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QUANTUM-CHEMICAL STUDIES OF PYRIMIDIN-4-ONES. 2*. STABILITY IN THE GAS PHASE OF TAUTOMERS OF PYRIMIDIN-2,4-DIONE, 2-THIOXO-, 2-SELENOXO-, 2-AMINO-, AND 2-ACETYLAMINOPYRIMIDIN-4-ONES, AND THEIR 6-METHYL- AND 6-PHENYL DERIVATIVES

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The relative stability in the gas phase and the most probable reaction centers for electrophilic attack for the tautomers of pyrimidin-2,4-dione, 2-thioxo-, 2-selenoxo-, 2-amino-, and 2-acetylaminopyrimidin-4-ones, and their 6-methyl- and 6-phenyl derivatives have been investigated on the basis of the results of quantum-chemical calculations, using the semi-empirical PM3 method, without taking solvent effects into account.

Keywords: 2-aminopyrimidin-2-one, 2-acetylaminopyrimidin-2-one, pyrimidin-2,4-dione, 2-selenoxo-pyrimidin-4-one, 2-thioxopyrimidin-4-one, quantum-chemical calculations, PM3 method, reactions with electrophiles, tautomerism.

The development of means for the synthesis of biologically active heterocyclic substances is of great practical and theoretical interest, since compounds of this type include almost two thirds of the currently recommended fungicides, herbicides, defoliants, and other similar preparations. In particular the study of the reactivity of 2-substituted pyrimidin-4-ones in electrophilic substitution is important.

6-Substituted 2-oxo-, 2-thioxo, 2-selenoxo-, 2-amino-, and 2-acetylaminopyrimidin-4-ones, the syntheses of which have been described [2-8] possess multiple reactivity. This is explained by the presence of mobile protons in the molecules and also atoms with high nucleophilicity, capable of readily adding protons. In our opinion there is an inseparable connection between the direction of reaction and the lactam-lactim tautomerism of the compounds under discussion. The tautomeric conversions and the stability of the heterocycles, and the results of quantum-chemical investigations of reactions involving them have been discussed frequently in the literature [9-11].

Some estimates of the stability of the tautomeric forms, their reactivity, and also predictions of further conversions of heterocyclic compounds, pyrimidin-2,4-diones in particular, have been carried out based on quantum-chemical calculations for both the gas phase [12-15] and also taking into account the influence of solvents [16], agree with experiment. The tautomeric equilibrium of the compounds under discussion can be controlled *via* their dependence on temperature, the type of solvent (protonic, polar, non-polar), and the

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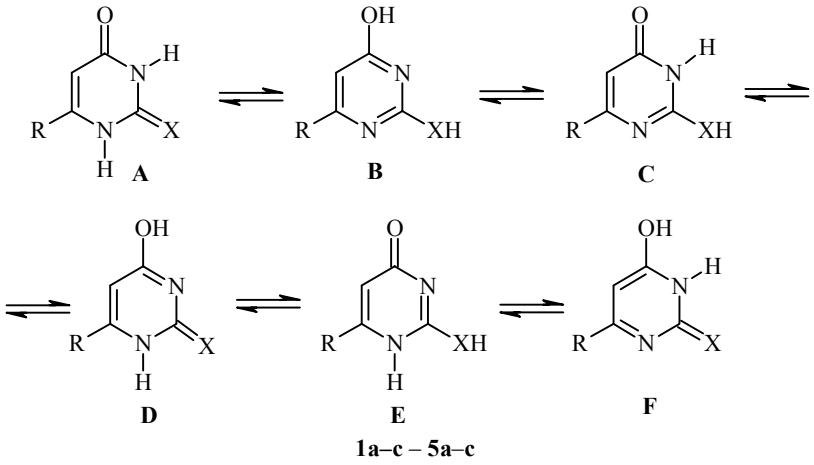
properties of the substituents in positions 2 and 6. In a monograph by Raikhardt [17] which takes into account literature published up the 90's, conclusions are drawn on the effects of solvents on tautomeric equilibria. These data have been updated with the appearance of new experimental and theoretical methods.

Generally the related semi-empirical quantum-chemical methods MNDO, AM1, and PM3 permit a sufficiently accurate estimate of the geometry and electronic structure of compounds with N, O, and S as heteroatoms. Consequently in this study of the tautomeric conversions (see the scheme) and probable reaction centers of pyrimidin-2,4-diones (**1a-c**), 2-thioxo- (**2a-c**), 2-selenoxo- (**3a-c**), 2-amino- (**4a-c**), and 2-acetylaminopyrimidin-4-one (**5a-c**) with respect to electrophiles we turned to the variant PM3 in the MOPAC suite of programmes [18] since it contained parameters for the selenium atom.



1 X = O, **2** X = S , **3** X = Se, **4** X = NH, **5** X = NAc; **1–5 a** R = H, **b** R = Me, **c** R = Ph

The geometries of the compounds studied were completely optimized in the PM3 approximation. In cases where it was necessary to take into account CO···HN and CN···HO hydrogen bonds, the corresponding calculation procedures included *in suite* were used.

The results of the calculations are given in Tables 1-3. In all cases the heat of formation of tautomer **A** was conditionally taken as the level from which energies were computed, which facilitated comparison of the tautomeric forms **A-F** of the compounds (Table 1). The relative heats of formation ΔH_f were correlated with the stabilities of the tautomers (the lowest heats for the more stable tautomers) and their reactivities. Since the calculations were carried out for isolated neutral molecules in the ground state, then the relative stability of one form or another corresponds to the evacuated gas phase. Nevertheless the relative heats of formation cited in Table can be used with confidence for comparative estimates of the fraction of tautomers **A-F** since they differ sufficiently greatly in the vast majority of cases.

EFFECT OF SUBSTITUENTS ON THE STABILITY OF THE TAUTOMERS 1A-F TO 5A-F

Pyrimidin-2,4-diones. For compounds **1a-c** the dioxo form **A** is always energetically most favorable, which is more stable than the dihydroxy forms **B** by 9.9, 8.4, and 10.7 kcal/mol respectively. It is necessary to note that a substituent in position 6 has little effect on the stability of the tautomers. Since both carbonyl groups are symmetrically placed relative to this position and the negative charge on atom N(3) is partially compensated by two neighboring electropositive atoms C(2) and C(4), the hydrogen in position 3 becomes more mobile. The conclusion that compounds **1a-c** exist preferably in form **A** is in agreement with data from [5] that characteristic bands of the NH and C=O groups appear in the IR spectrum of compound **1b**.

TABLE 1. Relative Heats of Formation ΔH_f and Energies of the HOMO E_f of the Tautomeric Forms of Compounds **1-5**

Com-pound	ΔH_f, kcal/mol						E_f, eV					
	A	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**
1a	0	9.9	13.1	12.4	14.8	10.7	-9.79	-9.91	-9.48	-9.50	-9.56	-9.33
1b	0	8.4	7.3	8.7	15.0	11.8	-9.62	-9.78	-9.38	-9.39	-9.43	-9.27
1c	0	10.7	13.9	12.0	14.6	12.0	-9.43	-9.54	-9.23	-9.27	-9.32	-9.26
2a	0	-8.9	-1.7	8.7	-0.6	11.2	-9.27	-9.32	-9.42	-8.82	-9.56	-8.84
2b	0	-7.7	-7.4	8.5	-0.2	12.2	-9.21	-9.25	-9.37	-8.76	-9.46	-8.75
2c	0	-5.3	-2.5	12.6	-0.4	12.2	-9.15	-9.21	-9.25	-8.68	-9.32	-8.71
3a	0	4.3	7.5	10.3	11.6	13.2	-8.83	-9.42	-9.51	-8.42	-9.57	-8.45
3b	0	5.5	5.2	10.1	12.4	13.9	-8.77	-9.36	-9.47	-8.36	-9.45	-8.34
3c	0	8.1	8.8	13.9	12.4	13.8	-8.72	-9.30	-9.32	-8.26	-9.34	-8.28
4a	0	-8.4	-7.1	4.8	2.6	1.7	-9.17	-9.11	-9.17	-8.65	-9.33	-8.72
4b	0	-9.1	-6.5	4.7	2.6	14.2	-9.11	-9.02	-9.11	-8.57	-9.24	-8.57
4c	0	-0.2	1.4	7.4	2.4	14.0	-9.02	-9.57	-9.30	-8.52	-9.15	-8.63
5a	0	38.9	-2.8	7.2	5.2	11.2	-9.38	-9.45	-9.14	-8.92	-9.36	-8.91
5b	0	-0.8	-2.5	6.4	4.8	11.7	-9.31	-9.20	-9.08	-8.86	-9.26	-8.83
5c	0	6.6	-1.0	10.2	5.7	13.1	-9.21	-9.14	-9.04	-8.81	-9.26	-8.83

TABLE 2. Difference in Energy (Δε) of the Frontier Orbitals in the Tautomeric Forms of Compounds **1-5**

Com-pound	Δε, HOMO–LUMO, eV					
	A	**B**	**C**	**D**	**E**	**F**
1a	9.2	9.5	8.9	8.8	9.3	8.7
1b	9.1	9.3	8.9	8.7	9.1	8.7
1c	8.3	8.6	8.3	8.1	8.3	8.4
2a	8.0	8.6	8.4	7.5	8.8	7.5
2b	7.9	8.5	8.5	7.6	8.8	7.4
2c	7.6	8.2	8.1	7.2	8.3	7.2
3a	7.2	8.2	7.7	6.8	7.9	6.7
3b	7.3	8.3	7.8	6.9	7.8	6.7
3c	7.0	8.3	7.5	6.5	7.7	6.5
4a	8.8	8.9	8.7	8.1	9.1	8.3
4b	8.7	8.8	8.6	8.2	9.0	8.3
4c	8.0	8.7	8.3	7.5	8.1	7.9
5a	8.8	8.7	8.5	8.2	9.0	8.2
5b	8.7	8.9	8.5	8.2	9.0	8.1
5c	8.0	8.3	8.2	7.8	8.7	7.8

2-Thioxopyrimidin-4-ones. In the case of the thioxopyrimidinones **2a** and **2c** the dihydroxy forms **B** predominate completely; it is favored by 8.9 and 5.3 kcal/mol respectively. In contrast to compounds **2a**, **2c**, and the pyrimidindiones **1**, the enthalpy of formation for tautomers **B** and **C** of methyl-substituted **2b** differ by only about 0.3 kcal/mol, which indicates that both forms probably exist. We note that an absorption band attributed to a carbonyl group appears in the IR spectrum of compound **2b** [5].

2-Selenoxypyrimidin-4-ones. The dioxo form **A** dominates for all the compounds **3a-c**. It is more stable than the dihydroxy forms **B** by 4.3, 5.5, and 8.1 kcal/mol respectively. Valence bands with $\nu_{C=O}$ = 1685 cm^{-1} occur in the IR spectra of compounds **3b,c** [5, 6].

2-Aminopyrimidin-4-ones. For the 2-amino-substituted compounds **4a,b** tautomers **B** and **C** are more stable than **A**. According to the data in Table 1 the dihydroxy form **B** is somewhat more stable than the monoxo form **C** for these compounds (by 1.3 and 2.6 kcal/mol respectively). In the case of the phenyl-substituted **4c** the difference in stability of tautomers **A**, **B**, and **C** is comparatively small and their existence may be considered more or less equally probable. We note that carbonyl absorption bands were observed in the IR spectrum of the neutral molecule **4b** [5], but the presence in the ^{1}H NMR spectra of compounds **4b** and **4c** of signals of the amino group confirms the conclusion reached above of the preference for tautomers **B** and **C**.

2-Acetylaminopyridin-4-ones. The monoxo form **C** predominates for compounds **5a-c** independent of the substituent at position 6. The energy barrier for the tautomeric transition **C**→**A** for these compounds is not less than 2.8, 2.5, and 1.0 kcal/mol respectively. For compound **5b** tautomer **B** is only 0.8 kcal/mol more stable than **A.**

Thus in the gas phase (in a vacuum) the dioxo form **A** is the more stable for all pyrimidin-2,4-diones and 2-selenoxypyrimidin-4-ones. The dihydroxy form **B** predominates for 2-thioxopyrimidin-4-ones and 2-amino-pyrimidin-4-ones. In all cases for acetylaminopyrimidin-4-ones the most stable tautomer is form **C.** Tautomers **D**, **E**, and **F** are almost always less stable than **A** and **B** (see Table 1) and are therefore not discussed above.

THE REACTIVITY OF COMPOUNDS 1A-C TO 5A-C WITH RESPECT TO ELECTROPHILES

It is very complicated to establish the reactivity of compounds **1-5**, which contain several reactive centers, with respect to electrophilic agents. It is considered that reaction controlled by an orbital mechanism occur with a small difference in energy of the frontier orbitals (FO), while reactions under charge control occur

TABLE 3. Charges on Atoms and π-Electron Density Distribution in the HOMO of Compounds **1-5**

Compound	Form	Charge on atoms, e				π-Electron density in the HOMO			
		N(1)	N(3)	X	O(4)	N(1)	N(3)	X	O(4)
1a	**A**	0.09	-0.01	-0.39	-0.35	0.42	0.00	0.07	0.08
1b	**A**	0.08	-0.01	-0.39	-0.36	0.39	0.00	0.07	0.08
1c	**A**	0.08	-0.01	-0.39	-0.36	0.25	0.00	0.05	0.07
2a	**B**	-0.18	-0.18	0.16	-0.21	0.10	0.04	0.63	0.01
2b	**B**	-0.12	-0.25	0.15	-0.21	0.10	0.04	0.62	0.01
2c	**B**	-0.12	-0.17	0.15	-0.18	0.07	0.06	0.61	0.00
3a	**A**	0.26	0.15	-0.29	-0.32	0.10	0.08	0.75	0.00
3b	**A**	0.26	0.15	-0.30	-0.33	0.10	0.08	0.75	0.00
3c	**A**	0.25	0.16	-0.30	-0.33	0.10	0.08	0.75	0.00
4a	**B**	-0.21	-0.27	0.13	-0.22	0.17	0.06	0.35	0.02
4b	**B**	-0.21	-0.27	0.13	-0.22	0.16	0.07	0.35	0.02
4c	**A**	0.15	0.01	-0.23	-0.37	0.27	0.06	0.22	0.01
5a	**C**	-0.24	0.05	0.05	-0.36	0.28	0.11	0.08	0.14
5b	**C**	-0.23	0.05	0.05	-0.37	0.26	0.10	0.08	0.15
5c	**C**	-0.23	0.05	0.05	-0.37	0.19	0.07	0.07	0.14

with a large difference (see Table 2). This tendency is defined in terms of Pearson's HSAB concept [19, 20] as "hard" or "soft" reaction systems.

To discuss the reactivity of compounds the energies of the HOMO and LUMO are frequently treated as an index of reactivity. According to the separation of these levels [21] reactions are separated into two types: charge-controlled and orbital-controlled. In the case of charge controlled reactions the probable reaction centers are atoms with maximum negative charge (q). For orbital control the maximum π-electron density (ρ) on centers which overlap the HOMO may serve to estimate the reactivity with respect to an electrophile.

Charge Control of a Reaction. According to Table 3, for compounds **1a-c** in the gas phase, the centres of electrophilic attack are the oxygen atoms in positions 2 and 4. The charge on the former is somewhat greater than that on the latter in all cases. Substituents at position 6 leave the charge distribution on these centers almost unchanged.

In compound **2a** the charge on the oxygen atom is greater (q = -0.21) than on atoms N(1) and N(3) (q = -0.18), while the sulfur atom lying between them has a positive charge (q = 0.16). In compound **2b** the -*I* effect of the methyl group at position 6 decreases the charge on atom N(1) (in comparison with compound **2a**) (see Table 2) and simultaneously increases to -0.25 the charge on atom N(2). The charges on the sulfur and oxygen atoms remain as before. Atoms N(3) and O(4) have the greatest charges. Since, thanks to conjugation with the aromatic ring, the phenyl group in compound **2c** has both -*I* and + *M* effects, it noticeably decreases the negative charges on those atoms (to -0.17 and -0.18 respectively) and lowers the probability of electrophilic attack at those centers.

In compounds **3a-c** the maximum charges are localised on the selenium and oxygen atoms, but in all cases the charge on atom O(4) is -0.03 greater than on atom Se(2).

In compounds **4a,b** the maximum negative charge is on atom N(3) and is -0.23, while atoms N(1) and oxygen have charges of q = -0.21 and -0.22 respectively. In compound **4c**, for which the dioxo form **A** predominates, the probable reactions centers are N(2) and oxygen with charges of -0.23 and -0.37 respectively, with electrophilic attack on the oxygen being preferred.

For compounds **5a-c** the reaction centers in all cases are the atom (N1) with q = -0.24 and oxygen with q = -0.36, with the probability of attack on the second being the higher. Reaction on the positively charged centers N(2) and N(3) is naturally not considered.

Orbital control of the reaction. It is seen from Table 3 that the maximum π-electron density on the HOMO of compounds **1a-c** is in the region of atoms N(1). In compounds **2a-c** and **3a-c** the π-electron density is greatest on the sulfur and selenium atoms respectively. The maximum π-orbital density in compounds **4a,b** is on the imine atom N(2), while in compound **4c** it is on the atoms N(1) and N(2). For all the compounds **5a-c** the maximum π-electron density corresponds to atoms N(1) and oxygen which may be considered as concurrent reaction centers with respect to electrophilic agents.

* * *

Experimental data [5-8] on the methylation of compounds **1-5** in different solvents with methyl iodide or methyl tosylate agree well with the predictions which may be interpreted as in favor of charge control of alkylation. In going from MeI as a "soft" reagent to methyl tosylate as a "hard" reagent only for compound **1b** is there observed some increase in formation of the product of methylation at N(1), and for the thione **2b** of the product of S-alkylation. In the remaining cases the direction of methylation with both reagents in general does not contradict charge control.

REFERENCES

1. M. Kh. Mamarakhmonov, M. A. Ashirmatov, and Kh. M. Shakhiloyatov, *Khim. Geterotsikl. Soedin.,* 1082 (2001).
2. I. I. Grandberg, *Practical Work and Seminar Problems in Organic Chemistry* [in Russian], Vysshaya Shkola, Moscow (1978), 148.
3. A. Murray and D. L. Williams, *Syntheses of Organic Compounds with Halogen, Nitrogen, Oxygen, Phosphorus, and Sulfur Isotopes.* [Russian translation], Izd-vi. Inostr. Lit., Moscow (1962), 429.
4. A. P. Phillips, *J. Am. Chem. Soc*., **76**, 6200 (1954).
5. K. A. Zakhidov, *Dissert. Kand. Khim. Nauk,* Tashkent (1963).
6. Kh. I. Nurbaev, K. A. Zakhidov, E. O. Oripov, R. A. Samiev, and Kh. M. Shakidoyatov, *Uzb. Khim. Zh.,* No.1-2, 96 (1966).
7. E. O. Oripov, K. A. Zakhidov, Kh. M. Shakidoyatov, *Abstr. V All-Union Conf. On Heterocycl. Cmpds.* [in Russian], Chernogolovka (1991), 299.
8. K. A. Zakhidov, E. O Oripov, Kh. M. Shakidoyatov, *Abstr. 18th Conf. On Chem. and Technol of Org. Sulfur Comp.* [in Russian], Kazan (1992), 69.
9. A. N. Nesmeyanov and M. I. Kabachnik, *Zh. Org. Khim.,* **25**, 41 (1955).
10. A. R. Katritskii, *Usp. Khim.,* **41**, 700 (1972).
11. O. A. Reutov and A. L. Kurts, *Usp. Khim.,* **46**, 1965 (1977).
12. M. A. Ashirmatov, and Kh. M. Shakhidolyatov, *Khim. Geterotsikl. Soed.,* 1246 (1993).
13. L. I. Belen'kii and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.,* 1535 (1996).
14. D. K. Danovich, V. G. Zakzhevskii, V. K. Voronkov, and E. S. Domnina, *Teoret. i. Eksperim. Khim.,* 716 (1989).
15. A. Z. Dzhumanazarova, I. A. Abronin, V. P. Litvinov, G. M. Zhidomirov, and V. A. Korsunov, *Khim. Geterotsikl. Soedin.,* 1461 (1979).
16. I. A. Abronin, K. Ya. Burshtein, and G. M. Zhidomirov, *Zhur. Strukt. Khim.,* **21**, 145 (1980).
17. K. Reichardt, *Solvents and Media Effects in Organic Chemistry* [Russian translation], Mir, Moscow (1991).
18. T. Clark, *Computer Chemistry* [Russian translation], Mir, Moscow (1990).
19. R. G. Pearson, *J. Chem. Educ.,* **45,** 581 (1968).
20. R. G. Pearson, *J. Chem. Educ.,* **45,** 643 (1968).
21. G. Klopman, *Reactivity and Reaction Pathways* [Russian translation], Mir, Moscow (1977).