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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-dimetylamino-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-dimetylamino-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.

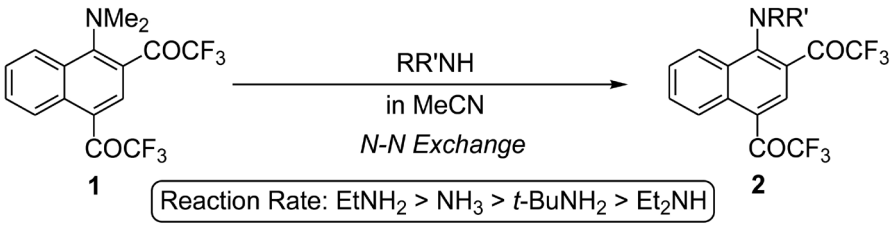
2. Results and Discussion

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

First, we calculated the optimized structure of 1-dimetylamino-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 (f_r^{LUMO}) at the 1-*C* of naphthalene ring and the carbonyl carbons of two trifluoroacetyl groups. The value of f_r^{LUMO} at the 1-*C* is considerably larger than the ones of both carbonyl carbons. This discrepancy of f_r^{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-dimetylamino-2,4-bis(trifluoroacetyl)-naphthalene **1** with ethylamine, ammonia, *t*-butylamine, and diethylamine respectively in acetonitrile solvent. These structures are varied, but



Scheme 1. The reaction of 1-dimetylamino-2,4-bis(trifluoroacetyl)naphthalene **1** with amines.

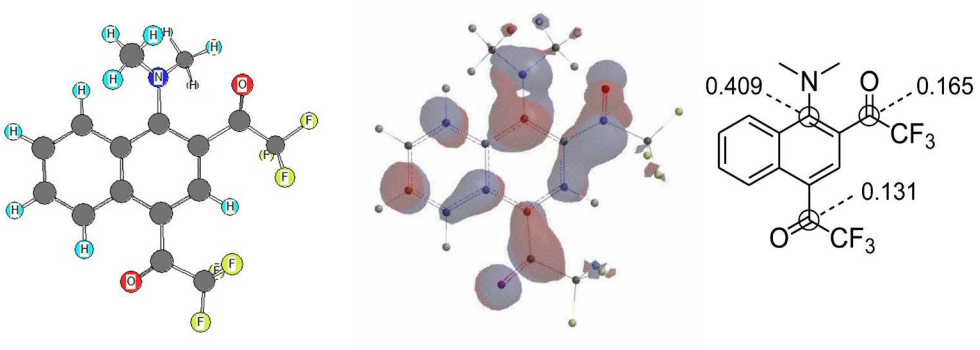
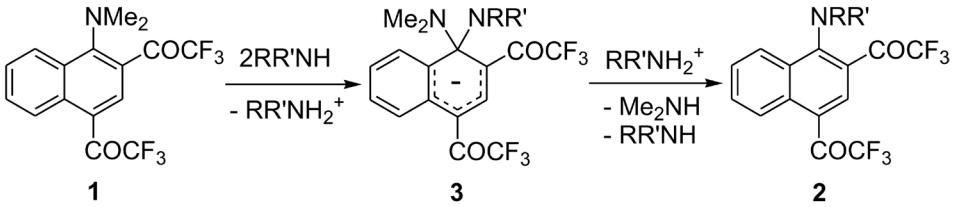


Figure 1. Optimized structure and the data concerning LUMO of the substrate **1**.



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

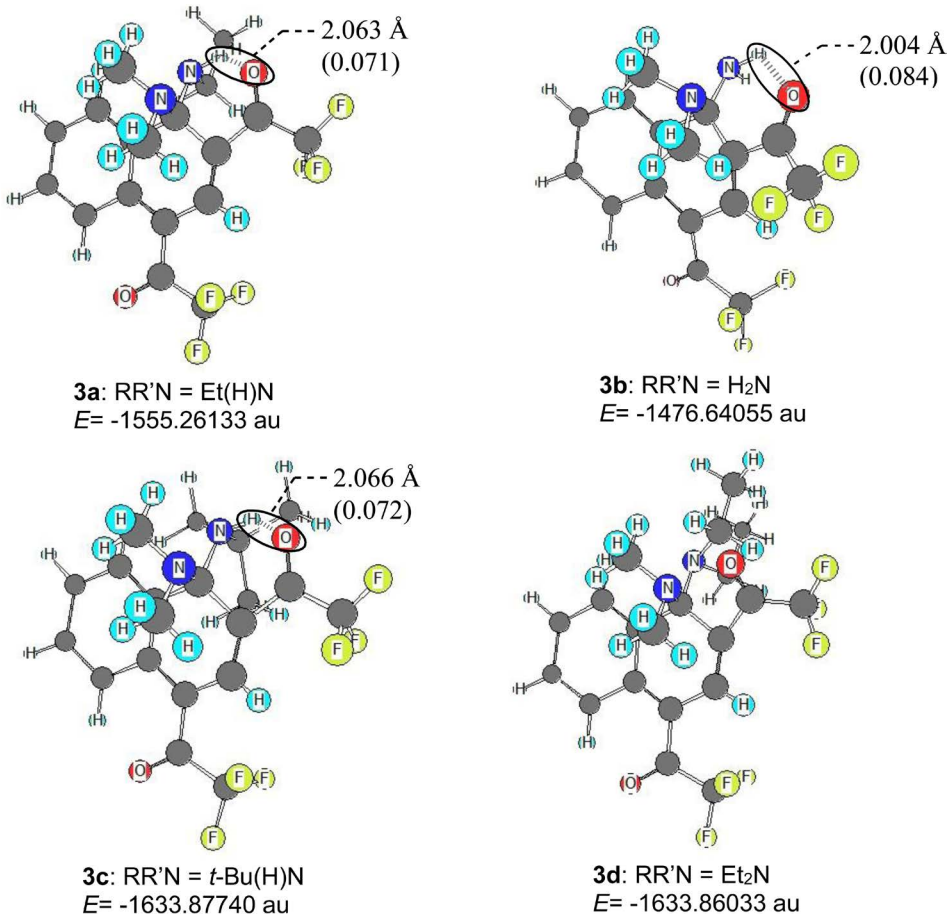


Figure 2. Optimized structure of Meizenheimer complexes **3a**-**d**.

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-dimetylamino-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.

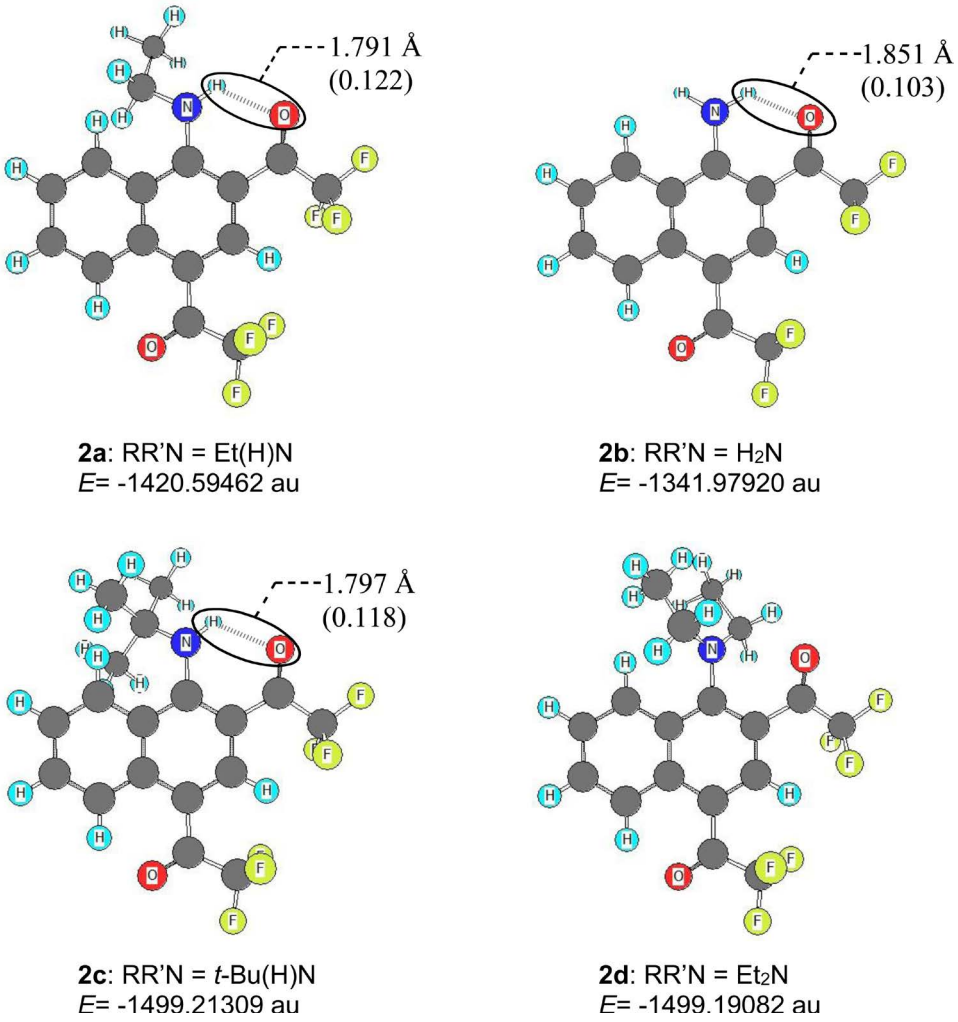


Figure 3. Optimized structure of *N*-*N* exchanged products **2a**-**d**.

2.4. Analyses for Reaction Processes

Energy diagrams of the present substitution course from 1-dimetylamino-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 (ΔE_1) 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

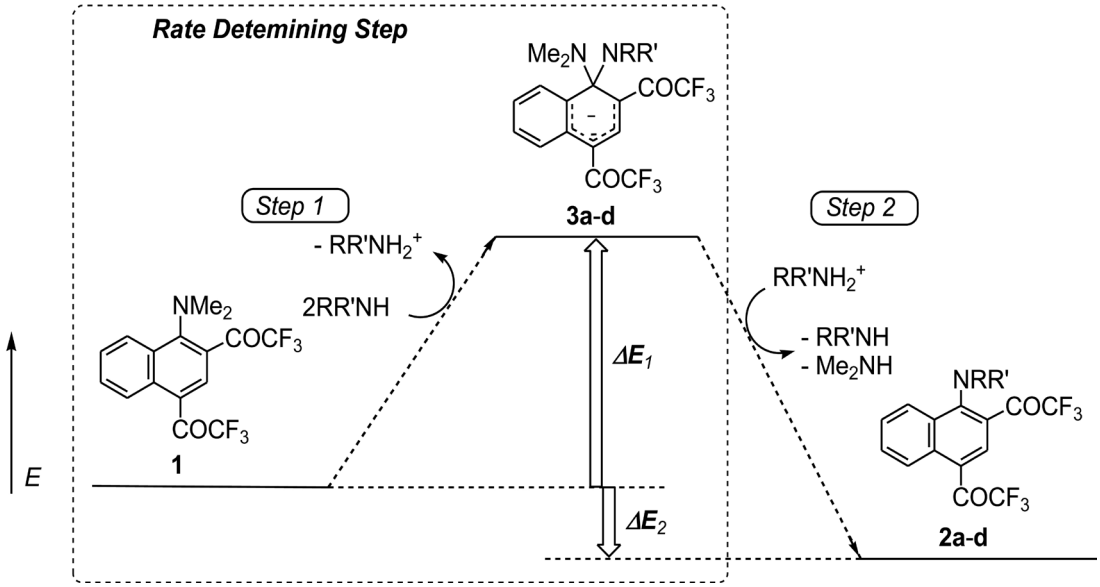


Figure 4. Energy diagrams from the substrate **1** to *N*-*N* exchanged products **2a**-**d**.

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 (ΔE_1) shown in Table 2 respectively. The largest ΔE_1 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, ΔE_1 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 (ΔE_2) 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 ΔE_1 for the reaction in acetonitrile is given by DFT calculations under solvation model. As a result, the increasing order of ΔE_1 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 ΔE_1 on the reaction affording **3a**-**c** are smaller than the case of **3d**.

We also calculated ΔE_1 about the reaction in toluene. As shown in Table 2, ΔE_1 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 ΔE_1 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 ΔE_1 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, ΔE_1 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 ΔE_1 on the rate determining steps from **1** to **3a**-**d**.

Nucleophile	Process	ΔE_1 (kcal/mol)		
		Solv.: None[a]	Acetonitrile	Toluene
$EtNH_2$	**1** → **3a**	101.8	7.2	45.8
NH_3	**1** → **3b**	114.4	10.1	52.2
t-$BuNH_2$	**1** → **3c**	105.6	16.7	53.1
Et_2NH	**1** → **3d**	109.1	20.9	57.0

a. Simple DFT calculation results without using solvation model.

Table 3. Solvent effects on ΔE_1.

Nucleophile	Process	ΔE_1 (kcal/mol)		ΔE_1(toluene) − ΔE_1(acetonitrile) (kcal/mol)
		Solv.: Toluene	Acetonitrile	
$EtNH_2$	**1** → **3a**	45.8	7.2	38.6
NH_3	**1** → **3b**	52.2	10.1	42.1
t-$BuNH_2$	**1** → **3c**	53.1	16.7	36.4
Et_2NH	**1** → **3d**	57.0	20.9	36.1

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 ΔE_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-dimetylamino-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.

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