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COMPUTATIONAL STUDY FOR THE SELECTIVE AROMATIC NUCLEOPHILIC SUBSTITUTION ON 4-DIMETHYLAMINO-2-METHOXY-3-TRIFLUOROACETYLQUINOLINE

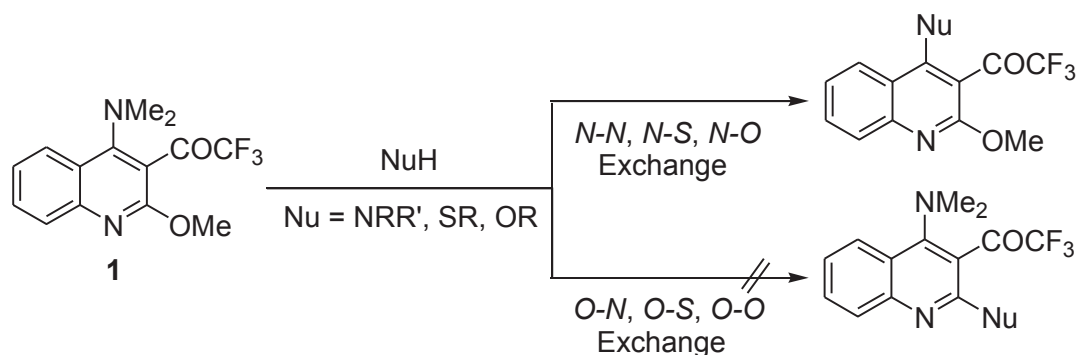
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Abstract – The selective nucleophilic substitution on aromatic ring occurs at the 4-position of 4-dimethylamino-2-methoxy-3-trifluoroacetylquinoline **1** by the reaction with various amines to afford the *N-N* exchanged products solely, and any *O-N* exchange reactions at the 2-position are not performed. Our DFT calculation study led to a rational explanation of this unique selectivity based on the frontier electron densities (LUMO) of **1** and energies of the Meisenheimer complexes which were assumed to be formed as the intermediates on such substitution course. It was also investigated about the reaction of related 4-dimethylamino-2-methoxyquinolines bearing various electron-withdrawing groups at the 3-position.

INTRODUCTION

In the last few decades, a lot of approaches have been taken on the exploration of synthetic methodologies for novel kinds of fluorine-containing heterocycles since their potential biological activity might be often focused as unique active ingredients in the various areas of life science research.¹⁻⁴ In recent years, we have proposed the convenient synthetic methods successfully accessing novel fluorine-containing 4-methoxypyrazolo[4,3-*c*]quinolines,⁵ 6-methoxy-1,4-diazepino[6,5-*c*]quinolines,⁵ 5-methoxypyrimido[5,4-*c*]quinolines,⁶ 5-methoxybenzo[*h*][1,6]naphthyridines,⁶ 6-methoxydibenzo[*b,h*][1,6]naphthyridines,⁷ and 6-methoxythiochromeno[3,2-*c*]quinolines.⁷ The key reaction in common for these synthetic process is a highly selective aromatic nucleophilic substitution of 4-dimethylamino moiety of trifluoroacetylated quinoline **1** with appropriate nucleophiles (Nu) (Scheme 1).^{7,8} At the 4-position occurs the aromatic nucleophilic substitution of **1** with various *N*-nucleophiles to afford the *N-N* exchanged products solely, while any *O-N* exchange reaction at the 2-position was not performed.⁸ In this work, DFT calculation



Scheme 1

(RB3LYP/6-31G*) study was examined for the reaction of **1** with *n*-butylamine as a representative model to find out an interesting outcome rationalizing the excellent selectivity on the present substitution of **1**. And, the influence by the 3-substituent on each ring was also discussed on analogous 4-dimethylamino-2-methoxyquinolines having 3-acetyl, 3-benzoyl, 3-cyano, and 3-nitro group instead of 3-trifluoroacetyl group.

RESULTS AND DISCUSSION

We started to clarify the relative reactivity of 2- and 4-position of trifluoroacetylated quinoline **1** with nucleophiles, which was the key substrate of the present aromatic nucleophilic substitution. At first, it was examined by evaluating the frontier electron densities (f_i) on LUMO of **1**. Figure 1 shows the computational optimized structure of **1** and its energy. Frontier and near frontier orbitals of **1**, LUMO, 2nd LUMO, and 3rd LUMO are depicted in Figure 2. Frontier electron densities on LUMO (f_i^{LUMO}) for 2- and 4-position of **1** are also indicated in Figure 1 together with the corresponding values on

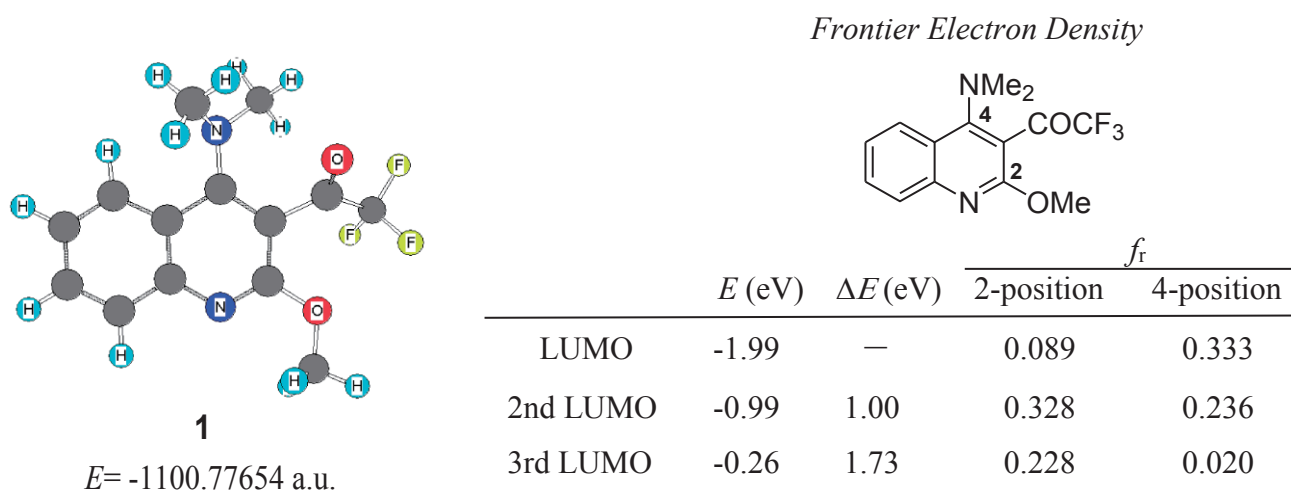


Figure 1

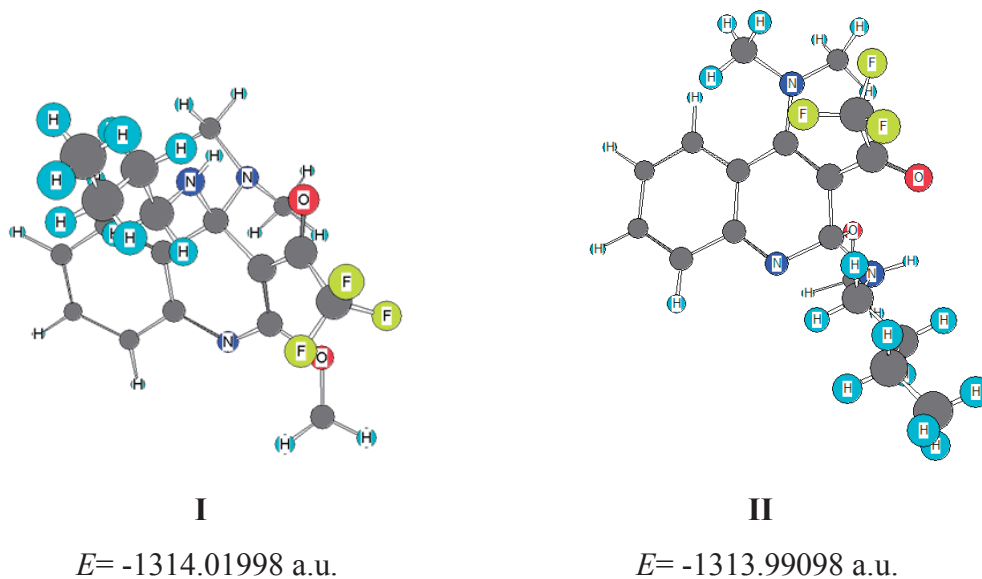


Figure 3

intermediate **I** gets preference over the route having the attack at the 2-position of **1** (*Step 1B*) affording **II**. On the other hand, 9.4 kcal/mol more energy was needed for the elimination step from **I** to the 4-substituted product **2** (*Step 2A*) compared with the course to 2-substituted product **3** via **II** (*Step 2B*). Energy diagrams of the present two substitution courses are depicted in Figure 4.

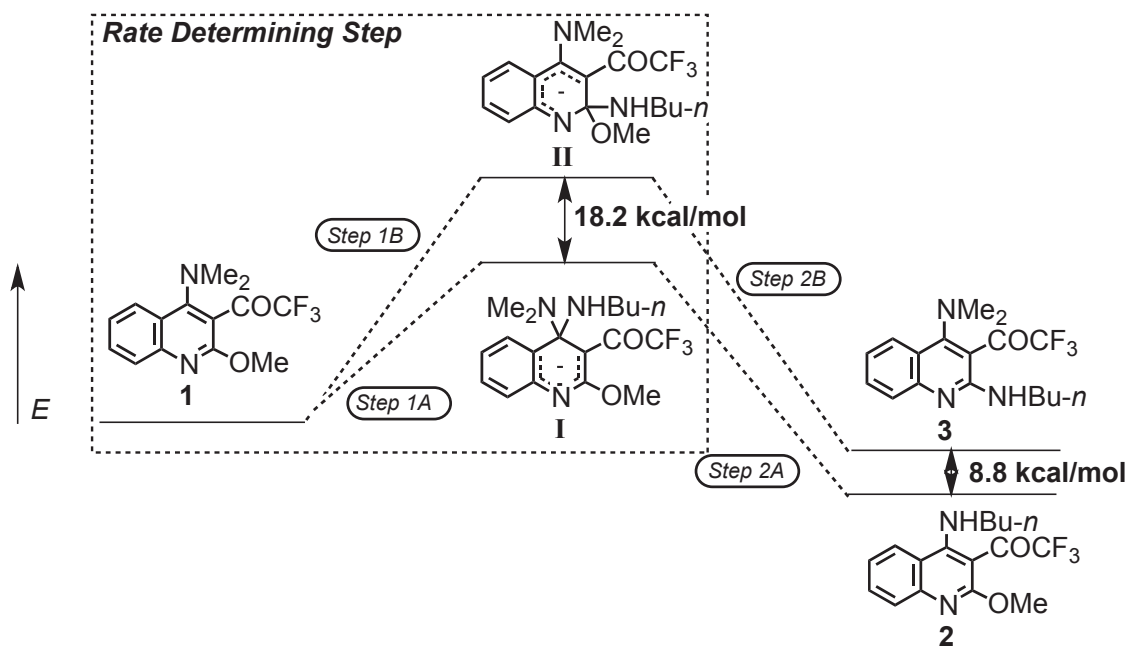


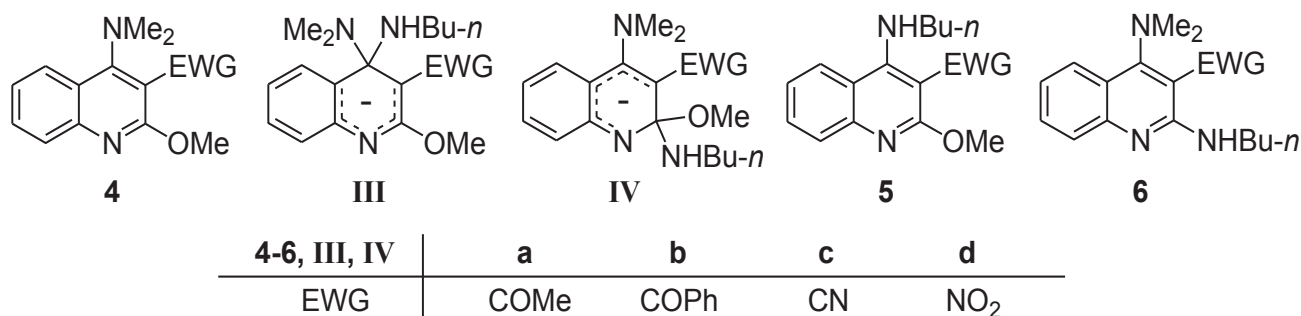
Figure 4

The rate determining steps of these substitution should be the former addition steps (*Steps 1A* and *1B*) giving the adducts **I** and **II** in which the aromatic pyridine-ring systems are destroyed. Even though

taking the subsequent elimination steps (*Steps 2A* and *2B*) into account, *N-N* exchange reaction at the 4-position accessing **2** via **I** is totally 8.8 kcal/mol more advantageous than *N-O* exchange reaction at the 2-position giving **3** via **II**.¹⁰

Consequently, the highly selective nucleophilic substitution of **1** at the 4-position is rationally explained by both frontier electron densities of the substrate **1** and the energy profiles on the whole substitution processes in Scheme 2.

We successively investigated the electron-withdrawing effect of the 3-substituent on this nucleophilic substitution (Scheme 3). It was performed on the reactions of 3-acetyl- and 3-benzoylquinolines, **4a,b**, with *n*-butylamine, which have more poor electron-withdrawing carbonyl substituents than trifluoroacetyl group. Additionally, we carried out calculations for the analogous reaction of 3-cyano- and 3-nitroquinolines, **4c,d**, which have other kinds of strong electron-withdrawing groups instead of trifluoroacetyl group. No experimental report about such type of nucleophilic substitution on **4a-d** has ever been known.



Scheme 3

The Table 1 shows frontier electron densities of LUMO (f_r^{LUMO}) and 2nd LUMO ($f_r^{2\text{nd LUMO}}$) at 2- and 4-position of quinolines **4a-d**, together with 3-trifluoroacetylquinoline **1** as a comparison. In all cases of **4a-d**, the values of f_r^{LUMO} at the 4-position is larger than the one at the 2-position respectively. It becomes to the prediction of predominant reactions at the 4-position as for these nucleophilic substitutions of **4a-d** according to these computed values.

The both 4-positions of acetylquinoline **4a** and cyanoquinoline **4c** have larger f_r^{LUMO} than the one of trifluoroacetylquinoline **1**. In contrast, **4a** and **4c** have much larger values than **1** as to the $f_r^{2\text{nd LUMO}}$ at the 2-positions. In addition, the 4-positions of **4a** and **4c** have very small $f_r^{2\text{nd LUMO}}$ less than 0.1 whereas the corresponding value at the 4-position of **1** is considerably large and comparable to the value of its 2-position. At the same time, benzoylquinoline **4b** and nitroquinoline **4d** have smaller f_r^{LUMO} of the 4-position compared with **1**, while $f_r^{2\text{nd LUMO}}$ at the same position of **4b** and **4d** are larger than the one of **1**.

As to the selectivity at the 4-position of **1**, it could not be accomplished by a simple comparison of these frontier electron densities between **1** and **4a-d**.

Table 1. Frontier electron densities f_r^{LUMO} and $f_r^{2\text{nd LUMO}}$ on quinolines **1** and **4a-d**

Compound	EWG	Orbital	E (eV)	ΔE^{a} (eV)	f_r	
					2-position	4-position
1	COCF ₃	LUMO	-1.99	1.00	0.089	0.333
		2nd LUMO	-0.99		0.328	0.236
4a	COMe	LUMO	-1.52	0.98	0.025	0.420
		2nd LUMO	-0.54		0.467	0.083
4b	COPh	LUMO	-1.59	0.49	0.101	0.132
		2nd LUMO	-1.10		0.091	0.424
4c	CN	LUMO	-1.96	1.24	0.006	0.519
		2nd LUMO	-0.72		0.523	0.030
4d	NO ₂	LUMO	-2.12	0.86	0.093	0.283
		2nd LUMO	-1.26		0.208	0.311

a) $\Delta E = (E \text{ of 2nd LUMO}) - (E \text{ of LUMO})$

Then, we computed energies of Meisenheimer complexes **IIIa-d** and **IVa-d**, which are summarized in Table 2 together with the corresponding trifluoroacetyl derivatives **I** and **II**. In all cases, Meisenheimer complexes **III** (the 4-position adducts giving the *N-N* exchange products **5**) are more stable than the other form **IV** (the 2-position adducts affording the *N-O* exchange products **6**). As a consequent, it gives preference to the nucleophilic substitutions at the 4-position over the same kind reactions at the 2-position on the route of **4a-d** to give the corresponding *Me*₂*N* - *n-BuNH* exchanged products **5a-d** selectively.

Table 2. Energies of Meisenheimer complexes **I**, **II**, **IIIa-d**, and **IVa-d**

Substrate	EWG	Energy of Meisenheimer Complex				Energy Difference ΔE^{2-4} (kcal/ mol) ^a
			E^4 (au)		E^2 (au)	
1	COCF ₃	I	-1314.01998	II	-1313.99098	18.2
4a	COMe	IIIa	-1016.29815	IVa	-1016.27264	16.0
4b	COPh	IIIb	-1208.03622	IVb	-1208.01026	16.3
4c	CN	IIIc	-955.89362	IVc	-955.88274	6.8
4d	NO ₂	III d	-1068.15768	IV d	-1068.13644	13.3

a) $\Delta E^{2-4} = E^2 - E^4$

The energy differences (ΔE^{2-4}) between **IIIa-d** and **IVa-d** are smaller than the one between **I** and **II**. Therefore, it is considered to provide poor selectivity for the reaction of quinolines **4a-d** to afford the corresponding *N-N* exchanged products **5a-d** compared with the reaction of trifluoroacetylquinoline **1** giving **2**. In addition, ΔE^{2-4} between **IIIc** and **IVc** derived from cyanoquinoline **4c** suggested the poorest selectivity on the substitution of **4c** due to the least ΔE^{2-4} value. The value of ΔE^{2-4} is increased in the order of trifluoroacetylquinoline **1** > acylquinolines **4a,b** > nitroquinoline **4d** > cyanoquinoline **4c**. The results suggest a selectivity for the substitution at the 4-position of these quinolines which is enhanced corresponding to this order.

In conclusion, an exclusive formation of the *N-N* exchanged products by selective nucleophilic substitution at the 4-position of 3-trifluoroacetylquinoline **1** with amines was rationally explained by our DFT calculation results. The high selectivity on this nucleophilic substitution at the 4-position of **1** was figured out by two factors. The first reason is much higher frontier electron density (LUMO) at the 4-position than the one at the 2-position on **1**. The comparison of energy difference gave the second reason that the Meisenheimer complexes **I** resulted by the attack of amines at the 4-position of **1**, which is assumed to be formed on the reaction course, is relatively more stable than the intermediates such as **II**. Our calculation results also suggested that the nucleophilic substitution with amines occurred selectively at the 4-position of acetyl-, benzoyl-, cyano-, and nitroquinolines **4a-d**. However, the selectivity on these quinolines was estimated to be inferior to the similar reactions of trifluoroacetylquinoline **1**.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 02 and PC SPARTAN 04.¹¹ For geometrical optimizations, it was performed with the 6-31G* basis set at B3LYP¹² level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL¹³ force field and subsequent semi-empirical PM3¹⁴ optimizations. The calculations for geometries of intermediates and their energies were also taken with the 6-31G* basis set at B3LYP level.

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9. 1 a.u. = 627.5 kcal/mol
10. Energy changes for *Steps 2A* and *2B* were calculated on the basis of the following equations.
$$\mathbf{1} + 2 n\text{-BuNH}_2 \longrightarrow \mathbf{I} + n\text{-BuNH}_3^+ \quad (\text{Step 1A})$$
$$\mathbf{I} + n\text{-BuNH}_3^+ \longrightarrow \mathbf{2} + \text{Me}_2\text{NH} + n\text{-BuNH}_2 \quad (\text{Step 2A})$$
$$\mathbf{1} + 2 n\text{-BuNH}_2 \longrightarrow \mathbf{II} + n\text{-BuNH}_3^+ \quad (\text{Step 1B})$$
$$\mathbf{II} + n\text{-BuNH}_3^+ \longrightarrow \mathbf{3} + \text{MeOH} + n\text{-BuNH}_2 \quad (\text{Step 2B})$$
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