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Mechanism of nucleophilic substitution reactions of 4-(4 -nitro)phenylnitrobenzofurazan ether with aniline in acetonitrile.

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Abstract:
Rate constants and activation parameters obtained for the nucleophilic aromatic substitution reactions (S_NAr) of 4-substitutedphenoxy-7-nitrobenzoxadiazole (1) with aniline in acetonitrile at varying temperature using Nuclear Magnetic Resonance (NMR) techniques were reported. These results were compared with the theoretical study which identifies transformations and intermediates using Density Functional Theory (DFT).

Keywords: Nucleophilic aromatic substitution, NMR, DFT
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1 Introduction

The 7-nitrobenzofurazan derivatives are a product of the nucleophilic aromatic substitution (S_NAr) of the activated chlorine atom on 4-chloro-7-nitrobenzofurazan (4-chloro-7-nitrobenzo-2-oxa-1,3-diazole, NBD chloride, NBD-Cl) **1** by primary or secondary amines, thiols and phenoxide tyrosine anions [1–7]. Hence, nitro-2,1,3-benzoxadiazoles, and related oxide derivatives (commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively) attracted much interest as typical 10 π electrons heteroaromatic substrates possessing an extremely high electrophilic character. The electrophilic character of nitro-2,1,3-benzoxadiazoles derivatives is particularly remarkable in the case of halo-nitrobenzofurazans that easily undergo S_NAr reactions, leading to several analytical and biochemical applications [8]. Some 4-aryloxy-7-nitrobenzofurazan derivatives have biologically active structural fragments, allowing their use in pharmacokinetics and pharmacodynamics. Some have also been reported to possess antileukemic and immunosuppressive activity [9].

The 4-chloro-7-nitrobenzofurazan **1** is a compound with variety of uses ranging from fluorescently labelling amino acids for diagnostic purposes [10, 11] through to the creation of highly sensitive fluorescent/colometric probes for use in analysis. Its use as a building block to generate much larger fluorescent systems justifies studies in the mechanism by which it reacts with nucleophilic molecules. Aromatic nucleophilic substitution of NBD-Cl has drawn attention in the literature and displays a range of reactivity. For instance, susceptibility to attack at position 5 by carbanions has been characterized kinetically [12]. However, the reactivity of NBD-Cl at position 7 is widely documented and the reactions at this position with indoles [13], indolizines [14] and series of substituted phenols [15] are good examples of this.

In this present work, the nitrophenoxy derivative **3** is first synthesized by reacting NBD-Cl **1** with 4-nitrophenol **2** (Figure 1). Activation parameters for the reaction of this derivative, 4-(4 -nitro)phenoxy-7-nitrobenzofurazan **3**, with aniline **4** (Figure 1) have been determined by performing this reaction at a variety of temperatures.

K. Lobb is the corresponding author.

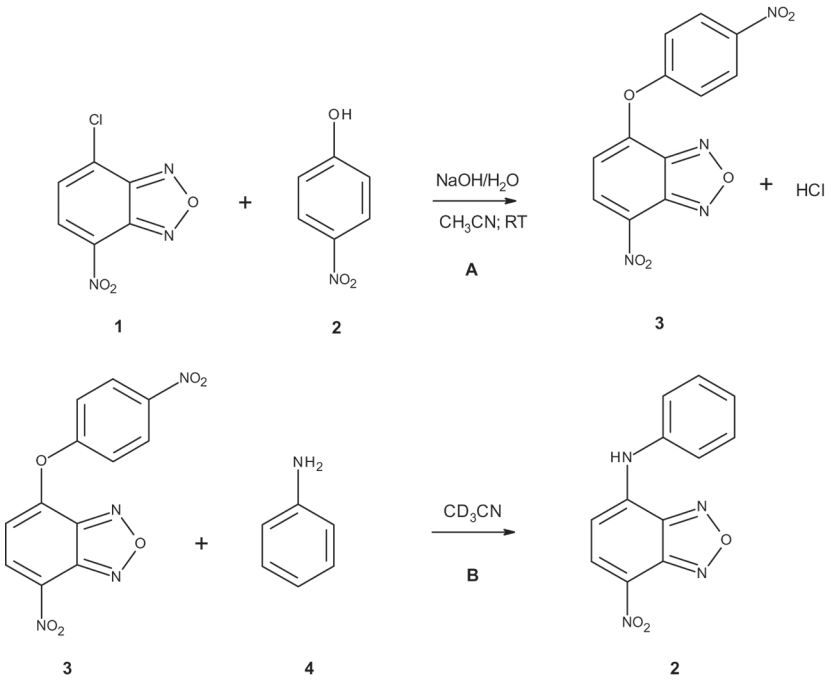

Figure 1: Synthesis **A** of the nitrophenoxy adduct, and its aminolysis **B**.

2 Results and discussion

The mechanism for S_NAr attack by the aniline is expected to follow the mechanism in Figure 2 [15]. A σ-complex is initially formed; subsequent to this, a proton transfer and loss of the leaving group results in the reintroduction of the aromaticity.

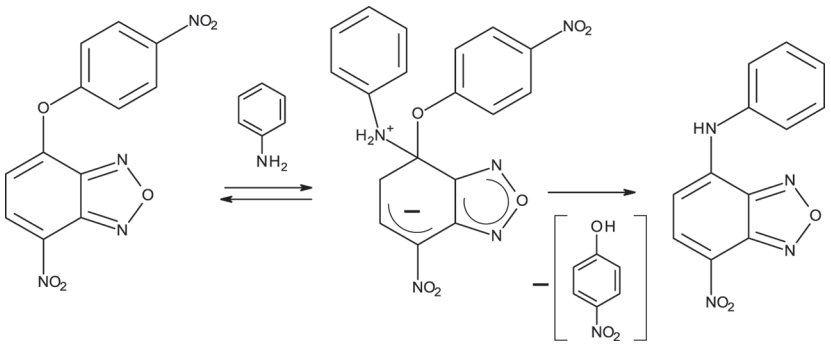

Figure 2: S_NAr mechanism forming the σ-complex intermediate, followed by loss of the leaving group.

In CDC_3N, the reaction between 4-(4 -nitro)phenoxy-7-nitrobenzofurazan **3** and aniline **4** is spontaneous at room temperature. Figure 3 illustrates the stacked 600 MHz ^1H Nuclear Magnetic Resonance (NMR) spectra obtained at time intervals at 328 K for this process. From this, the disappearance of the signal at 8.40 and 8.52 ppm from the phenoxy substrate disappears, while the aniline derivative forms as seen by the appearance of the signal at 7.28 and 8.10 ppm. Signals from the σ-complex intermediate were not observed in the NMR spectra.

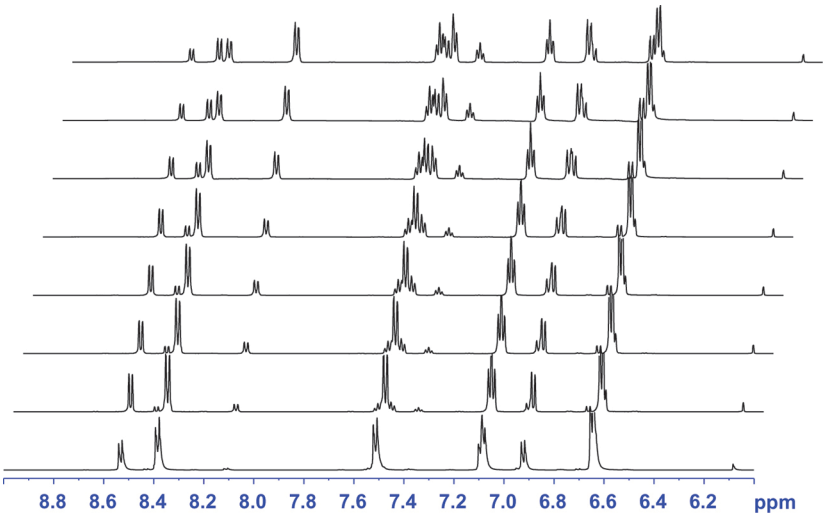

Figure 3: Stacked plot of the reaction of NBD-ether and aniline in CD_3CN at 328 K.

The trimethoxybenzene (TMB) signal at 6.13 ppm remains constant throughout the reaction as expected. The kinetics data were acquired for a range of temperatures (296 K–328 K) and were automatically integrated. The ^{1}H-NMR integral data were used to determine the rate of formation of product and the rate of consumption of the reactants. After conversion of the integrals to the concentrations of the various species in the reaction mixture, the graphs of these concentrations versus time were plotted against a theoretical concentration curve based on a second-order rate law. The plots of experimental versus theoretical concentrations are illustrated in Figure 4.

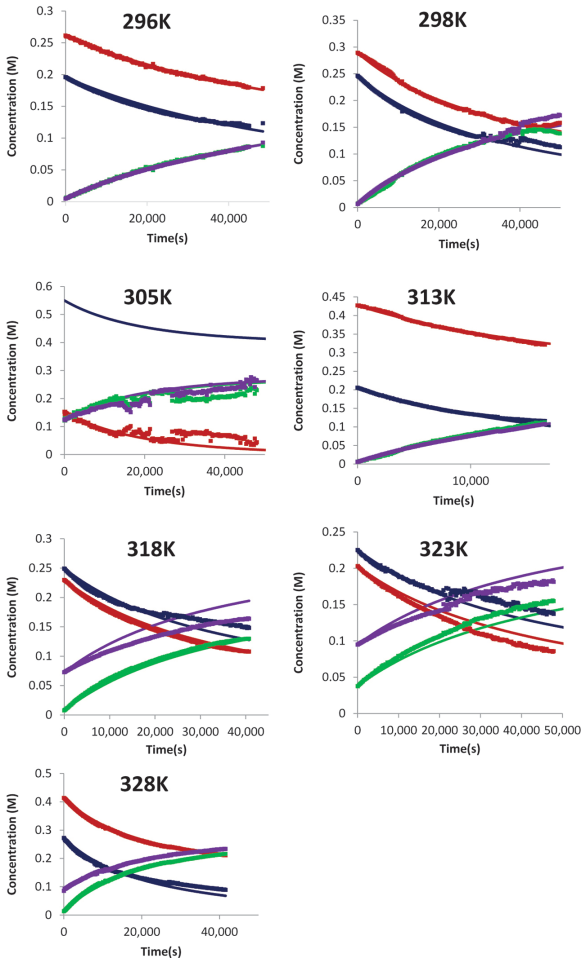

Figure 4: Theoretical and experimental superimposed graph of concentration versus time for the reaction of NBD ether with aniline at various temperatures.

Product **5** formation and decrease in the concentration of NBD ether **3** as well as the aniline **4** was evident from the ^{1}H-NMR integral (Figure 3).The shapes of the curves for the reactants and products of the theoretical concentration versus time graphs for the proposed model plotted were close to those of the experimental kinetic data (Figure 4). Rate constants determined showed a consistency with second-order kinetics. Figure 5 shows the Eyring plot for this process with $\Delta G^{\neq}$ = 23.1±1.9 kcal.mol^{-1}, $\Delta H^{\neq}$ = 2.27±0.95 kcal.mol^{-1} and $\Delta S^{\neq}$ = –69.8±3.1 Cal.mol^{-1}.K^{-1}.

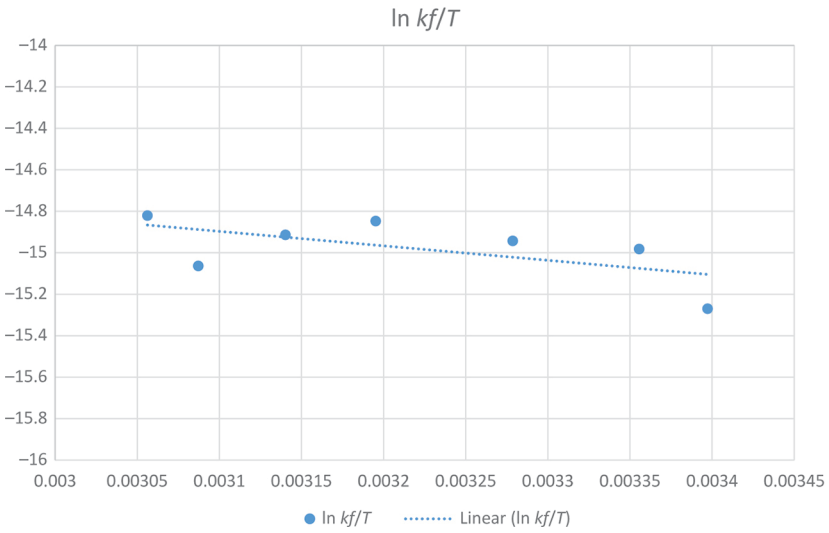

Figure 5: Eyring plot for the process.

The large negative $\Delta S^{\neq}$ value and small positive $\Delta H^{\neq}$ value suggests that the reaction proceeds through a typical rate-determining nucleophilic attack.

In a theoretical study, transition states and intermediates (Figure 6) were optimized for the reaction of aniline **4** with 4-(4 -nitro)phenoxy-7-nitrobenzofurazan **3** at the M06-2X/6-31+G(d,p) level [16], and the potential energy surface passing through the σ-complex intermediate is presented in Figure 7, with the values reported in Table 1. Under these conditions, the activation free energy for the rate-determining initial step was determined to be of the order of 50 kcal/mol. This is of the same order of magnitude as the experimental data, but a more accurate correlation might be obtained by investigation of the microscopic rate constants, or from MP2 or CCSD calculations. The σ-complex has been identified. Proton transfer in this intermediate is responsible for the final transition state and the formation of the final product.

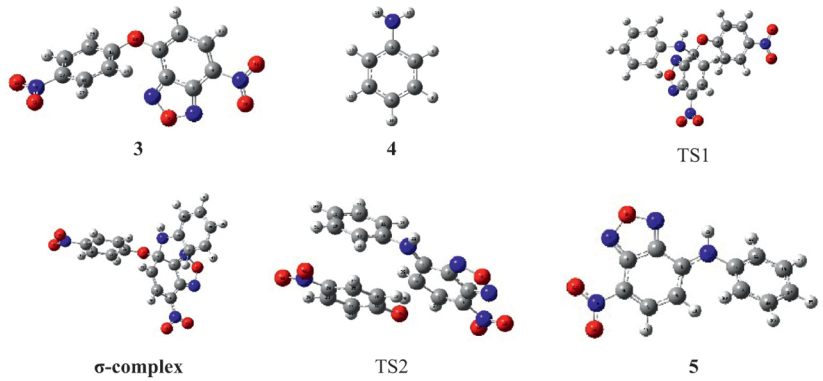

Figure 6: Optimized structures of molecules **3, 4**, TS1, the σ-complex intermediate, TS2 and **5** obtained at the DFT/M06-2x/6-31G+(d,p) calculation in acetonitrile.

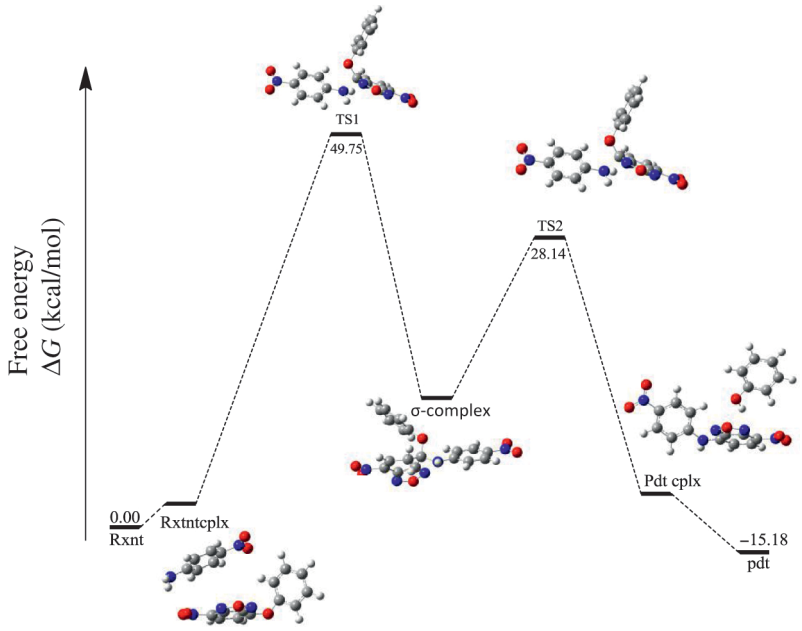

Figure 7: Potential energy surface for the transformation of 4-(4 -nitro)phenoxy-7-nitrobenzofurazan **3** to the adduct **5**.

Table 1: Thermodynamic and kinetic parameters for studied reaction calculated using DFT/M06-2x/6-31+G(d,p).

	In vacuo			In acetonitrile		
	TS1	TS2	5	TS1	TS2	5
ΔG^0 (kcal.mol^{-1})	51.42	34.68	–13.25	49.75	28.14	–15.8
ΔH^0 (kcal.mol^{-1})	37.83	21.55	–13.49	35.65	16.10	–15.92
ΔS^0 (cal.mol^{-1}.K^{-1})	–45.60	–44.06	–0.81	–47.31	–40.40	–2.48

3 Conclusion

The kinetic studies of the reaction of 4-(4 -nitro)phenyl-7-nitrobenzofurazan ether with aniline has been carried out in acetonitrile at a variety of temperatures. These results are consistent with a S_NAr-Ad.E reaction with a rate-limiting nucleophilic attack and formation of the intermediate σ complex followed by fast expulsion of the phenoxy leaving group proposed for the anilinolysis of 4-nitrophenyl-7-nitrobenzofurazan ether in acetonitrile. A potential energy surface has been calculated at the M06-2X/6-31+G(d,p) level in support of this mechanism.

4 Experimental section

Sodium hydroxide (0.02 g, 0.5 mmol) was dissolved in water (1 cm^3) and 4-nitrophenol (0.0695 g, 0.5 mmol) was dissolved in solution. 7-Chloro-4-nitrobenzofurazan (0.0998 g, 0.5 mmol) was dissolved in acetonitrile (2 cm^3) and added to the phenolate solution while stirring for 1 h. About 10 ml of distilled water was added to precipitate the ether which was then filtered and recrystallized from ethanol.

Kinetics: The progress of the reaction between 4-nitrophenylnitrobenzofurazan ether and aniline to form the corresponding nitrobenzofurazan amine derivative was monitored using the ^{1}H-NMR integral ratios of selected structure-specific signals. The integral data were generated as text and opened in MS-Excel. Trimethoxybenzene (TMB) was used as the internal standard. Kinetic experiments were carried out in CD_3CN at 296 K, 298 K, 305 K, 313 K, 318 k, 323 k and 328 k.

Calculations: All density functional theory (DFT) calculations were performed using the Gaussian 09 package [17]. Molecular geometries were optimized using DFT M06-2X method and 6-31+G(d,p). Vibrational frequencies of all optimized structures were calculated to inspect the nature of the stationary points (minimum or transition structure), and transition state structures are associated with only one imaginary frequency.

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