouracyl were obtained on an EMR-100/APDM-1 apparatus permitting to carry out simultaneous registration of electronograms and mass spectra of the vapour under investigation. Elec-

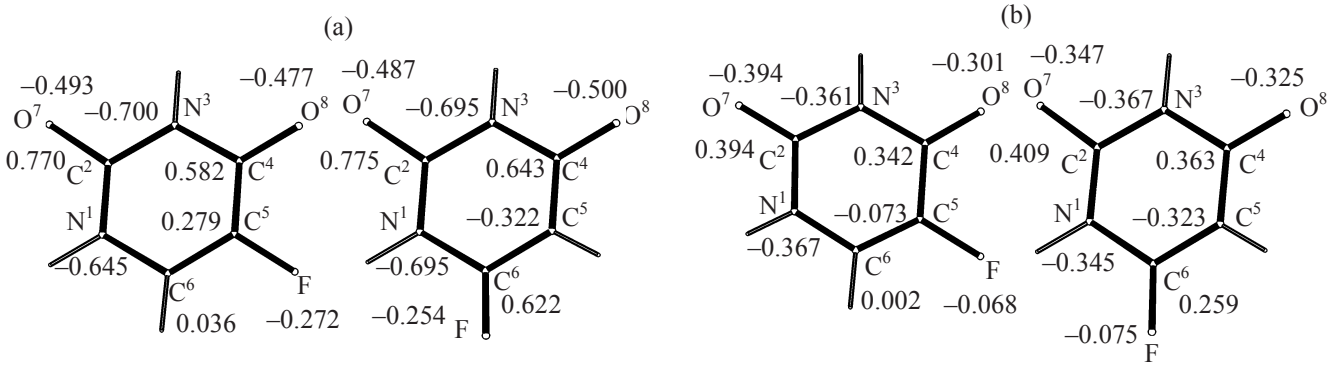

Fig. 4. Charges on atoms in 5- and 6-fluorouracyls according to quantum-chemical calculations by (a) AM1 and (b) B3LYP/6-31G* methods.

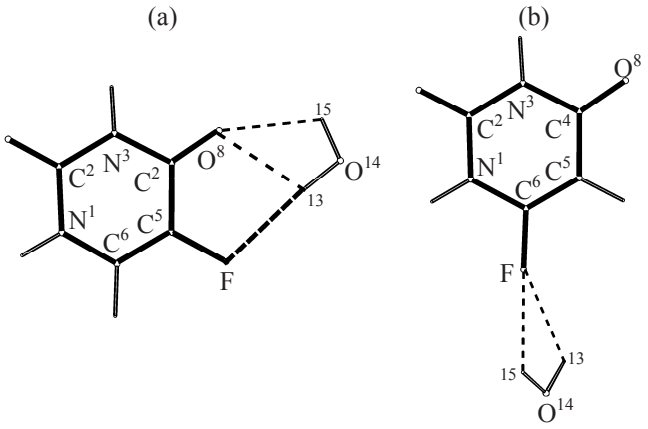

Fig. 5. Spatial arrangement of (a) 5-fluorouracyl and (b) 6-fluorouracyl complexes with water.

tronograms were taken under the accelerating voltage 81 kV at the effusive mesh-film distances L_1 338 mm and L_2 598 mm. Registration of each electronogram was accompanied by registration of the electron impact mass spectrum under the ionizing voltage 50 V. The wavelength of electrons was evaluated by means of the polycrystalline ZnO sample before and after taking the electronograms.

Photometering of electronograms was carried out on an automated MD-100 (Carl Zeiss, Germany) MD-100 microdensitometer. The function of intensity of the electron scattering $sM(s)$ was obtained in the ranges s 3.1–14.9 and s 4.0–24.0 with Δs 0.1 $Å^{-1}$ for the short and long distances between the nozzle and the film. IR spectra were recorded on a computerized BrukerVector-22 IR-Fourier complex. Commercial sample of 5-fluorouracyl (Fluka) was used. Authors express their gratitude to E.E. Zvereva for the help in calculations and to L.V. Avvakumova for obtaining the IR spectrum of 5-fluorouracyl.

REFERENCES

1. Heidelberger, C., Chaudhuri, N.K., Danneberg, P., Mooren, D., and Griesbach, L., *Nature*, 1957, vol. 179, p. 663.
2. *Fluorouracyl.http://en.wikipedia.org/wiki/Fluorouracyl.*
3. Borodulin, V.I., *Spravochnik prakticheskogo vracha* (Handbook of Practical Doctor), Moscow: Mir i Obrazovanie, 2004.
4. Vartanyan, R.S., *Sintez osnovnykh lekarstvennykh veshchestv* (Synthesis of the Essential Medicinal Substances), Moscow: MIA, 2005, p. 538.
5. Fallon, L., *Acta Cryst., B*, 1973, vol. 29, no. 11, p. 2549.
6. Hulme, A.T., Price, S.L., and Tocher, D.A., *J. Am. Chem. Soc*., 2005, vol. 127, no. 4, p. 1116.
7. Frish, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Stratmann, R.E., Buran, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, K.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Menucci, B., Pomeli, C., Adamo, C., Clifford, S., Ochterski, J., Peterson, G.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Oritz, J.V., Baboul, A.G., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonsalez, C., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Andres, J.L., Gonzalez, C., Head-Gordon, M., Replogle, E.S., and Pople, J.A., *Gaussian 98,* Revision A.7, Gaussian, Pittsburgh P.A., 1998.
8. Sipachev, V.A., *J. Mol. Struct. (Theochem),* 1985, vol. 121, p. 121.
9. Ferenzy, F., Horzonyi, L., Rozcondai, B., and Hargittai, I., *J. Mol. Struct*., 1986, vol. 140, p. 71.
10. Naumov, V.A., *Zh. Obshch. Khim*., 2008, vol. 78, no. 3, p. 447.
11. Geise, H.J. and Pyckhout, W., *Application of Gas-Phase Electron Diffraction*, VCH Publishers Inc., New York, 1988, part B, p. 321.
12. Portalone, G. and Colapietro, M., *Acta Cryst. C*, 2007, vol. 63, p. 423.
13. Katsuba, S.A. and Vandyukova, E., *Chem. Phys. Letters*, 2003, vol. 377, nos. 5–6, p. 658.
14. Lysenko, K.A., *Doctoral Sci. (Chem.) Dissertation,* Moscow, 2006.
15. Naumov, V.A., TafipolTskii, M.A., and Reznik, V.S., *Zh. Obshch. Khim*., 2004, vol. 74, no. 12, p. 2004.
16. Palafox, M.A., Iza ,N., and Gil, M., *J. Mol. Struct. (Theochem),* 2002, vol. 585, p. 69.