Based catalyzed phenylselenoetherification of 6-methylhept-5-en-2-ol

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Abstract

The mechanism of phenylselenoetherification of 6-methylhept-5-en-2-ol in the presence of some bases (pyridine, triethylamine, quinoline, 2,2'-bipyridine) as catalysts was examined through kinetic study of the cyclization under *pseudo*-first order conditions, by UV-VIS spectrophotometry. The obtained values for the rate constants show that there is a good agreement between those constants and the basicity of the catalyst. The fastest reaction is the one using the strongest base (triethylamine) and the smallest rate constant corresponded to the use of the weakest base as catalyst (2, 2'-bipyridine).

Keywords: Alcohols, cyclization, kinetics, oxygen heterocycles

Introduction

Organoselenium reagents and reactions have become well established in the repertoire of synthetic organic chemists.[1,2] The specific properties of organoselenium reagents, which fulfil requirements of modern organic synthesis, are the main reason for the explosive growth in interest in these compounds during the past decade. Most of these reagents are suitable for chemo-, regio- and stereo-selective synthesis.[3-5] Organoselenium compounds can be efficiently introduced into organic molecules, manipulated, and removed in many different ways under mild conditions and usually in good yields. In addition, organoselenium compounds, such as selenium-containing heterocyclic compounds, have been well recognized not only because of their chemical properties,[6-11] but also because of diverse pharmaceutical applications[12-15] associaed with their promising antioxidant,[16-18] anti-inflammatory[19,20] and neuroprotection activity.[21-25] They exhibit a broad range of biological profiles and therefore have been the targets of a number of synthetic programmes.

In the past few years, attention has been focused on the synthesis of the tetrahydropyrans and tetrahydrofurans as key starting materials for the preparation of numerous heterocyclic

compounds including physiologically active products. For some time we have been involved in the development and exploration of new methods for preparation of oxacyclic compounds through cyclofunctionalization of unsaturated alcohols.[26-32]

Recently, we investigated reactions between some Δ^4- and Δ^5-unsaturated alcohols and phenylselenenyl halides PhSeX (X=Cl, Br) in the presence of pyridine.[32] Due to its presence, which influences the cyclization, yields of ethers were almost quantitative. In continuation of that work, we have carried out a systematic kinetic study for determination of reaction mechanism[33] and additive influence on reaction rate. It was found that all the investigated reactions followed second order kinetics and rate constants depended on additive presence. Furthermore, reactions with pyridine were faster than without it.

Our efforts in this work were directed to exploration of kinetic aspects of reactions of the Δ^4-unsaturated secondary alcohol 6-methyl-hept-5-en-2-ol and PhSeCl in the presence of some additives with basic properties. For detailed examination of these reactions, we used a conventional kinetic method to determine the values of rate constants. It was of interest to compare the influences of various bases (pyridine, triethylamine, quinoline, 2,2'-bipyridine) on the yields and rate constants.

Results and Discussion

The influence of some basic additives on yields and rate constants in the reaction between 6-methyl-hept-5-en-2-ol and phenylselenenyl chloride was examined. We tried to compare the impact of various bases, which differ in steric size and basicity, on reaction flow and rate. For this purpose we used pyridine, quinoline, 2,2'-bipyridine and triethylamine as bases.

The reaction between the alcohol and phenylselenenyl chloride starts with electrophilic attack by the phenylselenenyl group on the double bond of alkenol which results in formation of selenonium cation (Figure 1). In the next phase of the reaction, nucleophilic oxygen from the hydroxyl group of alcohol attacks the selenonium cation with formation of a five- or six-membered ring, depending on reaction conditions, substrate structure and steric hindrance. Finally, generation of the five- or six-membered cyclic phenylseleno ether (Figure 1 **1a, 1b**,) ensues with elimination of a proton from the oxonium ion.

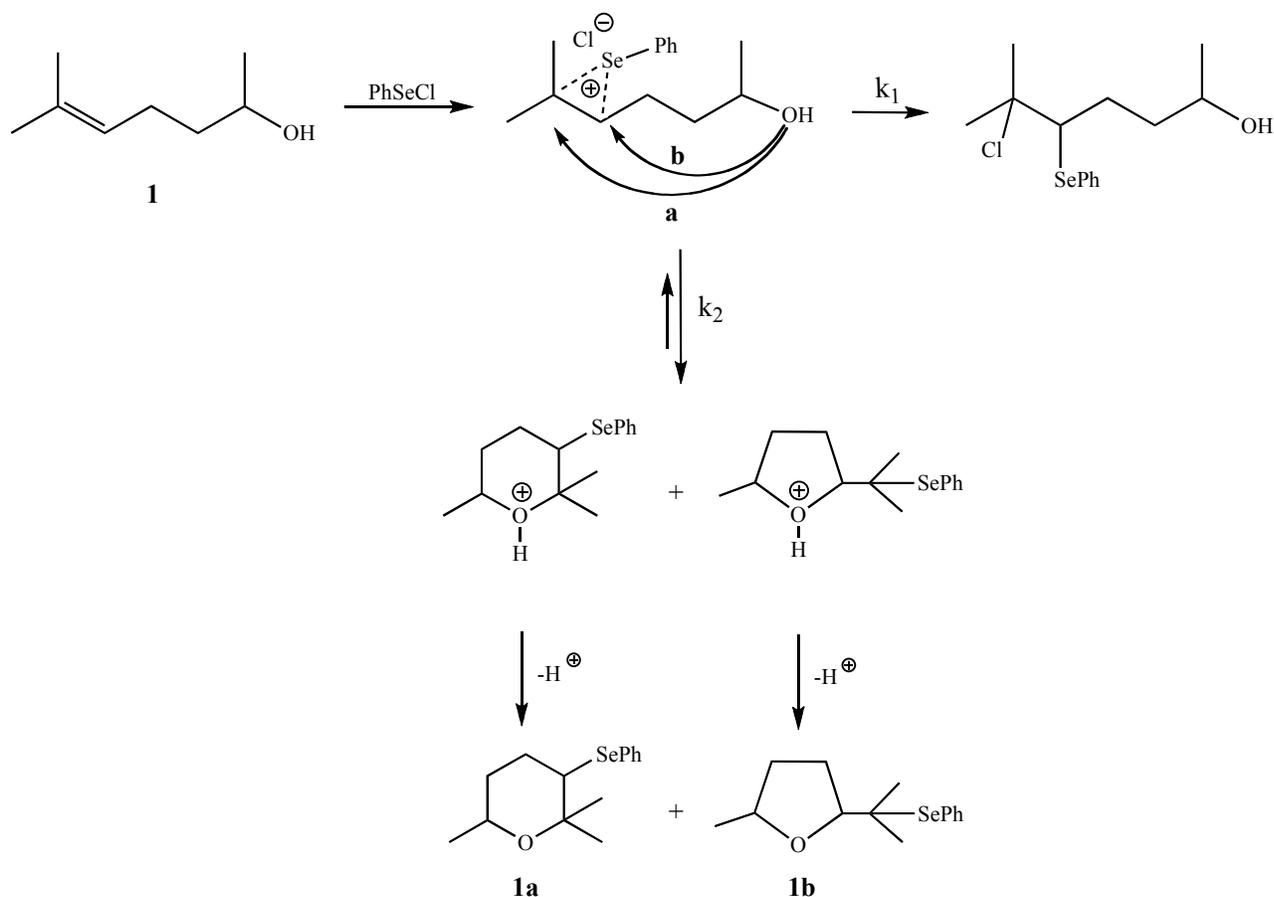**Figure 1.** Phenylselenoetherification of 6-methyl-hept-5-en-1-ol (k_2 – second order rate constant for forward reaction; k_1 – constant of parallel reaction).

At the beginning of the reaction, base can form a hydrogen bond with the hydroxyl proton and in that way it can increase oxygen nucleophilicity, therefore increasing the reaction rate. Also, at the same time, base decreases the influence of the halide ions, present in the reaction mixture. Finally base removes a proton from the oxonium ion and makes formation of final products easier. THF as a solvent, can also form a hydrogen bond with the proton of the hydroxyl group and in that way promote reaction.

The results that we obtained in synthetic part of our experiments showed that the cyclization process is more effective in the presence of the additives, which is reflected on the yields of obtained cyclic ether, Table 1. In the case of the reaction between alcohol and phenylselenenyl chloride without additive, only six-membered cyclic ether, in 70% yield, was obtained. In the reactions with additives, yields of cyclic ethers increased to almost quantitative. In addition, in these reactions, five-membered cyclic ether was also formed in a different ratio, Table 1.

Table 1. Base catalyzed phenylselenoetherification of 6-methyl-hept-5-en-2-ol with PhSeCl

Substrate	Products	Yields and ratio **1a**:**1b** of cyclic products (%)				
		A	B	C	D	E
1	**1a 1b**	70	99.6	99.9	99.5	98.8
		(100:0)	(57:43)	(54:46)	(73:27)	(91:9)

A-without additive. B-with pyridine. C-with quinoline. D-with 2,2'-bipyridine. E-with triethylamine.

For determination of the rate constants, conventional kinetic methods using UV/VIS spectroscopy were used. All reactions were studied as reactions of *pseudo*-first order at 15 ºC in THF as a solvent. Reactions were investigated by following the dependence of the absorbance on reaction time at suitable wavelength (Figure 2). The calculation of k_{obsd} is explained in the Experimental section. The observed rate constants as a function of total alcohol concentration can be described by the following equation:

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

In this equation, k_2 represents the second order rate constant for the forward reaction, which depends on alcohol concentration, and k_1 shows the effects of the parallel reaction on the substitution process. The rate constant k_1 is independent of the alcohol concentration. The values for k_2 were calculated from the slopes of the plots k_{obsd} versus of the alcohol concentration while the values for k_1 were determined from the intercept of the observed lines.
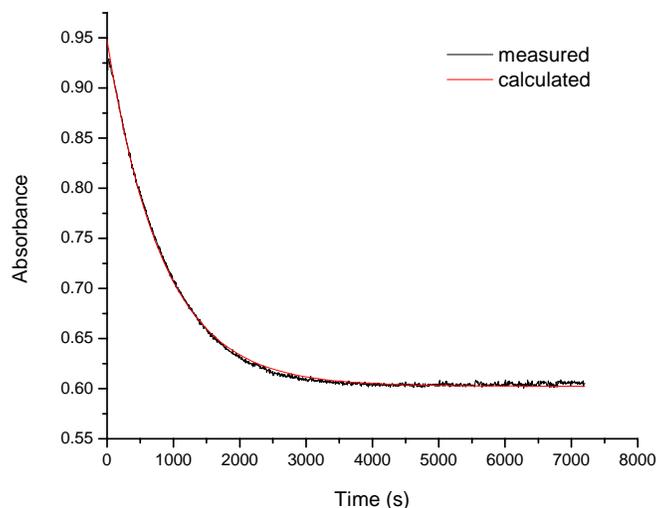

Figure 2. Kinetic traces for the reaction between 6-Me-hept-5-en-2-ol (2 mM) and PhSeCl (0.1 mM) at 298 K, $\lambda = 256$ nm in THF as a solvent.

On the base of kinetic measurements, the obtained values for the rate constants have shown that there is a good agreement between these constants and additive basicity, (Table 2 and Table 3). The fastest reaction is the one with additive that is the strongest base (triethylamine) and the smallest rate constant is in the case when the weakest base was used as catalyst (2,2'-bipyridine).

Table 2. Rate constants for phenylselenoetherification of 6-methyl-hept-5-en-2-ol with PhSeCl in THF at 288 K

	λ (nm)	k_2 ($M^{-1}s^{-1}$)	k_1 (s^{-1})
without additive	253	0.63 ± 0.02	$(1.1 \pm 0.3) \times 10^{-4}$
with triethylamine	257	0.77 ± 0.03	-
with pyridine	253	0.55 ± 0.02	-
with quinoline	256	0.49 ± 0.01	-
with 2,2'-bipyridine	259	0.48 ± 0.02	$(0.6 \pm 0.3) \times 10^{-4}$

Table 3. Relationship between rate constants and pKa of used additive in the reaction of 6-methyl-hept-5-en-2-ol and PhSeCl

Additive	pKa	k_2 ($M^{-1}s^{-1}$)
Triethylamine	10.64	0.77
Pyridine	5.23	0.55
Quinoline	4.94	0.49
2,2'-bipyridine	4.3	0.48

From the results in Table 3, unexpected rate constants in the presence of aromatic bases can be seen. The possible explanation for reaction being faster without the presence of pyridine, quinoline and 2,2'-bipyridine, could be steric hindrance, from rigid aromatic ring systems, which these additives make in the cyclization step. Since, aromatic base forms a hydrogen bond with the proton from hydroxyl group and together bonded they make the approach of oxygen in the ring closing phase difficult, which results in lower rate constant Figure 3.

It could be assumed that triethylamine as a much stronger aliphatic base then the other used aromatic bases, would have bigger influence on reaction rate, but due to the steric bulkiness from substrate and base in cyclization step, it is much lower then expected (1.4 times faster then pyridine catalyzed, 1.57 then quinoline, 1.6 then 2,2'-bipyridine). On the other hand, in the

reaction of phenylselenoetherification of stericly unprotected pent-4-en-1-ol in the presence of Et_3N, reaction rate is 4 times faster then uncatalyzed one (unpublished results).
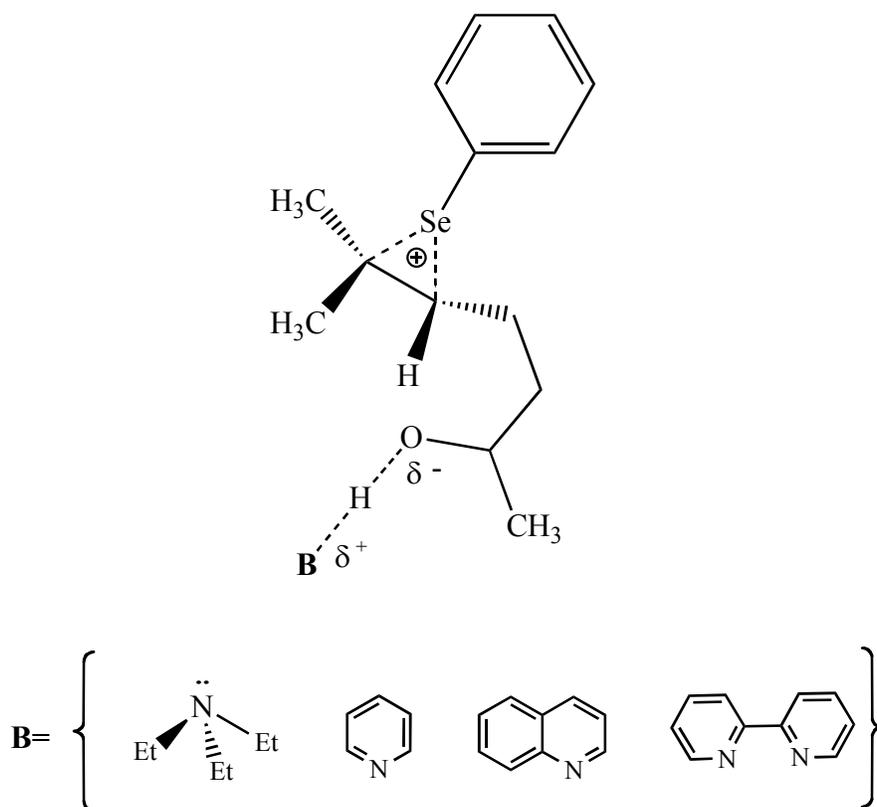

Figure 3. Steric hindrance in ring closing phase in the reactions with additive present.

From Figure 5 it can be seen that the lines, in the reactions with triethylamine, pyridine, quinoline, start from the origin. This means that these reactions have no parallel runs or they are reduced to insignificant value (in case of 2,2'-bipyridine), which is in agreement with the yields obtained synthetically, Table 1. On the other hand, in the case of the uncatalyzed reaction (Figure 4.) the intercept existed in the observed graph.
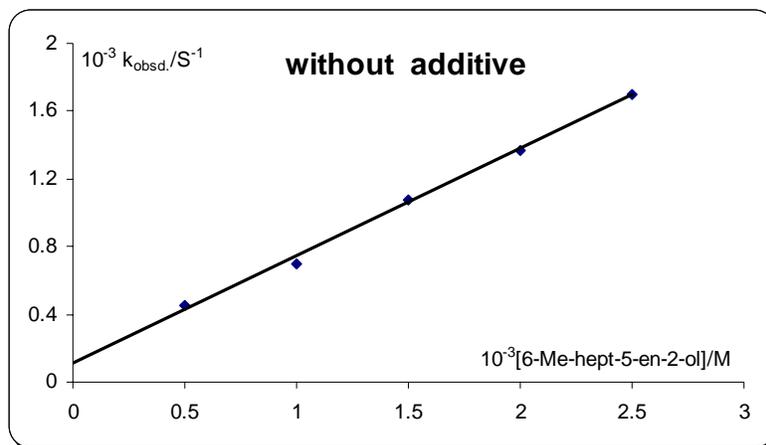
Figure 4. Pseudo-first order rate constant, $k_{obsd.}$, as a function of concentration of alkenol for reaction between PhSeCl and 6-Me-hept-5-en-2-ol in THF.

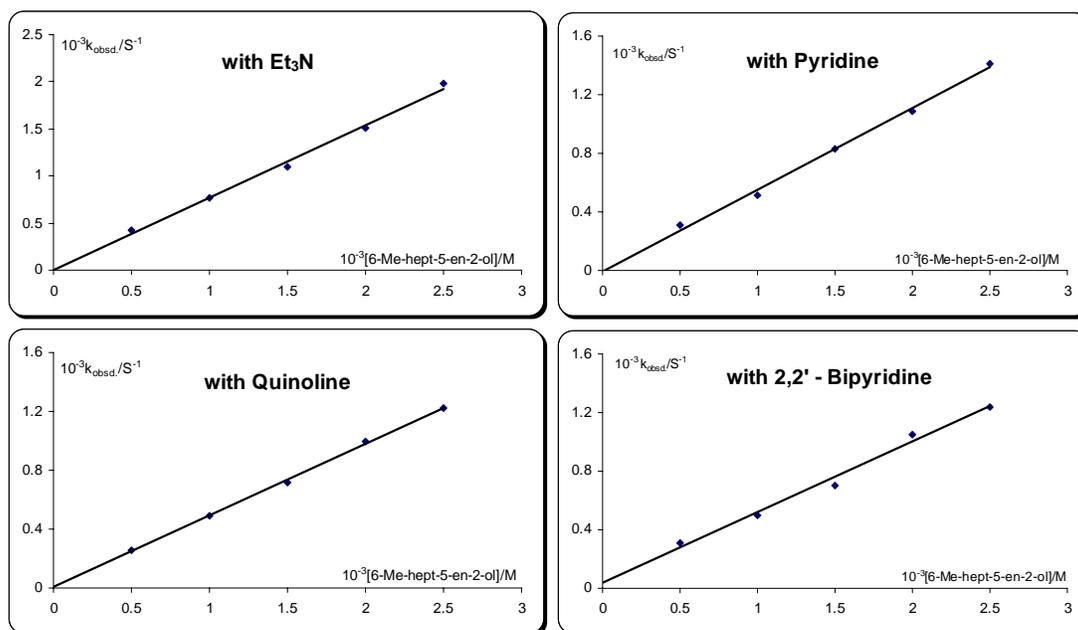**Figure 5.** Pseudo-first order rate constant, $k_{obsd.}$, as a function of concentration of alkenol for reaction between *Ph*SeCl and 6-Me-hept-5-en-2-ol with base additive present (triethylamine, pyridine, quinoline and 2,2'-bipyridine) in THF as a solvent.

From the Figure 6 it can be seen that plot log k_2 vs. pKa of additive is almost straight line, therefore the additives increase the rate and yields of reaction with the same reaction mechanism.
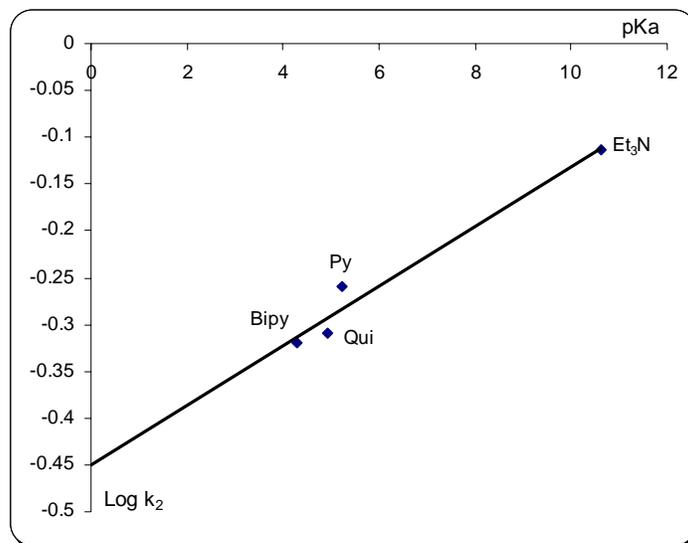
Figure 6. Plot of log k_2 vs. pKa of base additives for the reaction of phenylselenoetherification of 6-Me-hept-5-en-2-ol with additive present.

Conclusions

In conclusion, we have demonstrated a catalytic influence of additives on rate constants in phenylselenoetherification of 6-methyl-hept-5-en-2-ol. The results show that there is good agreement between rate constants and the basicity of the catalyst and the biggest catalytic effect was with the strongest base – triethylamine.

Experimental Section

General. GM analyses were obtained with an Agilent Technologies instrument, model 6890 N with HP-5NS columns (5% phenyl 95% methylpolysiloxane). ^{1}H and ^{13}C NMR spectra were run in CDCl$_3$ on a Varian Gemini 200 MHz NMR spectrometer. IR spectra were obtained with Perkin-Elmer Model 137B and Nicolet 7000 FT spectrophotometers. ''Dornis and Colbe'' laboratory performed microanalyses. Thin-layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel plates (60F-254) using UV light for visualization. For column chromatography, E. Merck silica gel (60, particle size 0.063-0.200 mm) was used. For kinetic measurements, UV-VIS Perkin Elmer Lambda 35 spectrophotometer equipped with thermostatted cell was used.

General procedure

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol) and additive (1 mmol) in dry dichloromethane (5 cm^3) solid PhSeCl (0.212 g, 1.1 mmol) was added at room temperature. The reaction went to completion in a few minutes. The pale yellow solution was washed with 1M HCl aqueous solution (5 ml), saturated NaHCO$_3$ aqueous solution and water. The organic layer was dried over Na$_2$SO$_4$, concentrated and subjected to chromatography. The product was obtained after the elution of traces of diphenyl diselenide from a silica gel-dichloromethane column. All products were characterized and identified on the basis of their spectral data.

Kinetic measurements

Reactions between phenylselenenyl chloride and 6-methyl-hept-5-en-2-ol in the presence of basic additives were observed as substitution reactions on bivalent selenium. For determination of the rate constants conventional kinetics was used. All investigated reactions were followed spectrophotometrically as *pseudo*-first order reactions, using UV-VIS Perkin Elmer Lambda 35 spectrophotometer equipped with thermostated cell. The temperature of reaction mixtures was controlled throughout all kinetic experiments to ± 0.1 ºC. Reactions were performed at 15 ºC. The solutions of reactants were prepared by measuring calculated amounts of substances in THF as a solvent. THF is more suitable than dichloromethane for kinetic experiments in terms of the boiling point, but for synthetic purpose it is better to use dichloromethane which is removed easily from reaction mixture and does not change yields. In a quartz cuvette, a certain volume of alcohol solution was added, then additive, and the reaction was initiated by adding phenylselenenyl chloride. During all experiments the concentration of phenylselenenyl chloride was kept constant ($1*10^{-4}$ M), while the concentration of alcohol was $2.5*10^{-3}$ M, $2*10^{-3}$ M, $1.5*10^{-3}$ M and $1*10^{-3}$ M. When the concentration of alcohol was $5*10^{-4}$ M, to maintain pseudo-first order kinetic conditions, the concentration of PhSeCl was lowered to $1*10^{-5}$ M. In the reactions with additives present, concentrations of additives were equimolar to phenylselenenyl halide concentration. All reactions were investigated 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 observed *pseudo*-first order rate constants were calculated as the average value from two to five independent kinetic runs using computational program Microsoft Excel and Origin 6.1. Obtained experimental data are reported in Table 2.

Acknowledgements

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