HETEROCYCLES, Vol. 103, No. 2, 2021, pp. 918 - 928. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 30th November, 2020, Accepted, 6th January, 2021, Published online, 1st February, 2021
DOI: 10.3987/COM-20-S(K)62

COMPUTATIONAL STUDY FOR THE AROMATIC NUCLEOPHILIC SUBSTITUTION OF 4-DIMETHYLAMINO-3-TRIFLUOROACETYL-QUINOLINE WITH VARIOUS NUCLEOPHILES

Norio Ota, Souma Nakagawa, Yasuhiro Kamitori, and Etsuji Okada*

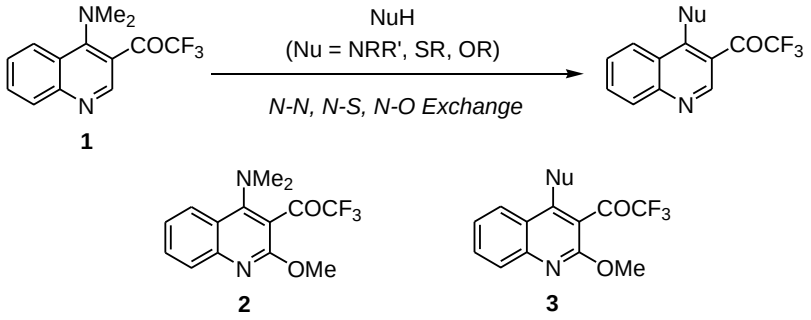
Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Kobe 657-8501, Japan, E-mail: okaetsu@kobe-u.ac.jp

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.[1-4] 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.[5] We also reported novel synthesis of 1*H*- and 2*H*-pyrazolo[4,3-*c*]quinolines,[6] isoxazoloquinolines,[6] 4-diazepino[6,5-*c*]quinolines,[6] pyrimido[5,4-*c*]quinolines,[7] and benzo[*h*][1,6]naphthyridines[7] 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).[8] Previously, we reported highly selective nucleophilic substitutions on

4-(dimethylamino)-2-methoxy-3-(trifluoroacetyl)quinoline **2** giving **3**[9,10] together with some computational studies on their reaction course.[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.

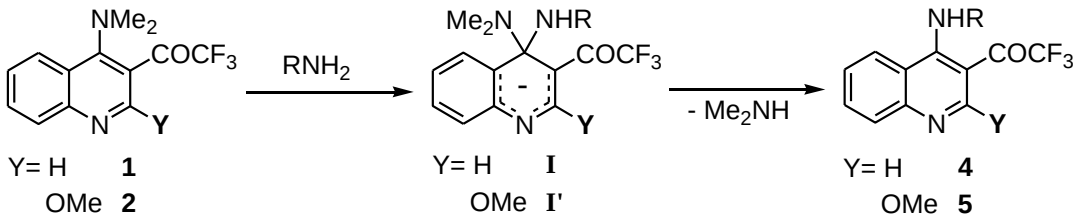


Scheme 1

RESULTS AND DISCUSSION

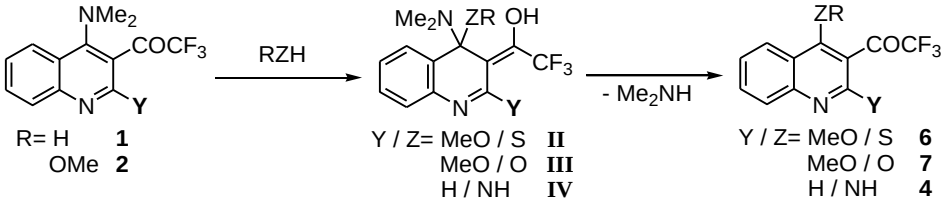
1. REACTION WITH AMINES

In our previous work,[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**.



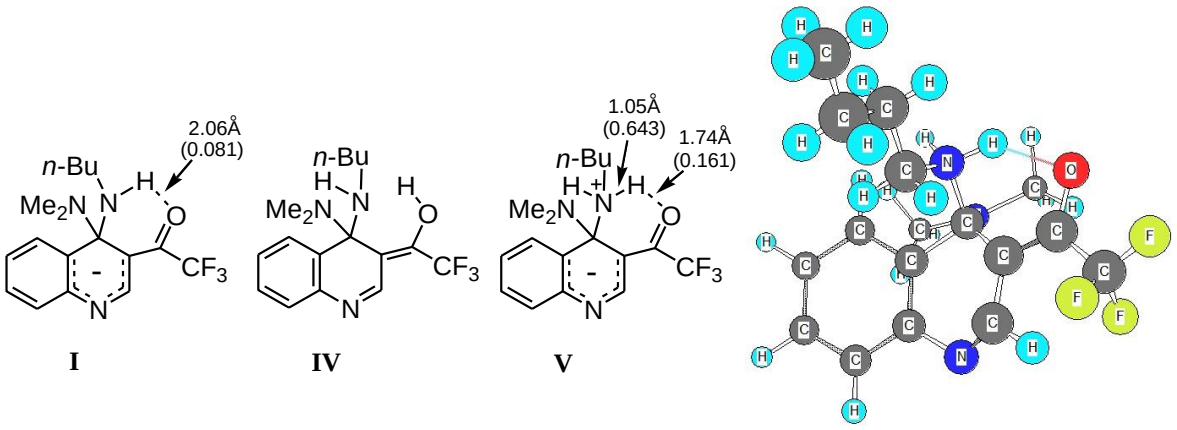
Scheme 2

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**.[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**.[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'**,[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**.

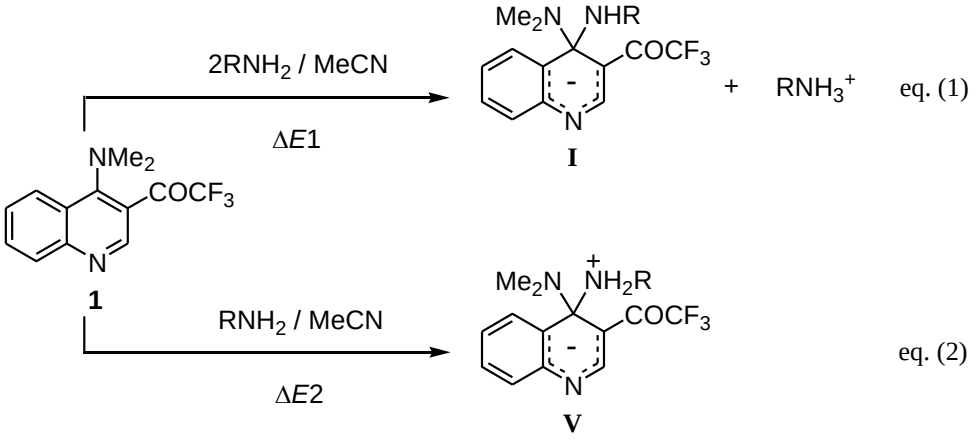


I **IV** **V**

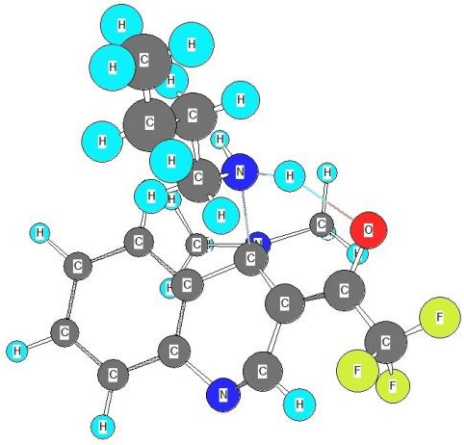
V
E = -1200.02246 a.u.

Figure 1

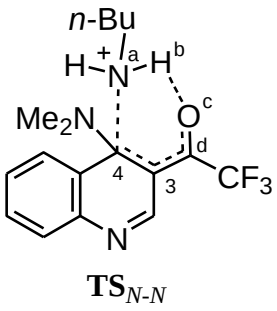
The energy changes from **1** to **I** ($\Delta E1$) and **1** to **V** ($\Delta E2$) are calculated based on the following eq. (1) and eq. (2), respectively.



In the case of the reaction with *n*-butylamine (R= *n*-Bu) in acetonitrile, Δ*E*2 (8.5 kcal/mol) is calculated as 6.2 kcal/mol less than Δ*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 methylamine from the intermediate **V**.



TS*N-N*
E = -1200.03326 a.u.



TS*N-N*

	Atomic distance (Å)	Mulliken bond order
N^a-C^4	2.05	0.374
N^a-H^b	1.02	0.744
H^b-O^c	1.97	0.087
O^c-C^d	1.24	1.575
C^3-C^d	1.43	1.163
C^3-C^4	1.48	1.068

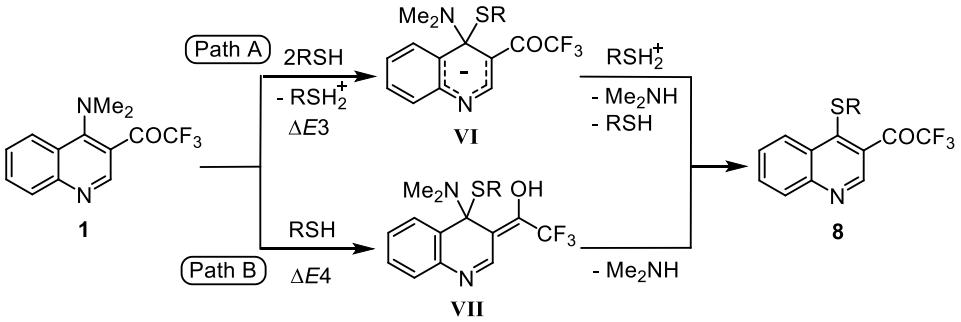
Figure 2

Next, we tried to pursue the transition state **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 **TS***N-N* (R= *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 **TS***N-N* similar to the case of intermediate **V**. On the basis of the energy value of **TS***N-N* on the process of eq. (2) is estimated activation energy E_a (R= *n*-Bu) as 16.8 kcal/mol. Quite similarly, it is calculated to be 16.3 kcal/mol for E_a (R= 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]

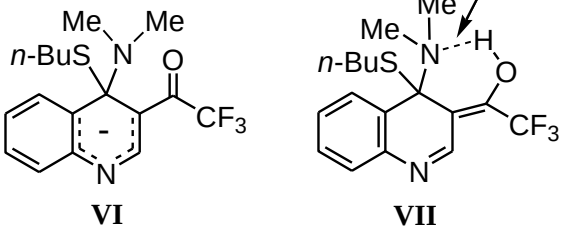
2. REACTION WITH THIOLS

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.



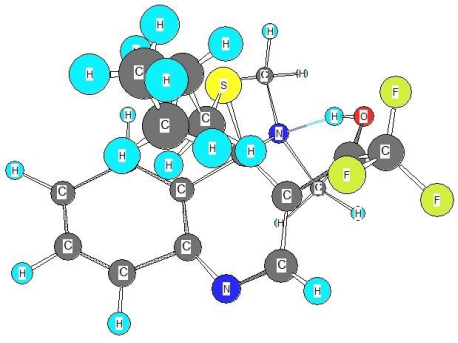
Scheme 4

Energy change Δ*E*3 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, Δ*E*4 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



E= -1542.39941 a.u. *E*= -1542.88287 a.u.

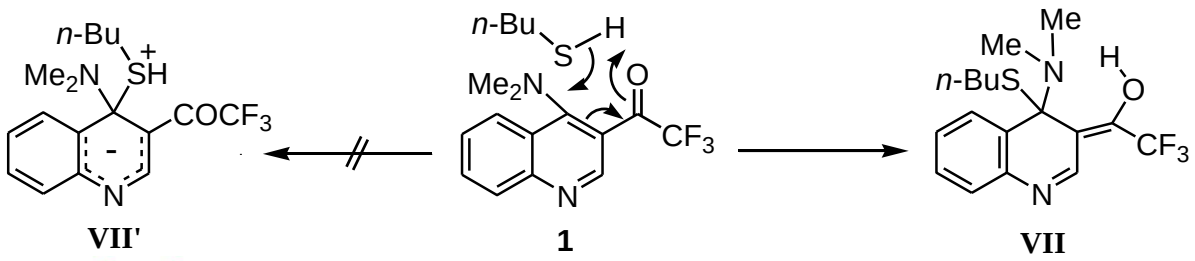
Figure 3

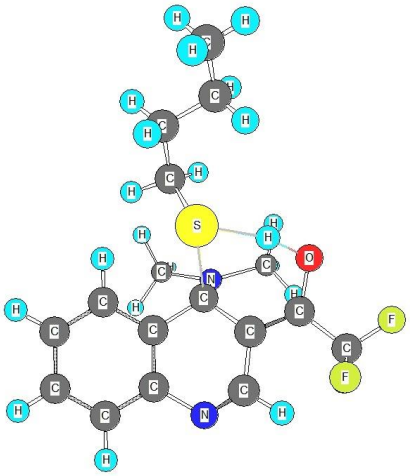


VII

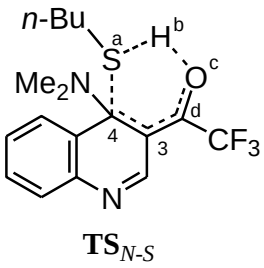
order (in parentheses) are also put up in Figure 3.

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**$_{N\text{-}S}$ together with its energy, and it is tabulated important atomic distances and Mulliken bond orders.[15] The structure of **TS**$_{N\text{-}S}$ clearly indicates the concerted process from **1** to **VII**.





TS$_{N\text{-}S}$
E= -1542.8534 a.u.



TS$_{N\text{-}S}$

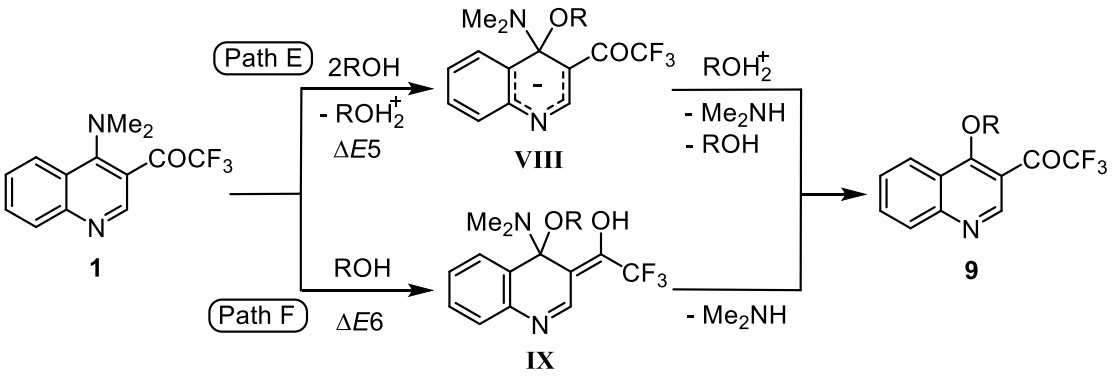
	Atomic distance (Å)	Mulliken bond order
S^a-C^4	2.34	0.547
S^a-H^b	1.91	0.322
H^b-O^c	1.04	0.501
O^c-C^d	1.32	1.149
C^3-C^d	1.37	1.510
C^3-C^4	1.51	0.943

Figure 4

Based on the energy value of **TS**$_{N\text{-}S}$, 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.[8]

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.[8] Energy values of geometrically optimized two intermediates **VIII** and **IX** are indicated in Figure 5.



Scheme 5

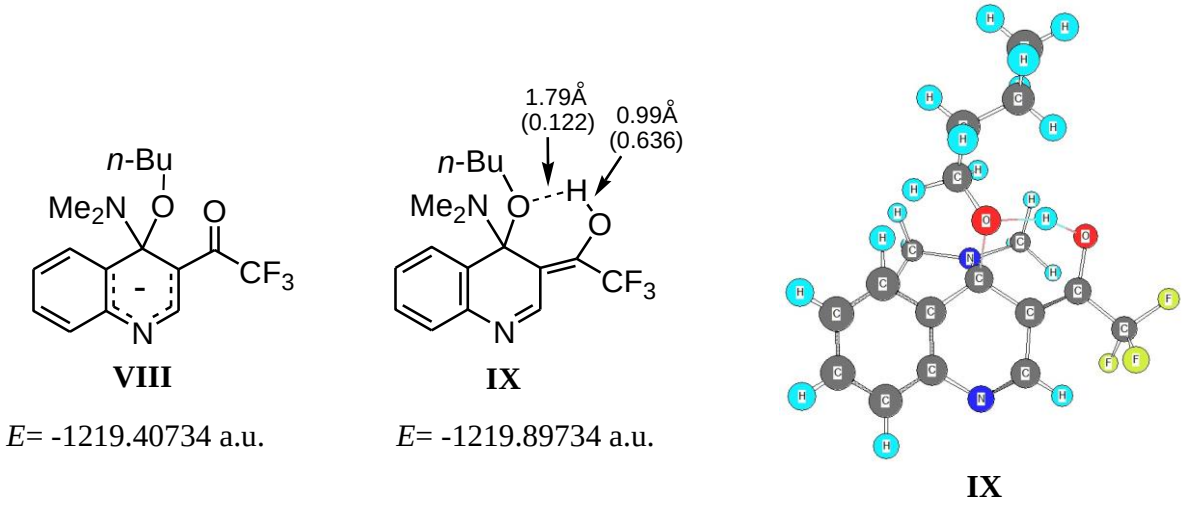
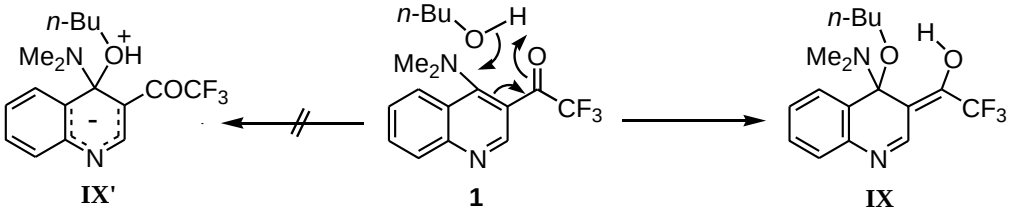
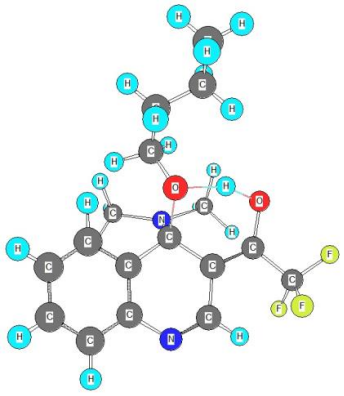


Figure 5

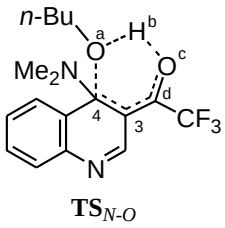
Similar to the case of the *N*-*S* exchange reaction (Scheme 4), energy change Δ*E*5 from **1** to Meisenheimer complex **VIII** is calculated as 78.8 kcal/mol.[14] This value is too large to undergo the reaction from **1** to **9** in refluxing *p*-xylene.[8] In contrast, the route via **IX** is rather suitable pathway suggested by its reaction conditions since Δ*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 $\mathbf{TS}_{N\text{-}O}$ for the present concerted reaction of **1** with *n*-butanol giving **IX**.[15] The energy and the atomic distances as well as Mulliken bond orders concerning the reaction centers on $\mathbf{TS}_{N\text{-}O}$ are also indicated in this Figure.





TS*N-O*
E= -1219.87618 a.u.



TS*N-O*

	Atomic distance (Å)	Mulliken bond order
O^a-C^4	1.75	0.509
O^a-H^b	1.17	0.364
H^b-O^c	1.24	0.332
O^c-C^d	1.29	1.241
C^3-C^d	1.38	1.437
C^3-C^4	1.52	0.966

Figure 6

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]

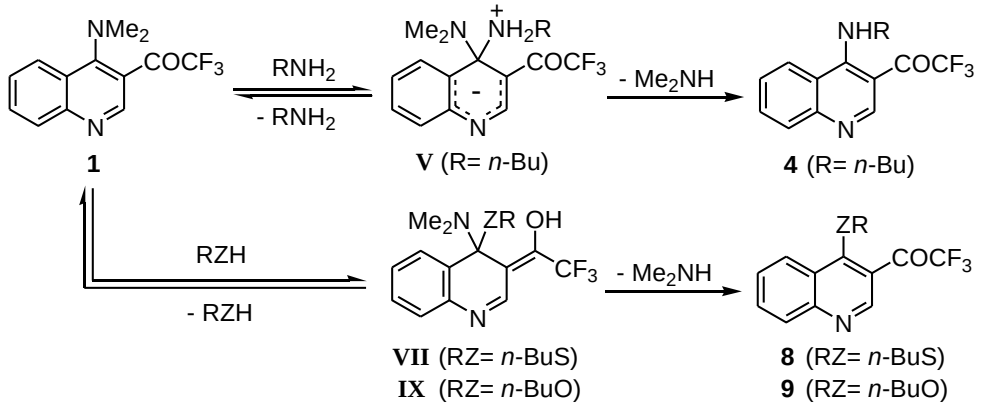
As shown in the Table, required experimental conditions for successful substitution reactions are enhanced in the order of *N*-*O* exchange > *N*-*S* exchange > *N*-*N* exchange. Similarly, the energy changes ΔE from **1** to the corresponding intermediates **IX** (ΔE6), **VII** (ΔE4), and **V** (ΔE2) are increased in the order of ΔE6 (*N*-*O* exchange) > ΔE4 (*N*-*S* exchange) > ΔE2 (*N*-*N* exchange). Temperatures required for the substitutions of **1** with the nucleophiles are consistent with each values of the energy changes ΔE 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 ΔE, 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

Nucleophile	Conditions	Product	Yield[a] %	ΔE (solvent) kcal/mol	E_a (solvent) kcal/mol
$MeNH_2$	rt, 4 h in MeCN	**4**[b]	96	8.1 (MeCN)	16.3 (MeCN)
n-$BuNH_2$	- [c]	**4**[d]	-	8.5 (MeCN)	16.8 (MeCN)
n-BuSH	100 °C, 96 h in PrCN	**8**[d]	62	11.0 (PrCN)	29.5 (PrCN)
				11.0 (MeCN)	29.6 (MeCN)
n-BuOH	refl (138 °C), 72 h in *p*-xylene	**9**[d]	89	11.7 (*p*-xylene)	25.0 (*p*-xylene)
				13.6 (MeCN)	25.7 (MeCN)

a) Isolated yields. b) R= Me. c) Although the experiment for the reaction of **1** with *n*-butylamine has not been reported, ΔE 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 ΔE 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.[16] For geometrical optimizations, it was performed with the 6-31G* basis set using B3LYP.[17] For a solvation calculation, C-PCM model[18] was used. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[19] force field and subsequent semi-empirical PM3[20] optimizations.

REFERENCES AND NOTES

1. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry', Kodansha & Elsevier Biomedical, Tokyo, 1982.
2. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications', ed. by R. E. Banks, Ellis Horwood, London, 1979.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications', Elsevier, Amsterdam, 1993.
5. E. Okada, M. Hatakenaka, M. Kuratani, T. Mori, and T. Ashida, *Heterocycles*, 2014, **88**, 799.
6. E. Okada, M. Hatakenaka, and T. Sakaemura, *Heterocycles*, 2015, **90**, 1072.
7. E. Okada, M. Hatakenaka, S. Nakano, T. Sakaemura, T. Mori, and T. Terauchi, *Heterocycles*, 2014, **89**, 2303.
8. E. Okada, M. Hatakenaka, T. Sakaemura, N. Shimomura, and T. Ashida, *Heterocycles*, 2012, **86**, 1177.
9. E. Okada, M. Hatakenaka, Y. Takezawa, and K. Iwakuni, *Heterocycles*, 2017, **95**, 322.
10. E. Okada, M. Hatakenaka, Y. Takezawa, and K. Iwakuni, *Heterocycles*, 2016, **93**, 474.
11. N. Ota, S. Sasakawa, Y. Kamitori, and E. Okada, *Heterocycles*, 2018, **97**, 451.
12. N. Ota, Y. Harada, Y. Kamitori, and E. Okada, *Heterocycles*, 2019, **99**, 694.
13. N. Ota, Y. Harada, Y. Kamitori, and E. Okada, *Heterocycles*, 2020, **101**, 692.
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 $\mathbf{TS}_{N\text{-}N}$, $\mathbf{TS}_{N\text{-}S}$, and $\mathbf{TS}_{N\text{-}O}$ has only one imaginary infrared vibration corresponding to the motion of the molecules at the transition state.
16. Wavefunction, Inc. Irvine, CA, USA.
17. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

18. V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995.
19. M. Clark, R. D. Cramer III, and N. Van Opdenbosch, *J. Comput. Chem.*, 1989, **10**, 982.
20. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.