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[G007]

The DFT reactivity estimation of amino-1,5-benzodiazepin-2-ones in the cyclization reaction with dimethyl-2-oxoglutaconate

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Abstract

The regioselectivity outcome of 7-(or 8 and 9)amino-1,5-benzodiazepin-2-ones cyclization reaction by Doebner–von Miller quinoline synthesis was estimated using the calculation of an average local ionization energies on molecular surface at the level of Density Functional Theory (DFT).

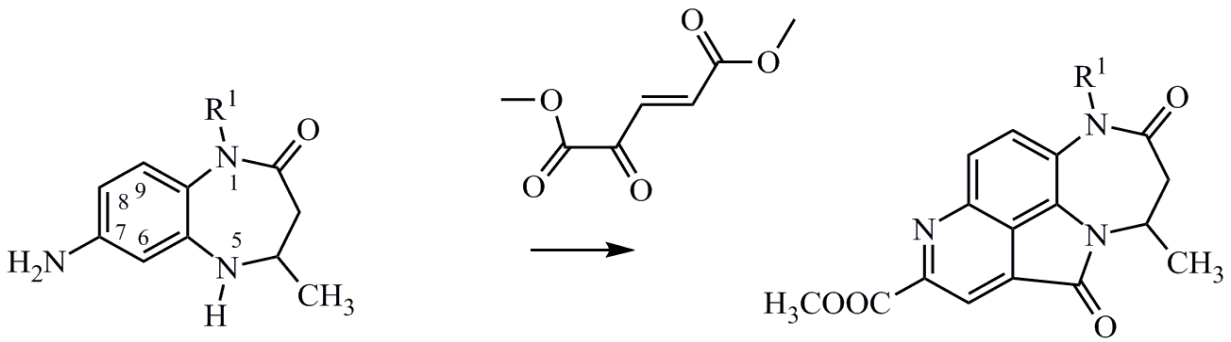
Keywords

Amino-1,5-benzodiazepinones, quinolines, local ionization energy, DFT

Introduction

Benzodiazepines and their polycyclic derivatives are known as medically active synthetic substances [1]. The quinoline ring system derivatives are important as antimalarial agents [2]. In the literature [3] we have described the synthesis of novel annelated heterocyclic systems, bearing 1,5-benzodiazepine as well as quinoline nucleus, from variously N_1 and N_5 substituted amino-1,5-benzodiazepinones employing Doebner–von Miller quinoline synthesis. In this experimental work 7-(or 8 and 9)amino-1-R^1-5-R^2-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a-h** (schemes 1-4) were used as starting amine components to prepare annelated heterocyclic derivatives. The cyclocondensation was accomplished by the reaction of amines **1a-h** with dimethyl-2-oxoglutaconate in a single step. A number of properly substituted tetracyclic 4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole and tricyclic 1*H*-[1,4]diazepino[2,3-*g*](or [2,3-*h*])quinoline derivatives were prepared **2a-c, 3d,e, 4f, 5g** . It was outlined that the structure of obtained cyclization product depends on the position of primary amino group and on the substituents of diazepine ring.

For example 1-alkylsubstituted amines **1a-c** in the reaction with dimethyl-2-oxoglutaconate afforded tetracyclic tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole derivatives **2a-c** (scheme 1). So the pyrido ring closure in 7-aminoderivatives **1a-c** takes place at 6-position of the benzodiazepine moiety.

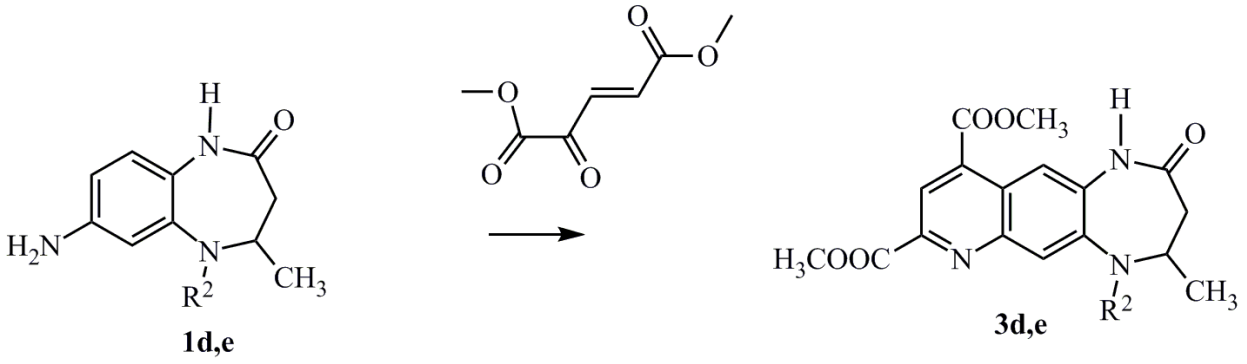


1a-c **2a-c**

R^1= H (a), CH_3 (b), C_3H_7 (c)

Scheme 1.

When 7-amino-5-alkyl-substituted benzodiazepinones **1d,e** were treated with oxoglutaconate (scheme 2) the cyclocondensation proceeds at 8-position of the bicyclic heterocycle and linear tricyclic diazepinoquinolines **3d,e** were obtained.

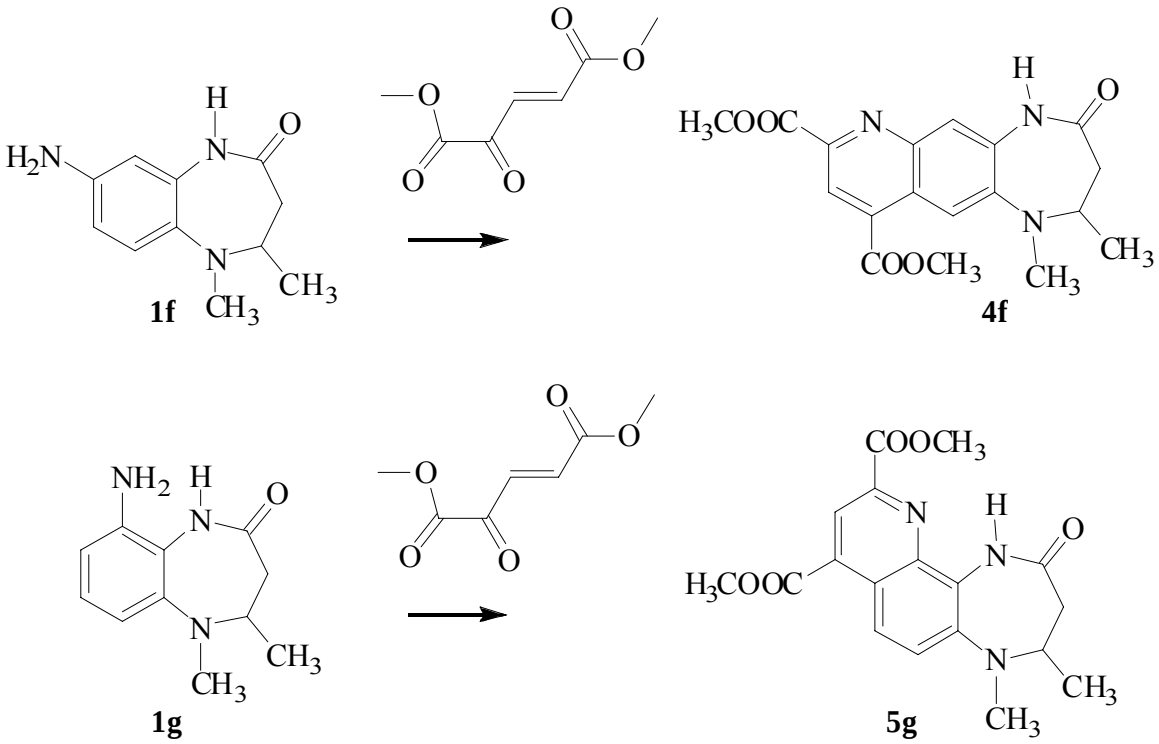


1d,e **3d,e**

R^2 = CH_3 (d), CH_2CF_3 (e)

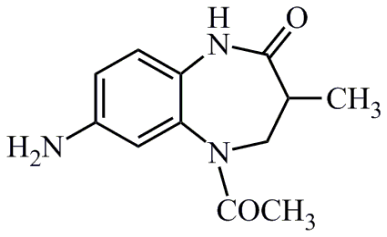
Scheme 2.

Analogously, cyclocondensation of 8(or 9)-aminoderivative **1f,g** with oxoglutaconate (scheme 3) under the same conditions gave linear [1,4]diazepino[2,3-*g*]quinoline **4f** and angular [1,4]diazepino[2,3-*h*]quinoline **5g**, respectively.



Scheme 3.

On the other hand, the reaction of 7-amino-5-acetylsubstituted benzodiazepinone **1h** with oxoglutaconate under parallel reaction conditions did not take place, and the starting N_5-acetylsubstituted amine **1h** was recovered.



1h

Scheme 4.

Moreover the synthetic work presented in [3] evidently pointed out that the formation of new pyrido ring takes place at *ortho*-position according to the primary amine group of the starting compound. However, the regioselectivity features of cyclization reaction for unsymmetricaly substituted aromatic amines remains unpredictable [2,4].

Results and Discussion

So far as we have described [2] the synthesis of novel heterocyclic systems from variously N_1 and N_5 substituted amino-1,5-benzodiazepinones **1a-h** employing Doebner–von Miller quinoline reaction, that leads to the formation of new pyrido ring and takes place at *ortho*-position according to the primary amine group of the starting compound.

In the current work we are presenting the investigation of electronic structure of the starting aminosubstituted benzodiazepinones with the succeeding explanation of regiochemical outcome of the studied cyclization process. The theoretical investigation of electronic structure of the starting variously N_1 and N_5 substituted amino-1,5-benzodiazepinones **1a,b,d.g,h** was executed in order to get more insight into the nature of the studied cyclization process.

The use of a molecular surfaces, based on the molecular electron density has a long tradition in the qualitative interpretation of chemical reactivity [5,6]. The best indicator of electrophilic attraction is provided by the local ionization potential map, an overlaying of the energy of electron removal (ionization) onto the electron density. Sjoberg P. et al and Politzer P. et al introduced the local ionization energy potential (*I(r)*) [7,8], defined as:

$$I(r) = \sum_i \frac{\rho_i(r)|\varepsilon_i|}{\rho(r)}$$

$\rho_i(r)$ is the electron density of the *i*-th molecular orbital (MO), and ε_i is its energy.

Murray J. S. and Politzer P. et al have discussed properties of the local ionization energy in detail and showed that it describes the electron donor properties of the molecule directly [8-10]. Results reported by Clark T. et al suggest that the local ionization energy can represent the visualization of reactivity properties of the aromatic substrate and the regioselectivity of the electrophilic substitution [6]. Also in the same publication it was shown that the absolute reactivity can be judged from the values of the local ionization energy at the π-surface of the aromatic compound. Luo J. reported that the DFT method provides more convenient and accurate way to calculate electron density surfaces and to estimate the ionization energy of a large molecular system than earlier proposed Hartree Fock method [11].

Since we are considering the synthesis of novel polycyclic systems accomplished by Doebner–von Miller quinoline synthesis method, noteworthy to say that cyclization reaction involves a stepwise mechanism and one of the steps is based on electrophilic addition to the aromatic ring [2-4]. This step determinates the regiochemical outcome of the reaction. Hence, our goal was to estimate the mostly reactive aromatic sites for an electrophilic attack. Therefore we used local ionization energy surfaces calculations, and attempted to show its applicability in predicting the most reactive sites and relative reactivities for electrophilic attack in aromatic part of the reactants.

In this study, we have computed *I(r)* for a series of N_1- and N_5-substituted amino-1,5-benzodiazepinones **1a,b,d.g,h**. These results have been discussed here in relation to the experimentally observed reactivity behavior of those molecules [2].

The DFT level of theory with B3LYP functional and 6-311G* basis set has been used to calculate *I(r)* on the three dimension surfaces corresponding to the contour of constant electronic density equal to 0.002 and 0.025 electron/bohr^3 [6,13,14]. In the literature [6,15] it has been shown that those contours give physically reasonable molecular dimensions and reflect molecular features such as bond formation, electron lone pairs, etc. Therefore, those surfaces can be useful to study molecular shape and the interactions of molecules with other molecules. The surface of value 0.002 electron/bohr^3 shows the outer edge of the molecule that is close to van der Waals surface. About 90% of the molecule electron density is inside this surface. The value 0.025 electron/bohr^3 displays a surface that indicates the electron density on the π-electron surface of the aromatic compounds. Our calculation results show that the local ionization potential calculated on the surface defined by the 0.025 electron/bohr^3 contour better permits to predict the direction of most reactive aromatic sites of compounds for an electrophilic attack. Therefore in this article we are presenting calculation results based on 0.025 electron/bohr^3 value surface.

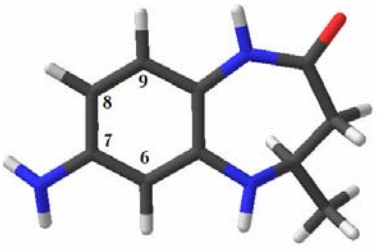
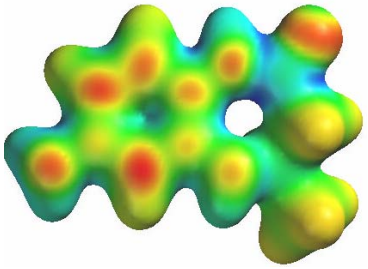
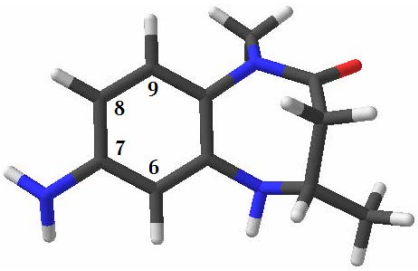
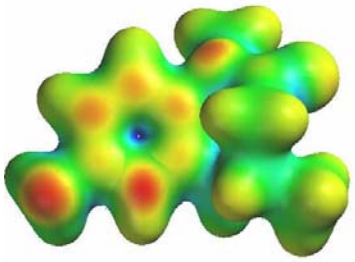
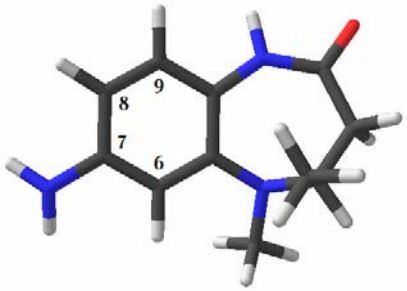
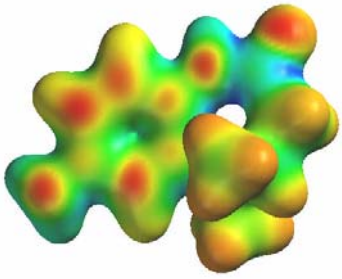
Table 1 presents optimized geometries of **1a,b,d,f,g,h** and shows local ionization energy surface maps *I(r)* plotted on the molecular surface of those heterocycles. The regions with red color represent the locations on the molecular surface where electron removal goes (with minimal energy) most easily. So the lowest average locations on local ionization energy maps *I(r)* are found on *ortho*-positions with respect to the aromatic primary amino group. The smallest *I(r)* values (I_{min}) are also presented in the table 1. I_{min} values are the points at which the least amount of energy is required to remove electron from the surface, thus these sites are expected mostly reactive towards electrophiles.

The lowest average locations of *I(r)* for 7-amino substituted **1a,b** are found on molecular surface over aromatic C_6 and C_8 atom. Furthermore as the I_{min} value is smaller for C_6 position than for C_8 it suggests the greater propensity of ring cyclization at C_6 position. In experiments with 7-aminoderivatives **1a-c** the pyridoring closure was observed at 6-position.

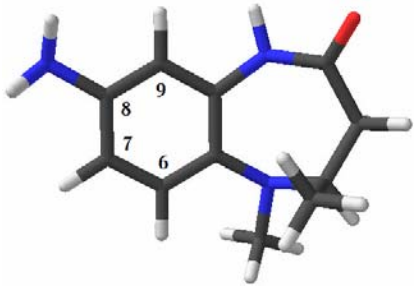
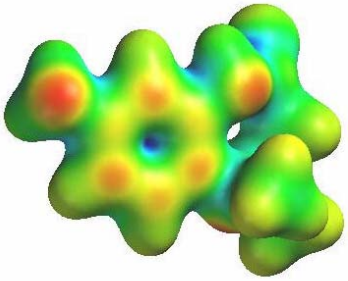
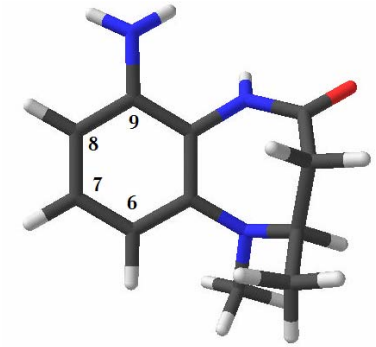
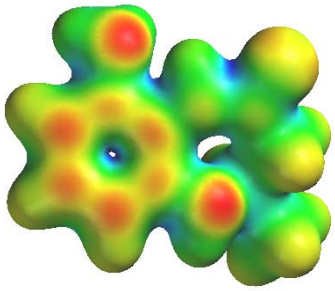
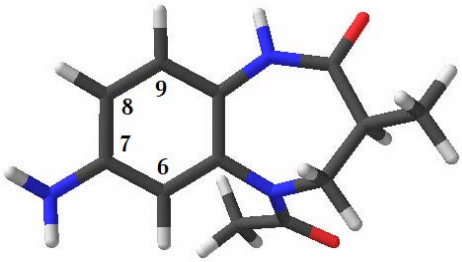
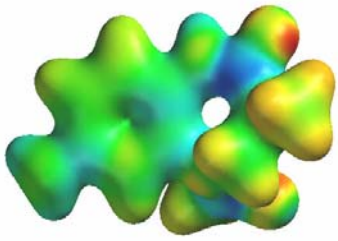
The smallest I_{min} values for 7-amino-5-methylsubstituted **1d** located above the C_8 atom. It shows the C_8-directing ring closure tendencies. Accordingly, experimental cyclocondensation of benzodiazepine **1d** proceeds at 8-position.

In the case of 7-amino-5-acetylsubstituted derivative **1h** the I_{min} values are greater than those of **1a,b,d**. Also the colored molecular surface shape of **1h** shows that aromatic ring is deactivated toward the electrophilic attack. Experimentally, the reaction of amine **1h** with oxoglutaconate did not lead to the cyclized product. These findings reflect the deactivating tendencies of acetyl group in **1h** for pending reaction. While the calculation results for **1a,b,d** compatible with activating effects of N_1- and N_5-alkylsubstituents in diazepine skeleton.

Table 1. Calculated local ionization energy surfaces *I(r)* on the molecular surfaces defined by the contour of constant electron density equal 0.025 electron/bohr^3 and the smallest *I(r)* values (I_{min}) for carbon atoms of aromatic ring and N atom of primary amino group for compounds **1a,b,d,f,g,h**

No	Optimized geometry	Local ionization energy surface *I(r)* (eV) [a]	I_{min} (eV)
1a			N – 15.55 C_6 – 15.53 C_7 – 17.32 C_8 – 16.50 C_9 – 16.55
1b			N – 12.48 C_6 – 13.07 C_7– 15.32 C_8 – 13.89 C_9 –14.25
1d			N – 15.98 C_6 – 16.46 C_7–17.32 C_8 – 16.00 C_9 – 16.30

Continuation of Table 1

No	Optimized geometry	Local ionization energy surface *I(r)* (eV)	I_{min} (eV)
1f			N – 12.48 C^6 – 14.30 C^7 – 13.60 C^8 – 15.30 C^9 – 13.89
1g			N – 12.71 C^6 – 13.67 C^7 – 14.26 C^8 – 13.65 C^9 – 15.65
1h			N – 18.95 C^6 – 18.70 C^7 – 19.14 C^8 – 18.50 C^9 – 19.06

[a] Color ranges for *I(r)*, in eV: from red 11.25 to blue 25.72. B3LYP functional and 6-311G* basis set.

The calculated I_{min} values for 8-aminosubstituted **1f** show that the smallest value located on C_7 carbon are consistent with the tendencies of ring closure at the C_7 position. The same consequence of calculated and experimental results is in accordance for 9-aminoderivative **1g** where the smallest values are located at C_8-position of aromatic ring.

Summarizing, our results suggest that the reaction behavior is governed by the difficulty of electron removal (ionization) from the definite π-electron density surface regions of molecules defined by the contour of constant electron density equal to 0,025 e/bohr^3. In addition, *I(r)* and I_{min} values are indicative for the calculation of relative activating and deactivating tendencies of the aromatic ring in the studied compounds.

Computational details

A conformational search was performed using Molecular Mechanics Force Field to identify the lowest-energy conformer for each structure of N_1- and N_5-substituted amino-1,5-benzodiazepinones **1a,b,d.g,h** [13]. The lowest-energy conformer structures were further optimized using quantum mechanics at the DFT level of theory with B3LYP functional and 6-311G* basis set [14]. This basis set then has been used to calculate *I(r)* on the three dimension surfaces corresponding to the contour of constant electronic density equal to 0.002 and 0.025 electron/bohr^3 [6,13,14].

Acknowledgements

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