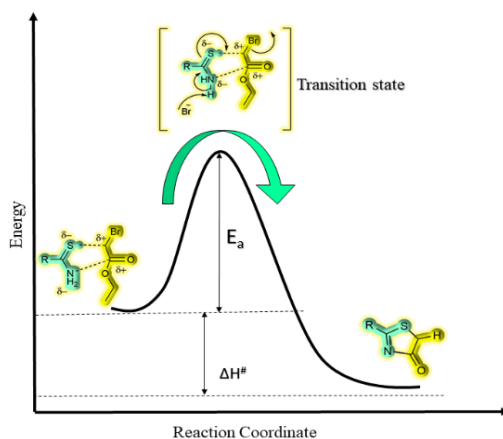


Chemical kinetics: cyclisation reaction of hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl 2-bromoacetate

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Transition state of the reaction

Substituted thiazolidine is formed from the cyclization reaction of hydrazine carbothioamide, thioacetamide, and thiobenzamide (thioamide) with ethyl 2-bromoacetate, and second-order reaction kinetics for both reactants are exhibited by the reaction, as determined by the Van't Hoff differential method. Thermodynamic parameter Energy of activation ($E_a = 65.1079$ kJ/mol/K, 54.54 kJ/mol/K, 36.87 kJ/mol/K), enthalpy ($\Delta H^\ddagger = 60.1195$ kJ/mol/K, 49.56 kJ/mol/K, 31.95 kJ/mol/K), entropy ($\Delta S^\ddagger = -65.862$ J/mol), Gibbs' free energy ($\Delta G^\ddagger = 79.87$ kJ/mol, 76.72 kJ/mol, 76.56 kJ/mol) and frequency factor ($A = 2.77 \times 10^{+09}$, $1.51 \times 10^{+08}$, $1.12 \times 10^{+05}$) was obtained by pH metric study of the reaction. According to the double-sphere mechanism, the distance between two atoms in solution with ethanol and isopropyl alcohol was calculated.

Keywords: kinetics, order, entropy, Gibbs' free energy, frequency factor, enthalpy.

INTRODUCTION

A link between medicinal chemistry and chemical synthesis is acted upon by thiazolidine structures, which encourage researchers to look at potential new therapeutic agents. The thiazolidine structure, which contains a five-membered heterocyclic ring with nitrogen in the third position and sulfur in the first position, is present. A variety of naturally occurring and biologically active molecules contain it as part of their structure. Its pharmacological aspects are improved by the presence of sulfur, making it useful as a carrier in the synthesis of important chemical combinations. A range of biological applications, such as antioxidant, anticancer, antispasmodic, antibacterial, anti-inflammatory, and neuroprotective effects, have

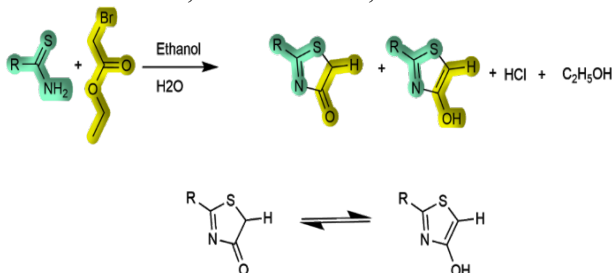
been demonstrated by it. It is highly valued as an ingredient because of its wide range of biological responses. Many synthetic methods have been applied to increase the selectivity, purity, product yield, and pharmacokinetic activity of thiazolidine and its derivatives, based on literature research. These methods include synthesis methods such as multicomponent reactions, click reactions, nano catalysis, and green chemistry. Reports have been made on the advantages of the green synthesis of thiazolidine and its derivatives, as well as their pharmacological activity [1]. 2-Hydrazinothiazolon-5-one (m.p. = 230°C) was produced under microwave irradiation in a solventless system by the condensation reaction of thiosemicarbazide with chloroacetic acid. A lengthy reaction period and a

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solvent is required for this reaction under normal heating [2]. Further reports of reactions between ethyl bromoacetate and substituted thiosemicarbazide and 1,1-dimethylsemicarbazides have been observed [3]. Previously, a kinetic study of thiazole formation using 3-chloroacetyl acetone and thioamides was reported by us [4]. The kinetics of 3-chloroacetyl acetone with various thioureas in ethanol has been reported [5]. The kinetics of the reaction between hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl 2-bromoacetate is yet to be investigated.

MATERIALS AND METHODS

Glass-distilled water was used in the investigation. All of the chemicals used in this work, including hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl 2-bromoacetate (Loba), are of analytical quality. A digital pH meter (Model: EQ-614A by Equiptronics) was employed to monitor the pH change as the reaction progresses. Absolute alcohol and glass-distilled water were used in the experiment. A standard solution (Scheme 1) was prepared using pure alcohol as the solvent, along with ethyl 2-bromoacetate and hydrazine carbothioamide, thioacetamide, and thiobenzamide:



Scheme 1. Reaction scheme

Kinetic measurements were carried out at different concentrations of reactants, temperatures, dielectric constants, and ionic strengths. A solution that contained the appropriate amount of hydrazine carbothioamide, thioacetamide, and thiobenzamide was added to an appropriate solution containing ethyl-2-bromoacetate at the same temperature. The pH meter readings were recorded at a particular time interval. According to the second-order integrated rate law, all the calculations were carried out. Equal amounts of hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl-2-bromoacetate were mixed and kept overnight under similar experimental conditions. Then the reaction mixture was neutralized with NaHCO₃ and extracted with diethyl ether. 2-hydrazineylthiazol-4-ol and 2-hydrazineylthiazol-4(5H)-one were characterized as the product, based on their spectral data and reported melting points of 230°C. The product was

recrystallized from ethanol and purified using column chromatography with n-hexane and ethyl acetate.

RESULTS AND DISCUSSION

The order *n* of the reaction [6] involving the following equation was determined using Van't Hoff's differential method (Table 1).

$$n = \frac{\log\left(\frac{dc}{dt}\right)_i - \log\left(\frac{dc}{dt}\right)_{ii}}{\log C_i - \log C_{ii}} \quad (1)$$

Table 1. Order concerning both reactant and reagent

Reactant	Reagent	Reactant	Reagent
Hydrazine-carbothioamide	Ethyl 2-bromoacetate	1.17002	0.89022
Thioacetamide	Ethyl 2-bromoacetate	0.967	0.984
Thiobenzamide	Ethyl 2-bromoacetate	0.9745	0.83873

The stoichiometric study indicated that one mole of ethyl 2-bromoacetate reacts with one mole of hydrazinecarbothioamide, thioacetamide, and thiobenzamide. The rates of reaction were measured for different concentrations of hydrazinecarbothioamide, thioacetamide, and thiobenzamide at a constant concentration of ethyl 2-bromoacetate. A straight line was observed on the plot of log₁₀(dc/dt) against log (thioamide) and the slope of the plot was nearly one (Fig. 1).

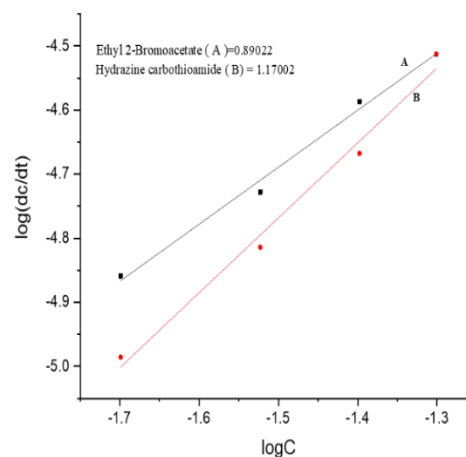


Figure 1. Order graph of hydrazinecarbothioamide with ethyl 2-bromoacetate.

Similarly, different concentrations of ethyl 2-bromoacetate determined the rates while keeping the concentration of hydrazinecarbothioamide, thioacetamide, and thiobenzamide constant. Van't Hoff's differential method [6] was used to determine the order of reaction concerning ethyl 2-

bromoacetate and hydrazinecarbothioamide, thioacetamide, and thiobenzamide.

The transition-state theory [8] of reactions in solution was first introduced by Wynne-Jones and Eyring [7]. The activation energy for the formation of the product when the molecule crosses the energy barrier was reported by Eyring and Laidler [9]. The Arrhenius equation [10] is applicable to the reactions in solution, and it is contributed to by the activation energy E_a and pre-exponential factor A.

$$k = Ae^{\frac{-E_a}{RT}} \quad (2)$$

Second-order rate constants were determined at five different temperatures. The energy of activation (E_a) was determined according to the Arrhenius relationship by plotting a graph of $\log_{10}k$ against $\frac{1}{T}$ and the thermodynamic parameter like activation energy, pre-exponential factor, activation entropy, and free energy were determined. The negative entropies of activation (ΔS^*) of these reactions indicated the rigid nature of the transition state. With decreasing entropy [11], an activated complex is formed. The negative entropy specifies that the molecules are bound to the solvent, limiting their free movement. Additionally, the negative value of entropies of activation (ΔS^*) indicates that stable cyclic products are formed from less stable noncyclic reactant.

Following equations were used to calculate the thermodynamic parameters (Table 2):

$$E_a = \frac{4.576 T_1 T_2 (\log k_2 - \log k_1)}{T_2 - T_1} \quad (3a)$$

The value of the entropy change of the activated complex can be calculated by equation (3b):

$$k = \frac{RT}{Nh} e^{-E_a^\ddagger/RT} * e^{\Delta S^\ddagger/R} \quad (3b)$$

But $R/N = kB$ (kB =Boltzmann constant)

$$k = \frac{kBT}{h} e^{-E_a^\ddagger/RT} * e^{\Delta S^\ddagger/R} \quad (3c)$$

Taking logarithms of both sides and simplifying them gives:

$$\frac{\Delta S^\ddagger}{4.576} = \log k - \log \frac{kB}{h} - \log T + \frac{E_a^\ddagger}{4.576T} \quad (3d)$$

$$\Delta H^\ddagger = E_a^\ddagger - 2RT \quad (4)$$

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (5)$$

According to equations from the literature, the effect of the salt was investigated, and it was found

that as the ionic strength increased, the rate of reaction was reduced, indicating that the reacting species were oppositely charged [12, 13] (Table 3, Figure 2).

$$I = \frac{1}{2} \sum c_i z_i^2 \quad (6)$$

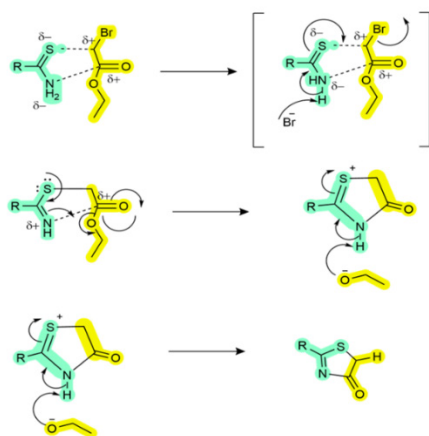
$$\log \frac{k}{k_0} = 1.02 z_A z_B \sqrt{I} \quad (7)$$

In a mixed solvent with variable dielectric constant, Scatchard's equation [14] was employed using the double-sphere model according to electrostatic theory. A straight line is obtained when the logarithm of the rate constant is plotted against the reciprocal of the dielectric constant. The colliding spheres are held together in the liquid phase by the surrounding solvent molecules, and multiple collisions occur before they finally separate, acting as a "cage" [15]. A reaction between uncharged species is resulted due to the development of an activated complex that is more polar than the reactants, and the rate constant rises with increasing dielectric constant [16]. The cyclization reaction between hydrazinecarbothioamide, thioacetamide, and thiobenzamide, and ethyl 2-bromoacetate in ethanol-water and isopropyl alcohol-water system is governed by the double sphere model. (Table 4 and Figure 3).

$$\ln k = \ln k_0 - \frac{z_A z_B e^2}{4\pi\epsilon\epsilon_0 d_{AB} k_B T} \quad (8)$$

- A rate of two is found for the reaction of ethyl 2-bromoacetate with hydrazinecarbothioamide, thioacetamide, and thiobenzamide.
- The rate of reaction being two is also shown by the suggested rate law.
- The same type of reaction mechanism as the cyclization of thiazole using thioamide and ethyl 2-bromoacetate is indicated by free energy (ΔG^*).
- Cyclic compounds are formed from open-chain compounds when there is a decrease in entropy (ΔS^*).
- The formation of nucleophiles and electrophiles in this reaction is indicated by the salt effect.
- Bimolecular reactions in the liquid phase of hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl 2-bromoacetate in an ethanol-water system and isopropyl alcohol-water system apply the double sphere model.

Expected reaction mechanism



S₁ - ethyl 2-bromoacetate
S₂ - thioacetamide or thiobenzamide

$$\text{Rate} = k_1[S_1][S_2] - k_{-1}[\text{Intermediate}]$$

On applying steady state approximation:

$$\frac{d}{dt}[\text{intermediate}] = 0$$

$$= k_1[S_1][S_2] - k_{-1}[\text{Intermediate}]$$

$$- k_2[\text{Intermediate}]$$

$$[\text{Intermediate}] = \frac{k_1[S_1][S_2]}{k_{-1} + k_2}$$

Substituting the value of [Intermediate] in equation:

$$\text{Rate} = k_1[S_1][S_2] - \frac{k_{-1} \cdot k_1[S_1][S_2]}{k_{-1} + k_2}$$

$$\text{Rate} = \left\{ k_{-1} - \frac{k_{-1} \cdot k_1}{k_{-1} + k_2} \right\} [S_1][S_2]$$

Scheme 2. Proposed general mechanism and rate expression

Table 2. Thermodynamic parameters for the reaction of hydrazinecarbothioamide, thioacetamide, and thiobenzamide with ethyl 2-bromoacetate. (T =300K)

	A	E_a^* kJmol ⁻¹	ΔH^* kJmol ⁻¹	ΔS^* Jmol ⁻¹	ΔG^* kJmol ⁻¹
Hydrazinecarbothioamide	$2.77 \times 10^{+09}$	65.10	60.11	-65.86	79.87
Thioacetamide	$1.51 \times 10^{+08}$	54.54	49.56	-90.53	76.72
Thiobenzamide	$1.12 \times 10^{+05}$	36.87	31.95	-148.70	76.56

Table 3. Slope values for the salt effect for the graph of logk versus $\sqrt{\mu}$

Reactant	Reagent	NaCl	LiCl
Hydrazinecarbothioamide	Ethyl 2-bromoacetate	-1.86125	-1.10995
Thioacetamide	Ethyl 2-bromoacetate	-0.44068	-0.46639
Thiobenzamide	Ethyl 2-bromoacetate	-0.25668	-0.31841

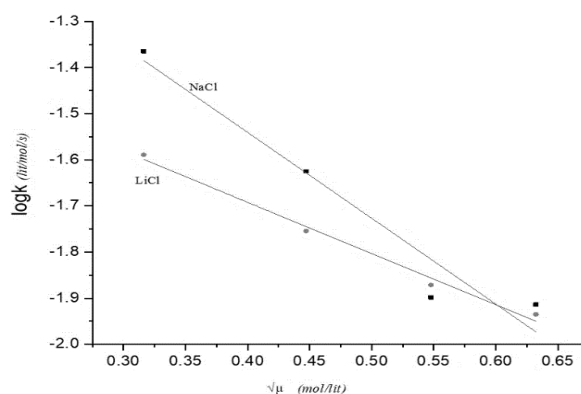


Figure 2. NaCl and LiCl effect on hydrazinecarbothioamide with ethyl 2-bromoacetate

Table 4. Solvent effect water-ethanol and water-isopropyl alcohol and d_{ab} values

Reactant	Reagent	d_{AB} = Ethanol (pm)	d_{AB} = Isopropyl alcohol (pm)
Hydrazinecarbothioamide	Ethyl 2-bromoacetate	$2.31 \times 10^{+03}$	$2.79 \times 10^{+03}$
Thioacetamide	Ethyl 2-bromoacetate	$3.86 \times 10^{+03}$	$3.10 \times 10^{+03}$
Thiobenzamide	Ethyl 2-bromoacetate	$1.60 \times 10^{+04}$	$1.11 \times 10^{+04}$

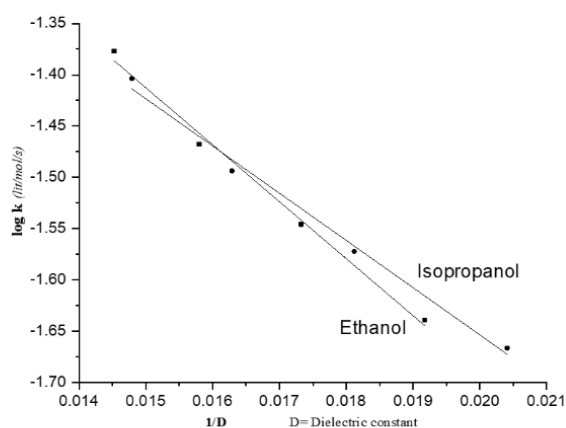


Figure 3. Solvent effect on hydrazinecarbothioamide with ethyl 2-bromoacetate

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