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The comparative quantum chemical study of the epoxidation reaction mechanism of eugenol and *iso*eugenol with peracetic and perbenzoic acids

Aim. To study the kinetics of the epoxidation reaction for eugenol and *iso*eugenol with perbenzoic acid, carry out the comparative quantum chemical study of the epoxidation reaction mechanism of eugenol and *iso*eugenol isomers (2-*cis* and 2-*trans*) with peracetic and perbenzoic acids.

Results and discussion. The kinetics of the epoxidation reaction of isomeric terpenoids eugenol and *iso*eugenol with perbenzoic acid in the medium of methylene chloride medium at 293 K was studied using the method of iodometric titration. It was shown that the rate constant of the epoxidation reaction for eugenol was in 5.5 times higher than for *iso*eugenol. According to the results of quantum chemical calculations using the UBH&HLYP/6-31G (d) approximation, the structures of transition states of eugenol and *iso*eugenol formed during the epoxidation reactions studied were proposed, and the activation energies for the corresponding reactions were calculated. Based on the results of the studies conducted it was found that the ratio of the activation energies during the interaction of eugenol and *iso*eugenol with peracetic and perbenzoic acids showed the higher reactivity of *iso*eugenol.

Experimental part. To study the kinetics of the epoxidation reaction the method of iodometric titration was used. The method of the functional density (software Gaussian 09, approximation UBH&HLYP/6-31G (d)) was applied for calculation.

Conclusions. The results of the quantum chemical study of the epoxidation reaction mechanism of eugenol and *iso*eugenol are consistent with the kinetic data experimentally obtained; it confirms the correctness of using the UBH&HLYP/6-31G (d) approximation for studying the features of epoxidation of isomeric terpenoids with organic peracids.

Key words: terpenoids; quantum chemical research; reaction mechanism; reaction kinetics; epoxidation; peracetic acid; perbenzoic acid

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Порівняльне квантово-хімічне дослідження механізму реакції епоксидування евгенолу та *ізо*евгенолу надацетатною та надбензойною кислотами

Мета. Дослідити кінетику реакції епоксидування евгенолу та *ізо*евгенолу надбензойною кислотою, провести порівняльне квантово-хімічне дослідження механізму реакції епоксидування евгенолу та двох ізомерів *ізо*евгенолу (2-*цис* та 2-*транс*) надацетатною та надбензойною кислотами.

Результати та обговорення. Методом йодометричного титрування вивчено кінетику реакції епоксидування ізомерних терпеноїдів евгенолу та *ізо*евгенолу надбензойною кислотою в середовищі метиленхлориду при 293 К і показано, що константа швидкості реакції епоксидування евгенолу в 5,5 разів вище, ніж для *ізо*евгенолу. За результатами квантово-хімічних розрахунків з використанням наближення UBH&HLYP/6-31G (d) запропоновано структури перехідних станів евгенолу та *ізо*евгенолу, що утворюються в ході вивчених реакцій епоксидування, і розраховано значення енергій активації для відповідних реакцій. Виходячи з результатів проведених досліджень встановлено, що співвідношення енергій активації при взаємодії евгенолу та *ізо*евгенолу з надацетатною і надбензойною кислотами свідчить про більш високу реакційну здатність *ізо*евгенолу.

Експериментальна частина. Для вивчення кінетики реакції епоксидування використовували метод йодометричного титрування. Для розрахунків використовували метод функціоналу густини (наближення UBH&HLYP/6-31G (d)) програми Gaussian 09.

Висновки. Результати квантово-хімічного дослідження механізму реакції епоксидування евгенолу та *ізо*евгенолу узгоджуються з експериментально отриманими кінетичними даними, що підтверджує коректність використання наближення UBH&HLYP/6-31G (d) для вивчення особливостей епоксидування ізомерних терпеноїдів за допомогою органічних надкислот.

Ключові слова: терпеноїди; квантово-хімічне дослідження; механізм реакції; кінетика реакції; епоксидування; надацетатна кислота; надбензойна кислота

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Сравнительное исследование механизма реакции эпоксидирования эвгенола и *изо*эвгенола перуксусной и пербензойной кислотами

Цель. Изучить кинетику реакции эпоксидирования эвгенола и *изо*эвгенола пербензойной кислотой, провести сравнительное квантово-химическое исследование механизма реакции эпоксидирования эвгенола и двух изомеров *изо*эвгенола (2-*цис* и 2-*транс*) перуксусной и пербензойной кислотами.

Результаты и обсуждение. Методом йодометрического титрования изучена кинетика реакции эпоксидирования изомерных терпеноидов эвгенола и *изо*эвгенола пербензойной кислотой в среде хлористого метилена при 298 К и показано, что константа скорости реакции эпоксидирования эвгенола в 5,5 раз выше, чем *изо*эвгенола. По результатам квантово-химических расчетов с использованием приближения UBH&HLYP/6-31G (d) предложены структуры переходных состояний эвгенола и *изо*эвгенола, образующиеся в ходе изученных реакций эпоксидирования, и рассчитаны значения энергий активации для соответствующих реакций. Исходя из результатов проведенных исследований установлено, что соотношение энергий активации при взаимодействии эвгенола и *изо*эвгенола с перуксусной и пербензойной кислотами свидетельствует о более высокой реакционной способности *изо*эвгенола.

Экспериментальная часть. Для изучения кинетики реакции эпоксидирования использовали метод йодометрического титрования. Для расчета использовали метод функционала плотности (приближение UBH&HLYP/6-31G (d)) программы Gaussian 09.

Выводы. Результаты квантово-химического исследования механизма реакции эпоксидирования эвгенола и *изо*эвгенола согласуются с экспериментально полученными кинетическими данными, что подтверждает корректность использования приближения UBH&HLYP/6-31G (d) для изучения особенностей эпоксидирования изомерных терпеноидов с помощью органических перкислот.

Ключевые слова: терпеноиды; квантово-химическое исследование; механизм реакции; кинетика реакции; эпоксидирование; перуксусная кислота; пербензойная кислота

The study of transformation reaction mechanisms is increasingly important to both among theoretic and experimental chemists. By the means of quantum chemical calculations one may predict the nature, character of interaction, energy and geometric parameters of a transition state and end products of a reaction [1–3]. The specified density functional theory is used to study the electronic and geometric structure and relative stability of different compounds [1–5]. The B3LYP functional is the most extensively used among all hybrid density functional methods; it allows describing correctly biradical structures and is quite economic in terms of cost of computer time, which allows its use in the study of sufficiently complex organic compounds and reactions [4–5].

Eugenol (**1**) is a natural compound obtained from various plants, particularly from black cloves. Although its consumption in a small amount provides antibacterial and antifungal benefits, exceeding the limit may cause various harmful effects [6–11]. Eugenol-rich cloves have been used for food preservation and in various medical areas, owing to its antibacterial, antiseptic and anti-inflammatory properties [6–14]. Eugenol sources, such as clove oil, cinnamon, basil and nutmeg oil, are some of the basic ingredients in mouth washes, soaps, tooth pastes, perfumes and in various veterinary medications [15]. Moreover, eugenol antibacterial and antifungal activities are very helpful in treating many digestive problems, such as diarrhea, gas bloating, ulcers and Candida [6–11]. Eugenol-rich black paper and clove can increase the release of gastric acid, which helps in digesting food and kills intestinal bacteria in the stomach. Clove tea can be used to dilate blood vessels, increase the circulation and the body temperature. As an antioxidant, eugenol can prevent or decrease harmful oxidations in the body [16–17].

Although eugenol has been nominated to be safe to consume in suggested limits by Food and Drug Administration, exceeding the limits may cause serious and fatal results, such as arrhythmia, kidney damage, digestive problems, increase in heart rate and blood pressure, dizziness, vomiting and liver failure [18]. Eugenol is quickly absorbed and digested in the liver, and 95 % of the dose is excreted within one day. However, it is reported that ingesting clove oil as small as 8 mL can cause fatal sickness by damaging the liver and nervous system [19]. The study of the eugenol epoxidation reaction mechanism of various isomers with organic peracids is of interest to scientists [20].

We earlier studied the epoxidation reaction mechanism of eugenol and *iso*eugenol with peracetic acid [21].

The aim of this article was to study the kinetics of the epoxidation reaction for eugenol (**1**) and isomers of *iso*eugenol – *cis*-2 (**2**) and *trans*-2 (**3**) – with perbenzoic acid and carry out the comparative quantum chemical study of the epoxidation reaction mechanisms of eugenol and *iso*eugenol with peracetic and perbenzoic acids (PBA) (Fig. 1).

The kinetic study of epoxidation reactions of both terpenoids with perbenzoic acid (PBA) was carried out in methylene chloride as a solvent in the second-order conditions under the temperature of 293 K. The reactions were studied by quantification of the unreacted PBA as a function of time using the method of iodometric titration. Fig. 2 shows the kinetic curves of the epoxidation reaction of eugenol and *iso*eugenol with perbenzoic acid.

By the results of titration the curves of dependence of $\ln[c/[b-(a-c)]]$ on time were plotted (a – is the initial molar concentration of PBA, mole/L; b – is the molar concentration of terpenes, mole/L; c – is the current molar concentration of PBA, mole/L).

The slope values for such curves were used for calculations of the second order rate constants k, L/(mole·min), for epoxidation reactions of eugenol and *iso*eugenol with perbenzoic acid in methylene chloride. The values of the rate constants were 0.44 L/(mole·min) for *iso*eugenol and 0.016 L/(mole·min)

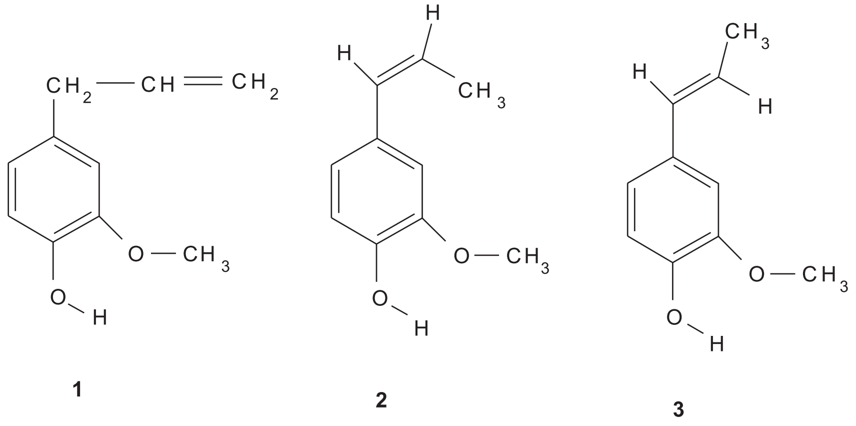


Fig. 1. The structure of terpenoids – eugenol (**1**) and *iso*eugenol isomers (**2–3**)

Table 1

The values of activation parameters of epoxidation of eugenol (**4**) and *iso*eugenol (**5, 6**) epoxidation with peracetic acid designed to approximate UBH&HLYP/6-31G (d)

Transition state	ΔH_{act}, kJ/mole	ΔG_{act}, kJ/mole
4	122.39	137.37
5	101.43	117.18
6	101.29	112.40

for eugenol, i. e. the rate constant of epoxidation of *iso*eugenol was in 5.5 times more than for its isomer (eugenol).

The method of the functional density (approximation UBH&HLYP/6-31G (d)) [22] was used for the quantum chemical calculation of activation parameters of the epoxidation reaction (Tab. 1–2) and modeling the transition states of molecules (Fig. 3–4).

As seen from Tab. 1, the values of activation barriers for epoxidation of *cis*- and *trans*-forms of *iso*eugenol were approximately 20 kJ/mole lower than that for eugenol coinciding with the experimental data.

The transition state of the eugenol epoxidation is in line with the synchronous process, in which the C–O-moeity of epoxide cycle has quite a close value. It is important to note that the structure has a closed electronic shell, i. e. in contrast to the reactions of epoxidation of other olefins the biradical transition state is not observed. According to the calculations, the activation parameters for epoxidation of *cis*- and *trans*-forms of *iso*eugenol have quite similar values, and it confirms the insignificant effect of stereoisomeric forms of molecules on their reactivity. The geometric parameters and spin density values on the corresponding atoms are also similar. As can be seen in Fig. 3, transition states **4** and **5** are close to planar character (see angles $C_\alpha C_\beta OH$), they are asymmetric

Table 2

The values of the activation parameters of epoxidation of eugenol (**7**) and *iso*eugenol (**8, 9**) with perbenzoic acid designed to approximate UBH&HLYP/6-31G (d)

Transition state	ΔH_{act}, kJ/mol	ΔG_{act}, kJ/mol
excluding the spin correction		
7	118.69	129.29
8	105.23	116.73
9	100.06	112.87
including the spin correction		
8	81.24	92.74
9	77.23	90.04

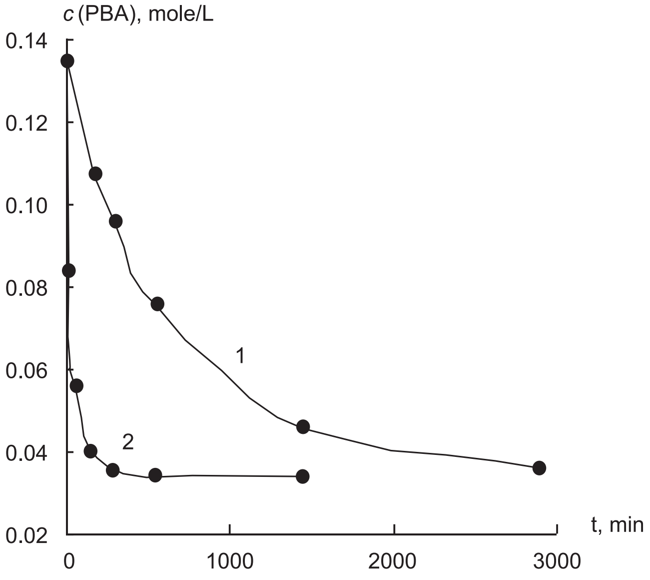
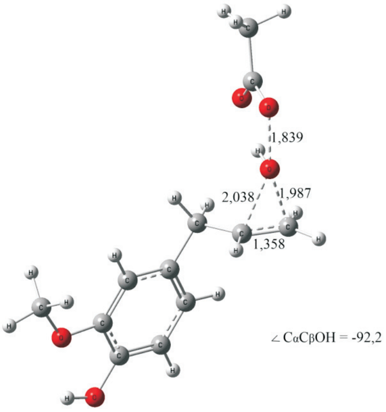


Fig. 2. Kinetic curves for the epoxidation reaction of eugenol and *iso*eugenol with perbenzoic acids (*c*(PBA) = 0.1350 mole/L; *c*(eugenol) = 1.65%; *c*(*iso*eugenol) = 1.65%; *T* = 293 K)



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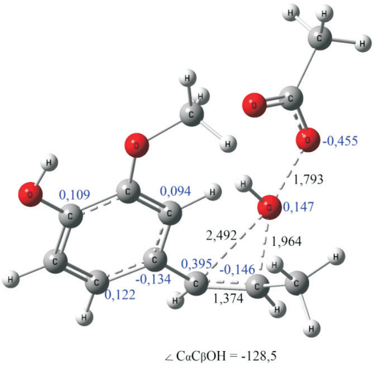
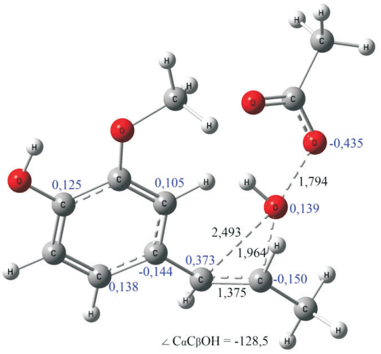
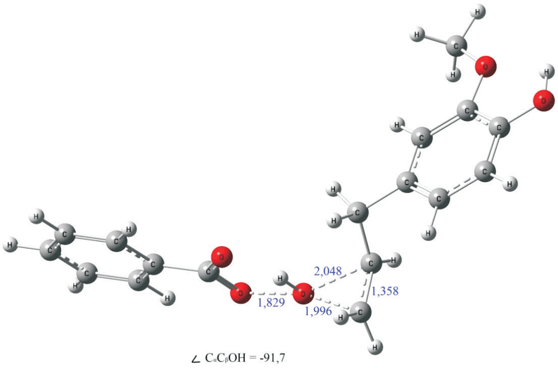




5 **6**

Fig. 3. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of epoxidation transition states of eugenol (**4**) and *iso*eugenol (**5, 6**) with peracetic acid



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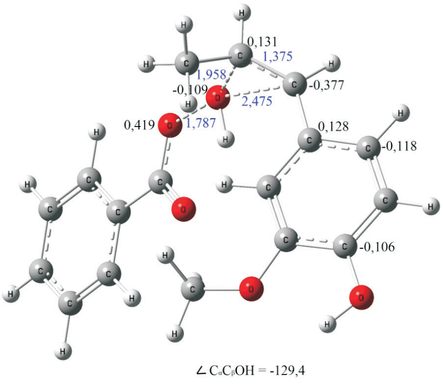

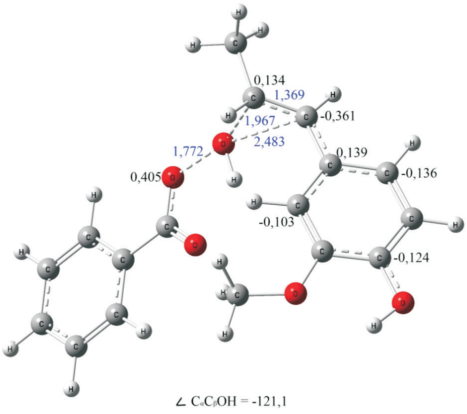

8 **9**

Fig. 4. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of epoxidation transition states of eugenol (**7**) and *iso*eugenol (**8, 9**) with perbenzoic acid

with a significant advantage in the bond formation of C_α–O above with C_β–O.

The analysis of the wave function transition states **5** and **6** show their biradicality. The highest spin density is localized on atoms C_2 and O_{27}. By coupling of the aromatic olefinic fragment there is a partial delocalization of the spin density at the *ortho*- and *para*-Carbon atoms.

The transition state **7** of eugenol epoxidation with perbenzoic acid is in line with the synchronous process, in which the C–O moeity of the epoxide cycle has quite similar value and a closed electronic shell. The analysis of the wave function transition states **8** and **9** shows their biradicality.

According to the calculation, the lowest activation barrier value is characterized by a reaction occurred through the transition state **9**. This trend persists even after consideration of the spin correction.

Experimental part

The following compounds were used in the work: eugenol (99 %, Sigma-Aldrich, *iso*eugenol (mixture of *cis*- and *trans*-isomers, 99 %, Sigma-Aldrich), benzoyl peroxide (≥ 98 %, Sigma-Aldrich), perbenzoic acid (98 % – determined by the iodometric titration), obtained by the method [23], acetic acid (at least 98 %), methylene chloride (p.a., LAB-SCAN).

To determine the *active oxygen content* for perbenzoic acid transfer 10.00 mL of its chloroform solution in a 100 mL Erlenmeyer flask, add 5 mL of 5 % KI solution and 5 mL of 30 % (w/w) acetic acid. Shake and allow to stand in a dark place for 30 minutes. Then titrate the liberated iodine with 0.1000 mole/L $Na_2S_2O_3$ solution using a 10 mL microburette (graduation is 0.02 mL). 1.00 mL of 0.1000 mole/L $Na_2S_2O_3$ solution corresponds to 0.0069 g of perbenzoic acid.

Diluted acetic acid: mix 31.3 wt. p. of acetic acid and 68.7 wt. p. of distilled water to obtain the acetic acid content of 29.5–30.5 % (w/w).

Potassium iodide solution, 5 %: dissolve 5.0 g of potassium iodide in 50 mL of freshly boiled and cooled water, and then dilute the solution obtained with the same solvent to 100 mL. The solution should be colorless.

Sodium thiosulphate standard solution ($c(Na_2S_2O_3 \cdot 5H_2O) = 0.1000$ mole/L): prepare from 0.1 M Normadose® (standard titer) in freshly boiled and cooled distilled water with addition of 0.5 g of sodium carbonate in a 1000 mL measuring flask and dilute to the volume at 293 K.

Air thermostat TS-80m was used for maintaining the desired temperature of the reaction mixture.

The study of the epoxidation reaction kinetics procedure*:* dissolve 0.8240 g of eugenol (or *iso*eugenol) in 49.2 mL of 0.1 mole/L solution of perbenzoic acid previously prepared in methylene chloride and mix to homogeneity. Over the determined period of time transfer 5.00 mL of the reaction mixture in a 150 mL Erlenmeyer flask using a pipette, add 2 mL of diluted acetic acid and 5 mL of 5 % potassium iodide solution while shaking. Titrate the liberated iodine with 0.1000 mole/L sodium thiosulphate solution using a microburette till the mixture becomes colorless. Repeat the titration without eugenol (control titration).

The method of the functional density (software Gaussian 09, approximation UBH&HLYP/6-31G(d)) was used for the quantum chemical calculation.

Conclusions

The study of epoxidation reaction mechanism of isomeric terpenoids eugenol and *iso*eugenol by density functional theory using the UBH&HLYP/6-31G (d) approach for the software Gaussian 09 has shown that the ratio of the activation energy for interaction of eugenol and *iso*eugenol with both acids (peracetic and perbenzonic) indicate higher reactivity of *iso*eugenol. These results are consistent with the kinetic data experimentally obtained; it confirms the correctness of the UBH&HLYP/6-31G (d) approach used to study the epoxidation characteristics of isomeric alkenes with peroxyacids.

Conflict of interests: authors have no conflict of interests to declare.

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