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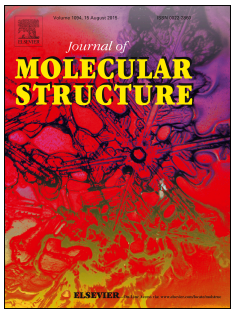

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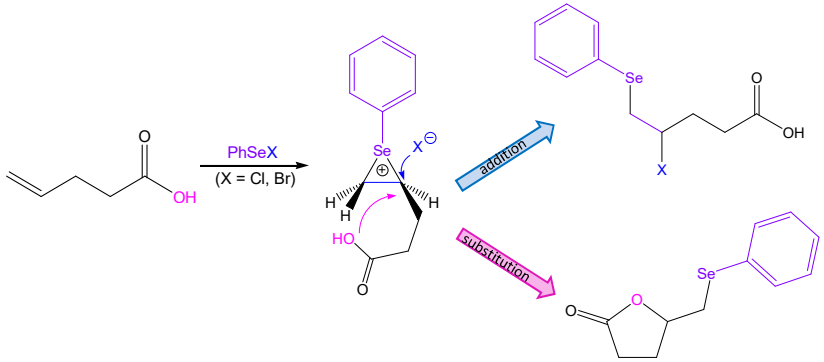

An Introduction to the Kinetics of the Triethylamine-Mediated Selenocyclofunctionalization of 4-Pentenoic Acid

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Abstract

The aim of this work is exploration of kinetic, thermodynamic and mechanistic aspects of triethylamine-mediated selenocyclofunctionalization of 4-pentenoic acid by means of phenylselenyl halides (PhSeCl and PhSeBr). The kinetics and mechanism for these reactions have been investigated by the UV-Vis spectrophotometry. The rate constants, as well as thermodynamic parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$) have been determined using UV-Vis method at three different temperatures (288, 298 and 308K) in THF as a solvent. All studied reactions gave negative values for entropy of activation, which is in agreement with the S_N2 mechanism of substitution. In addition, obtained values for the rate constants have indicated the higher reactivity of PhSeCl as reagent for cyclization.

Key words: Kinetics; Activation parameters; Selenocyclofunctionalization; Triethylamine.

1. Introduction

Lactones have become the subject of investigation in many research laboratories due to their unique physiological and structural properties. The occurrence of lactone motif in numerous biologically active and natural compounds [1], has given importance to all studies related to the methods for their preparation, as well as to mechanistic investigations of these reactions. Although, the great variety of methods for the lactone ring-construction has been reported [2-5], the synthetic strategy which involve the cyclization of unsaturated acids by means of electrophilic selenium species express many advantages, such as high yields of cyclic products, mild experimental procedure and wide transformational possibilities of organoselenium moiety [6-9]. Namely, organoselenium moiety from the side chain of a lactone can be further easily converted into the wide range of functionalities. PhSeCl and PhSeBr are, by the far, the two most widely employed reagents, which serve as sources of electrophilic selenium in these transformations [10-13]. Despite the utility of phenylselenyl halides in selenocyclization protocol, their use is frequently connected with some undesired reactions, such as addition of nucleophilic halide ion on double bond of unsaturated acid [10, 12, 13]. This side reaction has evoked several modifications of this cyclization method, such as the application of electrophilic selenium reagents with non-nucleophilic counter ion and the use of different additives, such as Lewis bases [13-15]. The mechanistic details of these transformations are not completely clear and they continue to stimulate research efforts in this field. The careful consideration and investigation of mechanistic and thermodynamic aspects of selenocyclofunctionalization reactions are important because they can bring

better insight into quintessence of the cyclization process, as well as into possibilities for its improvements.

We have been involved in a long-term mechanistic and synthetic study of the related reactions of selenocyclofunctionalization of unsaturated alcohols, in the presence of different Lewis bases as catalysts [16-25]. The present study is a result of our extended endeavors toward application of developed methodology into the selenocyclofunctionalization area. Therefore, herein we present the kinetic and mechanistic examination for the triethylamine-mediated selenocyclofunctionalization of 4-pentenoic acid by means of PhSeX (X = Cl, Br), as electrophilic reagents.

2. Experimental

2.1. General information

All reagents and solvent were purchased and used without further purification.

2.2. Synthetic procedure

In a solution of 4-pentenoic acid (1mmol) in CH_2Cl_2 or THF (10ml) was added triethylamine (1mmol), followed with fast addition of phenylselenyl bromide or chloride (1.1mmol). The mixture was stirred for 2h at room temperature. The solution was washed with 2M HCl, followed by saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/ AcOEt = 9:1) to give product **2**, without isolation of additional product **3**. The spectral data of the obtained product were in accordance with literature [26].

2.3. Kinetic measurements

UV-VIS Perkin Elmer Lambda 35 spectrophotometer equipped with a thermostatted cell was used for the kinetic measurements.

For determination of the rate constants conventional kinetics was used [27]. The temperature of reaction mixtures was maintained throughout all experiments to ± 0.1 ºC. Reactions were performed at 288, 298 and 308 K. The solutions of the reactants were prepared by the dissolution of the calculated amounts of the substances in THF as a solvent. First in a quartz cuvette a certain volume of acid solution was added, followed by the addition of the triethylamine solution, and the reaction was initiated by adding phenylselenyl halide. During all experiments the concentration of phenylselenyl halide was kept constant ($1 \cdot 10^{-4}$ M), while the concentration of acid was $5 \cdot 10^{-3}$ M, $4.5 \cdot 10^{-3}$ M, $4 \cdot 10^{-3}$ M, $3.5 \cdot 10^{-3}$ M and $3 \cdot 10^{-3}$ M. The concentrations of Et_3N were equimolar to phenylselenyl halide concentration. The reactions were elucidated by following the dependence of the absorbance on reaction time at suitable wavelength. The *pseudo*-first rate constants, k_{obsd}, were determined according to the equation by fitting all kinetic runs as single exponential function.

$$A_t = A_0 + (A_0 - A_\infty) \exp(-k_{obsd} t)$$

The obtained *pseudo*-first order rate constants present average value from two to five independent kinetic runs using Microsoft Excel and Origin 6.1. All experimental data are reported in Tables 1S and 2S (Supplementary material).

3. Results and discussion

4-Pentenoic acid **1** is the simplest representative of unsaturated acids whose $PhSe^{+}$-mediated cyclization provides the γ-lactone **2**, in accordance with preferred 5-*exo* trig model of cyclization (Scheme 1). Previous research has shown that without triethylamine present, at room temperature, the cyclization hasn't proceeded in satisfying yields and acceptable reaction time (>4h is required for the reaction completion). The reaction is further complicated due to the nucleophilicity of halide ion from PhSeX (X = Cl, Br) which can cause the side reaction and formation of product **3**. When the reactions are performed in the presence of equimolar amounts of triethylamine, the yield of lactone is increased up to 95% (in the case of both reagents). The progress of these reactions can be followed by the color change of the crude reaction mixture, whereas the characteristic color of reagents (PhSeCl-orange, PhSeBr-dark-red) disappears almost immediately upon the addition into the solution of pentenoic acid and triethylamine, in contrast to the reaction with no additive present where the color can be observed for hours. These findings have inspired us to examine the kinetic (rate constants) and thermodynamic (entropy and enthalpy of activation) aspects of these transformations.

Scheme 1

Proposed reaction mechanism is shown on the Scheme 2. Initially, an electrophilic atack of PhSeX (X = Cl, Br) on the double bond of 4-pentenoic acid generates seleniranium ion **I** (Scheme 2). In the next step of the reaction, the nucleophilic attack of carboxylic group causes the formation of intermediate **II**, rapidly followed by the elimination of proton resulting in a formation of a final product 2. In the presence of triethylamine, the formation of lactone is facilitated due to higher nucleophilicity of carboxylic group in intermediate **I**, in contrast to COOH group from intermediate **III**

where the triethylamine is not present in reaction. Our previous investigation, related to the pyridine-supported selenocyclofunctionalization of the pent-4-en-1-ol has also revealed that the proton migration (from alkenol OH to the nitrogen from the base) has drastic influence on the relative stability of the calculated mechanistic pathway (in contrast to very energetically unfavorable non-base supported cyclization) [18].

In order to examine kinetic aspects of these transformations, the triethylamine-mediated selenocyclofunctionalization between 4-pentenoic acid and phenyselenyl halides (PhSeCl and PhSeBr) has been investigated by means of UV-Vis spectroscopy with *pseudo*-first-order method at three diferent temperatures: 288, 298 and 308K, in THF as solvent. The nucleophilic atack of COOH group has been considered as the rate-determining step of reaction with the rate constant k_2.

Scheme 2.

The rate contants have been determined by measuring the change of absorbance at a suitable wavelength as a function of time (Figure 1). Since the reaction rates depend on the temperature it was controlled before and throughout the kinetic trials. The calculations for the k_{obsd} are explained in the Experimental section and the data are given in Tables 1S and 2S (Supplementary material).

Figure 1.

Under *pseudo*-first-order conditions, the observed rate constants are linearly dependent on a 4-pentenoic acid concentration as indicated in equation:

$$k_{obsd} = k_1 + k_2 \text{ [acid]}$$

In this equation, k_2 represents the second order rate constant for the forward reaction (the nucleophilic attack on seleniranium ion **I** leading to the cyclization process) which depends on acid concentration, while k_1 is the rate constant of the parallel reaction (reaction of addition). The rate constant k_1 is independent of the acid concentration. The values of k_2 were calculated from the slopes of the plots k_{obsd} versus the acid concentration, while the values for k_1 were determined from the intercept of the observed lines (Table 1, Figure 2) [27].

Figure 2.

Table 1. Rate constants and activation parameters for the selenocyclofunctionalization of 4-pentenoic acid with PhSeCl and PhSeBr in the presence of triethylamine

	PhSeCl				**PhSeBr**			
T (K)	k_2 ($M^{-1}s^{-1}$)	k_1	$\Delta H^{\#}$ (kJM^{-1})	$\Delta S^{\#}$ ($JK^{-1}M^{-1}$)	k_2 ($M^{-1}s^{-1}$)	k_1	$\Delta H^{\#}$ (kJM^{-1})	$\Delta S^{\#}$ ($JK^{-1}M^{-1}$)
308	1.36 ± 0.06	/			0.84 ± 0.02	/		
298	0.92 ± 0.04	/	25 ± 1	-176 ± 4	0.6 ± 0.03	/	21 ± 1	-193 ± 3
288	0.64 ± 0.02	/			0.44 ± 0.02	/		

From the rate constants presented in Table 1, a significant difference is apparent between the reactivity of the reagents (PhSeCl and PhSeBr). All reactions with PhSeCl as reagent are almost one and half order-of-magnitude faster than corresponding reactions with PhSeBr, indicating the higher reactivity of this reagent in selenocyclofunctionalization reactions.

The intercepts in Figure 2 confirms that, which represent the value of k_1, confirms that, under the conditions employed, there are no detectable side reactions, i.e. k_1 constants have insignificantly small values, and therefore not presented in Table 1.

Fitting the rate constants to the Eyring equation gave activation parameters (Figure 3) which are given in Table 1. All studied reactions gave negative values for entropy of activation, which is in agreement with the S_N2 mechanism of substitution.

$$\ln(\frac{k_2}{T}) = -\frac{\Delta H^{\neq}}{RT} + \left[\ln(\frac{k_t}{h}) + \frac{\Delta S^{\neq}}{R}\right]$$

Figure 3.

4. Conclusions

The kinetic and mechanistic details of the triethylamine-mediated selenocyclofunctionalization of 4-pentenoic acid have been described. Higher rate constants for PhSeCl-induced selenocyclofunctionalization have been observed in comparison to the PhSeBr ones. In addition, the obtained values for the activation parameters (the entropy of activation and the enthalpy of activation) support S_N2 mechanism of the nucleophilic COOH attack on the seleniranium ion. Presented results provide basis for further, more extensive kinetic and mechanistic studies with the great structural diversity of unsaturated acids as substrates, with a focus on the effects of various additives and reagent's counter ion on the reaction pathways.

Acknowledgements

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Conflict of interest

None

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Scheme and figure captions

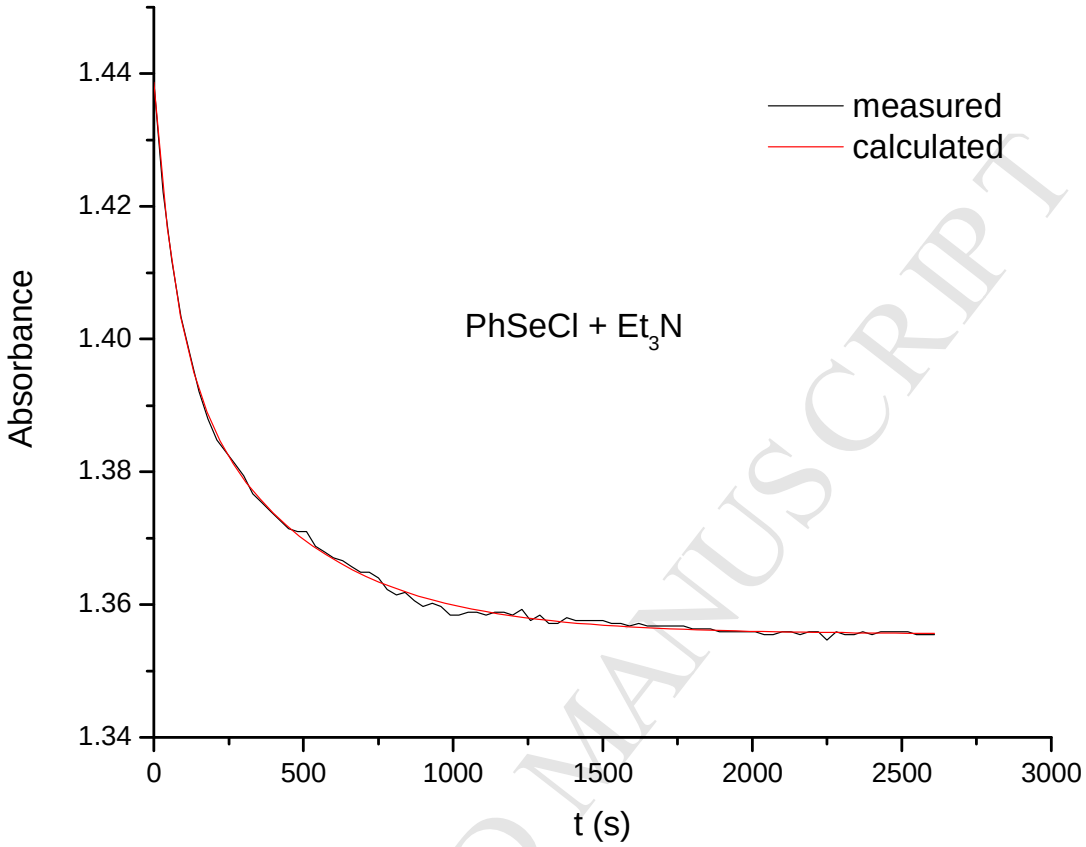
Scheme 1. Possible ways for the reaction between 4-pentenoic acid and PhSeX (X = Cl, Br).

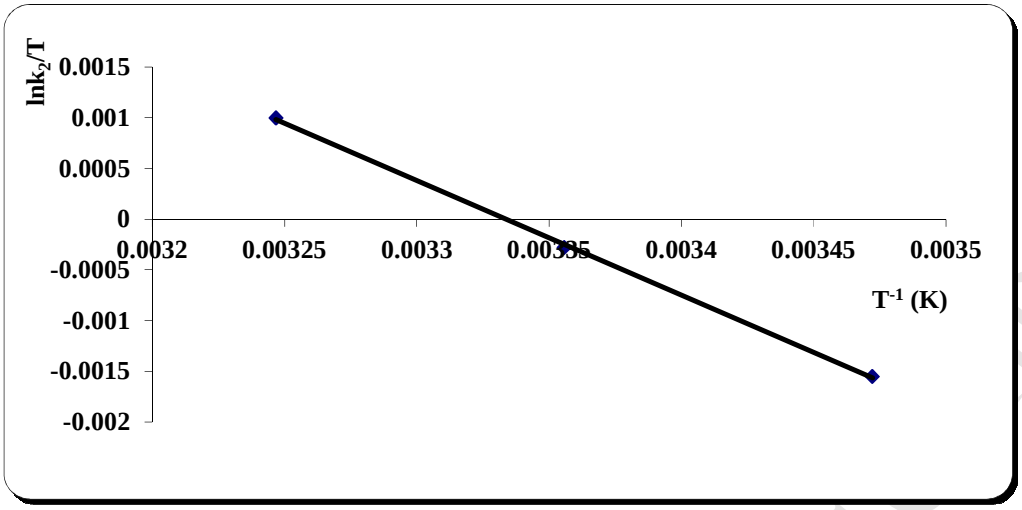
Scheme 2. Mechanism of the selenocyclofunctionalization of 4-pentenoic acid.

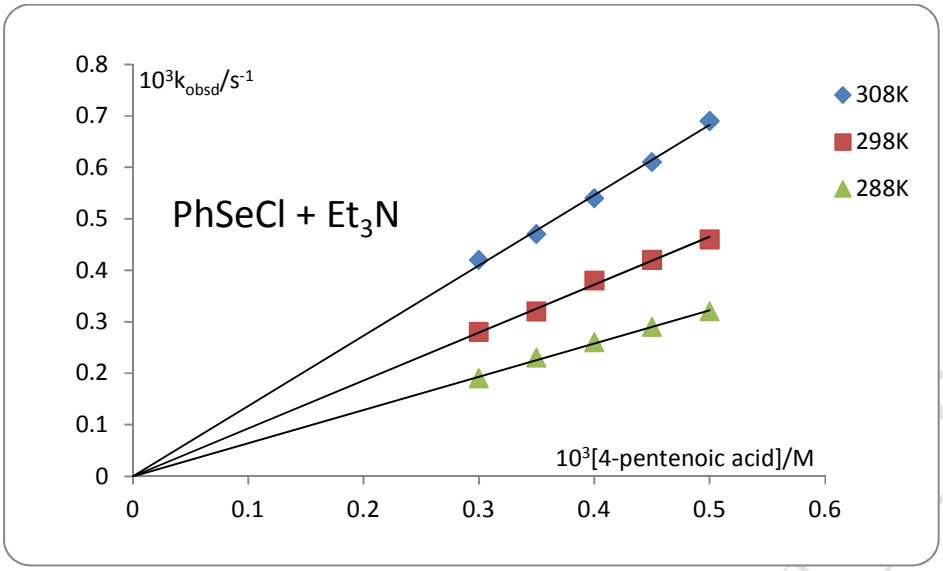
Figure 1. Absorbance dependence on time for the reaction between 4-pentenoic acid and PhSeCl in the presence of Et_3N in THF.

Figure 2. Observed rate constants for the *pseudo*-first order reaction as a function of 4-pentenoic acid concentration at different temperatures.

Figure 3. Linear dependence of ln(k/T) on 1/T for the reaction between 4-pentenoic acid and PhSeCl in the presence of triethylamine.



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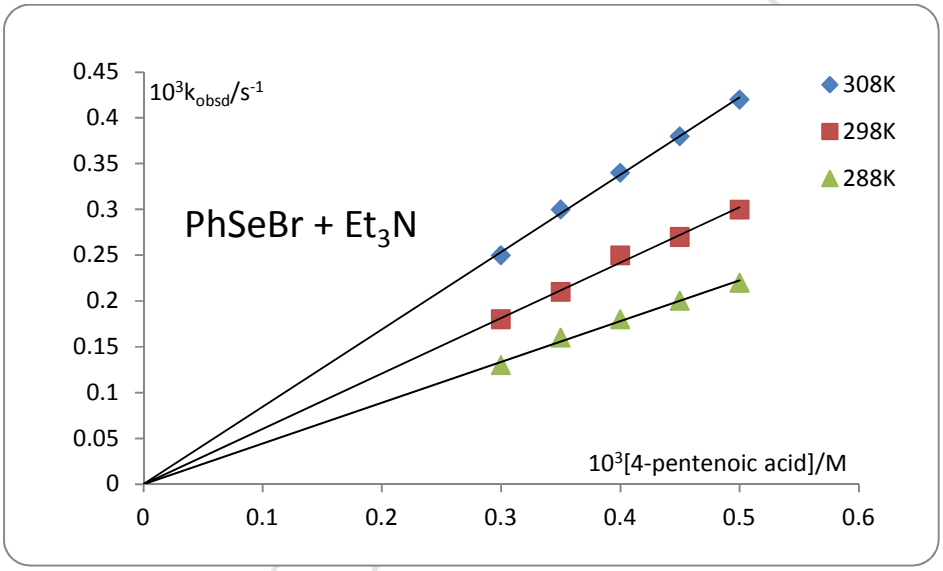
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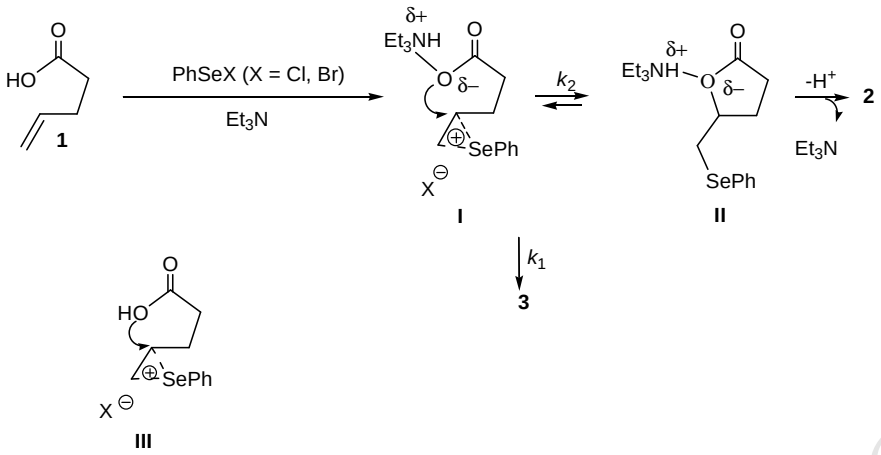

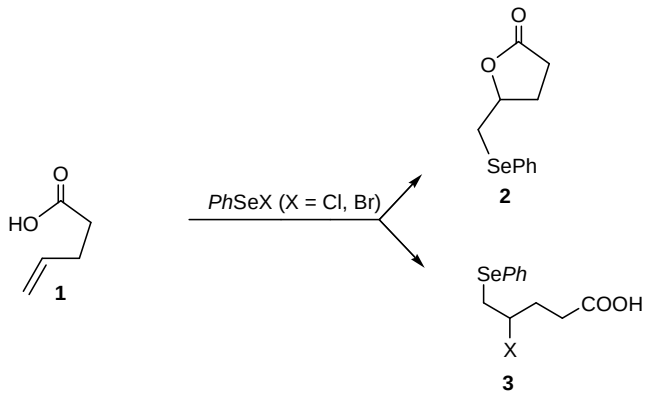

An Introduction to the Kinetics of the Triethylamine-Mediated Selenocyclofunctionalization of 4-Pentenoic Acid

Marina D. KOSTIĆ*[1], Vera M. DIVAC[a], Zorica M. BUGARČIĆ[a]

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- The kinetics of the selenocyclofunctionalization of 4-pentenoic acid was studied.
- The thermodynamic parameters have been determined by using the UV-Vis method.
- Activation parameters supported S_N2 mechanism of selenocyclofunctionalization.

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