Computational Study for the Aromatic Nucleophilic Substitution of 4-Dimethylamino-3-Trifluoroacetylquinoline with Various Nucleophiles

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Abstract – The aromatic nucleophilic substitutions of 4-dimethylamino-3-trifluoroacetylquinoline 1 with amines, thiols, and alcohols are elucidated on the basis of DFT calculations. Our calculation results suggest that the reaction of 1 with amines giving N-N exchanged products 4 occurs via Meisenheimer type adducts V whereas the ones with thiols and alcohols proceed via the enol type adducts VII and IX to afford N-S and N-O exchanged products 8 and 9, respectively. It is also clarified that the conditions required for the successful substitution are not controlled by the activation energies on these processes, but by the energy changes on the processes from 1 to each intermediates, V, VII, and IX.

Introduction

A number of researchers have engaged in exploring synthetic methodologies for novel kinds of fluorine-containing heterocycles because of their attractive character which often demonstrates high and unique biological activity in the field of life science research. In recent years, we have succeeded in establishing the convenient synthetic methods which enable us to access novel fluorine-containing dibenzo[b,h][1,6]naphthyridines, thiochromeno[3,2-c]quinolines, and chromeno[3,2-c]quinolines via 4-dimethylamino-3-trifluoroacetylquinoline 1 as a synthetic intermediate. We also reported novel synthesis of 1H- and 2H-pyrazolo[4,3-c]quinolines, isoxazoloquinolines, 4-diazepino[6,5-c]quinolines, pyrimido[5,4-c]quinolines, and benzo[h][1,6]naphthyridines using the reaction of 1 with bifunctional nucleophiles. The key step on the above studies is a unique aromatic nucleophilic substitution of 4-dimethylamino moiety of trifluoroacetylated quinoline 1 with N-, S-, and O-nucleophiles (Scheme 1). Previously, we reported highly selective nucleophilic substitutions on
4-(dimethylamino)-2-methoxy-3-(trifluoroacetyl)quinoline 2 giving 3\textsuperscript{9,10} together with some computational studies on their reaction course.\textsuperscript{11-13} Here we wish to describe the DFT calculation (RB3LYP/6-31G*) study on the reaction of 1 as the more simplified substrate than 2 bearing electron donative methoxy group at the 2-position in order to elucidate the essential reactivity of 3-trifluoroacetylquinoline system with various nucleophiles.

![Scheme 1](image)

**RESULTS AND DISCUSSION**

1. **REACTION WITH AMINES**

In our previous work,\textsuperscript{11} we proposed Meisenheimer complex I' as the most reasonable intermediate for the nucleophilic substitution of quinoline 2 with amines giving 5. Similarly, the reaction course via Meisenheimer complex I is also one of the most rational pathways for the nucleophilic N-N exchange reaction affording 4.

![Scheme 2](image)

Meanwhile, in Scheme 3 were suggested adducts, II and III, as the intermediates on the reactions of 2 with thiols and alcohols affording the corresponding N-S and N-O exchanged products, 6 and 7\textsuperscript{12,13}. In this work, the reaction path from 1 to 4 via intermediate IV was also examined. All calculations in this section are performed under the assumption using acetonitrile medium which used in the previously reported experiments for the N-N exchanged reaction from 1 to 4.\textsuperscript{8}
Scheme 3

The energy of geometrically optimized Meisenheimer complex I (R= n-Bu) is indicated in Figure 1. Definitely I has an intramolecular hydrogen bond between amino proton and carbonyl oxygen in 3-trifluoroacetyl group, and the computed result has revealed the values of distance and Mulliken bond orders (in parentheses) concerning this hydrogen boning. Like the case of 2-methoxy derivative I,\textsuperscript{12} a hydrogen bond has contributed to stabilize this complex I. In contrast to the case of I, our calculation study has suggested that the structure of IV is irrationalistic form, and it was given Meisenheimer type intermediate V as a preferable structure by the geometrical optimization process for IV. Figure 1 also indicates the steric structure and the energy of V. This intermediate V is corresponding to the proton adduct of I, and also carries the intramolecular hydrogen bond between amino proton and carbonyl oxygen. It is found that its Mulliken bond orders (in parentheses) is much more than the corresponding value of I. Such enhanced hydrogen bonding has favorable effect upon stabilizing the form of V.

\[ E = -1200.02246 \text{ a.u.} \]

The energy changes from 1 to I (\( \Delta E1 \)) and 1 to V (\( \Delta E2 \)) are calculated based on the following eq. (1) and eq. (2), respectively.
In the case of the reaction with \( n \)-butylamine (\( R = \text{n-Bu} \)) in acetonitrile, \( \Delta E_2 \) (8.5 kcal/mol) is calculated as 6.2 kcal/mol less than \( \Delta E_1 \) (14.7 kcal/mol).\(^{14}\) Even though both processes may be sufficiently possible at ambient temperature (reported experimental conditions)\(^{8}\), \( N \)-\( N \) exchanged product 4 is assumed to be given predominantly by elimination of methyamine from the intermediate V.

Next, we tried to pursue the transition state \( \text{TS}_{N-N} \) for the process from 1 to V (eq. (2)). As depicted in Figure 2, our calculation has resulted in the exhibited steric structure and the energy of \( \text{TS}_{N-N} \) (\( R = \text{n-Bu} \)).\(^{15}\) Some important bonds are also listed with the atomic distances and Mulliken bond orders. The bond order (0.087) on \( H^b \)-\( O^c \) suggests the presence of weak interaction between \( H^b \) and \( O^c \). Such hydrogen bond would contribute to stabilize \( \text{TS}_{N-N} \) similar to the case of intermediate V. On the basis of the energy value of \( \text{TS}_{N-N} \) on the process of eq. (2) is estimated activation energy \( E_a \) (\( R = \text{n-Bu} \)) as 16.8 kcal/mol. Quite similarly, it is calculated to be 16.3 kcal/mol for \( E_a \) (\( R = \text{Me} \)) on the reaction of 1 with methylamine. These \( E_a \) values no more than 17 kcal/mol suggest that the process of eq. (2) which is the
rate determining step of the \( N-N \) exchange reaction from 1 to 4 proceeds sufficiently at an ambient temperature in both cases of the reaction with methylamine and \( n \)-butylamine. These results are consistent with their previous experimental study.\(^8\)

2. REACTION WITH THIOLS

As for the \( N-S \) exchange reaction of 1 with \( n \)-butanethiol giving 8 (R= \( n \)-Bu) as a tentative case, there can be two plausible reaction pathways via Meisenheimer complex VI (Path A) and intermediate VII (Path B) (Scheme 4). Therefore, we started to simulate the both routes computationally. All calculation results in this section are afforded under butyronitrile medium condition which is adopted as a solvent for this \( N-S \) exchange.\(^8\)

Energy values of geometrically optimized two intermediates VI and VII are indicated in Figure 3.

Energy change \( \Delta E3 \) from 1 to VI (Path A) is calculated to be 59.2 kcal/mol\(^{14}\) which is deemed too large to undergo the reaction from 1 to 8 under the reported experimental conditions (100 °C).\(^8\) In contrast, \( \Delta E4 \) from 1 to VII (Path B) is mere 11.0 kcal/mol. These results strongly suggest that the reaction of 1 with S-nucleophile progresses to the formation of 8 proceeds via intermediate VII. This VII has a hydrogen bond between amino nitrogen and hydroxyl proton of which bond length and Mulliken bond

\[ \begin{align*}
\text{VI} & \quad E = -1542.39941 \text{ a.u.} \\
\text{VII} & \quad E = -1542.88287 \text{ a.u.}
\end{align*} \]
order (in parentheses) are also put up in Figure 3.

Our calculation indicated that it was impossible to form adduct VII’, suggesting concerted formation of VII from 1 and n-butanethiol but not stepwise formation of VII via VII’ (Figure 4). This concerted process has been also supported by analysis of the transition state from 1 to VII. In Figure 4 is depicted estimated transition state TS_{N-S} together with its energy, and it is tabulated important atomic distances and Mulliken bond orders. The structure of TS_{N-S} clearly indicates the concerted process from 1 to VII.

![Image of TS_{N-S}](image)

**Table 1**

<table>
<thead>
<tr>
<th>Atomic distance (Å)</th>
<th>Mulliken bond order</th>
</tr>
</thead>
<tbody>
<tr>
<td>S^a-C^4</td>
<td>2.34</td>
</tr>
<tr>
<td>S^a-H^b</td>
<td>1.91</td>
</tr>
<tr>
<td>H^b-O^c</td>
<td>1.04</td>
</tr>
<tr>
<td>O^c-C^d</td>
<td>1.32</td>
</tr>
<tr>
<td>C^3-C^d</td>
<td>1.37</td>
</tr>
<tr>
<td>C^3-C^d</td>
<td>1.51</td>
</tr>
</tbody>
</table>

**Figure 4**

Based on the energy value of TS_{N-S}, activation energy E_a of the process from 1 to VII is estimated to be 29.5 kcal/mol, which is compatible with the experimental fact that the N-S exchange reaction of 1 with n-butanethiol should be performed at 100 °C for reaction completion.

3. REACTION WITH ALCOHOLS

For computationally explaining the reaction of 1 with n-butanol as a representative case, we have examined two plausible pathways from 1 to N-O exchange product 9 (R= n-Bu) via Meisenheimer complex VIII (Path E) and intermediate IX (Path F) (Scheme 5). All calculation results in this section are afforded under the p-xylene medium condition which is adopted as a solvent for this N-O exchange by referring to our previous study. Energy values of geometrically optimized two intermediates VIII and IX are indicated in Figure 5.
Similar to the case of the N-S exchange reaction (Scheme 4), energy change $\Delta E_5$ from 1 to Meisenheimer complex VIII is calculated as 78.8 kcal/mol.\textsuperscript{14} This value is too large to undergo the reaction from 1 to 9 in refluxing $p$-xylene.\textsuperscript{8} In contrast, the route via IX is rather suitable pathway suggested by its reaction conditions since $\Delta E_6$ from 1 to IX is calculated to be 11.7 kcal/mol. The optimized structure of IX is also depicted in Figure 5. This intermediate IX has an intramolecular hydrogen bonding between $n$-butoxy oxygen and hydroxy proton. In this Figure 5 also put up the bond length and Mulliken bond order (in parentheses) of this hydrogen bond.

Our calculation also indicated that the structure of adduct IX$^*$ is impossible to be formed suggesting the concerted formation of IX from 1 and $n$-butanol as the case of the formation of intermediate VII from 1 and $n$-butanethiol (Figure 6). In Figure 6 is depicted the estimated transition state structure $\text{TS}_{N-O}$ for the present concerted reaction of 1 with $n$-butanol giving IX.\textsuperscript{15} The energy and the atomic distances as well as Mulliken bond orders concerning the reaction centers on $\text{TS}_{N-O}$ are also indicated in this Figure.
The activation energy $E_a$ of the process from 1 to IX is estimated to be 25.0 kcal/mol on the basis of the energy value of TS$_{N-O}$. It is consistent with the experimental fact that the $N$-$O$ exchange reaction of 1 with $n$-butanol proceeds in refluxing $p$-xylene to give 9 successfully.8

4. COMPARISON OF THE REACTIONS OF 1 WITH VARIOUS NUCLEOPHILES

Table 1 shows a summary of the present calculation results for the reactions of quinoline 1 with amines, thiols, and alcohols together with the corresponding experimental results previously reported.8 As shown in the Table, required experimental conditions for successful substitution reactions are enhanced in the order of $N$-$O$ exchange > $N$-$S$ exchange > $N$-$N$ exchange. Similarly, the energy changes $\Delta E$ from 1 to the corresponding intermediates IX ($\Delta E6$), VII ($\Delta E4$), and V ($\Delta E2$) are increased in the order of $\Delta E6$ ($N$-$O$ exchange) > $\Delta E4$ ($N$-$S$ exchange) > $\Delta E2$ ($N$-$N$ exchange). Temperatures required for the substitutions of 1 with the nucleophiles are consistent with each values of the energy changes $\Delta E$ from 1 to the corresponding intermediates IX, VII, and V. In contrast, activation energy $E_a$ of the process from 1 to IX ($N$-$O$ exchange) is less than the one from 1 to VII ($N$-$S$ exchange) whereas $N$-$O$ exchange requires higher temperature than $N$-$S$ exchange. These results suggest that the reactivity of 1 toward amines, thiols, and alcohols on the reactions from 1 to the substituted products 4, 8, and 9 are controlled by energy changes $\Delta E$, which means that it is not dominant for activation energies $E_a$ in the processes from 1 to the corresponding intermediates V, VII, and IX, respectively.
Table 1. Reaction of 1 with various nucleophiles

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield(^{a)}) (%)</th>
<th>(\Delta E) (solvent) kcal/mol</th>
<th>(E_a) (solvent) kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeNH(_2)</td>
<td>rt, 4 h in MeCN</td>
<td>4(^{b)})</td>
<td>96</td>
<td>8.1 (MeCN)</td>
<td>16.3 (MeCN)</td>
</tr>
<tr>
<td>(n)-BuNH(_2)</td>
<td>- (^{c)})</td>
<td>4(^{d)})</td>
<td>-</td>
<td>8.5 (MeCN)</td>
<td>16.8 (MeCN)</td>
</tr>
<tr>
<td>(n)-BuSH</td>
<td>100 °C, 96 h in PrCN</td>
<td>8(^{d)})</td>
<td>62</td>
<td>11.0 (PrCN)</td>
<td>29.5 (PrCN)</td>
</tr>
<tr>
<td>(n)-BuOH</td>
<td>refl (138 °C), 72 h in (p)-xylene</td>
<td>9(^{d)})</td>
<td>89</td>
<td>11.7 ((p)-xylene)</td>
<td>25.0 ((p)-xylene)</td>
</tr>
</tbody>
</table>

a) Isolated yields.  b) \(R=\) Me.  c) Although the experiment for the reaction of 1 with \(n\)-butylamine has not been reported, \(\Delta E\) and \(E_a\) values suggests that the conditions required for this reaction are quite similar to those for the reaction with methylamine.  d) \(R=\) \(n\)-Bu.

There undoubtedly exist equilibriums between substrate 1 and intermediates V, VII, and IX. It is understood from the viewpoint that the inverse reactions from these unstable intermediates to the stable substrate 1 proceed much more rapidly than the reactions from 1 to the intermediates (Scheme 6). Therefore, it results in the thermodynamic control which predominates on the processes from 1 to intermediates V, VII, and IX as the rate determining steps on the substitution reactions of 1 giving 4, 8, and 9, respectively. Less \(\Delta E\) on the process from 1 to VII than that from 1 to IX causes more concentration of VII than IX at the common temperature. And consequently, it leads up to a faster formation of N-S exchanged product 8 than N-O exchanged product 9 under the same conditions. This is one of the rational reasons explaining that the N-O exchange reaction of 1 with \(n\)-butanol requires higher temperature than the N-S exchange reaction of 1 with \(n\)-butanethiol.

Scheme 6
COMPUTATIONAL METHODS
All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 18. For geometrical optimizations, it was performed with the 6-31G\* basis set using B3LYP. For a solvation calculation, C-PCM model was used. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL force field and subsequent semi-empirical PM3 optimizations.

REFERENCES AND NOTES
14. The calculated energies of the nucleophiles, \(n\)-BuNH\(_2\), \(n\)-BuSH, and \(n\)-BuOH are -213.80498 a.u. (in acetonitrile), -556.64567 a.u. (in butyronitrile), and -233.66560 a.u. (in p-xylene), respectively. Those of the cations, \(n\)-BuNH\(_3^+\), \(n\)-BuSH\(_2^+\), and \(n\)-BuOH\(_2^+\) are -214.27540 a.u. (in acetonitrile), -557.05240 a.u. (in butyronitrile), and -234.048692 a.u. (in p-xylene), respectively.
15. Every transition state \(\text{TS}_{\text{N-N}}\), \(\text{TS}_{\text{N-S}}\), and \(\text{TS}_{\text{N-O}}\) has only one imaginary infrared vibration corresponding to the motion of the molecules at the transition state.
16. Wavefunction, Inc. Irvine, CA, USA.