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# The quantum chemical study of the mechanism of the epoxidation reaction of limonene and geraniol with peracetic and perbenzoic acids

**Aim.** To compare the mechanism of the epoxidation reaction of terpenes Geraniol and Limonene with peracetic acid and perbenzoic acid based on the quantum chemical study.

**Materials and methods**. For the calculation the density functional theory (approximation UBH & HLYP/6-31G (d) Gaussian 09) method was applied. The specified density functional allows to correctly describing biradical structures; it is rather economic in terms of the computer time cost, which allows its use in the study of sufficiently complex organic compounds and reactions.

**Results and discussion**. The quantum chemical study of mechanisms of the epoxidation reaction of such terpenes as Geraniol and Limonene with peracetic and perbenzonic acids using the density functional theory (approximation UBH & HLYP/6-31G (d) Gaussian 09 program) has been conducted. It has been shown that epoxidation of geraniol with both peroxyacids occurs preferably by the double bond $C_6$=$C_7$ due to stabilization of the corresponding transition state as a result of formation of hydrogen bond between the allyl hydroxyl group and the oxygen atom of the peroxy acid. Epoxidation of Limonene with perbenzoic and peracetic acids occurs via the cyclic double bond characterized by the lowest activation barrier, and it is consistent with the regioselectivity of the process generally known and experimentally proven.

**Conclusions**. The results obtained are consistent with the experimental data, confirming the correctness of the use of this UBH & HLYP/6-31G (d) approach to study the regiochemical pecularities of the epoxidation process of alkenes containing several isolated double bonds.

***Key words***: terpenes; Geraniol; Limonene; quantum-chemical studies; epoxidation mechanism; peroxy acid

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### Квантово-хімічне дослідження механізму реакції епоксидування гераніолу та лимонену надацетатною та надбензойною кислотами

**Мета** – з’ясування механізму реакції епоксидування терпеноїдів Гераніолу та Лимонену надацетатною (пероксіетановою) та надбензойною кислотами за результатами квантово-хімічного дослідження.

**Матеріали та методи**. Для розрахунку використовували метод функціоналу густини (наближення UBH&HLYP/6-31G(d)) програми Gaussian 09. Вказаний функціонал дозволяє коректно описувати бірадикальні структури і є достатньо економічним з точки зору витрат комп’ютерного часу, що дозволяє використовувати його для дослідження досить складних органічних сполук та реакцій.

**Результати та їх обговорення**. Здійснене квантово-хімічне дослідження механізму реакції епоксидування терпеноїдів Гераніолу та Лимонену надацетатною та надбензойною кислотами з використанням методу функціоналу густини (наближення UBH&HLYP/6-31G(d) програми Gaussian 09. Показано, що епоксидування Гераніолу обома пероксикислотами відбувається швидше за подвійним зв’язком $C_6$=$C_7$ завдяки стабілізації відповідного перехідного стану за рахунок водневого зв’язку між Гідрогеном гідроксильної групи алільної системи та атомом Оксигену пероксикислоти. Епоксидування Лимонену надацетатною та надбензойною кислотами відбувається за циклічним подвійним зв’язком і характеризується найменшим активаційним бар’єром, що узгоджується із загальновідомою експериментально встановленою регіоселективністю процесу.

**Висновки**. Отримані результати узгоджуються з експериментальними даними, що підтверджує коректність використання наближення UBH&HLYP/6-31G(d) для вивчення регіо-хімічних особливостей епоксидування алкенів з декількома ізольованими подвійними зв’язками.

***Ключові слова***: терпеноїди; Гераніол; Лимонен; квантово-хімічне дослідження; механізм; епоксидування; пероксикислота

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### Квантово-химическое исследование механизма реакции эпоксидирования терпеноидов гераниола и лимонена перуксусной и пербензойной кислотами

**Цель** – установление механизма реакции эпоксидирования терпеноидов Гераниола и Лимонена перуксусной и пербензойной кислотами на основании результатов квантово-химического исследования.

**Материалы и методы.** Для расчета использовали метод функционала плотности (приближение UBH & HLYP/6-31G (d)) программы Gaussian 09. Указанный функционал позволяет корректно описывать бирадикальные структуры и является достаточно экономичным с точки зрения затрат компьютерного времени, что позволяет использовать его для исследования достаточно сложных органических соединений и реакций.

**Результаты и их обсуждение.** Проведено квантово-химическое исследование механизма реакции эпоксидирования терпеноидов Гераниола и Лимонена перуксусной и пербензойной кислотами с использованием метода функционала плотности (приближение UBH & HLYP/6-31G (d) программы Gaussian 09. Показано, что эпоксидирование Гераниола обеими пероксикислотами происходит быстрее по двойной связи $C_6$=$C_7$ благодаря стабилизации соответствующего переходного состояния за счет водородной связи между водородом гидроксильной группы аллильной системы и атомом кислорода пероксикислоты. Эпоксидирование Лимонена перуксусной и пербензойной кислотами происходит по циклической двойной связи и характеризуется наименьшим активационным барьером, что согласуется с общеизвестной экспериментально доказанной региоселективностью процесса.

**Выводы**. Полученные результаты согласуются с экспериментальными данными, подтверждают корректность использования приближения UBH & HLYP/6-31G (d) для изучения регио-химических особенностей эпоксидирования алкенов с несколькими изолированными двойными связями.

***Ключевые слова***: терпеноиды; Гераниол; Лимонен; квантово-химическое исследование; механизм; эпоксидирование; пероксикислоты

Monoterpenes as objects of the chemical research have attracted great interest from the outset of organic pharmaceutical chemistry. These compounds were obtained from natural sources (e.g turpentine from conifers) by classic methods –fractional and steam distillation. The study of monoterpenes contributed to development of the experimental methodology of both organic synthesis and analysis, and made a significant contribution to its theoretical arsenal.

The study of transformation reaction mechanisms is becoming increasingly important to both 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. Of particular interest are epoxidation reactions of monoterpenoids having allyl alcohol functional groups with organic peroxy acids.

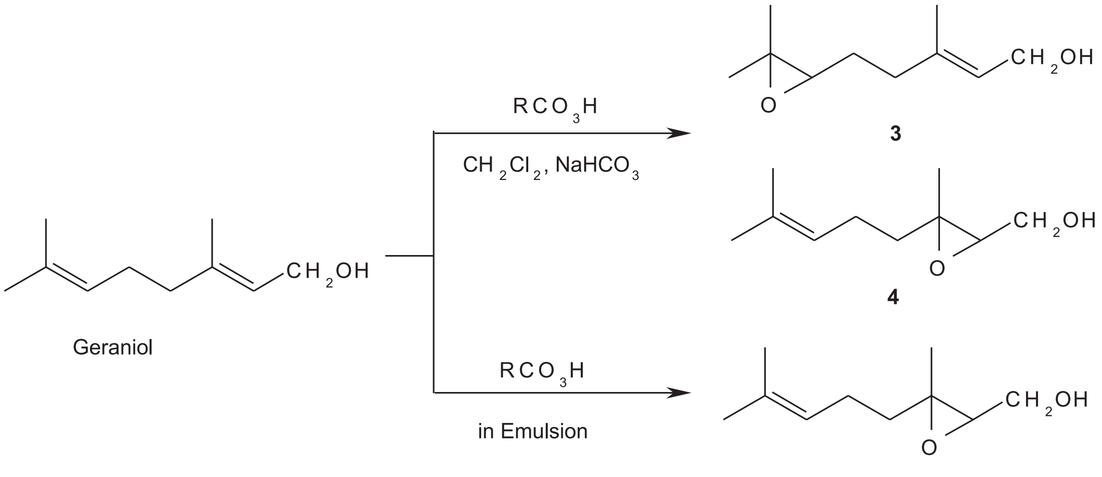
Thus, Geraniol (Fig. 1), which contains two trisubstituted C=C bonds, is epoxidated with meta-chloroperoxybenzoic acid (MCPBA) in the organic solvent (methylene chloride, chloroform) medium preferably at 6,7-double bond (3) (57 % vs. 30 % for 2,3-monoepoxide Geraniol (4)) (Scheme 1). Similarly, the interaction between MCPBA and Geraniol in an aqueous solution of $NaHCO_3$ (pH 8.3) (44 % versus 27 % for 2,3-monoepoxide), while in the presence of an emulsifier Geraniol is epoxidated exclusively selective with the allyl system which is apparently caused by different mechanisms of interaction (see Scheme 1) [1, 2].

It is not excluded that in the case of aprotic solvents the orientational effect of the hydroxyl group of the allyl system appears. As is known, Geraniol (1) (Fig. 1) is a *trans*-isomer (1-methyl-4 (1-methylethenyl)-cyclohexene); it is contained in palmarosa and citronella essential oils. It is used as a fragrant substance for perfume compositions, aromatization of soap and detergents [3].

Among menthene terpenes Limonene can be considered the most studied; it, obviously, is due to its prevalence in natural sources. Limonen (2) (Fig. 1) is a substance that is in relatively large amount in both lemon (where the name comes from) and in many other citrus fruits.

The natural Limonene occurs as a *d*-form isolated from orange oil. Like other terpenes, it is biologically active, possesses anticancerogenic properties, normalizes hepatic functions. It is used in perfumery, food industry and in the production of detergents.

Special attention is drawn to the relative reactivity of its endo- and exocyclic olefinic fragments. In most cases, electrophilic addition occurs easily at both π-bonds; hence, *bis*-products are isolated most often. In the situations when it is possible to stop the process at the stage of 1 : 1 adduct formation, usually there is a product of addition at the exocyclic bond, and some-



Scheme 1. Reactions of regioselective epoxidation of Geraniol

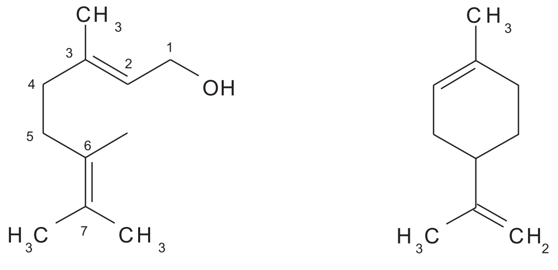


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Fig. 1. The structural formulas of Geraniol (1) and Limonene (2)

**Table 1**

The values of activation parameters of Geraniol epoxidation (1) with peracetic acid calculated to approximate UBH & HLYP/6-31G (d)

| The transition state | $\Delta H_{act.}$, kJ/mol | $\Delta G_{act.}$, kJ/mol |
|---|---|---|
| 7 | 102.36 | 115.11 |
| 8 | 121.61 | 139.66 |

times other products of further transformation are easily formed (Scheme 2) [4].

The aim of this work was to compare the mechanism of the epoxidation reaction of terpenes Geraniol and Limonene with peracetic acid and perbenzoic acid based on the quantum chemical study.

For the calculation the density functional theory (approximation UBH & HLYP/6-31G (d) Gaussian 09) method was applied. The specified density functional allows to correctly describing biradical structures; it is rather economic in terms of the computer time cost, which allows its use in the study of sufficiently complex organic compounds and reactions.

Comparison of the activation barrier values for Geraniol epoxidation at bonds $C_6=C_7$ and $C_2=C_3$ demonstrates the preference of the former bond to the latter (Tab. 1), which is consistent with the experimental data. In our opinion, one of the main causes for this regiochemistry of the process is formation of the hydrogen bond between the hydrogen atom of the alcohol group and the oxygen atom of peracetic acid in transition state (7), leading to its stabilization (Fig. 2).

It should be noted that transition states (7) and (8) differ in the character of their wave functions. In the first case, the structure has a closed electron shell, while transition state (8) has a biradical character with the most localized spin density on the atoms $C_2$ and $O_{32}$.

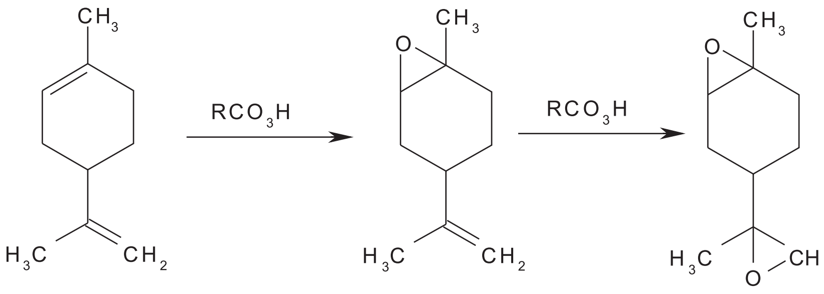
As shown in Fig. 2, transition states (7) and (8) are similar in their bond length between the oxygen atoms of the peroxide bond, but differ by the degree of the C-O bond formation; transition state (7) has a symmetrical structure, while in structure (8) there is preferential formation at one of the bonds. These activation parameter values of Geraniol epoxidation with peracetic acid are presented in Tab. 1, also confirming the preference of transition state (7).

In transition state (10) the formation of the hydrogen bond between the hydrogen atom of the alcohol group and the oxygen atom of perbenzonic acid is observed, it leads to stabilization of the corresponding transition state (Fig. 3). It should be noted that transition states (9, 10) differ in the character of wave functions. In the first case the structure has a biradical character with the most localized spin density on the atoms $C_2$ and $O_{32}$. And in the second case, the structure has a closed electron shell.

Fig. 3 shows that transition state (10) has a symmetrical structure since the bond lengths have similar values, while in structure (9) there is the preferential formation at one of the bonds. Comparison of activation barriers values of Geraniol epoxidation (Tab. 2) indicates that transition state (10) has a lesser probability for formation than transition state (9); thus, the reaction is faster in the latter as in the case with peracetic acid.

It is important to confirm regiochemistry of the Limonene epoxidation process studied back in 1961. According to the theory epoxidation should occur first (or preferably) at the cyclic double bond, therefore, this regularity will be confirmed.

In the case of Limonene epoxidation with perbenzonic acid we observe that transition states (16, 17) have also a biradical character, unlike structures (15, 18), and have a closed elecronic shell. Comparison of tran-



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Scheme 2. Limonene epoxidation with peracids

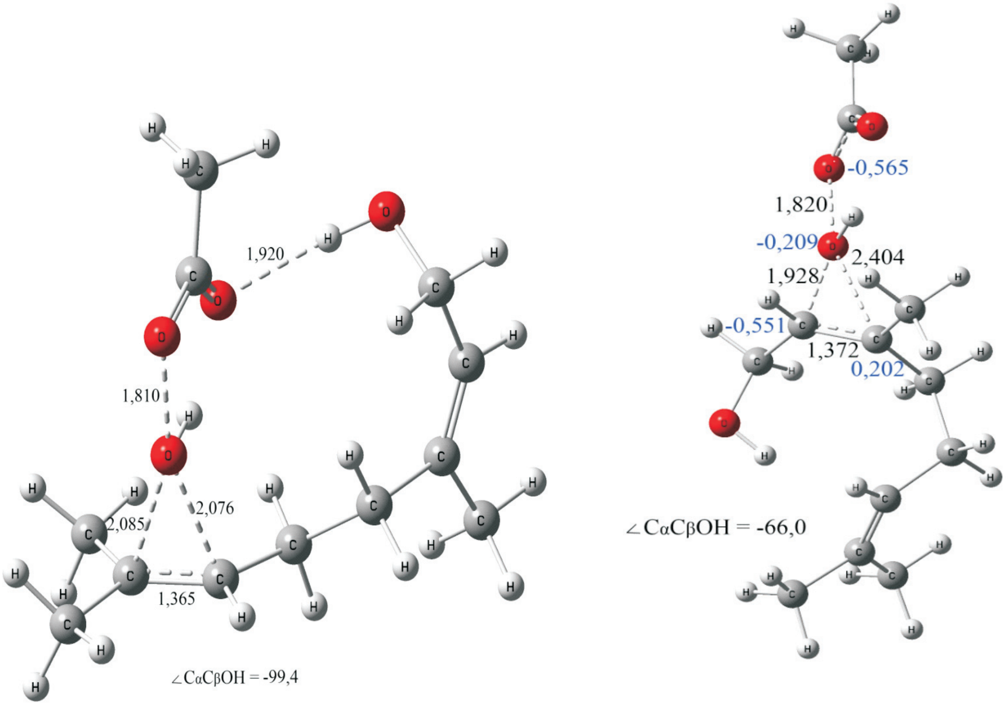

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Fig. 2. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of transition states of Geraniol epoxidation with peracetic acid

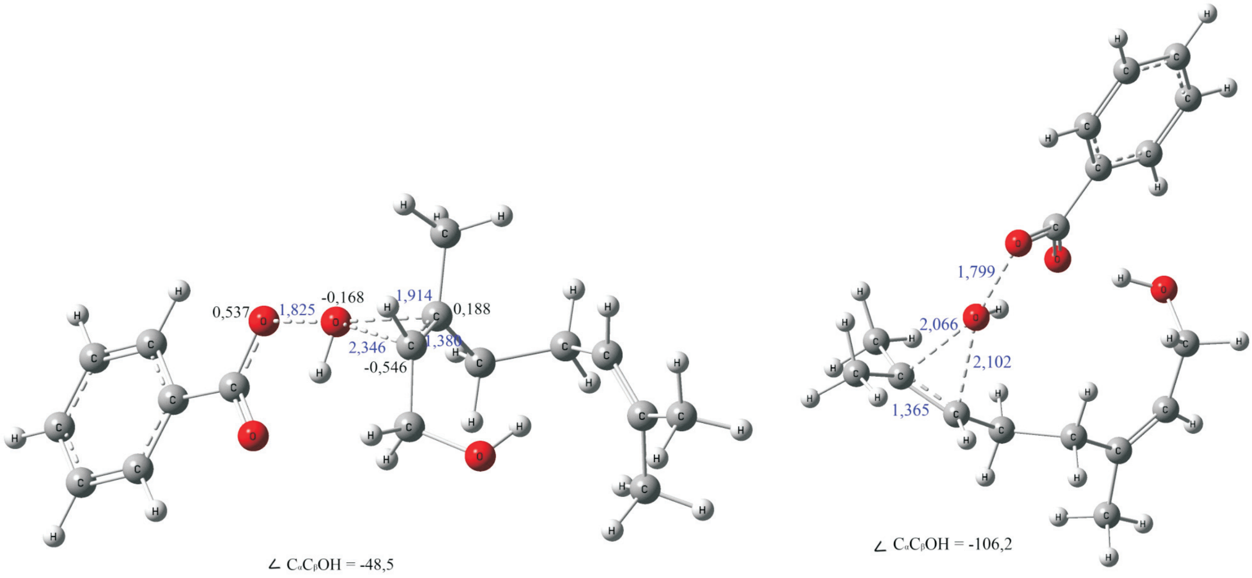

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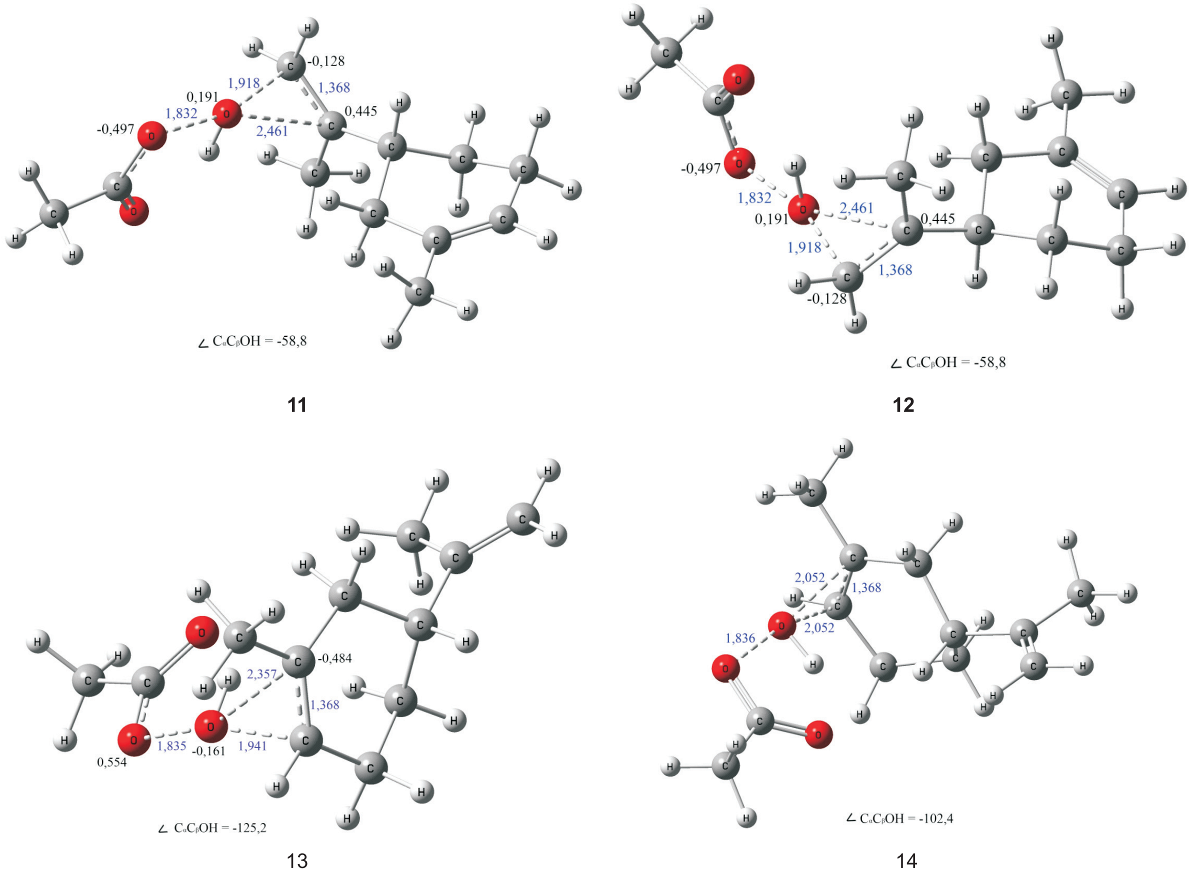
Fig. 3. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of transition states of Geraniol epoxidation with perbenzoic acid

sition state (14) and (18) shows that these structures are symmetrical, i.e. are close to the length of bonds between atoms of the oxygen peroxide bond. Based on the results of the calculation it can be concluded that Limonene epoxidation with peracetic and perbenzoic acids occurs via the cyclic double bond (transition states 13 and 17, respectively), and thus characterized by the lowest activation barrier, which is consistent with the regioselectivity of the process generally known and experimentally proven. These

**Table 2**

The values of activation parameters of Geraniol (1) epoxidation with perbenzoic acid using approximate UBH & HLYP/6-31G (d)

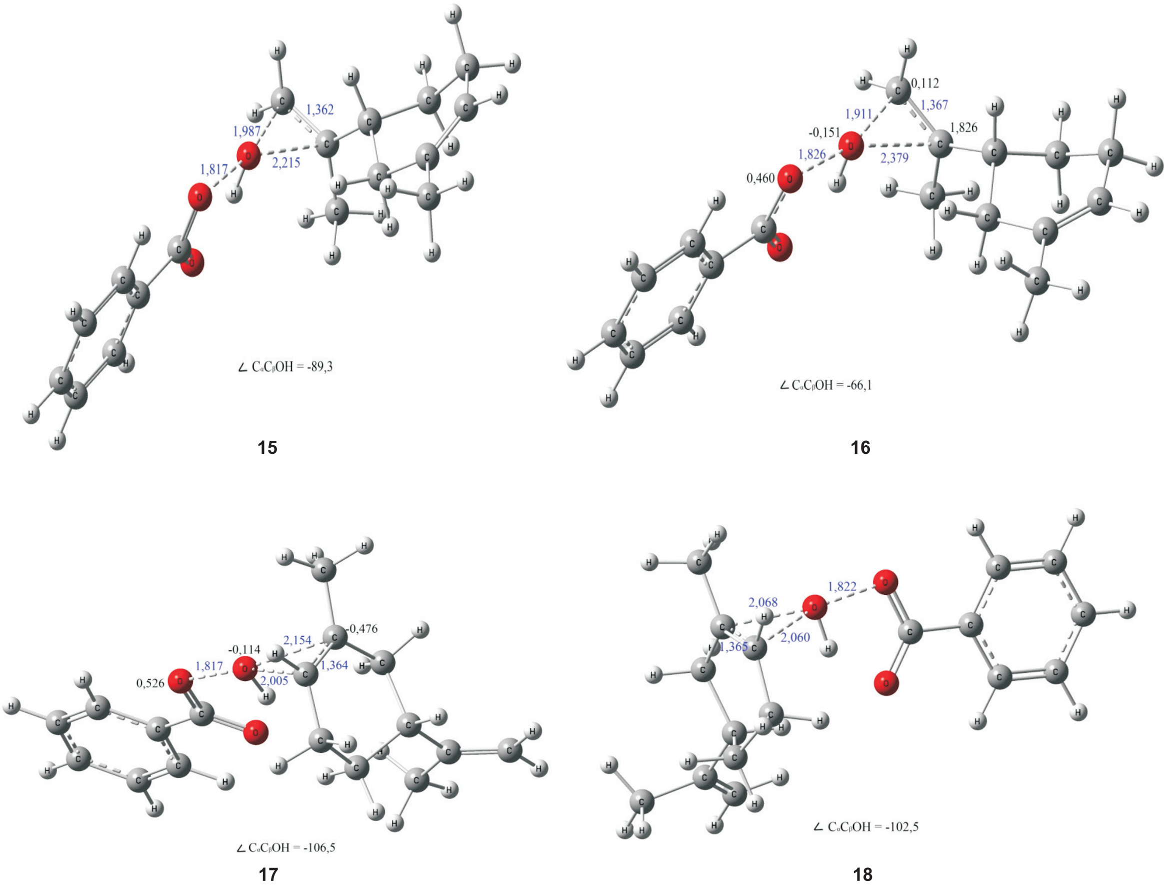
| The transition state | $\Delta H_{act.}$, kJ/mol | $\Delta G_{act.}$, kJ/mol |
|---|---|---|
| 9 | 106.4561 | 119.2948 |
| 10 | 98.06767 | 111.9067 |



**11** **12**

13 14

Fig. 4. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of transition states of Limonene epoxidation with peracetic acid



**15** **16**

**17** **18**

Fig. 5. The structure, geometric parameters (Å, deg.) and spin density values for some atoms of transition states of Limonene epoxidation with perbenzonic acid

**Table 3**

The values of activation parameters of Limonene epoxidation (2) with peracetic acid using approximate UBH & HLYP/6-31G (d)

| The transition state | $\Delta H_{act.,}$кJ/mol | $\Delta G_{act.,}$кJ/mol |
|---|---|---|
| Excluding spin correction | | |
| 11 | 112.12 | 115.42 |
| 12 | 115.41 | 115.41 |
| 13 | 106.15 | 118.02 |
| 14 | 110.33 | 124.35 |
| Including spin correction | | |
| 11 | 74.78 | 78.08 |
| 12 | 74.84 | 78.13 |
| 13 | 77.39 | 89.25 |

**Table 4**

The values of activation parameters of Limonene epoxidation (2) with perbenzoic acid calculated to approximate UBH & HLYP/6-31G (d)

| The transition state | $\Delta H_{act.,}$KJ/mol | $\Delta G_{act.,}$ KJ/mol |
|---|---|---|
| 15 | 109.93 | 121.27 |
| 16 | 111.18 | 116.29 |
| 17 | 104.03 | 117.30 |
| 18 | 106.51 | 122.29 |

values of activation parameters for limonene epoxidation with peracetic and perbenzoic acids are presented in Tab. 3 and 4, respectively.

The analysis of the wave function at the transition states of Limonene epoxidation with peracetic acid (Fig. 4, 5) indicates their biradical character (11-13), except for transition state (14), which has a closed electronic shell.

## Conclusions

As a result of the comparative quantum chemical study of mechanisms of the epoxidation reaction of terpenes, such as Geraniol and Limonene, with peracetic and perbenzonic acids using the density functional theory (approximation UBH & HLYP/6-31G (d) Gaussian 09 program), the following regularities have been determined:

1. Epoxidation of Geraniol with both peroxyacids occurs preferably by the double bond $C_6$=$C_7$ due to stabilization of the corresponding transition state as a result of formation of hydrogen bond between the allyl hydroxyl group and the oxygen atom of the peroxy acid and have a closed elecronic shell.
2. Epoxidation of Limonene with perbenzoic and peracetic acids occurs via the cyclic double bond characterized by the lowest activation barrier, and it is consistent with the regioselectivity of the process generally known and experimentally proven.
3. The results obtained are consistent with the experimental data, confirming the correctness of the use of this UBH & HLYP/6-31G (d) approach to study the regiochemical pecularities of the epoxidation process of alkenes containing several isolated double bonds.

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

### References

1. Frinquelli, F. pH–controlled Regioselectivity of the Epoxidation of Geraniol in Water / F. Frinquelli, F. Pizzo, R. Germani // Synlett. – 1991. – Vol. 1991 (07). – P. 475–476. https://doi.org/10.1055/s-1991-20765
2. Regioselective Epoxidation of Allylic Alcohols with Monoperoxyphtalic Acid in Water / F. Frinquelli, R. Germani, F. Pizzo et al. // J. Org. Chem. – 1992. – Vol. 57, № 4. – P. 1198–1202. https://doi.org/10.1021/jo00030a029
3. Гуринович, Л. К. Эфирные масла : Химия, технология, анализ и применение / Л. К. Гуринович, Т. В. Пучкова. – М. : Школа Косметических Химиков, 2005. – 192 с.
4. Племенников, В. В. Химия изопреноидов. Глава 5. Монотерпены (продолжение) / Химия растительного сырья. – 2006. – № 3. – С. 55–72.

### References

1. Fringuelli, F., Pizzo, F., & Germani, R. (1991). pH–Controlled Regioselectivity of the Epoxidation of Geraniol in Water. Synlett, 1991 (07), 475–476. https://doi.org/10.1055/s-1991-20765
2. Fringuelli, F., Germani, R., Pizzo, F., Santinelli, F., & Savelli, G. (1992). Regioselective epoxidation of allylic alcohols with monoperoxyphthalic acid in water. *The Journal of Organic Chemistry, 57 (4),* 1198–1202. https://doi.org/10.1021/jo00030a029
3. Gurinovich, L. K., Puchkova, T. V. (2005). *Jefirnye masla: Himija, tehnologija, analiz i primenenie.* Moscow : Shkola Kosmeticheskih Himikov, 192.
4. Plemenkov, V. V. (2006). *Himija rastitel'nogo syr'ja, 3,* 55–72.

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