



QUANTUM CHEMICAL MODELING OF THE FORMATION OF 3-PHENYL-5-METHYL-1,2,4-OXADIAZOLE

E. R. Kofanov

Kofanov E.R., Doctor of Chemical Sciences, Professor

Institute of Chemistry and Chemical Technology, Yaroslavl State Technical University, Moskovsky ave., 88, Yaroslavl, Russia, 150023

E-mail: kofanover@ystu.ru

Keywords:

1,2,4-oxadiazole, acylation, cyclization, quantum chemical modeling

A quantum chemical simulation of the formation of 3-phenyl-5-methyl-1,2,4-oxadiazole was performed. The energy of intermediate particles and the transition state is calculated. The directions of acylation of amidoxime are considered.

Introduction

Substituted 1,2,4-oxadiazoles are used as biologically active substances. There are several known methods for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles based on amidoximes [1-9]. We have studied the reaction of formation of 1,2,4-oxadiazoles during the interaction of *N*-hydroxybenzamidine (*N*-HBA) with carboxylic acid chlorides [10, 11].

There are data in the literature on quantum-chemical modeling of 3,5-diaryl-substituted 1,2,4-oxadiazoles. Calculations were performed using the PM3, AM1, and HF / 6-31G methods (gas-phase approximation) [12]. The obtained parameters of the geometry of molecules correspond to the experimental values determined using X-ray diffraction analysis.

Main part

To test the assumptions made about the mechanism of formation of 1,2,4-oxadiazoles, we carried out a quantum-chemical study of the reaction of the interaction of *N*-HBA with acetyl chloride (ACh). Our calculations were performed using the AMSOL software package by the AM1 / SM2.1 method (AMSOL 7.1 in the liquid-phase approximation: SM5.42, pyridine solvent) [13, 14]. A complete optimization of the geometry of all calculated molecules and complexes has been performed. Transient states were found using a standard technique - minimization of the norm of the energy gradient with the subsequent solution of the oscillatory problem for the resulting structure (test for one pseudo-oscillation with a negative force constant). In most cases, the approximation of the restricted Hartree-Fock (RHF) method was used, but in some cases, for comparison, calculations were performed using the unrestricted Hartree-Fock (UHF) methods.

Enthalpy of formation $\Delta H_f = \Delta H_f^o + \Delta G_{sol}$, where ΔH_f^o - is the calculated standard enthalpy of formation, ΔG_{sol} , is the calculated free energy of solvation. The error in predicting the



heats of solvation of neutral molecules is on average 1.7 kJ/mol, for ions - 17.6 kJ/mol [13-15].

We have considered the following possible path of the reaction (Fig. 1).

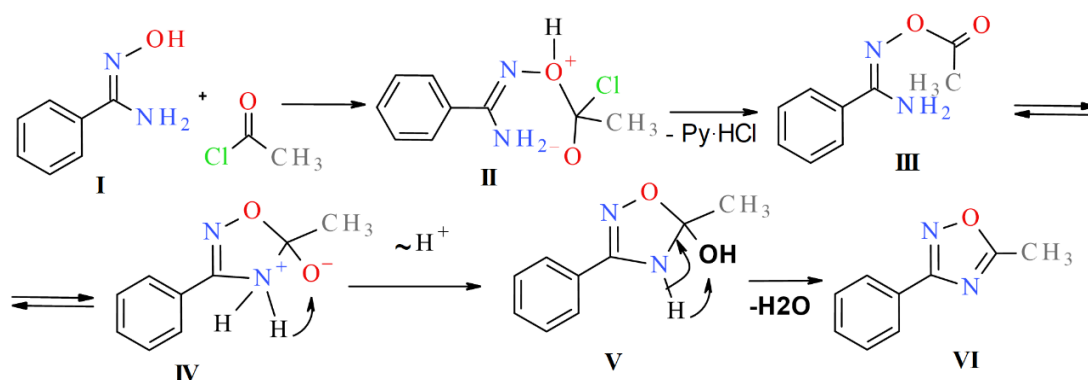


Fig. 1. A possible path of the reaction

The enthalpies of formation of the initial and final products, as well as intermediate complexes lying on the path of their formation, are shown in Table 1.

Table 1. Enthalpies of formation of compounds and complexes

	ΔH_f , kJ/mol
I	57,27
II	-151,05
III	-87,36
IV	16,57
V	-54,82
VI	254,50

ACh in the *N*-HBA (I) molecule can attack a nitrogen or oxygen atom (Fig. 2).

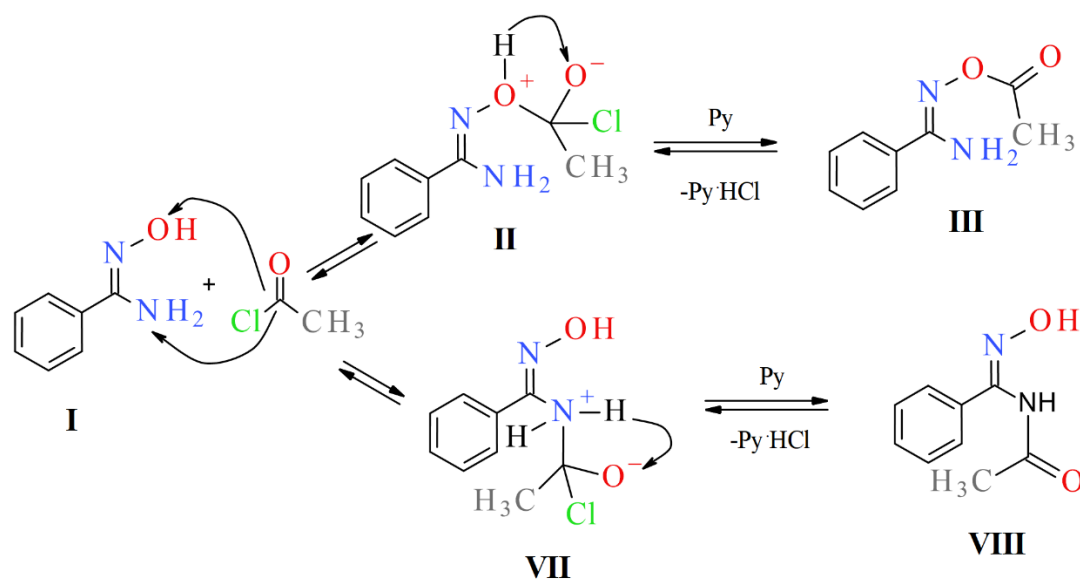


Fig. 2. Scheme of the formation of compounds III and VIII

Zwitterion II is a product of the interaction between *N*-HBA and AX (Fig. 3). The change in the energy of a supermolecule (*N*-HBA and AX) during the formation of II is shown in Table 2.

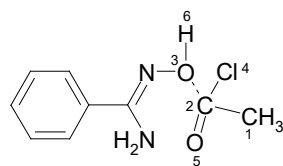


Fig. 3. Scheme of the supermolecule (N-HBA and ACh)

Table 2. Change in the energy of a supermolecule from a distance O(3)–C(2)

$l_{O(3)-C(2)}, \text{Å}$	$\Delta H_f, \text{kJ/mol}$	$l_{O(3)-C(2)}, \text{Å}$	$\Delta H_f, \text{kJ/mol}$
3	-151,05	2,2	-116,69
2,9	-149,00	2,1	-104,42
2,8	-146,61	2	-89,29
2,7	-146,86	1,9	-71,57
2,6	-143,59	1,8	-53,00
2,5	-139,40	1,7	-37,50
2,4	-133,79	1,6	-48,06
2,3	-126,37		

It was found that the maximum value of ΔH_f corresponds to the distance $O(3)-C(2) = 1,64 \text{ Å}$. The parameters of the transient state are shown in Table 3.

Table 3. Transient state parameters

$l_{O(3)-C(2)}, \text{Å}$	$\Delta H_f, \text{kJ/mol}$	$l_{C(2)-Cl(4)}, \text{Å}$	$q_{Cl(4)}$	$q_{O(3)}$	$q_{O(5)}$	Bonding structure C(2)=O(5)	Bonding structure C(2)–O(3)	$l_{O(13)-H(18)}, \text{Å}$	Bonding structure O(3)–H(6)	$q_{H(18)}$	Bonding structure C(2)–Cl(4)
1,64	-32,14	2,15	-0,718	-0,274	-0,510	1,87	0,50	0,96	0,89	0,423	0,352

It can be seen from the data obtained that the C(2)–Cl(4) bond was broken, and the order of the formed C(2)–O(3) bond was 0.5. The charge on the Cl(4) atom increases to $-0.718 e$, and the C(2)–Cl(4) distance increases to 2.15 Å . The transition state is characterized by a force constant $k = -45.82 \text{ n/m}$, the enthalpy of formation of the transition state (relative to the initial reagents) $\Delta\Delta H_f^\ddagger = 128,51 \text{ kJ/mol}$. The O(3) – H(6) remained almost unchanged.

The calculated enthalpies of formation of compounds III and VIII (see Fig. 2) were -163.95 and -145.81 kJ/mol , which indicates a high stability of intermediate III, which can be formed during O-acylation of N-HBA. This has been confirmed experimentally. We isolated an intermediate with the structure of an ester (III), which was confirmed by IR data (presence of an ester band $\nu_{C=O} = 1723 \text{ cm}^{-1}$) and PMR spectroscopy.

Conclusions

The transformation of compound III into product VI proceeds according to the scheme shown in Fig. 1, through intramolecular nucleophilic substitution during the transfer of a carbonyl carbon atom followed by a proton and the formation of 5-methyl-3-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-ol (V), losing water, passes the product is 5-methyl-3-phenyl-1,2,4-oxadiazole. The transfer of a proton to IV and the formation of V occurs practically without an activation barrier (see Fig. 1).



Referense

1. **Sharonova T., Pankrateva V., Savko P., Baykov S., Shetnev A.** Facile room-temperature assembly of the 1,2,4-oxadiazole core from readily available amidoximes and carboxylic acids. *Tetrahedron Letters*. 2018. V. 59. P. 2824-2827. URL: <https://doi.org/10.1016/j.tetlet.2018.06.019>.
2. **Baykov S., Sharonova T., Shetnev A., Rozhkov S., Kalinin S., Smirnov A.V.** The first one-pot ambient-temperature synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acid esters. *Tetrahedron Letters*. 2017. V. 73. P. 945-951. URL: <https://doi.org/10.1016/j.tet.2017.01.007>.
3. **Wang Y, Miller R.L., Sauer D.R., Djuric S.W.** Rapid and Efficient Synthesis of 1,2,4-Oxadiazoles Utilizing Polymer-Supported Reagents under Microwave Heating. *Tetrahedron Letters*. 2005. V. 7. P. 925-928. URL: <https://doi.org/10.1021/ol050007r>.
4. **Tarasenko M., Duderin N., Sharonova T., Baykov S., Shetnev A.** Room-temperature synthesis of pharmaceutically important carboxylic acids bearing the 1,2,4-oxadiazole moiety. *Tetrahedron Letters*. 2017. V. 58. P. 3672-3677. URL: <https://doi.org/10.1016/j.tetlet.2017.08.020>.
5. **Tamura M., Ise Y., Okajima Y., Nishiwaki N., Ariga M.** Facile Synthesis of 3-Carbamoyl-1,2,4-Oxadiazoles. *Synthesis*. 2006. P. 3453-3461. URL: <https://doi.org/10.1055/s-2006-950210>.
6. **Amarasinghe K.K.D., Maier M.B., Srivastava A., Gray J.L.** One-pot synthesis of 1,2,4-oxadiazoles from carboxylic acid esters and amidoximes using potassium carbonate. *Tetrahedron Letters*. 2006. Vol. 47 P. 3629-3631. URL: <https://doi.org/10.1016/j.tetlet.2006.03.155>.
7. **Du W., Truong Q., Qi H., Guo Y., Chobanian H.R., Haggmann W.K., Hale J.J.** A one-pot synthesis of 3-substituted-5-carbonylmethyl-1,2,4-oxadiazoles from β -keto esters and amidoximes under solvent-free conditions. *Tetrahedron Letters*. 2007. V. 48. P. 2231-2235. URL: <https://doi.org/10.1016/j.tetlet.2007.02.005>
8. **Lin Y., Lang S., Lovell M.F., Perkinson N.A.** New synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles. *Journal of Organic Chemistry*. 1979. V. 44. P. 4160-4164. URL: <https://doi.org/10.1021/jo01337a031>
9. **Neidlein R., Li S.** Syntheses of 1,2,4-oxadiazole substituted pyrazole, isoxazole and pyrimidine heterocycles. *Journal of Heterocyclic Chemistry*. 1996. V. 33. P.1943-1949. URL: <https://doi.org/10.1002/jhet.5570330663>
10. **Karunnaya M.V., Sosnina V.V., Krasovskaya G.G., Danilova A.S., Kofanov E.R.** Sintez 3-(3-nitrofenil)-5-stiril-1,2,4-oksadiazola. *Izvestiya vuzov. Khimiya i khim. Tekhnologiya*. 2014. V. 57. N. 12. P. 15-16 (in Russian).
11. **Tsiulin P.A., Sosnina V.V., Krasovskaya G.G., Danilova A.S., Baikov S.V., Kofanov E.R.** Formation and cyclization of N'-(benzoyloxy)benzenecarboximidamides. *Russian Journal of Organic Chemistry*. 2011. V. 47. N 12. P. 1874-1877. URL: <https://link.springer.com/article/10.1134/S10704280111201531877>. DOI: 10.1134/S1070428011120153.
12. **Rajendra M. Srivastava, Wagner M. Faustio, Ira M. Brin.** Semi-empirical (PM3 and AM1) and ab initio molecular orbital calculations of 1,2,4-oxadiazoles, 4,5-dihydro-1,2,4-oxadiazoles and 4,4-di-n-butyl-2-phenylbenzo-1,3-oxazine. *Journal of Molecular Structure (Theochem)*. V. 640(2003). P. 49-56. URL: [https://doi.org/10.1016/S0166-1280\(03\)00511-6](https://doi.org/10.1016/S0166-1280(03)00511-6).
13. **David J. Giesen, Gregory D. Hawkins, Daniel A. Liotard, Christopher J. Cramer, Donald G. Truhlar.** A universal model for the quantum mechanical calculation of free energies of solvation in non-aqueous solvents. *Theoretical Chemistry Accounts*. 1997. V. 98. P. 85-109. URL: <https://doi.org/10.1007/s002140050283>.
14. **Cramer C.J., Truhlar D.G.** AM1-SM2 and PM3-SM3 parameterized SCF solvation models for free energies in aqueous solution. *Journal of Computer-Aided Molecular Design*. 1992. V. 6. P. 629-666. URL: <https://doi.org/10.1007/BF00126219>.
15. **Daniel A. Liotard, Gregory D. Hawkin, Gillian C. Lynch, Christopher J. Cramer, Donald G. Truhlar.** Improved methods for semiempirical solvation models. *Journal of Computational Chemistry*. 1995. V. 16. N 4. P. 422-440. URL: <https://doi.org/10.1002/jcc.540160405>.

Received 22 January 2021

Accepted 10 March 2021