MNDO, AM1 AND PM3 CALCULATIONS IN THE STUDY OF THE ENERGY AND STRUCTURE OF QUINAZOLONE TAUTOMERS

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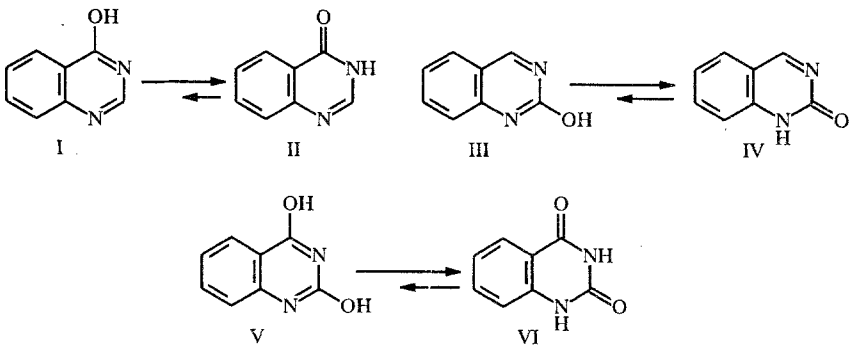
MNDO, AM1, and PM3 calculations were used to study the tautomeric forms of quinazolones. The relative energy of the tautomers closest to the experimental value was obtained using the AM1 and PM3 methods. The keto—enol tautomeric equilibrium of quinazolones in the gas phase is shifted toward the ketone form.

In the present work, we continued our systematic study of the interrelationship of the reactivity of condensed aromatic heterocycles and their structure.

Quinazoline derivatives with hydroxyl groups at $C_{(2)}$ and $C_{(4)}$ exist in several tautomeric forms [1, 2]. The existence of a molecule in some specific form has a significant effect on the reactions of these systems. Data on the geometrical and electronic structure of quinazolones are required for studying the structure of the tautomeric forms of these molecules in the amide and hydroxy forms. However, the experimental determination of the structure is rather difficult since the clarification of reactivity relative to the tautomeric nature of quinazolones is complicated and often unpredictable. The reaction products obtained, for example, in alkylation and acylation, are usually the result of the reaction of both forms. We undertook a quantum chemical study of the tautomeric forms of 4-hydroxyquinazoline (I), 4-oxo-3,4-dihydroquinazoline (II), 2-hydroxyquinazoline (III), 2-oxo-1,2-dihydrodihydroquinazoline (IV), 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (V), and 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (VI) and their analogs in order to clarify the tautomeric interconversions. MNDO [3], AM1, and PM3 LCAO MO calculations [5] were carried out using the MNDO85 program package with complete optimization of the molecular geometry.

We should note that I—VI hold interest as polydentate cyclic systems containing several competing reaction sites capable of reacting with nucleophilic reagents [7-10].



There is no information in the literature on the use of quantum chemical calculations to study the tautomeric forms of 2-hydroxy-, 4-hydroxy-, and 2,4-dihydroxyquinazolines. Thus, we must initially select the most satisfactory method for studying the tautomeric systems of I—VI by studying analogous compounds with geometrical and energy data derived from experiment and *ab initio* calculations. 2-Hydroxypyridine (VII) and 2-pyridone (VIII) are such compounds, for which data on their relative stability in the gas phase ([11-13] and the references cited therein) have been obtained by both semiempirical (CNDO/2, MINDO/2, MINDO/3, MNDO, and AM1) and nonempirical calculations with different bases (STO-3G, 3-21G, 6-31G, and

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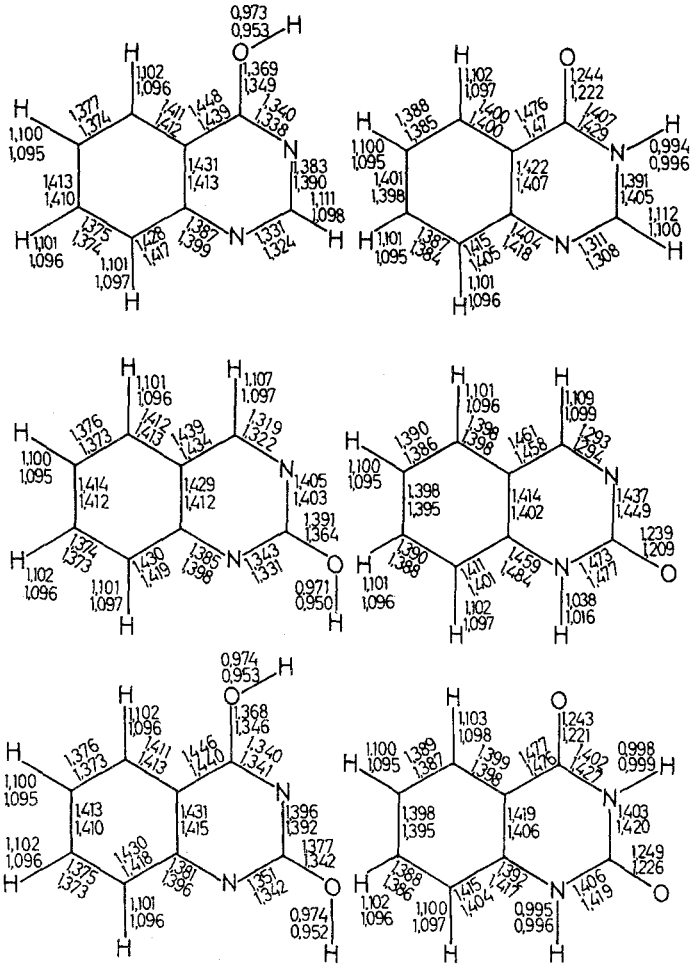


Fig. 1. Bond lengths of the tautomeric forms of quinazolines I—VI (from an AM1 calculation).

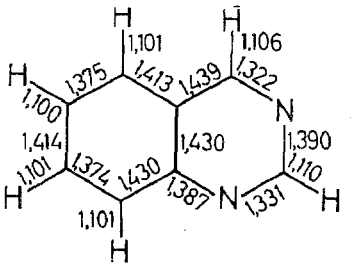


Fig. 2. Bond lengths and angles of the quinazoline molecule (from an AM1 calculation).

TABLE 1. Relative Tautomerization Energies of 2-Pyridone (VII) and 2-Hydroxypyridine (VIII) Obtained by Theoretical and Experimental Methods (kcal/mole)*

VII VIII

CNDO/2	MINDO/2	MINDO/3	MNDO	AM1	P M3	STO-3G	3-21G	6-31G [16]	6-31G [16]	Exp.
11,3 [14]	-14,2 [15]	-3,7 [16]	-9,8	-0,5	-2,5	-15,4 [16]	1,7 [16]	2,1 (HF)*2	0,6 (HF//3-21G)	0,3 + 2,5 [20]
			-9,8 [17]	0,4 [18]				2,9 (MP2)*3	1,4 (MP2//3-21G)	-0,6 + 0,3 [21]
				3,8 [19] (ℓ)*4					0,4 (HF//6-31G)	-4,2 [19] (ℓ)
									1,2 (MP2//6-31G)	

*The minus sign indicates the energetic preference of the enol tautomer.

*2The Hartree-Fock SCF approximation.

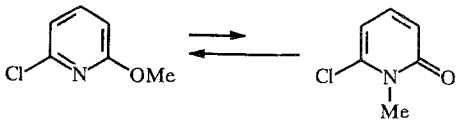
*3Calculation of the correlation correction to the total energy using the Meller-Plessette scheme.

*4Liquid state.

6-31G*) as well as experimental methods. In addition to the experimental and theoretical data, we carried out MNDO, AM1, and PM3 calculations for VII and VIII. According to the data in Table 1, the overwhelming majority of quantum chemical methods give data close to the experimental results (within experimental error) [19-21]. Some methods lead to somewhat overestimated tautomerization energies in favor of the enol form (STO-3G, MINDO/2, and MNDO) or ketone form (CNDO/2). The relative energy is closest to experiment in the 6-31G* and AM1 methods and nonempirical 6-31G method. Good results were also obtained from 3-21G, PM3, and MINDO/3 calculations. Thus, the AM1 and PM3 methods are entirely suitable for studying tautomers I—VI and actually reflect the final states of the model systems of VII and VIII.

The data in Table 2 show that the relative energies of tautomers I—VI obtained in MNDO, AM1, and PM3 calculations differ significantly. Thus, while the MNDO data indicate preference for the hydroxy form in all three systems, the AM1 and PM3 data, on the other hand, indicate preference for the amide form. Opposite conclusions concerning the structure of the tautomers containing enol and ketone forms are also encountered in the literature. Recently, Ivanovskii [22] has cast doubt on the stability of the enol, for example, of 2-, 6-, and 8-hydroxypurines in solution.

The tautomeric series of chemical systems in different phase states has been studied calorimetrically [23]. These measurements permitted calculation of the equilibrium, which is shifted toward the amide form (X) in the gaseous phase and toward the enol (IX) in the liquid phase.



IX X

Mathier and Panicot [24] analyzed many structures featuring prototropy and found that the ketone is usually more stable in the keto—enol tautomerization. The extent of enolization may be enhanced by steric and electronic factors. Thus, the AM1 and PM3 data on the preference of the ketone form in the keto—enol tautomerization of systems I—VI in the free state are entirely acceptable. The conjugation of the π-electrons of the carbonyl groups with the π-system of the molecular skeleton

TABLE 2. Heats of Formation (ΔH_f) and Energy Difference (ΔE) of Tautomeric Forms I-VI (kcal/mole)

Methanol	ΔH_f		ΔE	ΔH_f		ΔE	ΔH_f		ΔE
	I	II		III	IV		V	VI	
MNDO	-3,4	0,0	-3,4	-2,9	3,5	-6,4	-57,3	-53,1	-4,2
AM1	19,0	11,6	7,4	24,8	17,9	6,9	-19,1	-40,9	21,8
PM3	6,0	6,0	4,5	6,0	2,7	3,3	-42,9	-57.7	4,8

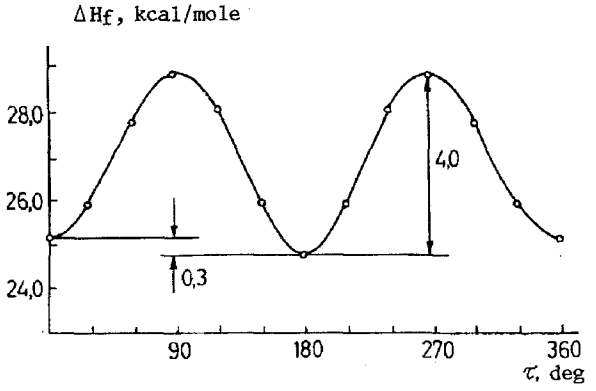


Fig. 3. Dependence of the heat of formation of III on the torsion angle of the OH group.

probably enhances the resonance energy of the ketone, which leads to its predominance over the enol. This effect is most pronounced in the case of 2,4-quinazolinedione, where the presence of two C=O groups enhances the resonance energy. Thus, relative energy of system VI, according to the AM1 data, exceeds the energies of II and IV by a factor of approximately three.

Let us examine the results of quantum chemical calculations of the structure of tautomers I—VI. The results of the AM1 calculations were taken as the basis of the our analysis of their geometry. Comparison of the bond angles of the pyridine and naphthalene molecules, which are the most well-known and closest to I—VI, and the values calculated using various methods in the present work (with the experimental data of Vilkov [25] as a test case) shows that the best agreement is achieved by the AM1 and PM3 methods. Furthermore, the results of the calculation of the geometry of 138 compounds given in the original work of Dewar et al. [4] provide support for using this method.

Proton migration in the systems examined leads to significant changes in geometry. Thus, going from the enol form to the ketone form leads to a decrease in the bond lengths over the entire perimeter of the benzene part of molecules I—VI by about 0.01 Å (Fig. 1). On the other hand, the bonds are significantly extended in the pyrimidine part of these molecules. Thus, in going from tautomeric form I to II, the $C_{(4)}$—$C_{(10)}$ and $N_{(1)}$—$C_{(9)}$ bonds lengths increase by 0.028, 0.067, and 0.018 Å, while the $N_{(1)}$—$C_{(2)}$ bond length is reduced by 0.019 Å. Analogous changes were observed for the pairs III—IV and V—VI. Figure 1 shows that the most noticeable changes are found for the amide group bonds. For example, the change in the $N_{(3)}$—$C_{(4)}$ bond in II is 0.067 Å, while the changes in the $N_{(1)}$—$C_{(2)}$ and $N_{(3)}$—$C_{(2)}$ bonds in IV are 0.083 and 0.024 Å, respectively. The changes in the $N_{(1)}$—$C_{(2)}$, $C_{(2)}$—$N_{(3)}$, and $N_{(3)}$—$C_{(4)}$ bonds in VI are 0.055, 0.007, and 0.061 Å, respectively. We should note that the geometrical parameters of the quinazolones in enol form I, III, and V are similar to the parameters of the original quinazoline molecule obtained in an AM1 calculation (Fig. 2).

Since the molecular heats of formation depend significantly on the orientation of the OH groups, we analyzed ΔH_f as a function of the torsion angles of the C—OH bond for I and III. According to the values of the potential energy surface, the orientation, in which hydrogen atom, for example, in III, has *cis* orientation relative to $N_{(1)}$, is preferable for the OH group proton (Fig. 3). The relative energies of the *cis* and *trans* orientation of the hydroxy group differ only slightly (0.03 kcal/mole), which permits the coexistence of both forms. Analogous results were obtained for the tautomers I and V. The relative energy of the *cis* and *trans* configuration of the OH groups for I is 5.8 kcal/mole in favor of the *cis* orientation.

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