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Maryna Stasevych[1], Viktor Zvarych[1], Rostyslav Musyanovych[1], Volodymyr Novikov[1] and Mykhailo Vovk[2]

SYNTHESIS OF N-BENZOYL-N′-(9,10-DIOXO-9,10-DIHYDROANTHACEN-1-YL)-THIOUREAS AND QUANTUM-CHEMICAL ANALYSIS OF THE REACTION PASSING

[1] Lviv Polytechnic National University
12, S. Bandera str., 79013 Lviv, Ukraine; vnovikov@polynet.lviv.ua
[2]Institute of Organic Chemistry of National Academy of Scieces of Ukraine,
5, Murmanska str., 02660 Kyiv, Ukraine

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Abstract. Interaction of an order of aminoanthraquinones with benzoylisothiocyanate resulting in the formation of new N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthacen-1-yl)-thioureas was investigated. Quantum-chemical calculations using *Gaussian 03W* and *HyperChem 8* were carried out. On their basis nucleophilic addition of aminoanthraquinones to benzoylisothiocyanate (charge control) was confirmed. A probable mechanism of nucleophilic addition was suggested. Influence of ortho-substituents on the passing of the reaction was explained. Values of absolute hardness and softness of aminoanthraquinones were calculated.

Keywords: aminoanthraquinones, benzoylisothiocyanates, benzoylthioureas, quantum-chemical calculations.

1. Introduction

N-Aroyl-N'-substituted thioureas belong to synthetic blocks of a wide range of preparative application. They are important reagents for the synthesis of heterocycles. Many of these substances possess interesting biological activities and can be used as source of materials for development of agrochemical and pharmaceutical products [1]. In particular, preparation of imidazolidine-2-thiones [2,3], 2-aroyliminothiazolines [4-6], 1,2,4-triazoles [7], 1,3-thiazines [8], and indeno[1,2-d][1,3]thiazepines [9] on their basis was described. 2-Iminothiazolines and 2-aminothiazoles deserve special attention as important structural scaffolds that provide a wide range of biological properties [10-13]. Significant role in manifestation of biological action also belongs to the nature of substituent in position 1 of thiazole (thiazoline) cycle.

The benzoylthiourea derivatives possess a wide range of biological activities including antiviral [14], antibacterial [15-17], antifungal [18], antitubercular [19,20], herbicidal [21], insecticidal [22], and pharmacological properties [23] and can act as chelating agents [24, 25].

Various methods of synthesis of substituted thioureas, obtained by reaction of 1(2)-amino-9,10-anthraquinone with aroylisothiocyanates in different conditions, were described in the literature [26-31]. We carried out interactions of aminoderivatives of 9,10-anthraquinone with ammonium thiocyanate in acetic acid, ammonium thiocyanate in the presence of hydrochloric acid, and aroylisothiocyanate in pyridine according to the known methods [32-34], but failed to obtain thioureas derivatives. However, these methods have several disadvantages such as necessity of high reaction temperature or the duration of the reaction. The development of mild efficient methods is still desired. Therefore, synthesis of new N-benzoylthioureas with pharmacophore fragment of 9,10-dioxo-9,10-dihydroanthacene [35] as precursors for further obtaining of various potentially bioactive azole and azine systems is reasonable.

2. Experimental

^{1}H NMR spectra were obtained on the device Varian Mercury-400 (399.9601 MHz) in solutions of DMSO-d_6, internal standard TMS. Chromato-mass spectra were recorded on the device Agilent 110\DAD\HSD\VLG 119562. Individuality of the obtained compounds was controlled by TLC in solvent systems benzene-acetonitrile, 6:1.

N-Benzoyl-N'-(9,10-dioxo-9,10-dihydro-anthacen-1-yl)-thioureas IIa-e. 0.009 mol of aminoanthraquinone was added to a solution of benzoylisothiocyanate in 50 ml of acetone, obtained by interaction of 0.87 g (0.009 mol) of potassium thiocyanate and 1.25 g (0.009 mol) of benzoylchloride by the method [36]. Reaction mixture was stirred at room temperature for 1 h and then boiled for 6 h. The reaction mixture was cooled, the precipitate was filtered, washed with a small amount of acetone and then with water. The residue was dried in air and crystallized from toluene.

N-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)-carbamoyl)benzamide IIa. Yield 78 %. Mp. = 487–488 K. ^{1}H NMR spectra, δ ppm: 7.58-7.69 (m, 4H, CH_{Ar}); 7.92-8.17 (m, 7H, CH_{Ar}); 8.72 (d, 1H, J = 8.0 Hz, CH_{Ar}); 11.80 (s, 1H, NH); 13.88 (s, 1H, NH). Chromato-mass spectra, *m/z* (I_{rel},%): 387 [M +1] (100). Found, %: C 68.50; H 3.51; N 7.32; S 7.81. $C_{22}H_{14}N_2O_3S$. Calculated, %: C 68.38; H 3.65; N 7.25; S 8.03.

N-((4-Amino-9,10-dioxo-9,10-dihydroanthracen-1-yl)carbamoyl)benzamide IIb. Yield 61 %. Mp. = 477–478 K. ^{1}H NMR spectra, δ ppm: 7.23 (d, 1H, J = 8.3 Hz, CH_{Ar}); 7.57-7.69 (m, 4H, CH_{Ar}, NH_2); 7.84-8.18 (m, 9H, CH_{Ar}); 11.67 (s, 1H, NH); 13.64 (s, 1H, NH). Chromato-mass spectra, *m/z* (I_{rel},%): 402 [M +1] (80). Found, %: C 65.70; H 3.59; N 10.32; S 7.87. $C_{22}H_{15}N_3O_3S$. Calculated, %: C 65.82; H 3.77; N 10.47; S 7.99.

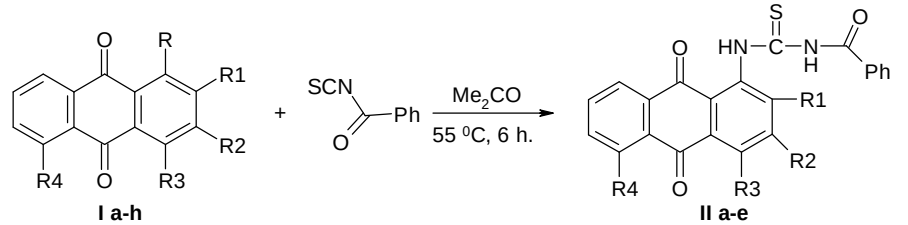
N-((5-Amino-9,10-dioxo-9,10-dihydroanthracen-1-yl)carbamoyl)benzamide IIc. Yield 64 %. Mp. = 555–556 K. ^{1}H NMR spectra, δ ppm: 7.10 (d, 1H, J = 7.9 Hz, CH_{Ar}); 7.19-7.21 (m, 2H, CH_{Ar}); 7.37-7.59 (m, 8H, CH_{Ar}, NH_2); 7.68-8.05 (m, 5H, CH_{Ar}); 8.15 (d, 1H, J = 7.7 Hz, CH_{Ar}); 8.69 (d, 1H, J = 8.0 Hz, CH_{Ar}); 11.72 (s, 1H, NH); 13.89 (s, 1H, NH). Chromato-mass spectra, *m/z* (I_{rel},%): 402 [M +1] (82). Found, %: C 65.68; H 3.61; N 10.37; S 7.82. $C_{22}H_{15}N_3O_3S$. Calculated, %: C 65.82; H 3.77; N 10.47; S 7.99.

N-((4-Benzamido-9,10-dioxo-9,10-dihydroanthracen-1-yl)carbamoyl)benzamide IId. Yield 60 %. Yield Yield 60 %. Mp. = 521–522 K. ^{1}H NMR spectra, δ ppm: 7.42 (d, 1H, J = 8.1 Hz, CH_{Ar}); 7.55-7.69 (m, 5H, CH_{Ar}); 7.72-7.93 (m, 3H, CH_{Ar}); 8.18-8.25 (m, 3H, CH_{Ar}); 8.91 (s, 1H, NH); 11.81 (s, 1H, NH); 13.35 (s, 1H, NH). Found, %: C 65.72; H 3.59; N 8.39; S 6.11. $C_{29}H_{19}N_3O_4S$. Calculated, %: C 65.90; H 3.79; N 8.31; S 6.34.

N-((2-Methyl-9,10-dioxo-9,10-dihydroanthracen-1-yl)carbamoyl)benzamide IIe. Yield 75 %. Mp. = 481–482 K. ^{1}H NMR spectra, δ ppm: 2.44 (s, 3H, CH_3); 7.57-7.61 (m, 2H, CH_{Ar}); 7.69-7.73 (m, 1H, CH_{Ar}); 7.86-7.91 (m, 3H, CH_{Ar}); 8.08-8.19 (m, 5H, CH_{Ar}); 11.79 (s, 1H, NH); 12.57 (s, 1H, NH). Chromato-mass spectra, *m/z* (I_{rel}, %): 401 [M +1] (100). Found, %: C 68.81; H 3.85; N 6.83; S 7.90. $C_{23}H_{16}N_2O_3S$. Calculated, %: C 68.98; H 4.03; N 7.00; S 8.01.

3. Results and Discussion

We have thoroughly studied the reaction of several aminoanthraquinones **Ia-h** and freshly obtained acetone solution of benzoylisothiocyanate. Benzoylisothiocyanate was prepared by the interaction of benzoylchloride with potassium thiocyanate. It was established that the possibility of passing of this reaction depends on the structure of aminoanthraquinones. Boiling of reagents in acetone during 6 h turned out positive only for compounds **Ia-e**, containing in position 2 no substituents or a methyl group. As a result N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracen-1-yl)thioureas **IIa-e** (Scheme 1) were obtained with 60–78 % yields. Instead, amino-anthraquinones **If** and **Ig,** containing carboxyl group or a chlorine atom in position 2, in similar conditions and also during long-term (10 h) heating and excess of benzoylisothiocyanate, did not enter into the reaction. A similar situation takes place in the case of 2-amino-3-chloroanthraquinone **Ih**.



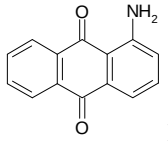
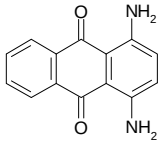
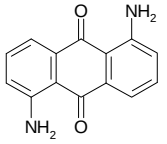
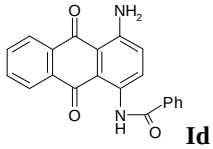
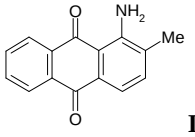
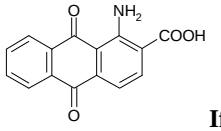
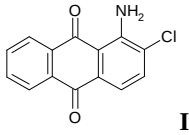
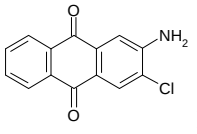
I a-h **II a-e**

R = NH_2, R_1 = R_2 = R_3 = R_4 = H(a)
R = R_3 = NH_2, R_1 = R_2 = R_4 = H (b)
R = R_4 = NH_2, R_1 = R_2 = R_3 = H (c)
R = NH_2, R_1 = R_2 = R_4 = H, R_3 = NHCOPh (d)
R = NH_2, R_2 = R_3 = R_4 = H, R_1 = Me (e)
R = NH_2, R_1 = COOH, R_2 = R_3 = R_4 =H (f)
R = NH_2, R_1 = Cl, R_2 = R_3 = R_4 =H (g)
R = H, R_1 = NH_2, R_2 = Cl, R_3 = R_4 =H (h)

Scheme 1

Table 1

Data of quantum-chemical calculations and absolute softness and hardness of anthraquinones Ia-h

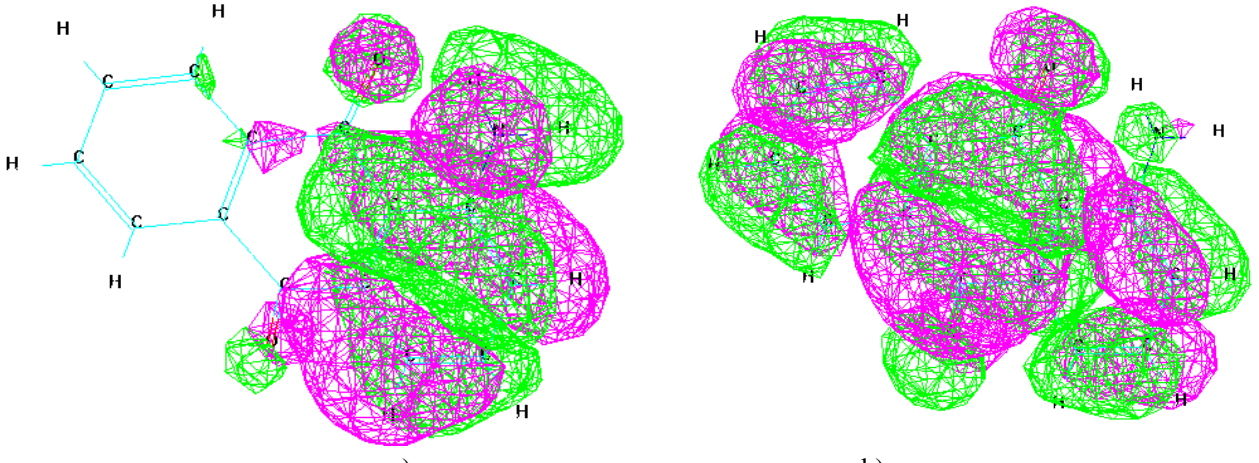
Compound	Energy HOMO, a.u.	Energy LUMO, a.u.	Charge on the nitrogen atom, eV	Density on the nitrogen atom	Softness S, eV^{-1}	Hardness η, eV
 **Ia**	-0.30075	0.02342	-0.998	1.380847	3.086	0.162
 **Ib**	-0.26513	0.02834	-0.996	1.389392	3.413	0.147
 **Ic**	-0.29306	0.02697	-0.998	1.380728	3.125	0.160
 **Id**	-0.26497	0.02975	-0.995	1.389291	3.387	0.158
 **Ie**	-0.29625	0.02587	-1.010	1.384657	3.106	0.161
 **If**	-0.31062	0.00611	-1.012	1.362399	3.155	0.158
 **Ig**	-0.31338	0.01220	-1.003	1.372947	3.067	0.163
 **Ih**	-0.31974	0.01862	-1.000	1.375253	2.959	0.169

The following quantum-chemical calculations of compounds **Ia-h** by using *Gaussian 03W* and *HyperChem 8* software were carried out to determine the causes of different reactivity of the amino group in an order of selected anthraquinones: preparation of structural objects, creation of initial approximation by method MM with next geometry optimization of molecules by *ab initio* method, and basic set 6-31G**. Optimized geometry of the studied molecular compounds as internal formats and Cartesian coordinate, their energy parameters and eigenvalues of vectors of molecular orbitals were obtained in the result of these calculations. In addition, absolute values of hardness η and softness S within Pearson theory of MO [37] for these structures were calculated. It allows

to take into account the influence of the nature of the substituent in the *ortho*-position on the reactionary ability of amino group (Table 1).

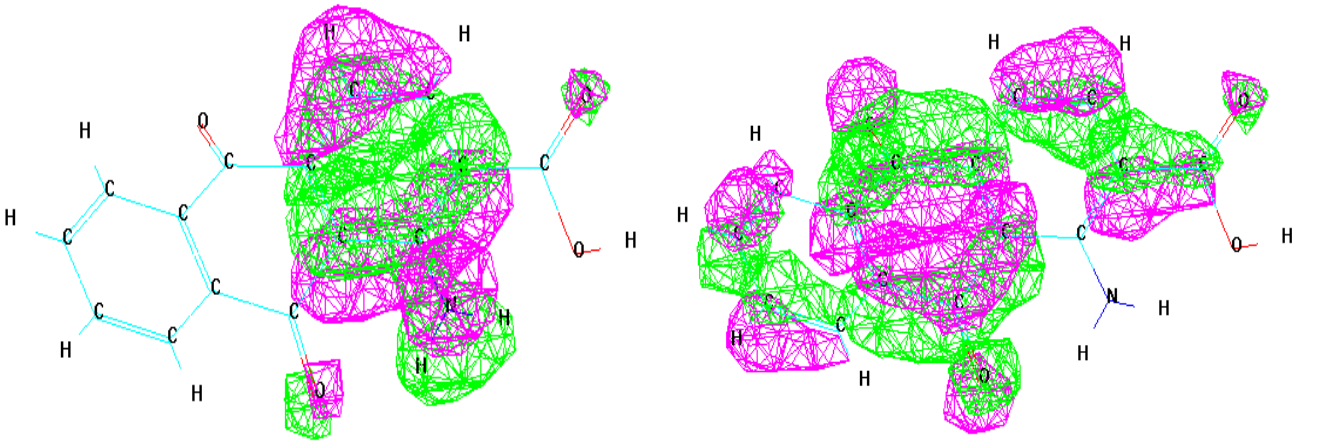
Attack by the nitrogen atom of the amino group on the atom of carbon of benzoylisothiocyanate (0.134 eV charge, HOMO = -0.36648 a.u., LUMO = 0.03431 a.u.) is initial stage of interaction of aminoanthraquinone. However, a problem in determining of relative reaction ability of specific nucleophile towards the sp^2-hybridized atom of carbon arises for compounds **If-h**. NH_2-group in the anthraquinones possesses a negative *-I* effect and large *+M* effect, while the presence of *p*-π-conjugation with the quinonic ring in molecules of aminoanthraquinones explains its electron-donor properties. Reaction of nucleophilic addition should be typical for the series of anthraquinones **Ia-h** (charge-controlled reaction) according to the calculated values of the effective charges on the atoms of nitrogen calculated by the *ab initio* method (basis set 6-31G **, Table 1). Besides, amino-anthraquinones are hard bases and benzoylisothiocyanate (S = 2.500, η = 0.200) is hard acid according to the calculated data of hardness η and softness S within Pearson theory of MO (Table 1). LUMO values are 0.02342–0.03483 a.u. for compounds **Ia-e** and for anthraquinones **If-h** they are in the range from 0.00611 to 0.01862 a.u. (Table 1). Values of energies of highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of molecules of aminoanthraquinones **Ia-h** were calculated by software package *Gaussian 03W* (Hartree-Fock method, basis set 6-31G **). The value of the energy gap, which separates HOMO of nucleophile (aminoanthraquinone) and LUMO of electrophile (isothiocyanate) from other occupied and vacant MO, is much less than 1 eV. It is typical of charge-controlled reaction. Data of Table 1 show that the density on the nitrogen atom weakly depends on the influence of substituents in *o*-position towards the aminogroup. It confirms passage of reactions which are controlled by the distribution of charges on the atoms. Moreover, solvation effects influence the distribution of charges on the atoms. Acetone improves the formation of an activated complex between nucleophiles **Ia-e** and substrate in the transient state. Given the above, it can be concluded that this reaction is charge-control type. Besides, the sharp decrease of the reactivity of aminoanthraquinone **If-h** and absence of interaction with benzoylisothiocyanate can be explained by the influence of the carboxyl group (*-I* and *-M* effects) and chlorine atom (*-I, + M* effects) in *o*-position to the NH_2-group, influence of quinonic coupling in molecules of anthraquinones and steric factors. As the result, the basicity of compounds **If-h** is decreased in comparison with compounds **Ia-e**. Such a sharp decrease of reaction ability of amino-group in aminoanthraquinones **I f,g** can be explained as follows. In the compounds **If** and **Ig** like in the compounds **Ia-e** hydrogen bonds between the hydrogen atoms of NH_2-group and the oxygen atom of the carbonyl group are present. Increase of enolic form of solvent (content of enol form is $1.5 \cdot 10^{-4}$ under normal conditions [38]) takes place in acetone during reaction of compounds **If** and **Ig**, which contain substituents –Cl and –COOH in *o*-position. Solvation of nucleophilic center with the molecules of the solvent takes place. As the result the energy of nucleophile decreases and shell from molecules of acetone is formed around it, which blocks the interaction between nucleophile and electrophile [39].

HOMO of 1-amino-9,10-anthraquinone **Ia** is localized mainly along C-C bonds of benzene and quinonic rings, as well as on 2*p*-orbital of amino-group, conjugated with quinonic fragment (Fig. 1a). The COOH-group does not participate in the formation of HOMO of 1-amino-2-carboxy-9,10-anthraquinone **If** (Fig. 2a). View of LUMO for molecules **Ia** and **If** is slightly different (Figs. 1b and 2b).



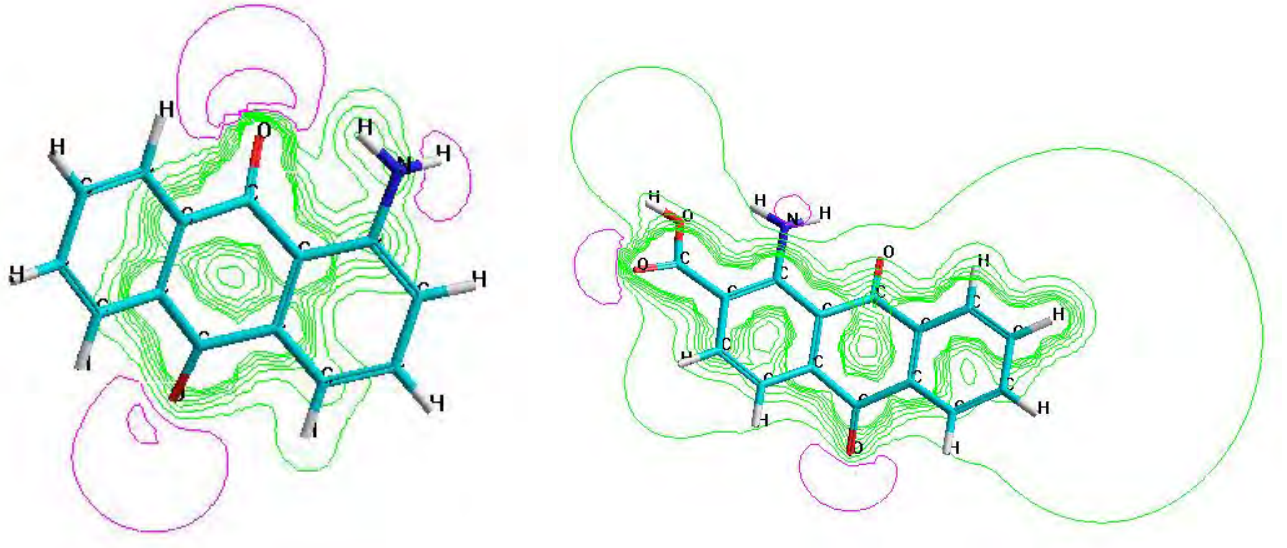
a) b)

Fig. 1. View of boundary orbitals of 1-amino-9,10-anthraquinone **Ia** in 3D: HOMO (a) and LUMO (b)



a) b)

Fig. 2. View of boundary orbitals of 1-amino-2-carboxy-9,10-anthraquinone (**If**) in 3D: HOMO (a) and LUMO (b)



a) b)

Fig. 3. Electrostatic potential of 1-amino-9,10-anthraquinone **Ia** (a) and 1-amino-2-carboxy-9,10-anthraquinone **If** (b)

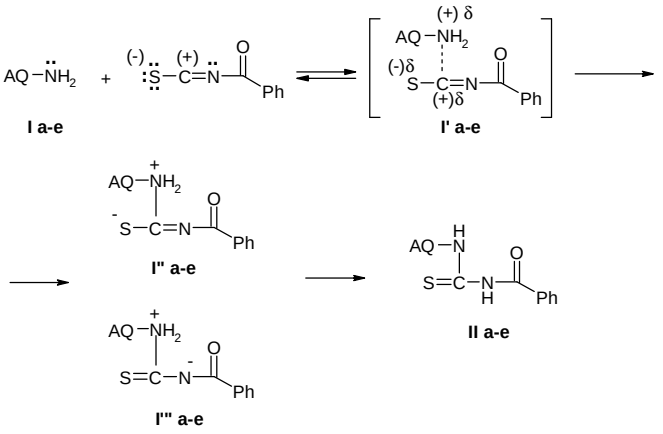
In addition, electrostatic potentials of 1-amino-9,10-anthraquinone **Ia** and 1-amino-2-carboxy-9,10-anthraquinone **If** were calculated in the approximation by PM3 software package *HyperChem 8* (Fig. 3). It allows predicting the interaction of the molecule with the solvent (acetone). Fig. 3 shows that a large area of negative potential (marked with red) is located on the oxygen atom of quinonic fragment and on the nitrogen atom of amino group of 1-amino-9,10-anthraquinone (Fig. 3a). Region of negative potential on the nitrogen atom in molecule of 1-amino-2-carboxy-9,10-anthraquinone is less than in molecule **Ia**.

Thus, it can be concluded that there exists complete correlation of the obtained experimental data of reaction ability of aminoanthraquinones **Ia-e** and the results of quantum chemical calculations.

The mechanism of interaction of aminoanthraquinones and isothiocyanate can be proposed as follows: attack of nucleophilic amino group takes place first on the carbon atom of benzoylisothiocyanate forming complex **I′a-e**. Two types of transient zwitterions **I″a-e** [40] and **I‴a-e** [41] can form during this reaction. Proton transfer passes the next stage and substituted thioureas **IIa-e** form as the result (Scheme 2).

Data of quantum-chemical calculations in approximation by PM3 of zwitterions **I″a-e** and **I‴a-e** for thiourea derivative **IIa** show that the heat of formation for zwitterion **I″a** is 34.391 kcal/mol and for zwitterion **I‴a**

is 29.603 kcal/mol. A similar tendency is observed for anthraquinones **I b-e**. Taking this into account it can be concluded that the formation of substituted thioureas passes with formation of zwitterion of type **I′′a-e**.



Scheme 2

4. Conclusions

Nucleophilic addition of aminoanthraquinones **Ia-e** to benzoylisothiocyanate (charge control) was confirmed by using of quantum-chemical calculations. Significant influence of *o*-substituents (–Cl and –COOH) on passing of this reaction was established. Values of absolute hardness η and softness S for the considered order of compounds were calculated. It was found that amino-anthraquinones are less hard nucleophiles and bases in comparison with aromatic amines.

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СИНТЕЗ N-БЕНЗОЇЛ-N'-(9,10-ДІОКСО-9,10-ДИГІДРО-АНТРАЦЕН-1-ІЛ)-ТІОСЕЧОВИН ТА КВАНТОВО-ХІМІЧНИЙ АНАЛІЗ ПЕРЕБІГУ РЕАКЦІЇ

Анотація. *Досліджено взаємодію ряду аміноантрахінонів з бензоїлізотіоціанатом з утворенням нових N-бензоїл-N'-(9,10-діоксо-9,10-дигідроантрацен-1-іл)-тіосечовин. Проведені квантово-хімічні розрахунки за допомогою Gaussian 03W та HyperChem 8, на основі яких підтверджено нуклеофільне приєднання аміноантрахінонів до бензоїлізотіоціанату (зарядовий контроль) та запропоновано його ймовірний механізм і обґрунтовано істотний вплив орто-замісників на перебіг цієї реакції. Розраховані значення абсолютної жорсткості та м'якості аміноантрахінонів.*

Ключові слова: *аміноантрахінони, бензоїлізотіоціанат, бензоїлтіосечовини, квантово-хімічні розрахунки.*