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FULL PAPER

Kinetic Study of the Reaction of Benzofuroxans with 2-Acetylthiophene: Effect of the Substituents on the Reaction Rate Using Hammett Equation

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Abstract:

The present work reports kinetic study of the reaction of benzofuroxan and its derivatives with 2-acetylthiophene. Hammett equation was used to determine the rate of the reaction and substituent effect. Specifically, chloro, nitro and methyl substituted benzofuroxans react with α-carbonyl compounds to form a fungicidal product quinoxalines-di-*N*-oxide (phenazine *N*5, *N*10-dioxides). The effect of the benzofuroxan substituents on the reactivity was performed and monitored by a UV/Visible spectrophotometer. The rate constants of the benzofuroxan, 5-chlorobenzofuroxan, 4-nitrobenzofuroxan, 5-methylbenzofuroxan and 4,6-dinitrobenzofuroxan reactions were found to be $3.32x10^{-3}$, $4.24x10^{-3}$, $3.48x10^{-3}$, $8.03x10^{-3}$ and $9.41x10^{-3}$ min^{-1} respectively. Moreover, Log k/k_0 against the substituent constant σ gave a linear relationship, which indicates positive effect of electron withdrawing substituent on the reaction. Therefore, the substituents have substantial effect on the reaction of benzofuroxans with 2-acetylthiophene.

Keywords: 2-acetylthiophene; benzofuroxan; Hammett equation; substituent effect

1. Introduction

Furoxans and benzofuroxans are well known compounds that continue to attract particular attention due to a broad spectrum of biological activity, including antibacterial, antifungal, antileukemic, acaricide and immunodepressive properties. These compounds are widely used in organic chemistry as intermediate compounds for the synthesis of numerous heterocycles due to their electronic behaviors and remarkable substituent effect [1]. Therefore, furoxans and benzofuroxans have been described as promising prototypes to design new systems which can be used for biological and/or pharmaceutical purposes. Consequently, intense works in the field of medicinal chemistry of these systems have produced hybrid compounds containing moieties of both furoxans/benzofuroxans and classical drug in a single molecule [2].

Quinoxalines-di-*N*-oxides are known as potent biologically active agents. Therefore, subtherapeutic levels of quinoxalines-di-*N*-oxides have been used as animal growth promoters. Quinoxaline derivatives show interesting biological properties. The quinoxaline ring has been described as a bioisoster of quinolein, naphthalene and some other heterocycles which are the base of many antimalarial, antibacterial or antitumor agents such as quinine, mefloquine, pyrazinamide or tirapazamine. Therefore, quinoxalines are receiving increasing interest in the field of medicinal chemistry [3].

Lewis and Kluge reported that the reaction of benzofuroxan **1** with α,β-unsaturated aldehydes and ketones under base catalysis (amine) gave quinoxaline-mono-oxide. Thus, **1** reacted with trans-4-phenyl-3-buten-2-one in the presence of

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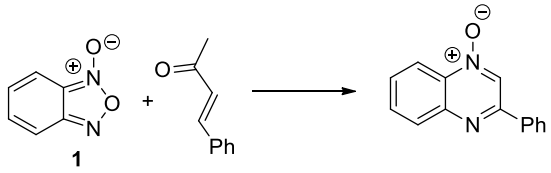
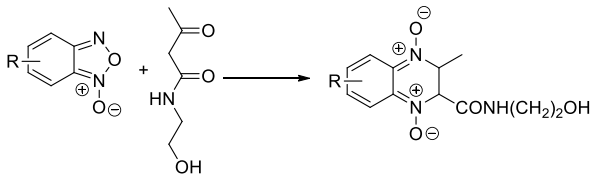
morpholine to give 3-phenylquinoxaline-*N*-oxide (Scheme 1) [4].

Issidorides and Haddadin studied the cycloaddition between **1** with enamines, β,α-unsaturated ketones, 1,3-dinitriles [5] or enolates [6] to produce quinoxaline-*N,N*'-dioxides. A variety of enamines and enolate anions have been found to react with **1**, giving quinoxaline-di-*N*-oxides, whereas Messmer and Hajos reacted benzofuroxan with hetaryl dienamines as activated olefins. Specifically, the reaction of 5-(4-aminobutadienyl) tetrazole derivatives with **1** gave quinoxaline-1,4-dioxide [7].



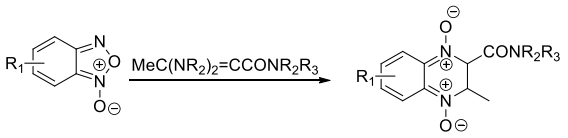
Scheme 1. The reaction of **1** with *trans*-4-phenyl-3-buten-2-one [4].

Stumm and Niclas prepared 2-methyl-3-(2-hydroxyethyl carbamoyl) quinoxaline-1,4-di-*N*-oxides as animal growth promoters by carrying out the condensation of benzofuroxans (R = H, MeO) with $MeCOCH_2CONHCH_2CH_2OH$ over catalyst consisting of calcium salt and $HOCH_2CH_2NH_2$ (Scheme 2) [8, 9].



Scheme 2. The preparation of 2-methyl-3-(2-hydroxyethyl carbamoyl) quinoxaline-1,4-di-*N*-oxides [8, 9].

2-methyl-3-aminocarbonylquinoxaline-1,4-di-*N*-oxides or feed additive olaquindox, which exhibits wide spectrum of antibacterial effect, was formed by cyclocondensation of MeC(NR2)=CHCONRR(R= H, alkyl) with benzofuroxans, (R =H, alkyl, alkoxy) in an organic solvent in the presence of ammonia or a primary amine (Scheme 3) [9].

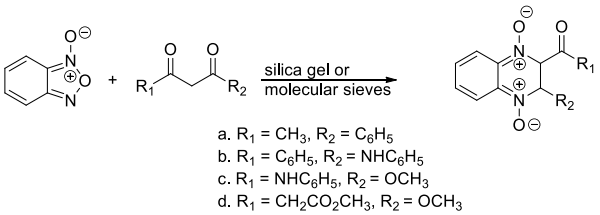


Scheme 3. Cyclocondensation of MeC(NR2)=CHCONRR(R= H, alkyl) with **1** to form 2-methyl-3-aminocarbonylquinoxaline-1,4-di-*N*-oxides.

Andrés *et al*., showed that ethyl and benzyl 3-methylquinoxaline-2-carboxylate 1,4-dioxide derivatives with the chlorine group and the unsubstituted derivatives have good antitubercular activities principally depend on the substituents in the carboxylate group [10].

Atfah and Hill studied the Beirut reaction of 2,1,3-benzoxadiazole-1-oxide and ethyl-2,4-dioxo-4-phenylbutyrate, which gave 2-benzoyl-quinoxaline-1,4-dioxide [11]. They also prepared aryl(4-methoxyphenyl and 2-naphthyl) and hetaryl (2-furyl, 3-pyridyl and 2-thienyl)3-methyl-2-quinoxalinyl ketone via reaction of **1** with 1-aryl and 1-hetaryl-butane-1,3-diones [12].

Miyazawa *et al*., synthesized quinoxaline-1,4-dioxide derivatives, phenazine-5,10-dioxide derivatives and pyrido[2,3-b]pyrazine derivatives from the corresponding **1** catalyzed over silica gel or molecular sieves (Scheme 4) [13].



Scheme 4. Synthesis of derivatives of quinoxaline-1,4-dioxide, phenazine-5,10-dioxide and pyrido[2,3-b]pyrazine using silica gel or molecular sieves [13].

Soliman (2013) synthesized and evaluated a series of quinoxaline 1,4-di-*N*-oxides for their antibacterial and antifungal activities [14]. The best result was demonstrated by 3-amino-*N*-(4-methoxyphenyl)-2-quinoxalinecarboxamide 1,4-di-N-oxide against *Aspergillus fumigatus* and *Streptococcus pneumonia*.

Cercetto *et al*., studied the effects of benzofuroxan substituents in the outcome of

their expansion reaction with phenolates and found that the electron donating substituents decrease the electrophilic characteristic of the benzofuroxans nitrogen at position 3 in the favored 5-substituted tautomers, whereas, the electron withdrawing substituents have been found to increase the electrophilic characteristic of benzofuroxans [15].

Although the reaction kinetic of **1** and substituted benzofuroxans with 2-acetylthiophene is very important, however, it has not been reported in literature. Therefore, the present paper reports the reaction rate and the effect of substituent of precursor compound benzofuroxans in the formation of quinoxalines using Hammett equation.

2. Results and Discussion

The preparation of benzofuroxans (chlorobenzofuroxan **1a**, methylbenzofuroxan **1b**, nitrobenzofuroxan **1c** and 4, 6-dinitrobenzofuroxan **1d** proceeded as described in literature. The melting points and physical characteristics of the synthesized compounds were identical to the reported literature [16-19].

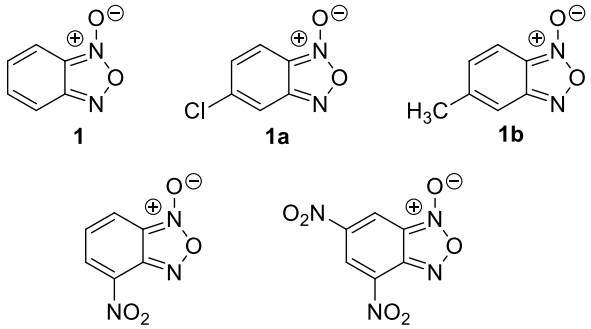


Figure 1. Benzofuroxan **1** and their substituted derivatives.

The kinetic reactions of benzofuroxans (chlorobenzofuroxan, methylbenzofuroxan, nitrobenzofuroxan and 4, 6-dinitrobenzofuroxan) were conducted at room temperature under pseudo-first order conditions in DMSO to establish an appropriate rate law for the reaction.

$$\Delta C = ([BFO]_o - [BFO]_t)\ M \quad (1)$$

where $[BFO]_o$ and $[BFO]_t$ are concentrations of benzofuroxan at time 0 and t minutes respectively. ΔC represents the change in concentration. Therefore, the reaction rate, R,

$$R = \Delta C/\Delta t\ M/s \quad (2)$$

The rate constant (k) for the reaction of benzofuroxan (BFO), 2-acetylthiophene and TEA in DMSO was determined by the integrated rate law for first order reaction.

$$k = 1/t\ \ln\alpha \quad (3)$$

where $\alpha = [BFO]_t/[BFO]_0$. Thus, for each reaction the average values of k (min^{-1}) and R (M/s) were obtained as described above.

From the kinetic experiment, the average value of rate (R) M/s and the rate constants (k) were obtained. The rate constants (k) of reactions were found to be $3.32x10^{-3}$, $4.24x10^{-3}$, $3.48x10^{-3}$, $8.03x10^{-3}$ and $9.41x10^{-3}$ min^{-1} as calculated by the integrated rate law.

The plots of $ln[BFO]_t$ against time (Figure 2) resulted in straight lines with rate constants (k) as slopes. These values are in good agreement with the values obtained by integrated rate law.

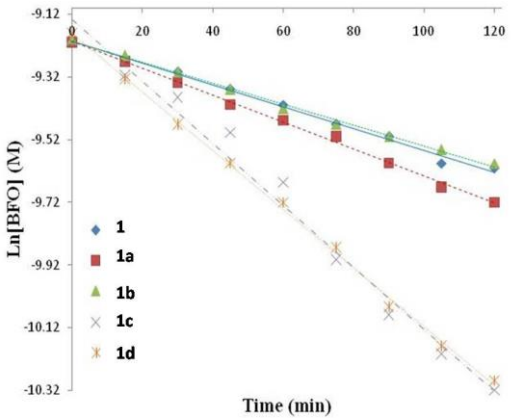


Figure 2. The kinetic reaction of benzofuroxans, ln[BFO] vs time (min).

The effects of substituent on the reaction rate of benzofuroxan with 2-acetylthiophene as demonstrated by the kinetic measurements were correlated to Hammett constants of the chlorobenzofuroxan, methylbenzofuroxan, nitrobenzofuroxan or and 4,6-dinitrobenzofuroxan.

Structure reactivity relationships

The study of the effect of substituents on the

reaction rate was carried out by the reaction of **1a**, **1b**, **1c** and **1d** with 2-acetylthiophene and compared with that of **1**.

Table 1 presents the effect of substituents on the reaction rate of benzofuroxans with 2-acetylthiophene. Obviously, the substituents have considerable effect on the reaction rate. The order of reactivity, starting with the most reactive first: 4,6-dinitrobenzofuroxan, nitrobenzofuroxan, chlorobenzofuroxan, benzofuroxan, methylbenzofuroxan. Interestingly, these results resemble values arrived by Hammett equation.

$$\text{Log}k/k_o = \sigma\,\rho \quad (4)$$

where k_o, is the specific rate constant for a given reaction with an unsubstituted reactant, k is the rate constant of the reaction using a substituted reactant, ρ and σ are constants determined by reaction and substituent respectively 20]. Specifically, the rate constants of benzofuroxans reactions were related to the structure and composition of the parent molecule. Notably, the electron density of the ring influenced the reaction reactivity of both **1** and its substituents.

As seen in Table 1, the electron donating group (CH_3) has a negative σ value. The negative σ value was anticipated as **1b** has small rate constant. Alternatively, the electron withdrawing groups (Cl, NO_2) have positive σ values. The reactivities of **1a**, **1c** and **1d** followed their high rate constants. Thus, σ values reveal specific substituent effects.

Table 1. Reaction rate of benzofuroxans with 2-acetylthiophene at R.T in DMSO.

Substituent (X)	k (min-1x 10-3)	Logk/k0	σ	ρ
H	3.32	0.0000	0.00	0.00
CH_3	3.48	0.0204	-	-1.20×10^{-3}
Cl	4.24	0.1062	0.17	0.46
NO_2	8.03	0.3836	0.23	0.48
4,6-(NO_2)	9.41	0.4524	0.80	0.58
			0.78	

As shown in Table 1 and Figure 3, the plotting of Log k/k_0 of electron withdrawing substituents versus σ gives straight line. While the electron donating group gives negative value. Thus, the positive value indicates that the substituents enhance the reaction. Alternatively, the negative value affects the reaction in the opposite way. Obviously, these relationships describe the susceptibility of the reaction to substituents, characteristic of Hammett plot [20]. Moreover, these results resemble that of Cercetto *et al*., [15].

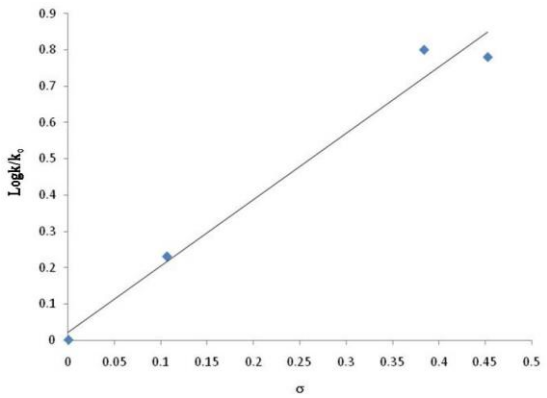


Figure 3. The effect of electron withdrawing substituents on the reaction rate of benzofuroxans; plotting Logk/k_o vs σ.

3. Material and Methods

3.1 Chemicals

Triethylamine (TEA) and o-nitroaniline were purchased from Koch-light laboratories Ltd. Colnbrook Bucks, England. Sodium nitrite, sodium azide and dimethyl sulphoxide (DMSO) were obtained from Hopkin and Williams Ltd. Chadwell Health Essex, England. Hydrochloric acid, nitric acid, sulphuric acid, glacial acetic acid, 2-acetylthiophene, ethanol and ether were purchased from Lancaster Synthesis, Eastgate, White Lundmore Camb, England. The chemicals were of analytical reagent grade and used without further purification.

3.2 Synthesis of benzofuroxan (BFO)

It was prepared by the method of diazotization of *o*-nitroaniline followed by thermal decomposition of *o*-nitrophenylazide. A dark yellow cluster was formed, recrystallized from 75% ethanol, melting point: 71-72 °C [16]. IR ν/cm^{-1}: 2225, 1345, 1333; ^{1}H-NMR δ/ppm: 7.38 (1H, H4`), 7.87 (1H, H3`), 8.69 (1H, H5`), 7.92 (1H, H7), 8.03 (1H, H6), 8.61 (1H, H8), 8.74 (1H, H5).

3.3 Synthesis of 5-chloro, and 5-methylbenzofuroxan

5-chlorobenzofuroxan was synthesized by diazotization of 4-chloro, 2-nitroaniline followed by thermal decomposition of the 4-chloro, 2-nitrophenylazide in glacial acetic acid, A pale yellow precipitate of 5-chlorobenzofuroxan was formed; melting point 46-48 °C. Similarly, 5-methylbenzofuroxan, was prepared by diazotization of 4-methyl, 2-nitroaniline followed by thermal decomposition of the corresponding azide; melting point 98-100 °C [16, 17].

5-chlorobenzofuroxan: IR ν/cm^{-1}: 2226, 1352, 1312; ^{1}H-NMR δ/ppm: 7.89 (1H, H3`), 7.39 (1H, H4`), 8.66 (1H, H5`), 8.77 (1H, H5), 7.94 (1H, H7), 8.59 (1H, H8).

5-methylbenzofuroxan: IR ν/cm^{-1}: 2234, 1345, 1310; ^{1}H-NMR δ/ppm: 2.67 (3H, CH_3), 8.63 (1H, H5), 7.83 (1H, H7), 7.86 (1H, H3`), 8.37 (1H, H8), 7.35 (1H, H4`), 8.60 (1H, H5`).

3.4 Synthesis of 4-nitrobenzofuroxan

A mixture of fuming nitric acid (0.01 mole, 4.95 mL) and H_2SO_4 (10 mL) was added drop wise to benzofuroxan (0.01 mole, 1.36 g) in H_2SO_4 (50 mL) at 0 °C , the solution was poured on crushed ice (200 g), the precipitate was filtered and recrystallized from ether, melting point: 143 °C [18]. IR ν/cm^{-1}: 2231, 1351, 1313; ^{1}H-NMR δ/ppm: 7.35 (1H, H4`), 7.53 (1H, H6), 7.81 (1H, H3`), 7.88 (1H, H8), 8.62 (1H, H5`), 8.63 (1H, H7).

3.5 Synthesis of 4,6-dinitrobenzofuroxan

It was prepared by nitration of 4-nitrobenzofuroxan as reported in the literature, melting point: 171-172 °C [19]. IR ν/cm^{-1}: 2238, 1536, 1357, 1331; ^{1}H-NMR δ/ppm: 7.33 (1H, H4`), 7.59 (1H, H6), 7.79 (1H, H3`), 7.87 (1H, H8), 8.64 (1H, H5`).

3.6 Kinetic measurements

Kinetic measurements were performed on 6505 UV/Vis. spectrophotometer, at room temperature. All kinetic runs were carried out in triplicate under pseudo-first order conditions with a mixture of benzofuroxan 1 x10^{-4} M and 2-acetylthiophene 0.004 M and TEA 0.1 mL in DMSO through suitable interval time at λ max 365 nm of the parent benzofuroxan as a function of time. The same procedure was repeated for the rate measurements of substituted benzofuroxans. The initial concentrations of 2-acetylthiophene were 40 times concentration of benzofuroxan. TEA was used as a catalyst for the reaction.

The pseudo first order rate constants (k) were calculated by the integrated rate law for first order reaction (Equation 6).

$$kt = - \ln([BFO]_t / [BFO]_o) \quad (6)$$

3.6 Preparation of solutions

0.0001 M of **1** was prepared by dissolving 0.0014 g in DMSO (50 mL). Similarly, equal concentrations of **1a**, **1b**, **1c** and **1d** were prepared.

3.7 Preparation of reaction products (Reaction of benzofuroxans with 2-acetylthiophene)

A mixture of **1** (0.0001 M), 2-acetylthiophene (0.004 M) and 0.1 mL of TEA was formed to give 2(2`-thienyl) quinoxaline-1,4-di-N-oxide. The same procedure was followed with other benzofuroxans [21].

4. Conclusions

The reactions of **1** and its derivatives (Cl, NO_2, CH_3) with 2-acetylthiophene to form quinoxaline-di-*N*-oxide proceed by the first order kinetics and the reaction rate depends on the reactivity of substituent, so that the reaction occurred more rapidly in the presence of an electron withdrawing group while the opposite occurs with an electron donating group.

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