| **タイトル** | Computational Study for the Aromatic Nucleophilic Substitution Reaction on 1-Dimethylamino-2,4-bis(trifluoroacetyl)-naphthalene with Amines |
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| **掲載誌・巻号・ページ** | International Journal of Organic Chemistry,8(3):273-281 |
| **刊行日** | 2018-09 |
| **資源タイプ** | Journal Article / 学術雑誌論文 |
| **版区分** | publisher |
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| **DOI** | 10.4236/ijoc.2018.83020 |
| **JaLCDOI** | |
| **URL** | http://www.lib.kobe-u.ac.jp/handle_kernel/90007052 |

PDF issue: 2020-11-05
Computational Study for the Aromatic Nucleophilic Substitution Reaction on 1-Dimethylamino-2,4-bis(trifluoroacetyl)-naphthalene with Amines

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Abstract

Our previous research showed that aliphatic amines were put in order of high reactivity as “ethylamine > ammonia > t-butylamine > diethylamine” on the aromatic nucleophilic substitution of 1-dimethylamino-2,4-bis(trifluoroacetyl)-naphthalene 1 in acetonitrile. The DFT calculation study (B3LYP/6-31G* with solvation model) for the reactions of 1 with above four amines rationally explained the difference of each amines reactivity based on the energies of their Meisenheimer complexes 3 which are assumed to formed as the reaction intermediates in the course of the reaction giving the corresponding N-N exchange products 2. Intramolecular hydrogen bond between amino proton in 1-amino group and carbonyl oxygen in 2-trifluoroacetyl group stabilizes Meisenheimer complexes 3 effectively, and accelerates the substitution reaction from 1 to 2. Our calculation results also predicted that the above order of amines is also true if less polar toluene is used as a solvent instead of acetonitrile even though more enhanced conditions are required.

Keywords

1-Amino-2,4-bis(trifluoroacetyl)naphthalenes, Aliphatic Amines, Meisenheimer Complexes, Aromatic Nucleophilic Substitution, DFT Calculation

1. Introduction

In our previous research, we found that dimethylamino group on naphthalene system activated by two trifluoroacetyl groups is easily substituted with various nucleophiles, even though such substituent is commonly understood to have a
poor leaving-group ability [1] [2] [3]. This unique aromatic nucleophilic substitution has provided diverse synthetic methods having capability to access a lot of kinds of fluorine-containing heterocycles [4]-[14]. These are the class of fluorine-containing heterocycles of which potential biological activities might be focused on as unique active ingredients in the various life science fields [15] [16] [17] [18]. On the above investigations was attained a newfound knowledge in which the N-N exchange reaction rate of aliphatic amines resulted in order of decreasing as “ethylamine > ammonia > t-butylamine > diethylamine” by making observations for the reaction of 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene 1 in acetonitrile (Scheme 1) [19]. This reactivity order is hard to be understood by traditional electronic theories of organic chemistry.

Therefore, these situations prompted us to demonstrate the DFT calculation (RB3LYP/6-31G*) study on the reaction of 1 with the above four kinds of amines to have led to an interesting outcome rationalizing the reaction rate order of the four amines. Moreover, we discuss an elucidation of the solvent effect on the present substitution by making use of C-PCM model calculation.

2. Results and Discussion

2.1. Calculations for 1-Dimethylamino-2,4-bis(trifluoroacetyl)naphthalene

First, we calculated the optimized structure of 1-dimethylamino-2,4-bis(trifluoroacetyl)-naphthalene 1 which is the key substrate of the present nucleophilic substitution. In Figure 1 is depicted an estimated most stable structure of 1 in acetonitrile together with its energy. It also shows LUMO of 1 and its frontier electron densities (LUMO) at the 1-C of naphthalene ring and the carbonyl carbons of two trifluoroacetyl groups. The value of LUMO at the 1-C is considerably larger than the ones of both carbonyl carbons. This discrepancy of LUMO suggests the predominant attack by amino nucleophiles on the 1-C of 1 giving the Meisenheimer complex 3 which are assumed to be formed as the intermediates on the present substitution course (Scheme 2).

2.2. Calculations for Meisenheimer Complexes

Figure 2 shows four computed structures of Meisenheimer complexes 3a–d and each energies, which are formed by the reaction of 1-dimethylamino-2,4-bis(trifluoroacetyl)-naphthalene 1 with ethylamine, ammonia, t-butylamine, and diethylamine respectively in acetonitrile solvent. These structures are varied, but
Figure 1. Optimized structure and the data concerning LUMO of the substrate 1.

Scheme 2. The substitution pathway from 1 to N-N exchanged products 2.

Figure 2. Optimized structure of Meisenheimer complexes 3a-d.
within the margin of error, from ones estimated by the simple DFT calculations without using solvation model. The Meisenheimer complexes 3a-c have intramolecular hydrogen bond between amino proton and carbonyl oxygen in 2-trifluoroacetyl group respectively, but 3d does not due to the absence of amino proton. In respect to these hydrogen bonds, in Figure 2 are indicated the computed values of distance and Mulliken bond orders (in parentheses).

2.3. Calculations for N-N Exchanged Products

Figure 3 shows the optimized structures of four N-N exchanged products 2a-d afforded by the reaction of 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene 1 with ethylamine, ammonia, t-butylamine, and diethylamine in acetonitrile. Similar to the cases of Meisenheimer complexes 3a-c, intramolecular hydrogen bonding between amino proton and carbonyl oxygen of 2-trifluoroacetyl group are formed in 2a-c. Moreover, the exhibited values are the estimated energies and bond lengths as well as Mulliken bond orders (in parentheses) of hydrogen bonds.

Figure 3. Optimized structure of N-N exchanged products 2a-d.
2.4. Analyses for Reaction Processes

Energy diagrams of the present substitution course from 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene 1 to the corresponding N-N exchanged products 2a-d are depicted in Figure 4. The rate determining step of this substitution would be the first addition step (Step 1) giving the corresponding adducts 3a-d in which one of the aromatic benzene-ring systems is destroyed. It is hard to estimate directly the transition state structures and their energies in the rate determining step since the present available computational methods cannot enable us to access an exact transition state structure of ionic reaction in polar solvents. However, it is possible to approximate activation energies of the rate determining step using energy changes (ΔE₁) from substrate 1 to Meisenheimer complexes 3a-d which have the structures relatively close to each transition states.

Table 1 summarizes the computed energies of the substrate 1 and Meisenheimer complexes 3a-d, in which values are worked out under the two conditions. The one is using solvation model and the other one is not using it. Acetonitrile (aprotic polar solvent) and toluene (aprotic less polar solvent) was adopted as

![Figure 4](image)

**Figure 4.** Energy diagrams from the substrate 1 to N-N exchanged products 2a-d.

**Table 1.** Energies of the substrate 1 and Meisenheimer complexes 3a-d.

| Compound | \( E \) (au.) | Solv.: None \(^a\) | Acetonitrile | Toluene |
|----------|---------------|------------------|-------------|---------|
| 1        | \(-1420.55312\) | \(-1420.56579\) | \(-1420.55988\) |
| 3a       | \(-1555.19499\) | \(-1555.26133\) | \(-1555.23358\) |
| 3b       | \(-1476.57275\) | \(-1476.64055\) | \(-1476.61229\) |
| 3c       | \(-1633.81209\) | \(-1633.87740\) | \(-1633.84997\) |
| 3d       | \(-1633.79469\) | \(-1633.86033\) | \(-1633.83274\) |

\(^a\) Simple DFT calculation results without using solvation model.
the solvation models. The energy values of Table 1 lead to the estimated energy increments (ΔE₁) shown in Table 2 respectively. The largest ΔE₁ value is given in the case of the reaction of 1 with ammonia based on the simple DFT calculation without the use of solvation model. Additionally, ΔE₁ of the reaction of 1 with amines decreases according to the order of “ammonia > diethylamine > t-butylamine > ethylamine” (Table 2). The results predicts that amines are put in order of high reaction rate as “ethylamine > t-butylamine > diethylamine > ammonia” on the N-N exchange reaction of 1 though this assumption is not compatible with the experimental results (ethylamine > ammonia > t-butylamine > diethylamine). We also calculated overall energy changes (ΔE₂) from 1 to 2a−d to afford the computed values as the order of “ammonia (−16.1 kcal/mol) < ethylamine (−12.6 kcal/mol) < t-butylamine (−4.3 kcal/mol) < diethylamine (4.1 kcal/mol)”. This order is also not coincident with the experimental results even if this N-N exchange reaction of 1 is affected by thermodynamic control. In contrast, in the case of the reaction of 1 with ethylamine to afford 3a, the least ΔE₁ for the reaction in acetonitrile is given by DFT calculations under solvation model. As a result, the increasing order of ΔE₁ becomes computationally evident as “ethylamine < ammonia < t-butylamine < diethylamine”, which suggests the acceleration of the N-N exchange reaction on 1 in the order of “ethylamine > ammonia > t-butylamine > diethylamine”. This order is completely consistent with our experimental evidence examined previously. It allows us to explain that stabilization by intramolecular hydrogen bond in Meisenheimer complexes 3a−c would be one of the reasons why ΔE₁ on the reaction affording 3a−c are smaller than the case of 3d.

We also calculated ΔE₁ about the reaction in toluene. As shown in Table 2, ΔE₁ in toluene are larger than ones in acetonitrile in all cases. It follows that the substitution reaction of 1 with amines in less-polar toluene is predicted to require more enhanced conditions than the one in polar acetonitrile.

The ΔE₁ values in toluene predict that the order of amines on the substitution rate in toluene is the same as the one in acetonitrile. Differences of ΔE₁ values between the reactions in toluene and the corresponding ones in acetonitrile are summarized in Table 3. In the case of the reaction with ammonia, ΔE₁ is obviously more decreased than the cases using the other three amines in acetonitrile solvent instead of toluene. Meisenheimer complex 3b has one more amino

### Table 2. Energy changes ΔE₁ on the rate determining steps from 1 to 3a−d.

| Nucleophile | Process | ΔE₁ (kcal/mol) | Solv.: None | Acetonitrile | Toluene |
|-------------|---------|----------------|-------------|--------------|---------|
| EtNH₂       | 1 → 3a  | 101.8          | 7.2         | 45.8         |
| NH₃         | 1 → 3b  | 114.4          | 10.1        | 52.2         |
| t-BuNH₂     | 1 → 3c  | 105.6          | 16.7        | 53.1         |
| Et₂NH       | 1 → 3d  | 109.1          | 20.9        | 57.0         |

a. Simple DFT calculation results without using solvation model.
proton in addition to the other one which is used for intramolecular hydrogen bond (Figure 2). It is explained rationally that stabilization by such hydrogen bond of this free amino proton in 3b surrounded by acetonitrile would contribute to additional decrement of $\Delta E_1$ on the reaction of 1 with ammonia compared to the cases using the other three amines.

2.5. Conclusion

The unexpected order of the reaction rate (ethylamine > ammonia > t-butylamine > diethylamine) on the aromatic nucleophilic substitution of 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene 1 with nucleophiles (ammonia and three kinds of aliphatic amine) giving the corresponding N-N exchanged products 2 is rationalized by the energy changes for forming the corresponding Meisenheimer complexes 3, i.e. the rate determining step of the present substitution reaction. These energy changes are closely correlated with the relative stabilities of 3 under the reaction conditions. Intramolecular hydrogen bond between amino proton in 1-amino group and carbonyl oxygen in 2-trifluoroacetyl group stabilizes Meisenheimer complexes 3 effectively, and accelerates the substitution reaction from 1 to 2, consequently. Our calculation results also predict that the above order of amines is also true if less polar toluene is used as a solvent instead of acetonitrile even though more enhanced conditions are required.

3. Computational Methods

All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 16 [20]. For geometrical optimizations, it was performed with the 6-31G* basis set at B3LYP [21] level. For a solvation calculation, C-PCM model [22] was used. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL [23] force field and subsequent semi-empirical PM3 [24] optimizations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hojo, M., Masuda, R. and Okada, E. (1987) Nucleophilic Nitrogen-Nitrogen Ex-
change Reaction at Aromatic Carbon Atoms—Reaction of N,N-Dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine with Various Amines. *Tetrahedron Letters*, **28**, 6199-6200. https://doi.org/10.1016/S0040-4039(00)61845-2

[2] Hojo, M., Masuda, R., Okada, E. and Miya, H. (1989) Aromatic Nucleophilic N,S- and N,O-Exchange Reactions of N,N-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with Various Thiols and Alcohols: A Facile Synthetic Method for Alkyl and Aryl 1-[2,4-Bis(trifluoroacetyl)napthyl] Sulfides and Ethers. *Synthesis*, **1989**, 870-873. https://doi.org/10.1055/s-1989-27418

[3] Hojo, M., Masuda, R., Okada, E. and Miya, H. (1990) Unusual High Reactivity of Dimethylamino as a Leaving Group in Aromatic Nucleophilic Substitutions at the 1-Position of 2,4-Bis(trifluoroacetyl)naphthalenes. *Chemistry Express*, **5**, 569-572. https://doi.org/10.1002/chin.199048045

[4] Hojo, M., Masuda, R. and Okada, E. (1988) Acid Catalyzed Cyclization of N,N-Dialkyl-2,4-bistrifluoroacetyl-1-naphthylamines to Naphtho[1,2-d][1,3]oxazines. *Tetrahedron Letters*, **29**, 4599-4602. https://doi.org/10.1016/S0040-4039(00)80558-4

[5] Hojo, M., Masuda, R., Okada, E. and Miya, H. (1989) Aromatic Nucleophilic Nitrogen-Nitrogen Exchange Reaction of N,N-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with Amino Acid Derivatives: A Facile Synthesis of Fluorine-Containing 1H-Benz[g]indolines and 1H-Benz[g]indoles. *Synthesis*, **1989**, 550-552. https://doi.org/10.1055/s-1989-27315

[6] Hojo, M., Masuda, R. and Okada, E. (1987) A Convenient and Facile Synthesis of Fluorine-Containing 1H+, 2H-Benz[g]indazoles and Naphthosoxazoles by Aromatic Nucleophilic N-N-Exchange Reaction of N,N-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with Hydrazines and Hydroxylamine. *Synthesis*, **1990**, 481-483. https://doi.org/10.1055/s-1990-26911

[7] Hojo, M., Masuda, R., Okada, E., Tomifujii, T. and Imazaki, N. (1990) A Facile and Convenient Synthetic Method for Fluorine-Containing Benz[c]acridines and Dihydrobenz[c]acridines from N,N-Dimethyl-1-naphthylamine. *Synthesis*, **1990**, 1135-1137. https://doi.org/10.1055/s-1990-27114

[8] Okada, E., Masuda, R., Hojo, M., Imazaki, N. and Miya, H. (1992) A Simple Route to 2,3-Dihyronaphtho[1,2-b]thiophenes and Naphtho[1,2-b]thiophenes Bearing Trifluoromethyl Groups by Aromatic Nucleophilic Substitution of N,N-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine. *Heterocycles*, **34**, 103-110. https://doi.org/10.3987/COM-91-5897

[9] Okada, E., Masuda, R., Hojo, M., Imazaki, N. and Takahashi, K. (1992) Facile and Convenient Synthetic Methods for Fluorine-Containing Benz[c]thioxanthenes and Benzo[c]xanthenes from N,N-Dimethyl-1-naphthylamine. *Synthesis*, **1992**, 536-538. https://doi.org/10.1055/s-1992-26156

[10] Okada, E., Masuda, R., Hojo, M. and Tomifujii, T (1993) Facile and Convenient Synthesis of Fluorine-Containing Naphth[1,2-][1,3]oxazines by Novel Cyclization of N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines. *Heterocycles*, **36**, 845-856. https://doi.org/10.3987/COM-92-6250

[11] Okada, E., Masuda, R., Hojo, M., Tone, H. and Tomifujii, T. (1994) A Convenient Synthetic Method for Fluorine-Containing Naphtho[1,2-][1,3]thiazines from N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines. *Heterocycles*, **37**, 157-162. https://doi.org/10.3987/COM-93-512

[12] Okada, E., Tone, H., Tsukushi, N., Otsuki, Y., Takeuchi, H. and Hojo, M. (1997) A Simple and Efficient Synthetic Method for Fluorine-Containing Benzo[b]quinolines. *Heterocycles*, **45**, 339-346. https://doi.org/10.3987/COM-96-7680
[13] Okada, E., Tsukushi, N., Kunihiro, N. and Tomo, Y. (1998) A Facile and Convenient Synthetic Method for Fluorine-Containing Naphtho[1,2-\(e\)][1,4]diazepines, Naphtho[1,2-\(e\)][1,4]dithiepins and Naphtho[1,2-\(e\)][1,4]dioxepins. *Heterocycles*, **49**, 297-304. [https://doi.org/10.3987/COM-98-S33](https://doi.org/10.3987/COM-98-S33)

[14] Lamarque, J.-F., Lamarque, C., Lassara, S., Médebielle, M., Molette, J., David, E., Pellet-Rostaing, S., Lemaire, M., Okada, E., Shibata, D. and Pilet, G. (2008) Copper Catalyzed 1,3-Dipolar Cycloaddition Reaction of Azides with N-\((2\text{-trifluoroacetylaryl})\) propargylamines. A Mild Entry to Novel 1,4-Disubstituted-[1,2,3]-triazole Derivatives. *Journal of Fluorine Chemistry*, **129**, 788-798. [https://doi.org/10.1016/j.jfluchem.2008.05.015](https://doi.org/10.1016/j.jfluchem.2008.05.015)

[15] Filler, R. and Kobayashi, Y. (1982) Biomedicinal Aspects of Fluorine Chemistry. Kodansha & Elsevier Biomedical, Tokyo.

[16] Filler, R. (1979) Organofluorine Chemicals and Their Industrial Applications. Ellis Horwood, London.

[17] Welch, J.T. (1987) Advances in the Preparation of Biologically Active Organofluorine Compounds. *Tetrahedron*, **43**, 3123-3197. [https://doi.org/10.1016/S0040-4020(01)90286-8](https://doi.org/10.1016/S0040-4020(01)90286-8)

[18] Filler, R., Kobayashi, Y. and Yagupolskii, L.M. (1993) Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications. Elsevier, Amsterdam.

[19] Hojo, M., Masuda, R., Okada, E. and Miya, H. (1990) Importance of Steric Acceleration in Nucleophilic Nitrogen-Nitrogen Exchange Reaction of 1-Amino-2,4-Bistrifluoroacetylnaphthalenes with Amines. *Chemistry Express*, **5**, 485-488.

[20] Spartan'16, Version 2.07, Aug. 1, 2017. Wavefunction Inc., Irvine.

[21] Becke, A.D. (1993) Density-Functional Thermochemistry. III. The Role of Exact Exchange. *Journal of Chemical Physics*, **98**, 5648-5652. [https://doi.org/10.1063/1.464913](https://doi.org/10.1063/1.464913)

[22] Barone, V. and Cossi, M. (1998) Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *Journal of Physical Chemistry A*, **102**, 1995-2001. [https://doi.org/10.1021/jp9716997](https://doi.org/10.1021/jp9716997)

[23] Clark, M., Cramer III, R.D. and Van Opdenbosch, N. (1989) Validation of the General Purpose Tripos 5.2 Force Field. *Journal of Computational Chemistry*, **10**, 982-1012. [https://doi.org/10.1002/jcc.540100804](https://doi.org/10.1002/jcc.540100804)

[24] Stewart, J.J.P. (1989) Optimization of Parameters for Semiempirical Methods. I. Method. *Journal of Computational Chemistry*, **10**, 209-220. [https://doi.org/10.1002/jcc.540100208](https://doi.org/10.1002/jcc.540100208)