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Investigation on the preparation of 2,2-difluoroethylamine by amination of 1-halo-2,2-difluoroethane

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Graphical Abstract – Pictogram



Highlights

- The amination of CHF₂CH₂X (X = Cl or Br) without catalyst and solvent was reported.
- The theoretical study on the amination of CHF₂CH₂X was performed.
- The mechanism of the amination of CHF₂CH₂X with NH₃ was proposed.
- CHF₂CH₂Cl was easier to be aminated than CHF₂CH₂Br.

Abstract

The synthesis of 2,2-difluoroethylamine via the amination of 1-halo-2,2difluoroethane (halogen = Cl or Br) without catalyst and solvent was studied by experiment and theoretical calculation. In order to compare the difficulty in the amination of 1-halo-2,2-difluoroethane with NH₃, experimental investigations were carried through changing reaction temperature, molar ratio and reaction time. And experimental evidence demonstrated that 1-chloro-2,2-difluoroethane was more prone to amination than 1-bromo-2,2-difluoroethane under the same conditions. In addition, the reaction mechanism was investigated, and the formation complexity evaluated. Calculation of the transition states and rate constants, and analysis of the frontier molecular orbitals, indicated that the reaction rate of the amination of 1-chloro-2,2-difluoroethane was higher than that of 1-bromo-2,2difluoroethane, which was consistent with the results of the experiment.

Keywords: 2,2-difluoroethylamine; 1-chloro-2,2-difluoroethane; Density functional theory; 1-bromo-2,2-difluoroethane; Kinetic modeling.

1. Introduction

2,2-Difluoroethylamine is an important fluoroaliphatic compound of significant industrial value, and is widely used as a synthetic raw material or intermediate in the manufacture of numerous pharmaceuticals and pesticides, among other products [1]. A difluoroethylamine group can replace the trifluoroethylamine group found in cathepsin K inhibitors such as odanacatib [2]. Downstream products synthesized from 2,2-difluoroethylamine, including amine amides sulfo acyl pyrrole derivatives, aminobenzophenones, trifluoroethyl sulfide derivatives, etc, which are widely used, such

as disease treatment and pest control. Amine amides sulfo acyl pyrrole derivatives have excellent effect in the treatment of hepatitis B [3], while aminobenzophenones were applied in the treatment of inflammatory ophthalmic diseases or cancer [4]. In addition, trifluoroethyl sulfide derivatives played an important role in killing animal pests [5]. In recent years, 2,2-difluoroethylamine were used as the raw material to produce difluorodiazoethane (CF₂HCHN₂), a novel reagent applied in [3+2]-cycloadditions, esterification and carbene transfer reaction[6-8]. The downstream products synthesized from 2,2-difluoroethylamine were summarized in scheme 1.



Scheme 1 Downstream products synthesized from 2,2-difluoroethylamine.

Thus far, 2,2-difluoroethylamine was prepared from various starting materials via different synthetic routes [9-18], which were summarized in scheme 2. The direct fluorination of ethylamine with trifluoromethyl hypofluorite [9] was not suitable for industrial production because of the high toxicity and pyrophoricity of diborane and trifluoromethyl hypofluorite. In addition, reduction of 2,2-difluoroacetamide [10], 1,1-difluoro-2-nitrosoethane [11], or 1,1-difluoro-2-nitroethane [12] were unattractive synthetic routes because of the difficulty in obtaining the necessary raw materials. For the

same reason, synthetic routes involving hydrogenolysis of 2,2-difluoroethylbenzylamine [12], or reaction of *N*-(2,2-difluoro-ethyl)prop-2-en-1-amine with 2-aminoethanol [13] were disadvantageous. 2,2-difluoroethylamine can be also synthesized in two steps by hydrogenation of 2,2-difluoroacetonitrile [14] followed by acidic hydrolysis of the resulting *N*-(2,2-difluoroethyl)acetamide. However, this approach had the following disadvantages: it was a longer route, and the end product was 2,2-difluoroethylamine hydrochloride, such that 2,2-difluoroethylamine can only be obtained after neutralization reaction of 2,2-difluoroethylamine hydrochloride with a base. Preparation of 2,2-difluoroethylamine by addition of the appropriate amine to *endo-cis*-5-norbornene-2,3-dicarboxylic anhydride [15] was tedious and not suitable for industrial application. Furthermore, the amination of 1-bromo-2,2-difluoroethane with ammonium acetate [16] was unattractive because of the deliquescent character of the latter, which affected reaction efficiency, in addition to the long reaction time. Thus, the methods discussed above for the synthesis of 2,2-difluoroethylamine were not suitable for industrial use.

In addition, 2,2-difluoroethylamine can be prepared by the amination of 1-chloro-2,2difluoroethane [17-18]. When the reaction was controlled at 140-145°C for 9h over KBr catalyst, the yield of 2,2-difluoroethylamine was 59% after extraction separation by Nmethlpyrroliding and water [14]. While the reaction was carried out at 143-145°C for 5.5h over KI catalyst in N-methylpyrrolidine, the yield of 2,2-difluoroethylamine was 88% [18]. In the above amination method, solid catalysts and large amount of solvents were used, which generated a lot of liquid waste and solid waste. Thus, this method was environmentally unfriendly, and its reaction mechanism was not clear.



Scheme 2 Known routes for the preparation of 2,2-difluoroethylamine.

In this work, 2,2-difluoroethylamine was prepared by reacting 1-halo-2,2difluoroethane with excess NH₃ in the absence of catalyst and solvent, and the reaction was studied both experimentally and computationally. 1-halo-2,2-difluoroethane were reacted with NH₃ under the same reaction conditions. Compared with routes 9-12, the raw materials used in this method were easily obtained and low toxicity. The route was short to obtain 2,2-difluoroethylamine via the amination of 1-halo-2,2-difluoroethane, which was better than routes 14-15. In addition, no catalysts and solvents were used in this method, without waste generation, and was beneficial to the environment. The reaction conditions were changed to obtain the conversion rate of reactants and the selectivity of products. A comparison of the experimental results determined which 1-halo-2,2-difluoroethane was more likely to react with NH₃. Generally, various reaction pathways for the preparation of 2,2-difluoroethylamine were studied, and two transition states were predicted to be located along the process. In addition, analysis of the frontier molecular orbitals, was performed in order to compare the ease of the two reactions [19, 20]. The molecular electrostatic potential (MESP) was used to visualize charged regions of molecules [21]. Furthermore, thermal rate constants for temperatures between 298.15K and 2500K were calculated by conventional TST [22, 23] and canonical variational TST (CVT) [24], considering the Wigner and Eckart tunneling corrections.

2. Results and discussion

2.1 Synthesis of difluoroethylamine

In this experiment, 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane were reacted with ammonia, with changing the material ratio, temperature conditions and reaction time to prepare difluoroethylamine. The results were shown in Fig. 1, Fig. 2 and Fig. 3, respectively.



Fig. 1 Conversion of 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane and selectivity to 2,2-difluoroethylamine with changing molar ratio. (Reaction conditions: molar ratio $(NH_3/CHF_2CH_2X) = 2/1-6/1$, reaction temperature = 160°C, reaction time = 12h)

From Fig. 1 (corrected by gas chromatography), 160°C was selected as the reaction temperature, while the molar ratio (NH₃/CHF₂CH₂X) increased from 2:1 to 6:1, the conversion of 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane rose with the increasing molar ratio. When the molar ratio reached 6:1, the upward trend tended to be flat. The rate of formation of 2,2-difluoroethylamine in the amination of 1-chloro-2,2-difluoroethylamine in the amination of 1-chloro-2,2-difluoroethylamine in the amination of 1-chloro-2,2-difluoroethylamine in the amination of 2,2-difluoroethylamine always approached 100% in the two reactions.



Fig. 2 Conversion of 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane and selectivity to 2,2-difluoroethylamine with changing temperature. (Reaction conditions: molar ratio $(NH_3/CHF_2CH_2X) = 6/1$, reaction temperature = 80-180°C, reaction time = 12h)

As shown in Fig. 2 (corrected by gas chromatography), the reaction temperature was increased from 80°C to 180°C and the molar ratio was 6:1 (NH₃/CHF₂CH₂X), the conversion of 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane rose significantly as the reaction proceeded in the two reactions. At the beginning, the progress of the each of the two reactions was relatively low, as the conversion of the two raw materials was less than

10%. With the reaction progressing, the conversion increased significantly, and finally the upward trend tended to be flat. The rate of formation of 2,2-difluoroethylamine in the amination of 1-chloro-2,2-difluoroethane was higher than that of 1-bromo-2,2-difluoroethane. Besides, the selectivity of 2,2-difluoroethylamine always approached 100% in the two reactions, which indicated that the reaction produced no by-products.



Fig. 3 Conversion of 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane and selectivity to 2,2-difluoroethylamine with changing time. (Reaction conditions: molar ratio (NH_3/CHF_2CH_2X) = 6/1, reaction temperature = 160°C, reaction time = 2-12h)

Choosing a representative temperature point of 160°C and a molar ratio point of 6:1, the reaction time was changed to observe the effect on the two groups of reactions. As shown in Fig. 3 (corrected by gas chromatography), with the longer reaction time, the conversion increased significantly, and finally the upward trend tended to be flat respectively. And the conversion of reactant in the amination of 1-chloro-2,2difluoroethane was always higher than that of 1-bromo-2,2-difluoroethane, which demonstrates that 1-chloro-2,2-difluoroethane was more prone to amination than 1-bromo2,2-difluoroethane. When the reaction time was 12h, the yield of 2,2-difluoroethylamine was 59.5% in the amination of 1-chloro-2,2-difluoroethane without catalyst and solvents, which was slightly higher than that in the presence of KBr catalyst (yield: 59%) [17]. Thus, the present experiments provide another facile method to synthesize 2,2-difluoroethylamine without catalyst and solvent.

In the above single factor experiments, it can be found that at the same reaction condition, the conversion of 1-chloro-2,2-difluoroethane was always higher that of 1-bromo-2,2-difluoroethane in the amination with NH₃. Thus, 1-chloro-2,2-difluoroethane was more easily aminated compared to 1-bromo-2,2-difluoroethane. In order to find the reason for the above results, the chemical computations in the amination of 1-halo-2,2-difluoroethane were then performed.

2.2 Computation

2.2.1 Geometries

The optimized structures of all located stationary points and selected geometrical parameters at the B3LYP/6-311+G level were shown in Fig. 4 and Fig. 5. Attack on the carbon atom of the $-CH_2X$ group by NH₃ proceeded via the transition states leading to intermediates $CHF_2CH_2NH_3^+Cl^-$ and $CHF_2CH_2NH_3^+Br^-$, respectively. Subsequently, another NH₃ molecule reacted as a base to abstract the proton and deliver $CHF_2CH_2NH_2$.



Fig. 4 Selected geometrical parameters of the optimized reactants, transition states and products of the first step at the B3LYP/6-311+G level. Bond lengths are in Å, and angles are in degrees.

 $CHF_2CH_2NH_3^+Br^-$

94.56

TS2

Fig. 4 showed that the C–Cl bond in 1-chloro-2,2-difluoroethane must elongate by 0.410 Å to reach TS(1), while from CHF₂CH₂Br to TS(2) the corresponding value for the C–Br bond was 0.482 Å. In contrast, the lengths of the forming C–N bonds in the TS1 and TS2 geometries (2.216 Å and 2.145 Å respectively) were both longer than those in the corresponding products (1.496 Å and 1.497 Å respectively). The fact that the C–N bond shortened from transition state to product was possibly attributed to an interaction between the unpaired electron of the N atom of ammonia and the C atom, leading to an electron transfer. During the reaction, the C–C–N bond angle increased from 93.33° in TS1 to 111.4° in CHF₂CH₂NH₃+Cl⁻, forming a relatively stable structure, while it increased from 94.56° in TS2 to 111.5° in CHF₂CH₂NH₃+Br⁻.

As displayed in Fig. 5, the C–N and the C–C bond lengths in the transition state were 1.486 Å and 1.505 Å respectively, and the C–C–N bond angle were 112.5°. While the C–N bond shortened to 1.459 Å in CHF₂CH₂NH₂, the length of the C–C bond changed only slightly to 1.506 Å, and the C–C–N bond angle increased to 113.6°, leading to a relatively stable structure.



Fig. 5 Selected geometrical parameters of the optimized reactants, transition states and products of the second step at the B3LYP/6-311+G level. Bond lengths are in Å, and angles are in degrees.

2.2.2 Molecule Electrostatic Potential Analysis

Molecule electrostatic potential was associated with the electronic density, and was a well-suited descriptor for identification of sites for nucleophilic and electrophilic reactions, in addition to hydrogen bonding interactions [25]. Mapped electrostatic potential (ESP) surfaces of the optimized structures of the three reactants and the product at DFT-B3LYP level were shown in Fig. 6.



Fig. 6 B3LYP/6-311+G optimized structures and Multiwfn calculated mapped electrostatic potential (MESP) surfaces of CHF₂CH₂Cl (A), CHF₂CH₂Br (B), NH₃ (C), and CHF₂CH₂NH₂ (D). Red, white and blue represent positive, zero and negative electrostatic potential values (kcal mol⁻¹) respectively.

For 1-chloro-2,2-difluoroethane (A), the highest electron density was localized on the carbon atom which is attached to the chlorine atom (62.00kcal/mol), and was higher than that of the corresponding carbon atom in 1-bromo-2,2-difluoroethane (B) (57.69kcal/mol). The higher the ESP value, the more likely a nucleophilic reactionwas to occur, otherwise, the electrophilic reaction would contribute to the reaction. Thus, the carbon atom of 1-chloro-2,2-difluoroethane was more prone to reaction with an electron donating group [26]. Among all calculated values, the nitrogen atom of NH₃ (C) had the lowest electron density (-48.70kcal/mol), which indicated its ability to donate electrons. In contrast, the carbon atoms which were bound to the halogen atoms in 1-halo-2,2-difluoroethane (halogen = Cl or Br) had a relatively strong ability to attract electrons, which was reflected in their high

electrostatic potential.



2.2.3 Energetics

reaction A reaction B

Fig. 7 Potential energy profile for the reaction of CHF₂CH₂Cl+NH₃ (reaction A) and CHF₂CH₂Br+NH₃ (reaction B) at the B3LYP/6-311+G level of theory.

In order to understand the reaction mechanism, DFT calculations were performed to elucidate possible reaction paths. Based on B3LYP/6-311+G, the ZPVEs, energies, enthalpies and Gibbs free energies of various stationary points were calculated. The energies of the reaction pathways for the two substrates were shown Fig. 7. The reactions were predicted to occur in two steps, and the energy values of the reactants of each step $(CHF_2CH_2Cl + NH_3/CHF_2CH_2Br + NH_3 \text{ and } CHF_2CH_2NH_3^+ + NH_3)$ were set as zero for reference.

As shown in Fig. 7, the first step of the reaction for either substrate proceeded through transition states TS1 and TS2, forming intermediates IM1 and IM2, respectively. From Fig.7, the energy of TS1 was higher than that of the reactants $CHF_2CH_2Cl + NH_3$ by

59.33kJ/mol, while the difference in energy between TS2 and $CHF_2CH_2Br + NH_3$ was 87.44kJ/mol. As such, the activation energy barrier of the reaction 2 was higher than that of the reaction 1 by 28.11kJ/mol. In the second step, shown in Fig. 8, either reaction proceeds via the same transition state, which was higher in energy than the reactants $CHF_2CH_2NH_3^+ + NH_3$ by 2.01kJ/mol.



Fig. 8 Potential energy profile for the reaction of CHF₂CH₂NH₃⁺+NH₃ at the B3LYP/6-311+G level of theory.

According to the data and discussion provided above, it was concluded that the reaction proceeded preferentially by attack of the NH₃ molecule to the carbon atom of the $-CH_2X$ group, forming intermediate $CHF_2CH_2NH_3^+X^-$, with subsequent reaction of a second NH₃ molecule as a base to deprotonate the intermediate and deliver $CHF_2CH_2NH_2$. The discussion of the reaction energetics was consistent with structural implications and the Hammond's postulate, confirming the earlier character of TS1 when compared to TS2.

2.2.4 HOMO-LUMO analysis

Frontier molecular orbitals, namely highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), were the most important orbitals in a molecule. These orbitals determine how a molecule interacted with other species [27], and the frontier molecular energy gap aids the characterization of the chemical reactivity [28]. The higher the HOMO energy, the more facile it was for it to donate electrons, whereas LUMO was more prone to accept electrons when its energy was low [29]. In order to simulate the energetic behavior of the title reaction, HOMO-LUMO energy calculations of transition states were carried out by DFT theory level calculations using the B3LYP method with 6-311+G basis set.

Band
$$gap(E_b) = E_{LUMO} - E_{HOMO}$$
 (1)





Fig. 9 Calculated molecular orbital energy levels of transition states and intermediates with molecular orbital maps of LUMO and HOMO. Red and blue correspond to different phases of the molecular wave functions for the frontier molecular orbitals.

1-Halo-2,2-difluoroethanes were electrophilic in nature. The HOMO of NH₃ reacted with the LUMO of the 1-halo-2,2-difluoroethane molecules, a reaction in which the nitrogen atom participates as the electron donor. As shown in Fig. 9, the HOMO-LUMO band gap of TS1 was wider than that of TS2, and the difference in the band gaps was 0.7370eV. This contributed to the higher stability and indicateed that a lower energy barrier had to be overcome in order for the reaction to occur. In addition, the band gap of IM1 was larger than that of IM2 suggesting that IM1 possessed a lower energy, which was consistent with the energy calculations. According to I. Fleming, the HOMO represented the molecule's ability to donate electrons, while the LUMO represented the molecule's ability to accept electrons [30]. Consequently, by comparing the HOMO-LUMO band gap and stability of two transition states, it was concluded that preparation of 2,2-difluoroethylamine from amination of 1-chloro-2,2-difluoroethane was more facile than

from that of 1-bromo-2,2-difluoroethane.

2.2.5 Rate Constant

Wigner and Eckart tunneling corrections were plotted in Fig. 10. Analysis of the plot reveals that Wigner and Eckart tunneling contributions become more significant as the temperature decreases. While all values were in the range of 1.00–1.25, Eckart corrections were consistently larger than the corresponding Wigner values. Within the temperature range of 1000–2500K, both values were nearly the same for a given temperature, and vary only slightly within this range. In contrast, tunneling values increased sharply from approximately 1.02 to 1.24 as the temperature decreased from 1000K to 298K.



Fig. 10 Plots of tunneling coefficients for CHF₂CH₂Cl+NH₃ (A) and CHF₂CH₂Br + NH₃ (B) evaluated by different theoretical methods. W and E referred to Wigner and Eckart corrections, respectively.

Rate constants were calculated by TST (conventional transition state theory) and CVT (canonical variational transition state theory) at the B3LYP/6-311+G level for a wide temperature range of 298.15K–2500K. Fig. 11 showed the profiles of the logarithm of TST,

CVT, TST/W, CVT/W, TST/E, and CVT/E rate constants versus the reciprocal (1000/T) of reaction temperatures, taking into account the Wigner and Eckart tunneling corrections.



Fig. 11 Plots of rate constant expressions for the reactions $CHF_2CH_2Cl+NH_3(A)$ and $CHF_2CH_2Br + NH_3(B)$ evaluated by different theoretical methods, highlighting the sections in which the temperature ranges from 298.15K to 500K and from 1250K to 2500K in the bottom and right amplifications, respectively.

As displayed in Fig. 11, the data obtained by either calculation method for both reactions was similar. For the reaction $CHF_2CH_2Cl+NH_3$ (A), the distinction between the TST and the CVT rate constants was more pronounced than for reaction B in the wide temperature range. It was noticeable that the evaluated kTST values are larger than kCVT in both cases. In contrast, the amplified figure at the bottom (temperature range: 298.15 K–

500 K) shows that nearly the same values were obtained by the two computing methods for reaction B, while a small difference was observed for reaction A. In addition, the order $kTST \ge kCVT$ for the reactions described herein conforms with the theoretical definition by Fernández-Ramos et al. [31].

From Figure 11, the rate constants of the two reactions obtained by the TST method and the CVT method can be obtained. Among them, the rate constant of CHF₂CH₂Cl+NH₃ (A) was much larger than that of CHF₂CH₂Br+NH₃ (B), between 298.15-500K. And as the temperature increased, the difference gradually decreased (1250-2500K), but the rate constant of CHF₂CH₂Br+NH₃ (B) is always smaller than CHF₂CH₂Cl+NH₃ (A). Therefore, the calculation result of the rate constant was consistent with the above calculation and experimental results, indicating that 1-chloro-2,2-difluoroethane was easily aminated than 1-bromo-2,2-difluoroethane.

3. Conclusions

The experiments on 1-chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane reacting with ammonia were carried out. The reaction temperature, molar ratio, and reaction time were changed to obtain the conversion rate and selectivity of the two reactions, respectively. By comparing the experimental results, it was found that the 1-chloro-2,2-difluoroethane was easier to be aminated with NH₃ than 1-bromo-2,2-difluoroethane. In order to understand the detailed mechanism and the kinetics of the formation of 2,2-difluoroethylamine by amination of 1-halo-2,2-difluoroethane with ammonia, the two reactions were calculated and simulated by various analysis theories, including energy calculation, geometry analysis, and band gap comparison. Results obtained by thermodynamic calculations indicated that the amination of 1-chloro-2,2-difluoroethane with ammonia was more facile than that of 1-bromo-2,2-difluoroethane. The results

reported herein can facilitate the screening for synthetic routes toward 2,2difluoroethylamine.

4. Experimental

4.1 Chemicals

1-Chloro-2,2-difluoroethane and 1-bromo-2,2-difluoroethane (purity > 98%) were purchased from Baokai Chemical Co., Ltd. (Jiangsu, China). Ammonia was purchased from Xinghua Group Co., Ltd. (Shaanxi, China).

4.2. Instruments

The synthetic reaction system consisted of a reaction kettle, a thermometer, and a programmable temperature control device.

Gas chromatography (GC) was performed on a GC9560 thermal conductivity detector (TCD) instrument equipped with a GS-GASPRO column of 30 m length and 0.320 mm inner diameter. The operating conditions for the gas chromatography were as follows: 40°C for 3min; 15°C min⁻¹ until 230°C; hold for 40min. Both the injection port and the thermal conductively were maintained at 200°C, and the nitrogen (N₂) carrier gas was introduced at a rate of 0.5mL min⁻¹. The content of the product was analyzed on-line.

To calculate the conversion rate of CHF₂CH₂NH₂ and the selectivity of CHF₂CH₂Cl and CHF₂CH₂Br, their GC relative response factors needed to be measured. Placed each 10mmol sample into a 5ml glass reagent bottle and mixed well. The above-mentioned mixture liquid was carried to the GC by a carrier gas under warm atmosphere and their relative GC areas were measured. Finally, the following ratio was: $CHF_2CH_2Br/CHF_2CH_2NH_2/CHF_2CH_2Cl = 0.92/1/1.34$, and obtain the GC relative response factor by relative calculation. The data were used to calculate the conversion of $CHF_2CH_2NH_2$ and the selectivity of CHF_2CH_2Cl and CHF_2CH_2Br in amination fluorination reaction.

4.3 Synthesis of 2,2-difluoroethylamine

Experiments were carried out in a reactor which was subjected to a leak test prior to introduction of the reactants. Once the absence of a leak was ensured, the container was evacuated. 1-Halo-2,2-difluoroethane and liquid ammonia were introduced sequentially. The reaction was carried out under stirring and certain temperature conditions and reaction conditions were: $(NH_3/CHF_2CH_2X) = 2/1-6/1$, reaction temperature = 80-180°C, reaction time = 2-12h. After the reaction was finished, the aliquot was collected and analyzed online by gas chromatography and the results are shown in Figures 1-3.

4.4 Computation methods

4.4.1 Theoretical calculations

In order to elucidate the reaction mechanism, theoretical calculations were performed with Gaussian 09 software packages [32]. Geometries of the reactants, products and transition states of the examined reactions were fully optimized with the density functional theory (DFT) with Becke three-parameter Lee-Yang-Parr correlation B3LYP [33] at the B3LYP/6-311+G level. Furthermore, single point energy including the zero-point vibrational energy (ZPE) corrections was performed on the optimized structures. By analyzing vibrational frequencies, the located stationary points could be confirmed at the same level. The intrinsic reaction coordinates (IRC) calculations [34, 35] with a step size of 0.100 Bohr confirmed the reaction from reactants to products. In addition, the HOMO-

LUMO energy calculations of transition states were carried out by DFT theory level B3LYP method with 6-311+G basis set to simulate the energetic behavior of the title reaction. Finally, electrostatic potential (ESP) surfaces were calculated with the Multiwfn [36] package as well as the molecular surface quantificationally [37] analysis, which was a valuable technique for analyzing non-covalent interactions, studying molecular recognition modes, and predicting reactive sites and reactivity.

4.4.2 Rate constant calculations

Thermal rate constants in the temperature range of 298K–2500K were calculated using conventional transition-state theory (TST) and canonical variational TST(CVT).

In the conventional transition-state theory (TST), the equation of thermodynamic equivalent was employed:

$$K^{TST}(T) = \sigma \frac{k_b T}{h} \left(\frac{RT}{P^0}\right)^{\Delta n} e^{-\frac{\Delta G^{*0}}{k_b T}}$$
(4)

This was the reaction path degeneracy, in which k_b (J/K) was the Boltzmann constant, T (K) was the temperature, h (J/s) was the Planck constant, N_A was the Avogadro number, and $G^{\neq 0}$ represents the standard Gibbs free energy of activation for the considered reaction (RT/P⁰ has a unit of the inverse of a concentration).

The canonical variational TST (CVT) was summarized in equation (5) and involved a generalized transition state [38] rate constant, which was obtained by performing an IRC calculation [39] using Gaussian 09:

$$K^{GT} = \sigma \frac{k_b T}{h} \frac{Q^{TS}(T,S)}{N_A Q^R(T)} e^{-\frac{v^*(s)}{k_b T}}$$
(5)

In the above equation, s was the distance along the MEP in isoinertial coordinates. In this theory (CVT), the rate constant $k^{CVT}(T)$ was obtained by minimizing k^{GT} with respect to s along the reaction path:

$$K^{CVT} = \min_{s} K^{GT}(T, s)$$
(6)

Taking quantum mechanical effects into consideration in the theoretical kinetic models, the TST and CVT rate constants were improved by a temperature-dependent tunneling coefficient, κ (T), which was approximated using the Eckart [40] and Wigner [41] correction methods. The corrected rate constants were computed by the following expressions:

$$K^{TST/T} = \kappa(T) \times K^{TST}(T)$$
⁽⁷⁾

$$K^{CVT/T} = \kappa(T) \times K^{CVT}(T)$$
(8)

Here, TST/T and CVT/T denote TST and CVT including the tunneling corrections, respectively.

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