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Quantum Chemical Estimation of Reactivity of 2,3,4,5-Tetrahydro-1,5-benzodiazepin-2(1*H*)-ones in Electrophilic Aromatic Substitution

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ABSTRACT: *DFT B3LYP calculation study was employed to estimate the regioselectivity of an electrophilic aromatic substitution in functionalized 2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-ones. Charge density, frontier molecular orbital study, energetics of σ-complex intermediates of electrophilic substitution reactions in the 2,3,4,5-tetrahydro-1,5-benzodiazepin-2(1H)-ones yield information on different reactivity of aromatic sites.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:263–270, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20015

INTRODUCTION

Recent years increasing interest has been directed towards synthesis of functionalized tetrahydro-1,5-(or 1,4)-benzodiazepinones due to their unique biological properties to act as inhibitors of HIV-1 replication [1,2]. Among the diversity of synthetic attempts, the literature provides data closely connected to functionalization reactions of substituted 2,3,4,5-tetrahydro-1,5 (or 1,4)-benzodiazepinones by direct electrophilic substitution of aromatic ring. In most cases described reactions demonstrate different activity of particular benzene carbons toward attacking electrophiles for differently substituted benzodiazepinones [3–8]. Nevertheless, literature provides no data concerning quantum chemical estimation of reactivity of 2,3,4,5-tetrahydro-1,5-benzodiazepinones. Therefore it would be useful to have theoretical approach of quantum chemical estimation of 2,3,4,5-tetrahydro-1,5-benzodiazepinones for initial prediction of most reactive benzene sites. Hence this paper is devoted to examine reactivity of the groups of substituted benzodiazepinones in nitration electrophilic substitution reaction. The investigation of quantum chemical descriptors for this reaction may be useful for experimental chemist in their future synthetic studies.

RESULTS AND DISCUSSION

In this context we concentrate our efforts on reactions described in the literature [9–11] and presented in Scheme 1. It indicates that 7-brominated tetrahydro-1,5-benzodiazepinones bearing variation of substituents at C-3, at C-4, and at N-5 yielded products with different orientation of entering electrophilic nitro group in the nitration electrophilic aromatic substitution reaction.

Experimentally 5-acetyl-7-bromo-2,3,4,5-tetrahydro-1,5-benzodiazepinone **1** and analogous C-3

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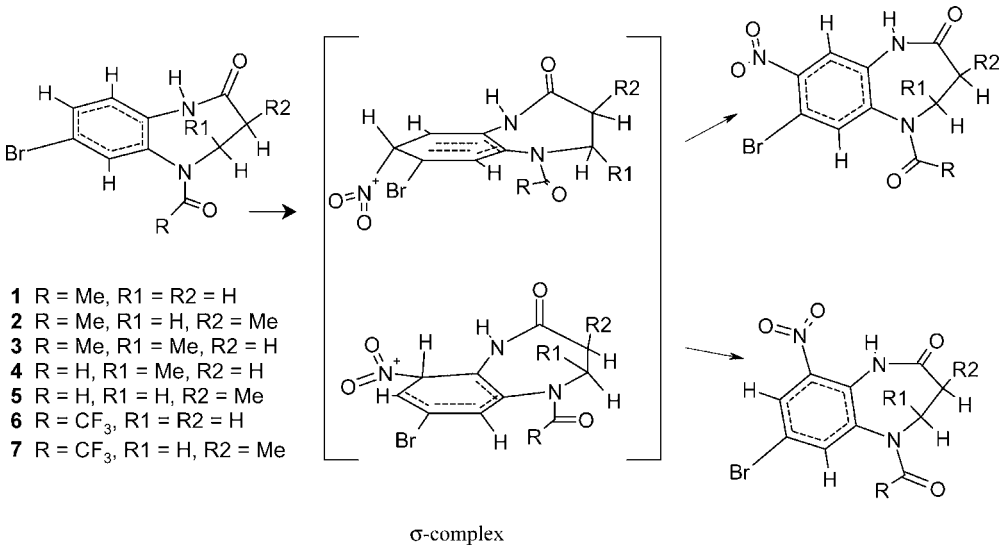


SCHEME 1 Representation of nitration reaction of 7-brominated tetrahydro-1,5-benzodiazepinones **1–7**.

and C-4 methyl substituted 1,5-benzodiazepinones **2** and **3** were nitrated exceptionally in position 9 [9]. Reaction of 5*N*-formyl-benzodiazepinone bearing C-4 methyl substitute **4** with nitration agent lead to the mixture of isomeric 8- and 9-mononitro benzodiazepinones in a ratio nearly to 1:1 [10,11]. While nitration of 5*N*-formylbenzodiazepinone **5** with C-3 methyl substitute, and 5*N*-trifluoroacetyl-benzodiazepinone **6**, and its C-3 methylated analogue **7** in the same fashion afforded the mixture of 8- and 9-mononitro products in a ratio from 1:4 to 1:3 [10,11].

In order to get more insight into nature of the observed regiochemistry we compared experimental data—the ratio of crude nitration reaction products obtained from ^{1}H NMR spectra analysis [9–11] presented in Table 1 with our theoretical study of calculated quantum chemical parameters.

Quantum chemical calculations were carried out to study geometry and electronic structure of starting 7-bromo-2,3,4,5-tetrahydro-1,5-benzodiazepinones **1–7**. In order to foresee observed regioselectivity the lowest energy stationary points along reaction coordinate for electrophilic aromatic substitution reaction of benzodiazepinones **1–7** with NO_2 as attacking electrophile were calculated. These attempts allowed to precisely locate σ-complex intermediates and calculate π-localization energies. Full geometry optimization of starting compounds **1–7** was performed by DFT calculations at the B3LYP/STO-4G level using GAMESS program package [12]. Optimized structures of **1–7** are shown in Fig. 1.

The analysis of obtained conformations for optimized structures **1–7** indicates that the benzene ring together with N-1 and N-5 causes planar conformation for all optimized structures. While remaining diazepine skeleton for tetrahydro-1,5-benzodiazepinones **1–4** and **6** adopts pseudochair conformation with the C-3 or C-4 methyl in axial-position. Optimized structures of tetrahydro-1,5-benzodiazepinones **5** and **7** bearing formyl and

TABLE 1 Difference of π-Localization Energies $\Delta\Lambda^+$, Total Energy of σ-Complex E_σ, and Experimental Data [9–11]—Ratio of Nitrated Products Obtained at C-8 and C-9 Carbon Positions in Crude Reaction Mixtures

	$\Delta\Lambda^+$ *(kcal/mol)*	E_σ *at C-8 (kcal/mol)*	E_σ *at C-9 (kcal/mol)*	*Exp. Data Ratio at C-8 to C-9 Positions*
1	5.057	−2156801.271	−2156806.329	Only at C-9
2	5.153	−2181181.215	−2181186.368	Only at C-9
3	6.075	−2181185.908	−2181191.983	Only at C-9
4	0.223	−2156787.089	−2156787.316	1 to 1
5	3.313	−2156793.911	−2156797.224	1 to 4
6	2.880	−2341555.739	−2341557.619	1 to 3
7	2.412	−2365937.107	−2365939.519	1 to 3

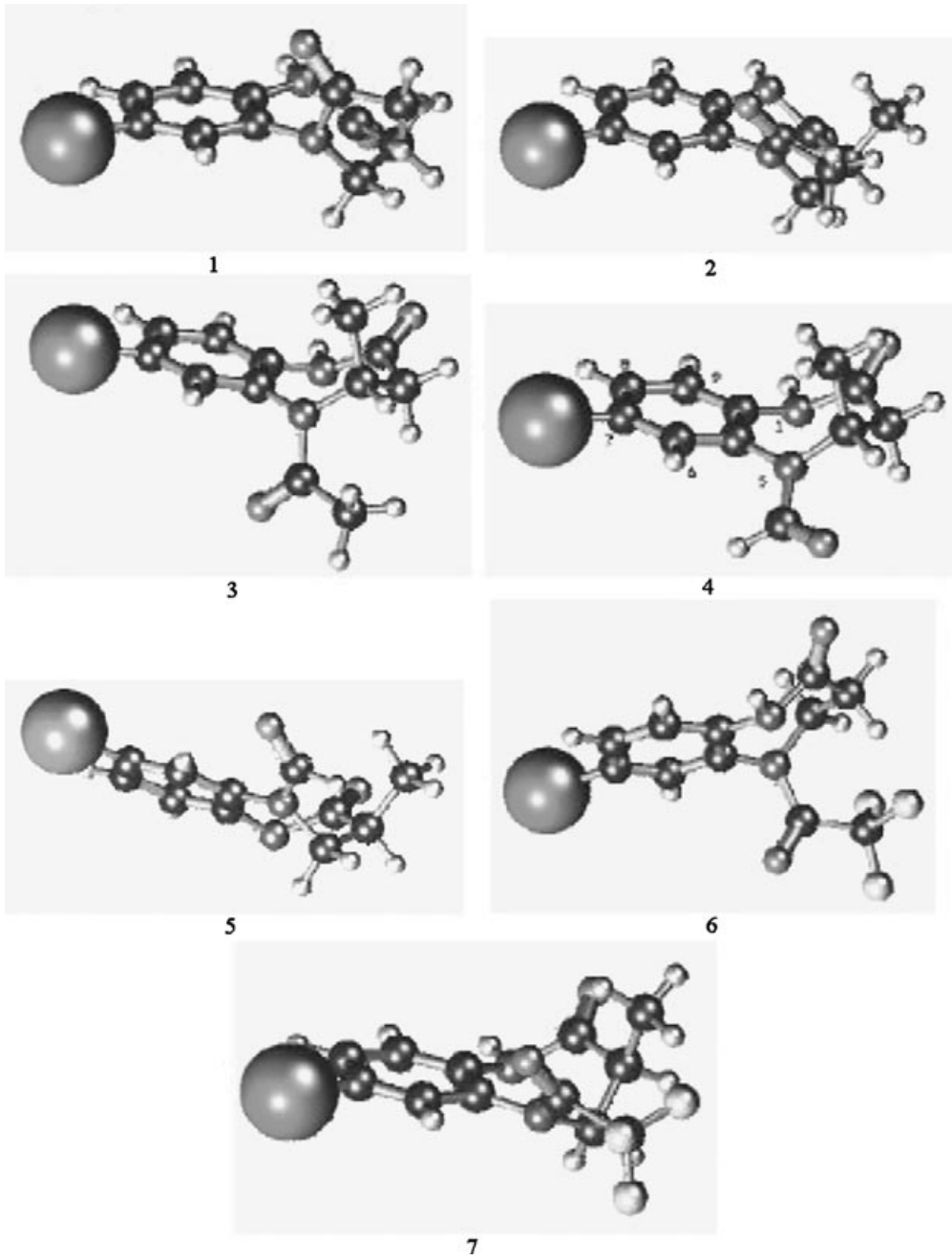


FIGURE 1 Optimized structures of derivatives **1–7**.

trifluoroacetyl groups at N-5 and methyl at C-3 gets twist conformations which are lowest in energy.

The planar conformation of benzene and nitrogen atoms N-1, N-5 on 1,5-benzodiazepinones **1–7** demonstrates that $2p_z$ orbitals of benzene and $2p_z$ lone electron pair orbitals of nitrogens create single system of delocalized π-molecular orbital. It suggests that differences in electronegativity of nitrogen atoms could make high impact on electron density of benzene nucleus. Hereafter, in the electrophilic aromatic substitution reactions, electrophiles attack the electron rich π-cloud of an aromatic system, forming an intermediate σ-complex. Therefore for interpretation of observed regioselectivity we performed the examination of spatial distribution of the highest bonding π molecular orbitals (MO) together with the examination of p_z atomic orbital electron population densities (p_z) for particular C-8 and C-9 atoms of benzene moiety involved in those MOs.

We obtained seven delocalized π bonding MOs that belong to the highest occupied molecular orbitals (HOMOs) for all **1–7** derivatives. In this article we pictured only the most important HOMOs for interpretation of observed regioselectivity. The HOMO-3 consisting of nonbonding orbital of bromine and HOMO-4 containing delocalized orbital on C6=C5 benzene bond and N-5 nitrogen atom are not noted in this article. The MOs spatial distribution, p_z values for C-8 and C-9 atoms, and MO energies of other essential highest π bonding MO are presented in Figs. 2–4. Figure 2 is common for the 5-acetyl substituted benzodiazepines **1–3**, Fig. 3—for 5*N*-formyl substituted **4**, **5**, and Fig. 4—for 5*N*-trifluoroacetyl substituted benzodiazepinones **6, 7** accordingly.

As shown in Figs. 2–4 the energy differences between the corresponding MOs for all benzodiazepines **1–7** are small. All represented highest occupied MOs are formed from out of benzene plane p_z orbitals, which render π aromacity. Among them HOMO-4 and HOMO-5 exhibit aromacity between two rings due to delocalization of π orbitals on benzene carbons and lone pair orbitals of N-1, N-5 nitrogen atoms, or bromine atom. The Figs. 2–4 show that the spatial distributions of corresponding HOMO - HOMO-5 for all represented derivatives **1–7** are similar. The HOMO of all compounds **1–7** is located on aromatic bond C7=C8 and also delocalized between C-9, C-10, and C-11 benzene ring atoms. The p_z electron population densities in HOMO for all derivatives **1–7** are mainly located at C-8 position comparing to that at C-9 atom. The positions of HOMO-1 and HOMO-2 are located on C8=C9 bond for all heterocycles **1–7**. Figures 2–4 show that p_z electron population density in HOMO-1 for all derivatives is mostly located at C-9 carbon comparing to that at C-8 carbon atom, while p_z electron populations in HOMO-2 at C-8 and C-9 are almost equal.

Presented HOMO-5 orbitals are similar for all derivatives **1–7** and consist of two parts. One of them exhibit π-molecular orbital delocalization between C-9 benzene carbon and N-1 nitrogen, while another part is delocalized between C8=C7 aromatic bond and bromine atom. However, the p_z electron population densities of derivatives **1–3** are different from those of derivatives **4–7**. While p_z electron population density in compounds **1–3** is mainly located at C-9 position, for compounds **4–7** that is predominantly located at C-8 atom. On the contrary, the spatial distribution of HOMO-6 is different for the groups of benzodiazepinones **1–7**. For 5*N*-formyl substituted **4, 5** and for 5*N*-trifluoroacetyl substituted benzodiazepinones **6, 7** the HOMO-6 consist from delocalized orbital between p_z lone pair of bromine and π orbital of C-8 benzene carbon, while HOMO-6 for

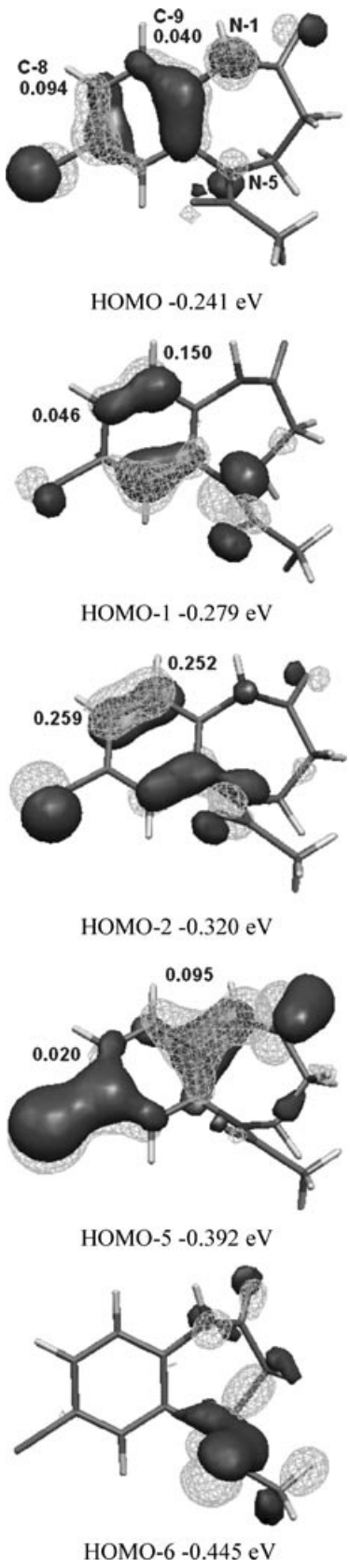
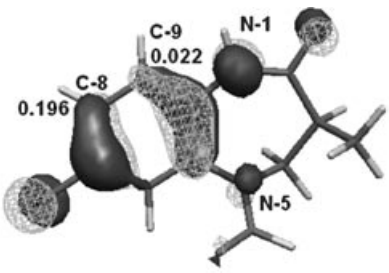
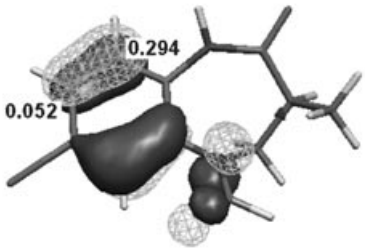


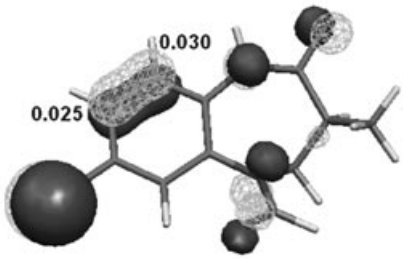
FIGURE 2 Main highest occupied molecular orbitals (HOMOs) of *N*-acetyl substituted benzodiazepinone **1**.



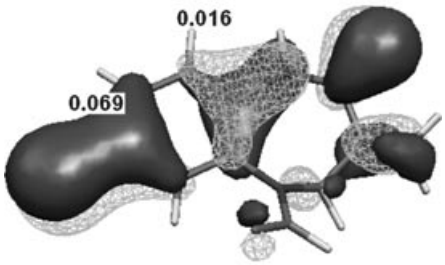
HOMO -0.273 eV



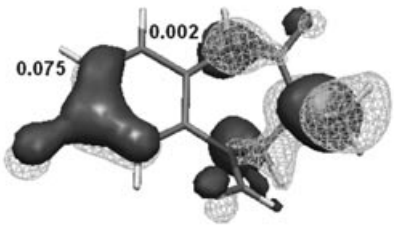
HOMO-1 -0.271 eV



HOMO-2 -0.323 eV

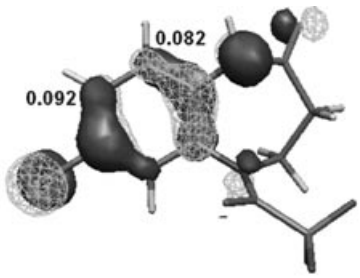


HOMO-5 -0.394 eV

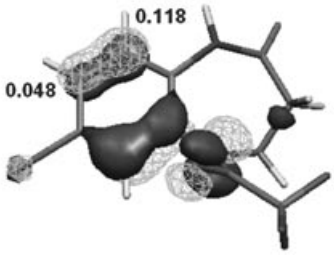


HOMO-6 -0.448 eV

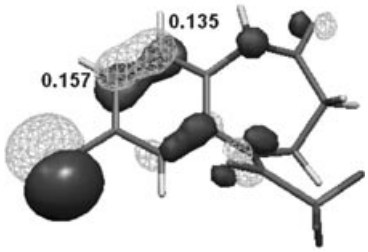
FIGURE 3 Main HOMOs of 5*N*-formyl substituted benzodiazepinone **5**.



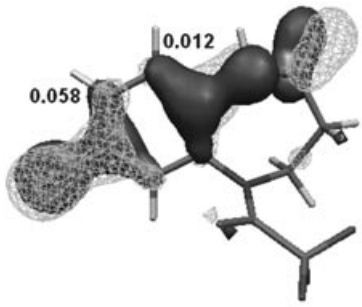
HOMO -0.241 eV



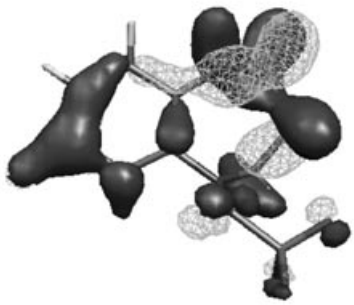
HOMO-1 -0.279 eV



HOMO-2 -0.320 eV



HOMO-5 -0.399 eV



HOMO-6 -0.461 eV

FIGURE 4 Main HOMOs of 5*N*-trifluoroacetyl substituted benzodiazepinone **6**.

5*N*-acetyl substituted heterocycles **1–3** is located on 5*N*-acetyl moiety, as pictured in Fig. 2.

The analysis of MOs presented in Figs. 2–4 suggests that p_z electron populations and positions of all HOMO's influence the regioselective manner of electrophilic substitution reaction for molecules **1–7**. However, estimation of MOs results permits to predict only common tendencies of nitration directions. The electron densities of few top HOMO's are mainly located at C-8 and C-9 carbons of benzene. Likewise, in experiments (see Table 1) the nitration process of all studied compounds took place predominantly at C-9 position, while substitution at C-8 position is also possible. Moreover, for derivatives with formyl and trifluoroacetyl residues **4–7** two π delocalized MOs (HOMO-5, HOMO-6) between bromine and C-8 was obtained, while acetyl substituted heterocycles **1–3** contains only single HOMO-3. Noteworthy to say that the nature of π molecular orbitals (HOMO-5, HOMO-6) delocalization suggests that electron populations on N-1 nitrogen could mostly reflect π electron population densities on C-9, while bromine influence upon electron population densities on C-8 position.

Differences observed in spatial distribution and p_z electron population densities of highest MOs show only common directions of nitration process that is in agreement with experiments but did not explain the regioselectivity of reaction.

Therefore, we used several approaches [14–16] to evaluate difference in the reactivity between 8 and 9 positions of aromatic moiety for the molecules **1–7**. The isolated molecule approach seeks correlation between rates of attack of an electrophilic reagent and the mostly negatively charged or high electron densities centers. The localization energy method employs the changes in π-energy between the aromatic molecule and benzene moiety σ-complex to be compared.

The Mulliken, Lowdin, and net atomic charges (restrained electrostatic potential charges—ESP charges) at B3LYP/STO-4G level were calculated and presented in Table 2 in order to explain experimental reactivity data [9–11] of nitration towards position C-8 and C-9 (Table 1).

The calculated Mulliken charges (results are presented only for C-8, C-9, N-1, and N-5 atoms in Table 2) indicate that for all derivatives the magnitude of negative charge at atom in the aromatic moiety decrease in the following succession: C-7 > C-9 > C-8 > C-6 suggesting that C-9 is possible position for electrophilic attack when C-7 is occupied. Lowdin and ESP charges presented in Table 2 are superior descriptors for predicting of most reactive sites. Calculations indicate the high differences in Lowdin charge distribution of derivatives **1–3** between benzene C-8 and C-9 carbons. The increase of negative charge density at C-9 atom comparing to C-8 site implies that position 9 should be more susceptible for electrophilic attack than position 8. This result correlates with experimentally observed regioselectivity (Table 1) showing exceptional reactivity of C-9 position for derivatives **1–3**. The smaller difference of Lowdin charge distribution between carbons C-8 and C-9 in compounds **5–7** corresponds experimental results of nitration process leading to the mixture of 8- and 9-mononitro products in ratio from 1:4 to 1:3 respectively. The almost equal Lowdin charge parameters for C-8 and C-9 atoms in compound **4** guess both positions to be similarly attractive for electrophiles, while experimentally nitration reaction also result in the formation of both the isomers in a ratio almost equal to 1:1. Obtained behavior for distribution of ESP charges on C-8 and C-9 atoms for **1–7** represents the same tendencies as it was discussed for Lowdin charges. It is worth to notice that substitutes in tetrahydro-1,5-benzodiazepinone skeleton yielded differences in ESP and Lowdin charge density on N-1 and N-5 atoms of **1–7** compounds. In case

TABLE 2 Mulliken, Lowdin, and ESP Charge Densities of Derivatives **1–7**

	Atom Number	*Mulliken Charges*	*Lowdin Charges*	*ESP Charges*
1	C-8	−0.0210	−0.0004	−0.0658
	C-9	−0.0461	−0.0305	−0.2365
	N-1	−0.2762	−0.1647	−0.6766
	N-5	−0.2521	−0.1601	−0.5014
2	C-8	−0.0200	+0.0025	−0.0478
	C-9	−0.0460	−0.0301	−0.2375
	N-1	−0.2763	−0.1663	−0.6328
	N-5	−0.2495	−0.1563	−0.4622
3	C-8	−0.0218	−0.0004	−0.0331
	C-9	−0.0470	−0.0310	−0.2724
	N-1	−0.2763	−0.1643	−0.6744
	N-5	−0.2565	−0.1663	−0.5651
4	C-8	−0.0316	−0.0127	−0.1473
	C-9	−0.0433	−0.0256	−0.1857
	N-1	−0.2781	−0.1695	−0.7165
	N-5	−0.2487	−0.1407	−0.0766
5	C-8	−0.0256	−0.0049	−0.0528
	C-9	−0.0460	−0.0291	−0.2279
	N-1	−0.2737	−0.1623	−0.7619
	N-5	−0.2534	−0.1520	−0.2402
6	C-8	−0.0255	−0.0046	−0.1123
	C-9	−0.0461	−0.0290	−0.1539
	N-1	−0.2737	−0.1643	−0.6823
	N-5	−0.2573	−0.1576	−0.1523
7	C-8	−0.0300	−0.0091	−0.0901
	C-9	−0.0420	−0.0247	−0.1859
	N-1	−0.2793	−0.1671	−0.6849
	N-5	−0.2459	−0.1448	−0.3291

of *N*-acetyl substituted derivatives **1–3** negative ESP and Lowdin charges on N-1 and N-5 nitrogens are almost equal, whereas *N*-formyl and *N*-trifloracetyl substituted 1,5-benzodiazepinones **5–7** exhibit increase of negative ESP charge on N-1 with decrease of ESP charge distribution on N-5. The highest difference in ESP charge distribution between N-1 and N-5 atoms was obtained for derivative **4**.

In order to further estimate the differences in reactivity between position 8 and 9, the π-localization energies for σ-complex with NO_2^+ (the attacking electrophile) were calculated according to the definition given for electrophilic aromatic substitution reaction [16,17]. The total energies E_σ of σ-complexes were located using B3LYP/STO-4G method. These parameters are presented in Table 1 with experimental data taken from the references [9–11]. Calculated differences $\Delta\Lambda^+$ of π-localization energies of σ-complex for NO_2^+ substitution indicates that *N*-acetyl derivatives **1–3** are favored to form σ-complexes at position C-9 instead to that at position C-8 by value $\Delta\Lambda^+ \sim 5.06$–$6.08$ kcal/mol. This result predicts that experimental exceptional reactivity at C-9 position for *N*-acyl 1,5-benzodiazepinones **1–3** confirms theory since substitution at C-8 was not detected. In the case of nitration of *N*-formyl derivative **4** π-localization energies differ only by 0.22 kcal/mol. It correlates with the experiment showing that two mononitro compounds were formed in almost equal ratio. The $\Delta\Lambda^+$ for compounds **5–7** is in the range of 2.41–3.31 kcal/mol. The smaller $\Delta\Lambda^+$ values for compounds **5–7** in comparison with those for **1–3** yielded satisfying correlation with experiments, which confirmed the formation of both possible nitro isomers, though the substitution at C-9 prevailed to form over C-8 (9-nitro isomers predominate in the crude nitration mixtures).

It could be stated that the calculations evidently point out to the suitability of π-localization energy of σ-complex intermediates parameters to predict the regioselectivity of differently substituted tetrahydro-1,5-benzodiazepinones in the electrophilic aromatic substitution. The most reactive benzene sites in electrophilic substitution reaction of heterocycles **1–7** could be rather well explained using Lowdin and ESP charges. Obtained results are in agreement with experiment.

Summarizing we can note that spatial distribution and p_z electron population on the highest MOs show common directions of nitration process at particular C-8 and C-9 benzene atoms of 1,5-benzodiazepinones **1–7** but could not directly explain the regioselectivity of the reaction. Nevertheless the π molecular orbital delocalization analysis for differently substituted tetrahydro-1,5-benzodiazepinones suggests that electronegativity effects and electron density differences on N-1 and partially on N-5 nitrogens could mostly reflect π cloud electron densities at C-9, while electron densities of bromine atom influence upon electron population densities at C-8 position. Otherwise, the π electron cloud on MOs affected the distinction in Lowdin and ESP charge densities on N-1 and N-5 atoms and successive differences of charge distribution on particular benzene nucleus for diverse of substituted diazepinones. Presumably, this may explain the distinct contribution of nitrogen and bromine atoms for the stability of σ-complex and the orientation of entering electrophiles by substitution reaction of aromatic moiety.

EXPERIMENTAL

All calculations were carried out using the GAMESS program package [12]. The stationary points were checked by a frequency analysis. The full geometry optimizations of derivatives **1–7** were carried out at the B3LYP/STO-4G level. The σ-complex intermediates were located using the same level of theory. π-localization energies of σ-complex intermediates were calculated in accordance with definition given in the references [16,17]. Visualization of optimized results was performed with ViewMol3D program [18] and MOLEKEL [19].

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