



Supercomputer technologies ,dynamic models/molecular basis of intelligence

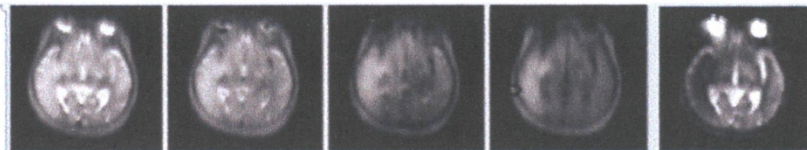
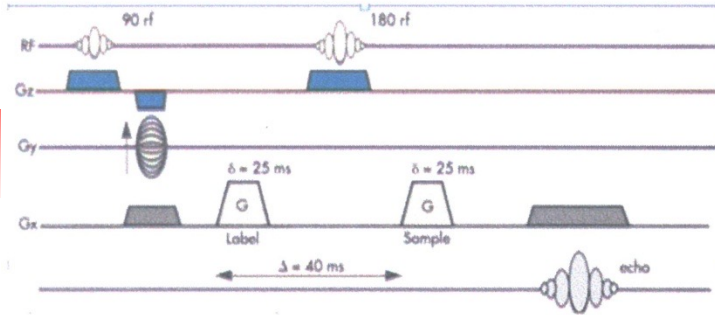
Sergey Varfolomeyev

Institute of Biochemical Physics,Russian Academy of Sciences

Moscow State University

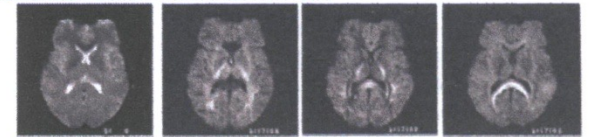






← diffusion coefficient image

Diffusion weighting

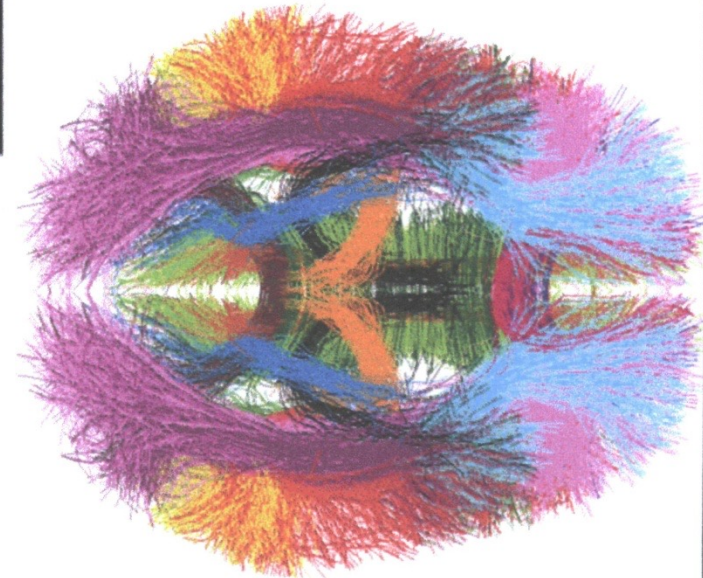
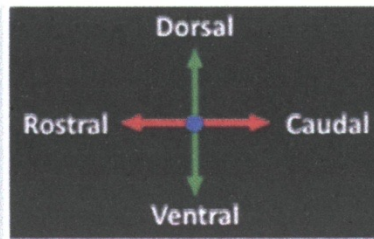
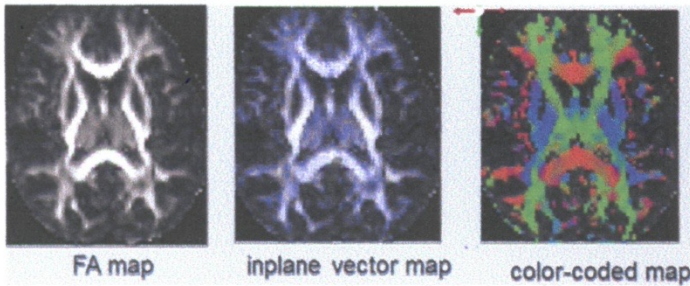


different gradient directions

DW along Read

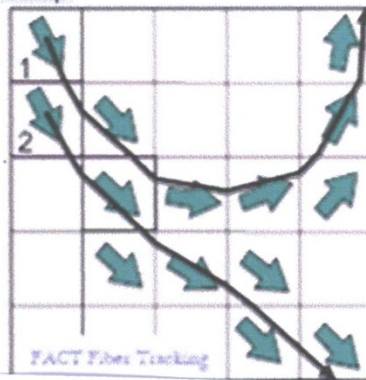
DW along Phase

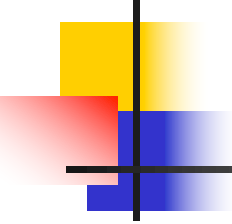
DW in Slice direction



$$FA = \frac{\sqrt{\frac{1}{3}((\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2)}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

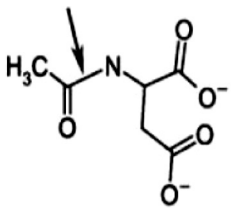
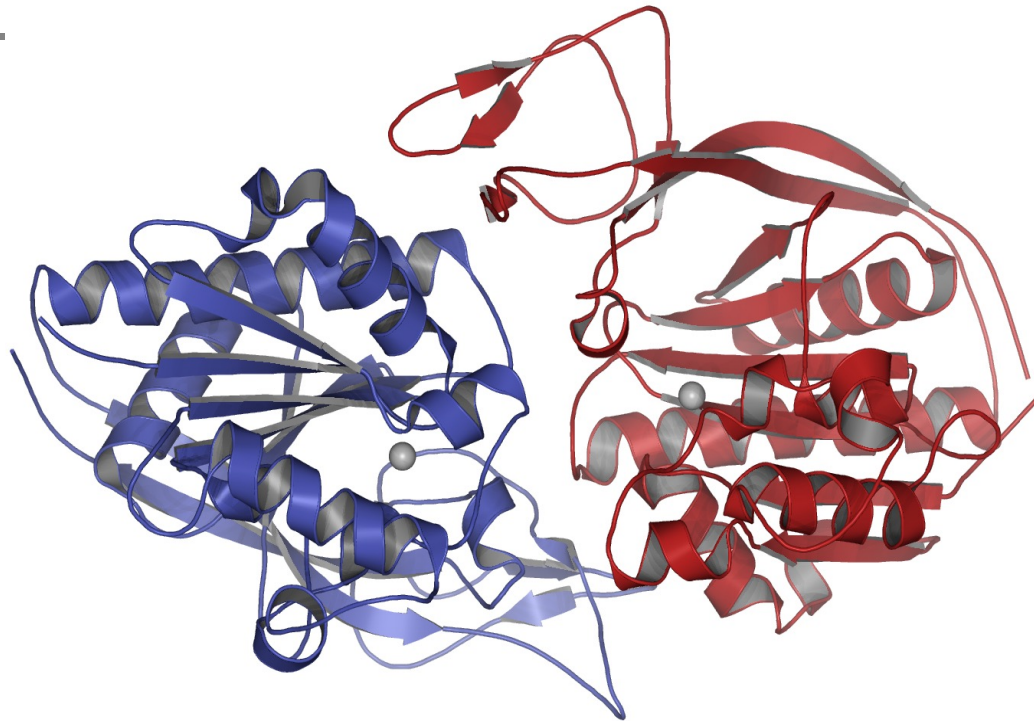
FA: fractional anisotropy



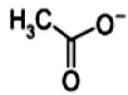


Молекулярные механизмы функционирования ферментов мозга

Brain N-Acetylaspartate hydrolase

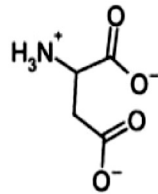


ASPA



Ацетат

+



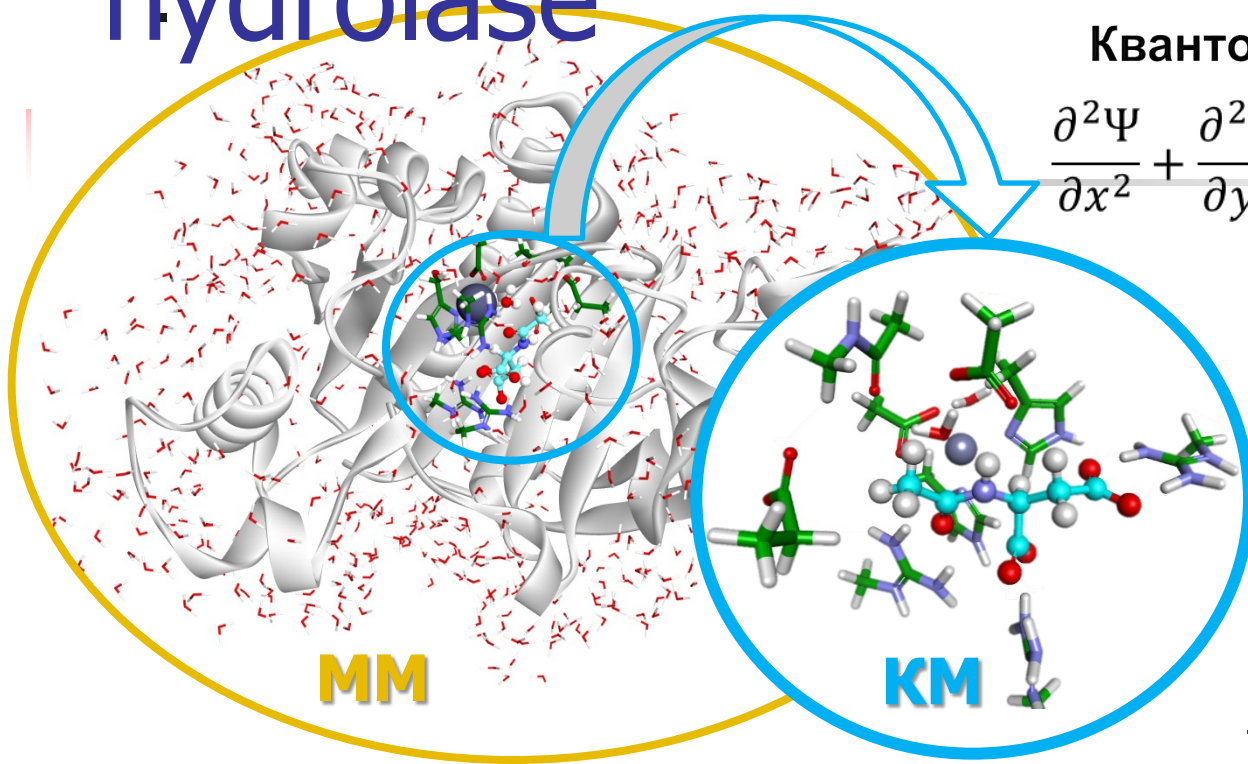
L-Аспарат

Н-ацетил-аспарат

Brain N-Acetylaspartate hydrolase

Квантово-механическая часть

$$\frac{\partial^2 \Psi}{\partial x^2} + \frac{\partial^2 \Psi}{\partial y^2} + \frac{\partial^2 \Psi}{\partial z^2} + \frac{8\pi^2 m}{h^2} (E - U) \Psi = 0$$



MM

QM

162 atoms , 714 electrons

Молекулярно-механическая часть

7127 atoms:
 4835 atoms of protein
 21 atoms of substrate
 757 water molecules

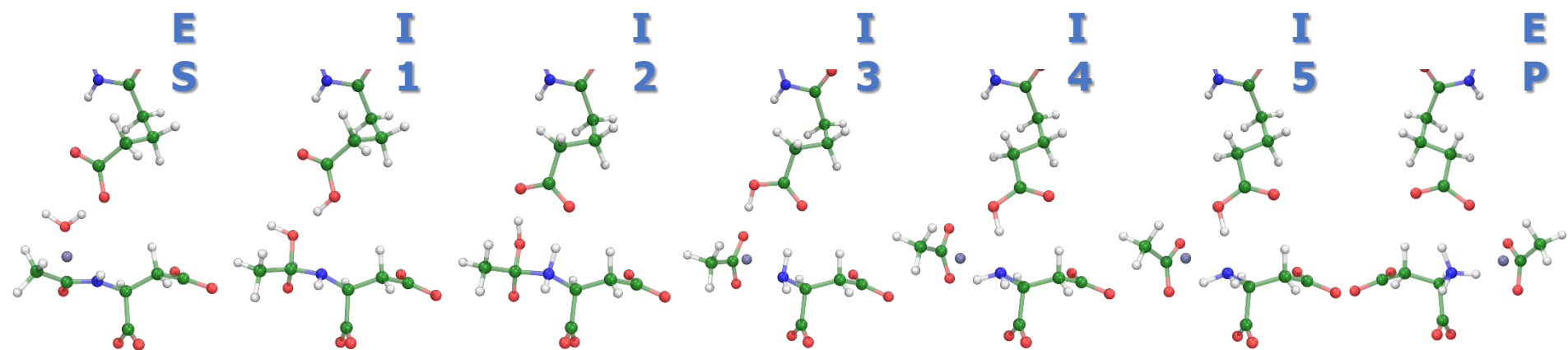
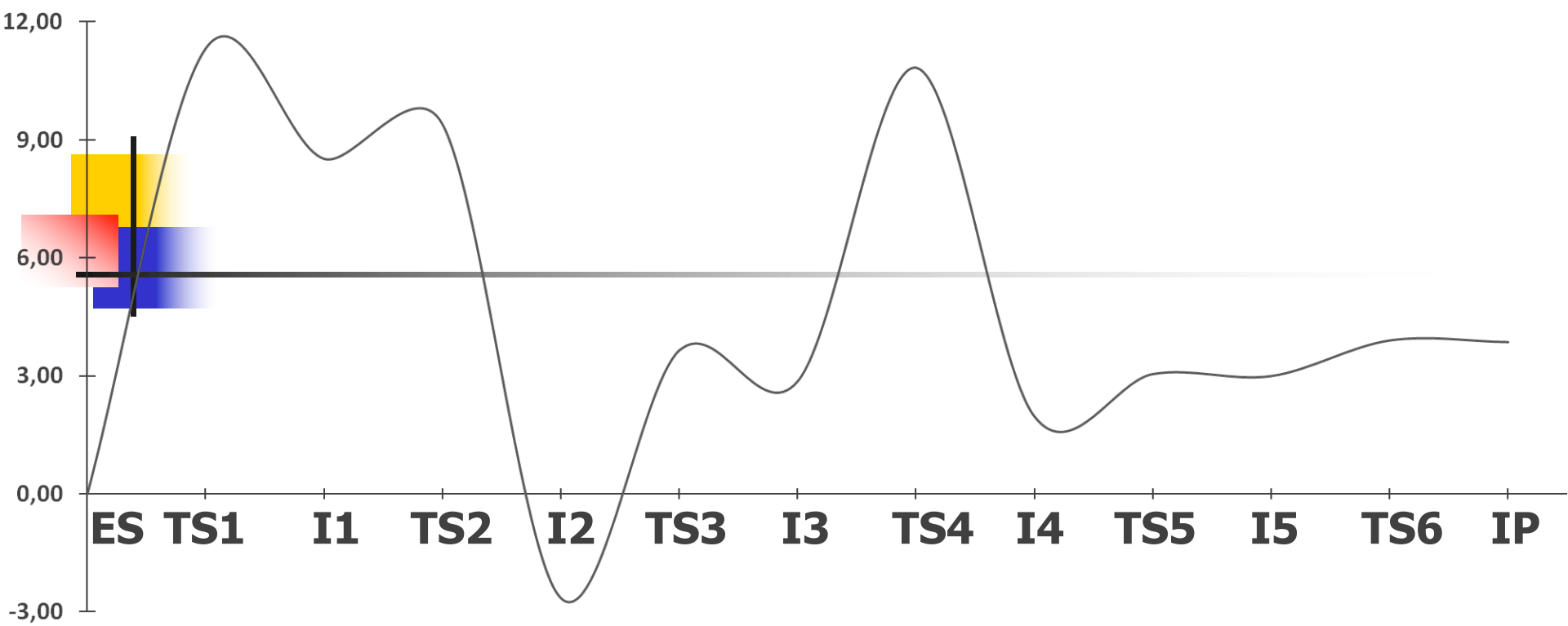
$$\hat{H}_{\text{электр.}} = \sum_i \hat{T}(i) - \sum_{iA} \frac{Z_A}{r_{iA}} + \sum_{i,j} \frac{1}{r_{ij}} + \sum_{A,B} \frac{Z_A Z_B}{R_{AB}}$$

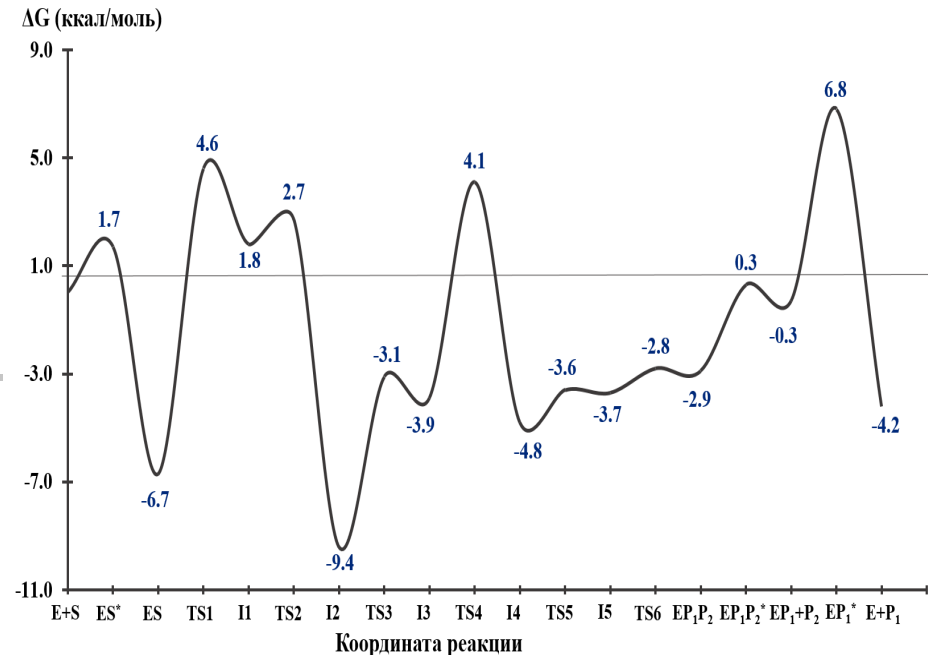
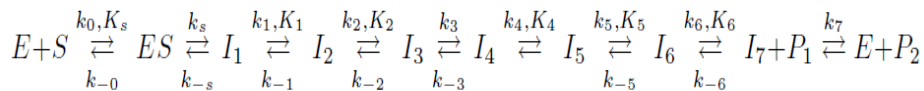
Kinetic energy of nucleus
 electrons

Interaction of
 electrons and

Negativ interaction of
 electrons

Negativ
 interaction of
 nucleus





- Structure of ALL labile intermediates and ALL transition states
- Calculation of ALL rate constants of ALL elementary steps

$$k_0 = 3.4 \cdot 10^{11} \text{ M} \cdot \text{s}^{-1}$$

$$k_3 = 8.03 \cdot 10^6 \cdot \text{s}^{-1}$$

$$k_{-0} = 4.07 \cdot 10^6 \cdot \text{s}^{-1}$$

$$k_{-3} = 1.74 \cdot 10^{-6} \cdot \text{s}^{-1}$$

$$k_s = 3.02 \cdot 10^4 \cdot \text{s}^{-1}$$

$$k_4 = 8.12 \cdot 10^{11} \cdot \text{s}^{-1}$$

$$k_{-s} = 5.4 \cdot 10^{10} \cdot \text{s}^{-1}$$

$$k_{-4} = 5.24 \cdot 10^{12} \cdot \text{s}^{-1}$$

$$k_1 = 1.35 \cdot 10^{12} \cdot \text{s}^{-1}$$

$$k_5 = 1.35 \cdot 10^{12}$$

$$k_{-1} = 7.7 \cdot 10^3 \cdot \text{s}^{-1}$$

$$k_{-5} = 5.24 \cdot 10^{12}$$

$$k_2 = 1.43 \cdot 10^8 \cdot \text{s}^{-1}$$

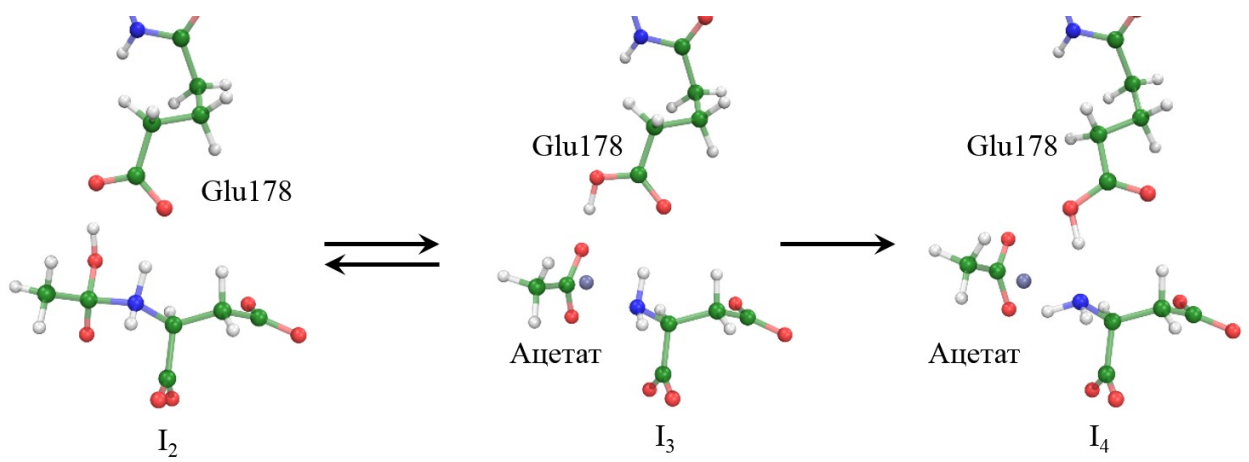
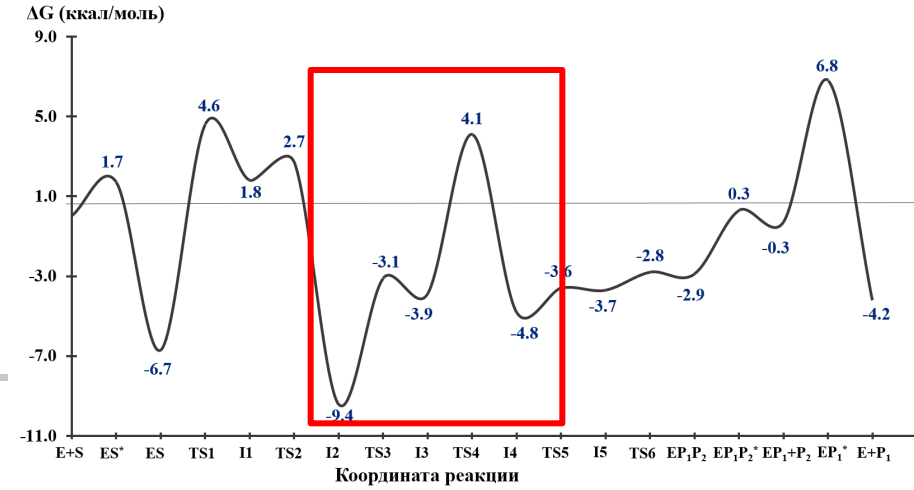
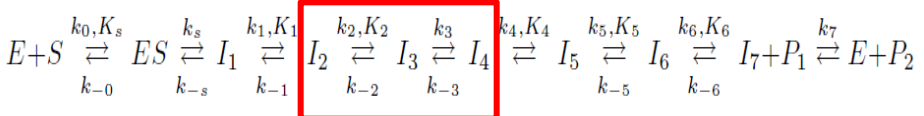
$$k_6 = 2.7 \cdot 10^{10} \cdot \text{s}^{-1}$$

$$k_{-2} = 1.6 \cdot 10^{12} \cdot \text{s}^{-1}$$

$$k_{-6} = 2.24 \cdot 10^{12} \cdot \text{s}^{-1}$$

$$k_7 = 3.69 \cdot 10^7 \cdot \text{s}^{-1}$$

Limiting step



$$\frac{1}{k_{\text{кат}}} = \frac{1}{k_s} + \frac{1}{k_s K_1 K_2} + \frac{1}{k_3} + \frac{1}{k_3 K_2} + \frac{1}{k_7 K_4 K_5 K_6} + \frac{1}{k_7 K_5 K_6} + \frac{1}{k_7 K_6} + \frac{1}{k_7}$$

$$k_{\text{кат}} \cong k_3 K_2 \cong 715 \text{ c}^{-1}$$

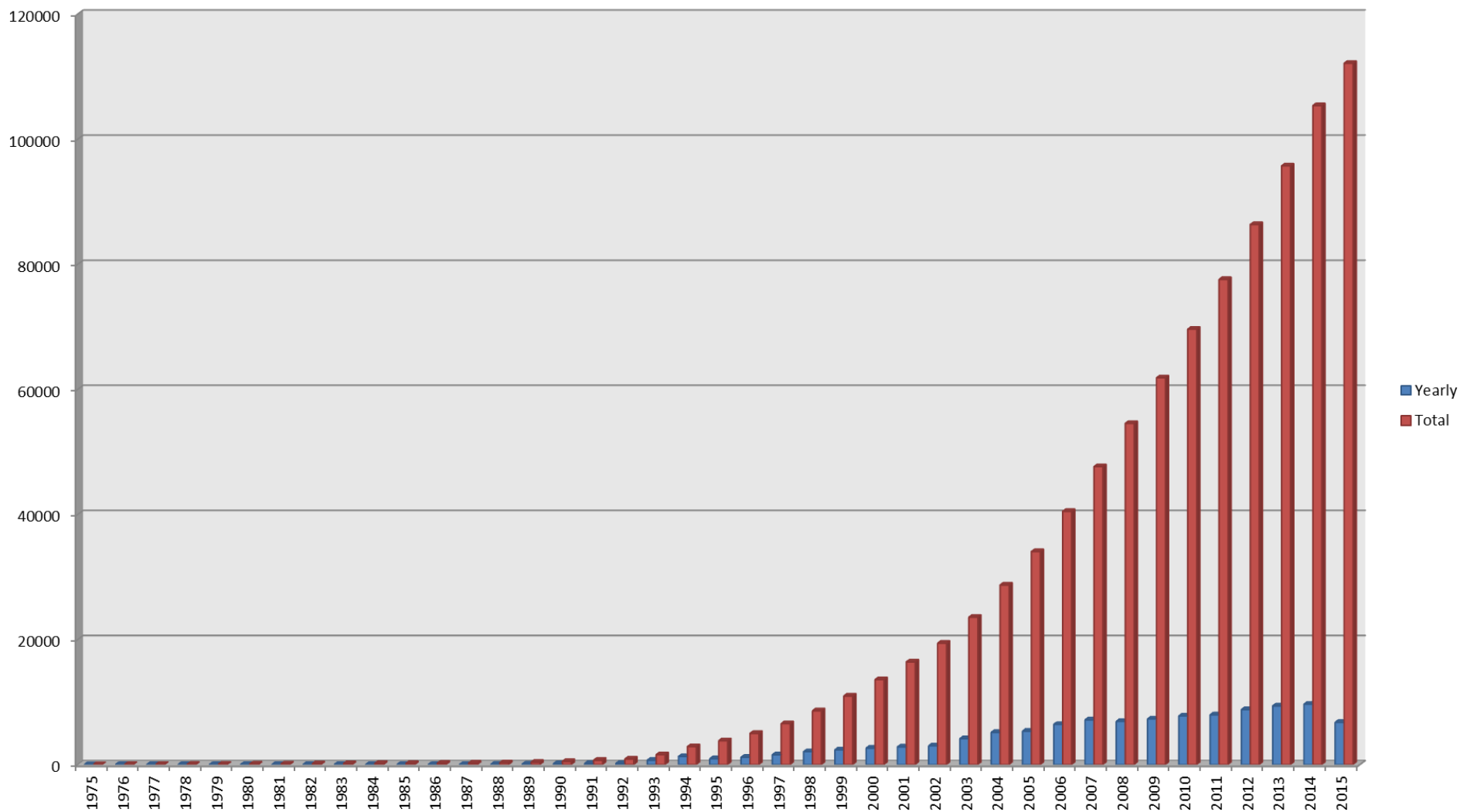


Applications



The most of the well-known
modern drugs passed through
computer design

PDB



<http://www.rcsb.org/pdb/statistics/>

Last update: *Tuesday Sep 15, 2015 at 5 PM PDT*



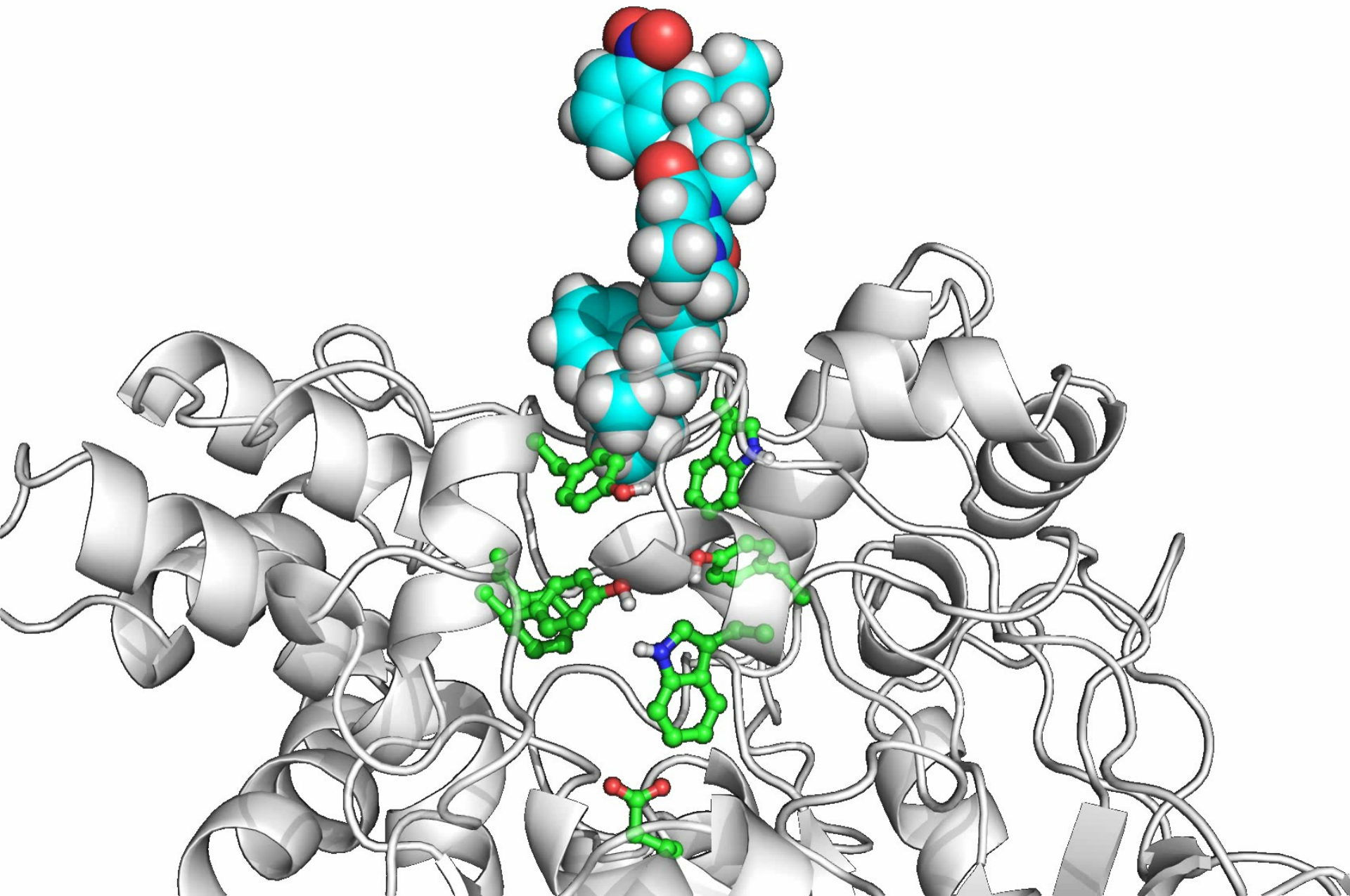
Molecular docking with molecular dynamics

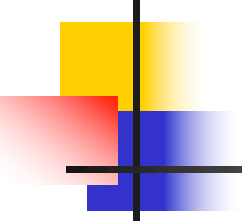
Reactivity on the basis of quantum chemical approach



Interaction of ligand

(substrate-inhibitor-
drug) with protein is very complex
dynamic process with
conformational changes of ligand
and protein





Molecular polymorphism-genetic
predisposition to different
diseases and individual sensitivity
to drugs



Identification of essential and not essential changes in protein structure

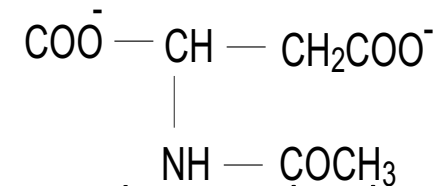
N-acetyl aspartic acid-key metabolite of central neural system

Canavan disease

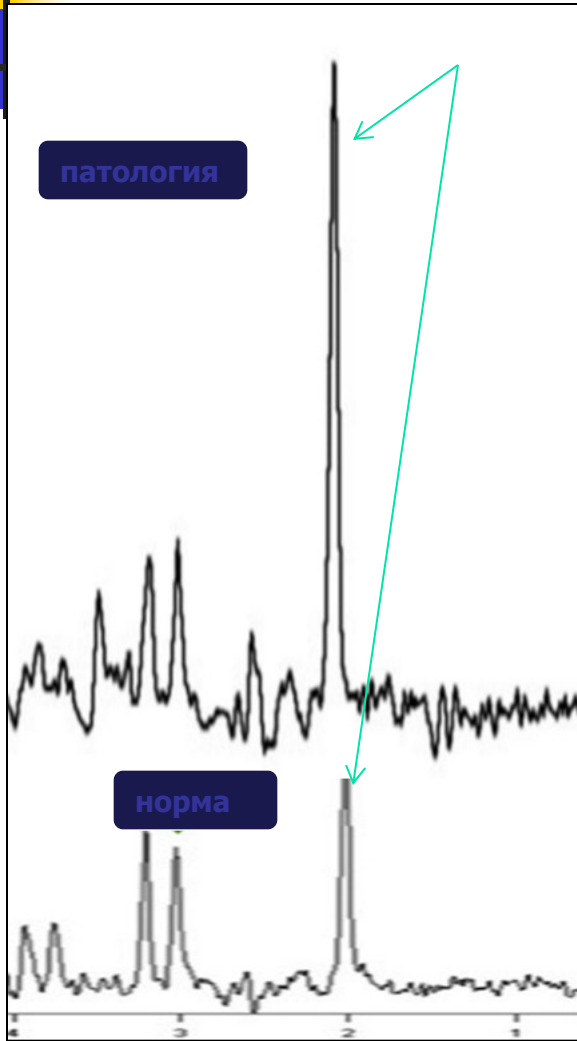
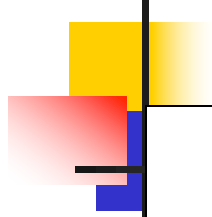
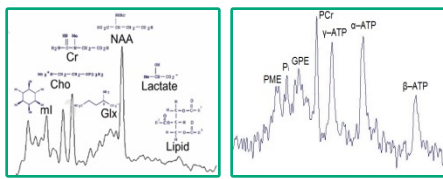
- Mental destruction - macrocephaly.
- 1 per 40 men (2.5%) for population ashkenazy
- Blocking of synthesis of mielyne covers of brain cells



Myrtelle May Canavan



Fundamental ground - single changes of amino acids in the structure of enzyme N-acetyl aspartate hydrolase



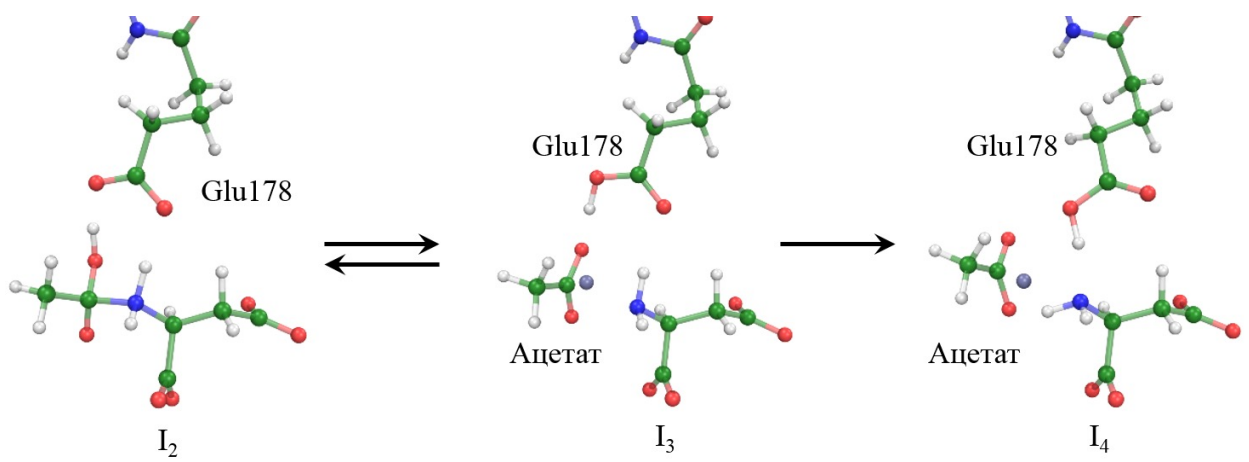
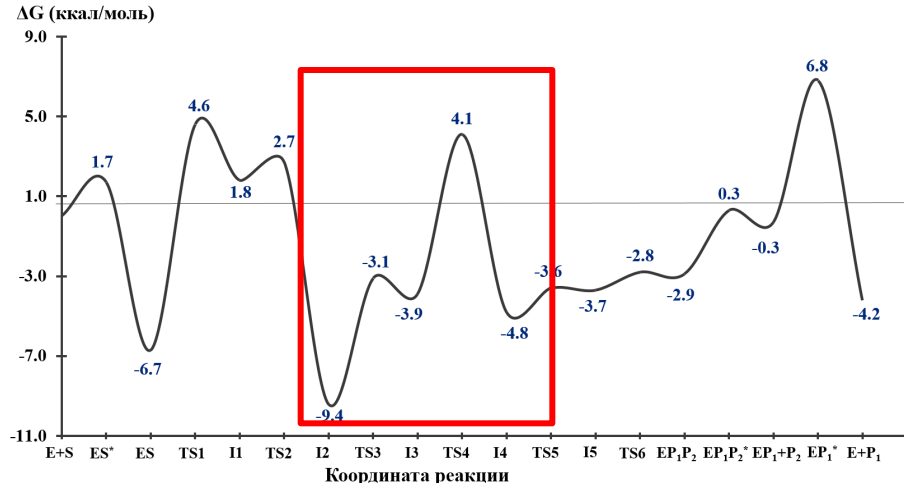
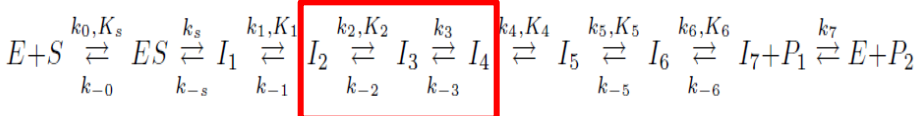
Canavan disease –level of N-acetyl aspartate in 5 TIMES higher normal



Supercomputer calculations

**Prediction of influence of point
amino acid polymorphic change on
structure and catalytic activity**

Limiting step

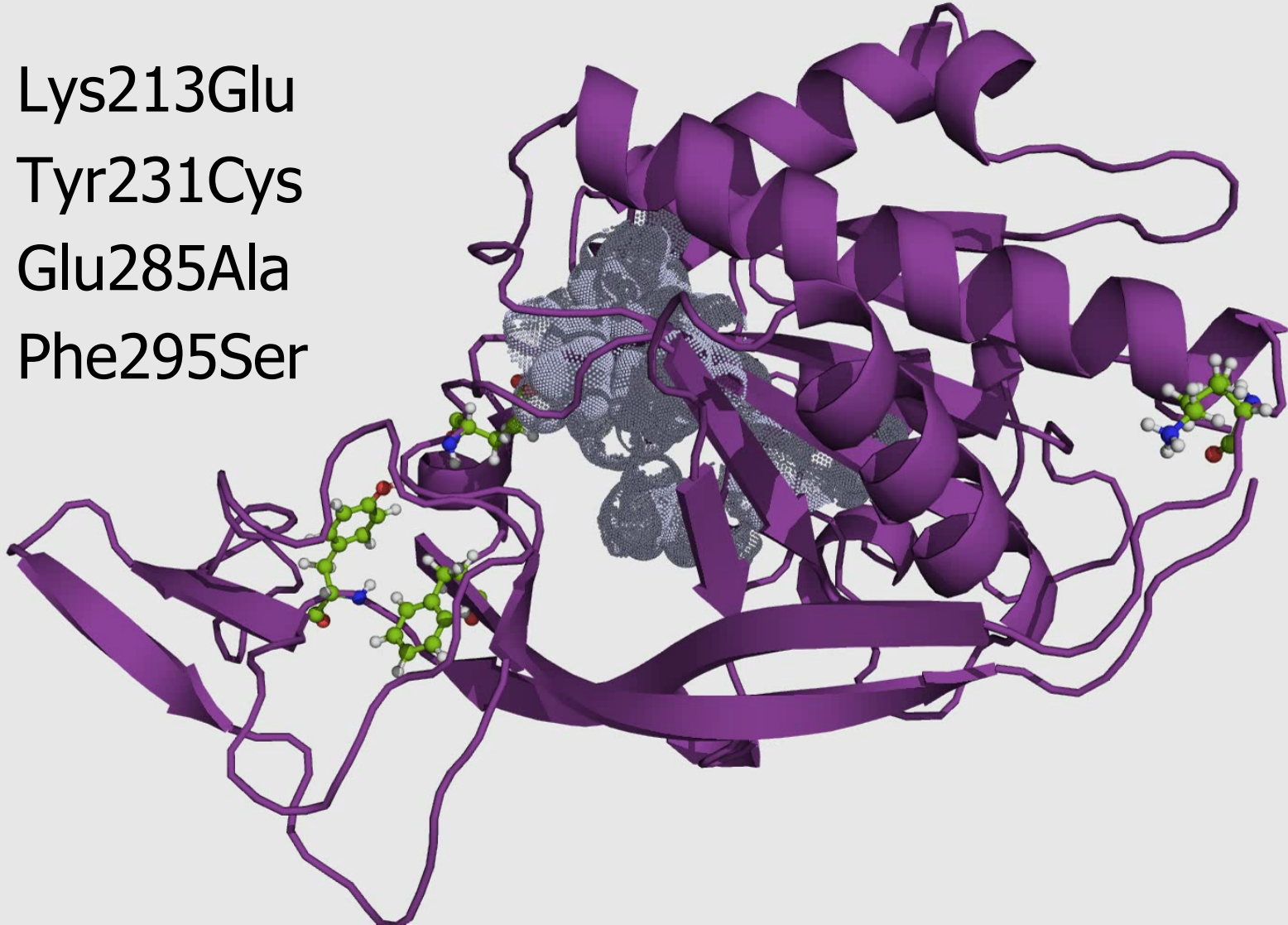


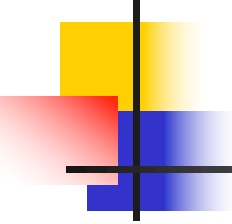
$$\frac{1}{k_{\text{кат}}} = \frac{1}{k_s} + \frac{1}{k_s K_1 K_2} + \frac{1}{k_3} + \frac{1}{k_3 K_2} + \frac{1}{k_7 K_4 K_5 K_6} + \frac{1}{k_7 K_5 K_6} + \frac{1}{k_7 K_6} + \frac{1}{k_7}$$

$$k_{\text{кат}} \cong k_3 K_2 \cong 715 \text{ c}^{-1}$$

Critical single amino acid changes in aspartoacylase at Canavan disease

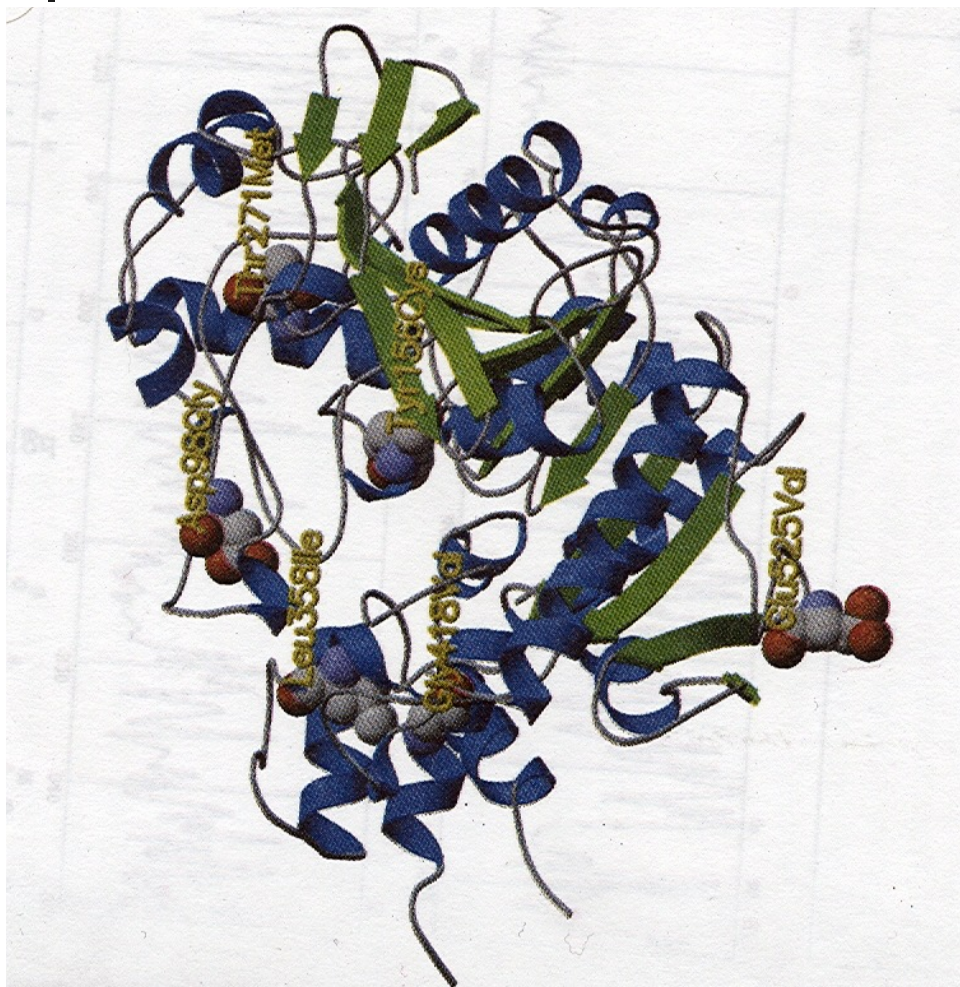
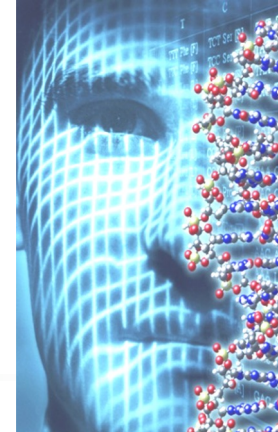
- Lys213Glu
- Tyr231Cys
- Glu285Ala
- Phe295Ser



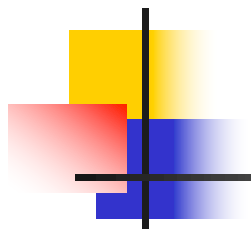


Critical mutations in protein structure decrease (in 10-1000 times) the catalytical activity of enzyme

Molecular polymorphism of human enzymes- individual sensitivity to drugs and toxins



Butyrylcholine esterase



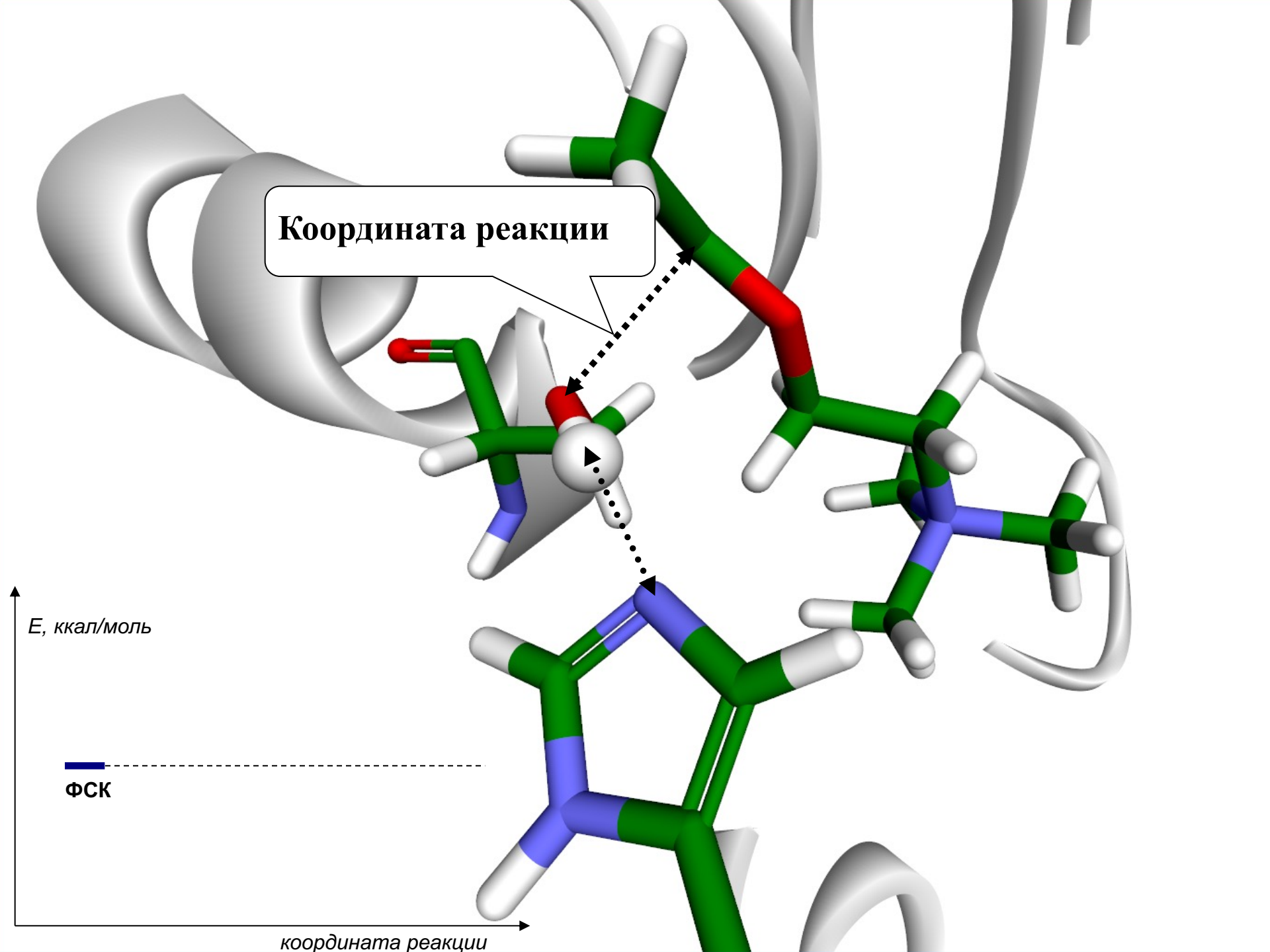
Acylation step

Координата реакции

E , ккал/моль

ФСК

координата реакции

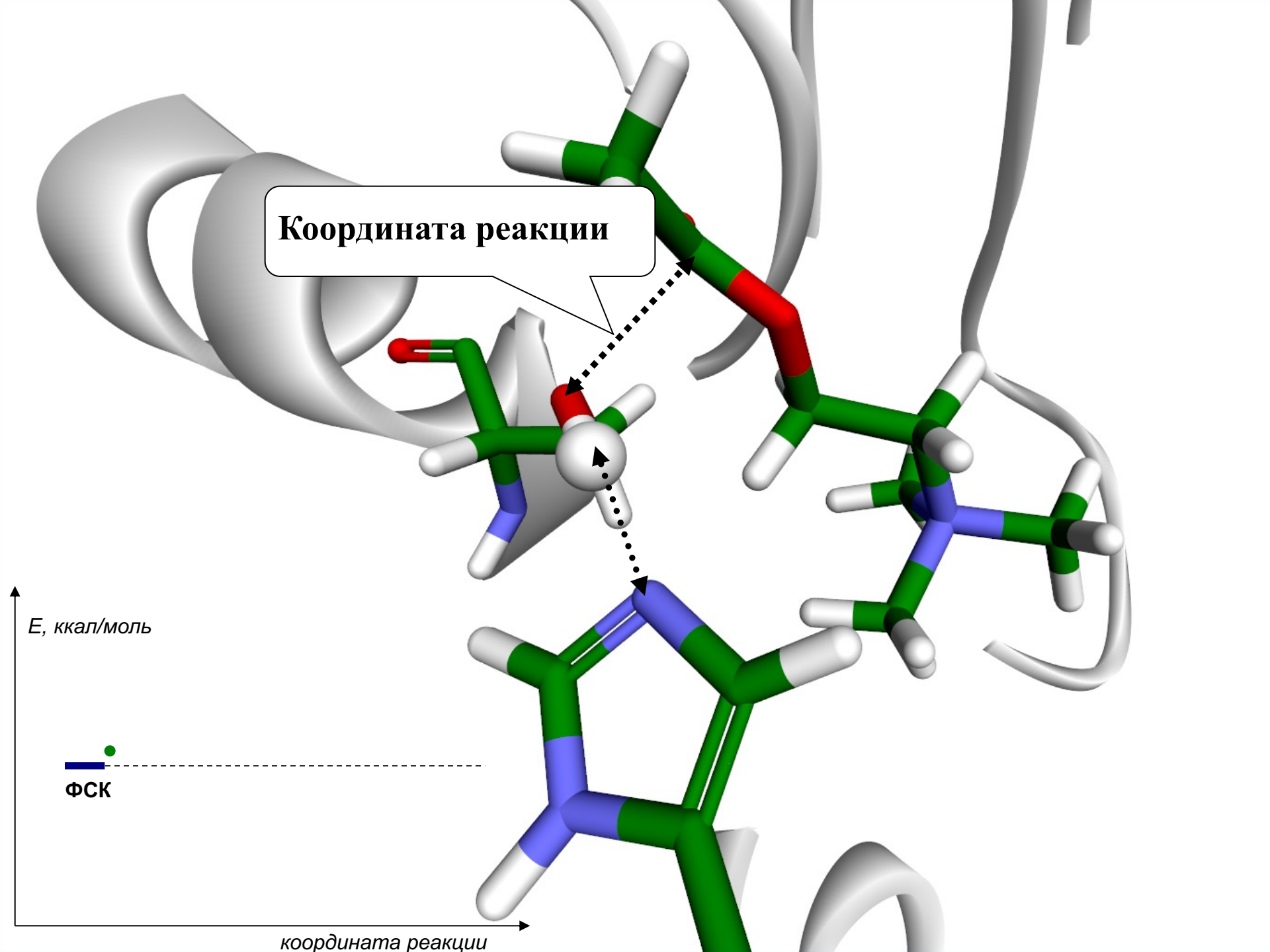


Координата реакции

E , ккал/моль

ФСК

координата реакции

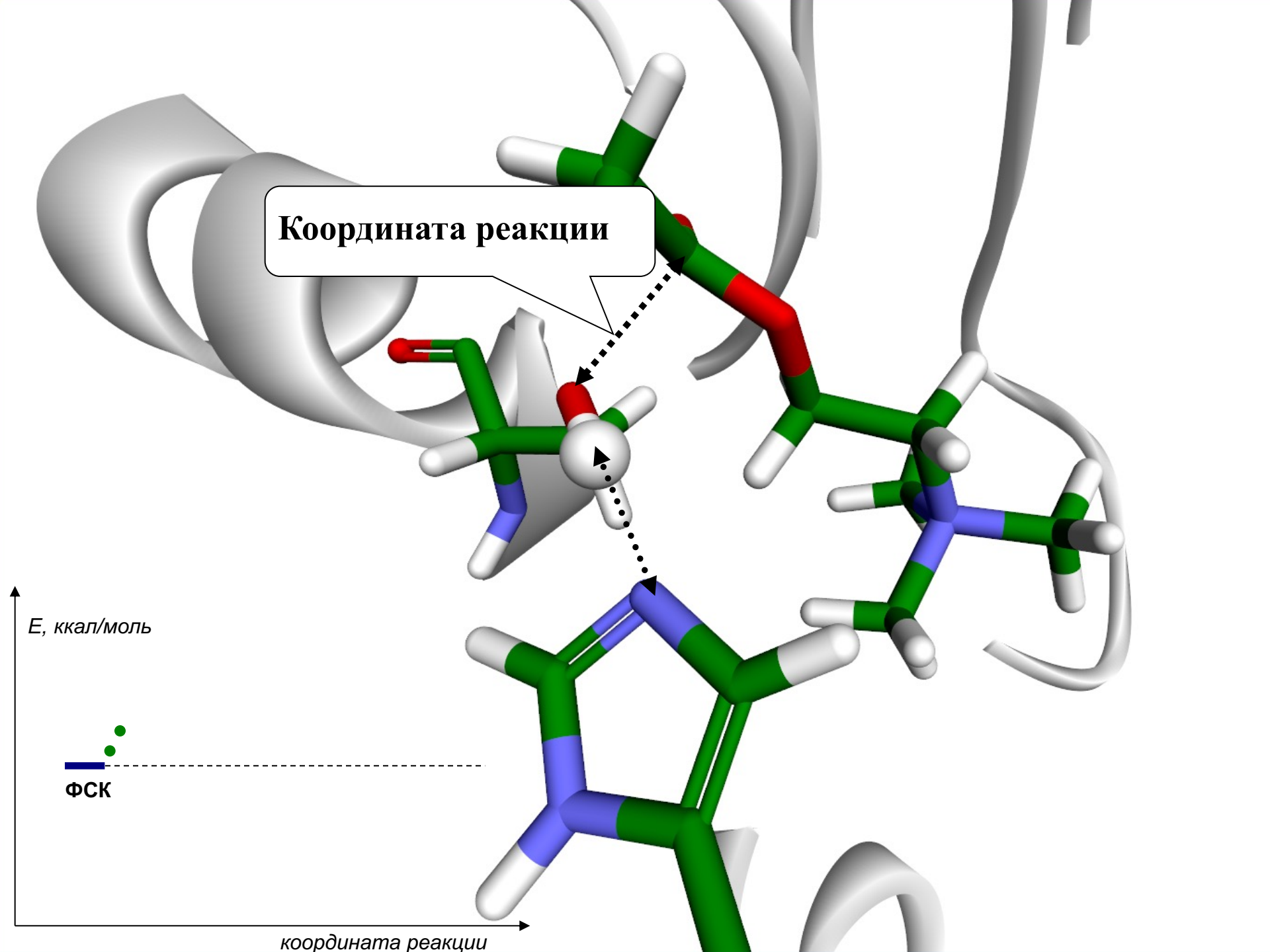


Координата реакции

E, ккал/моль

ФСК

координата реакции

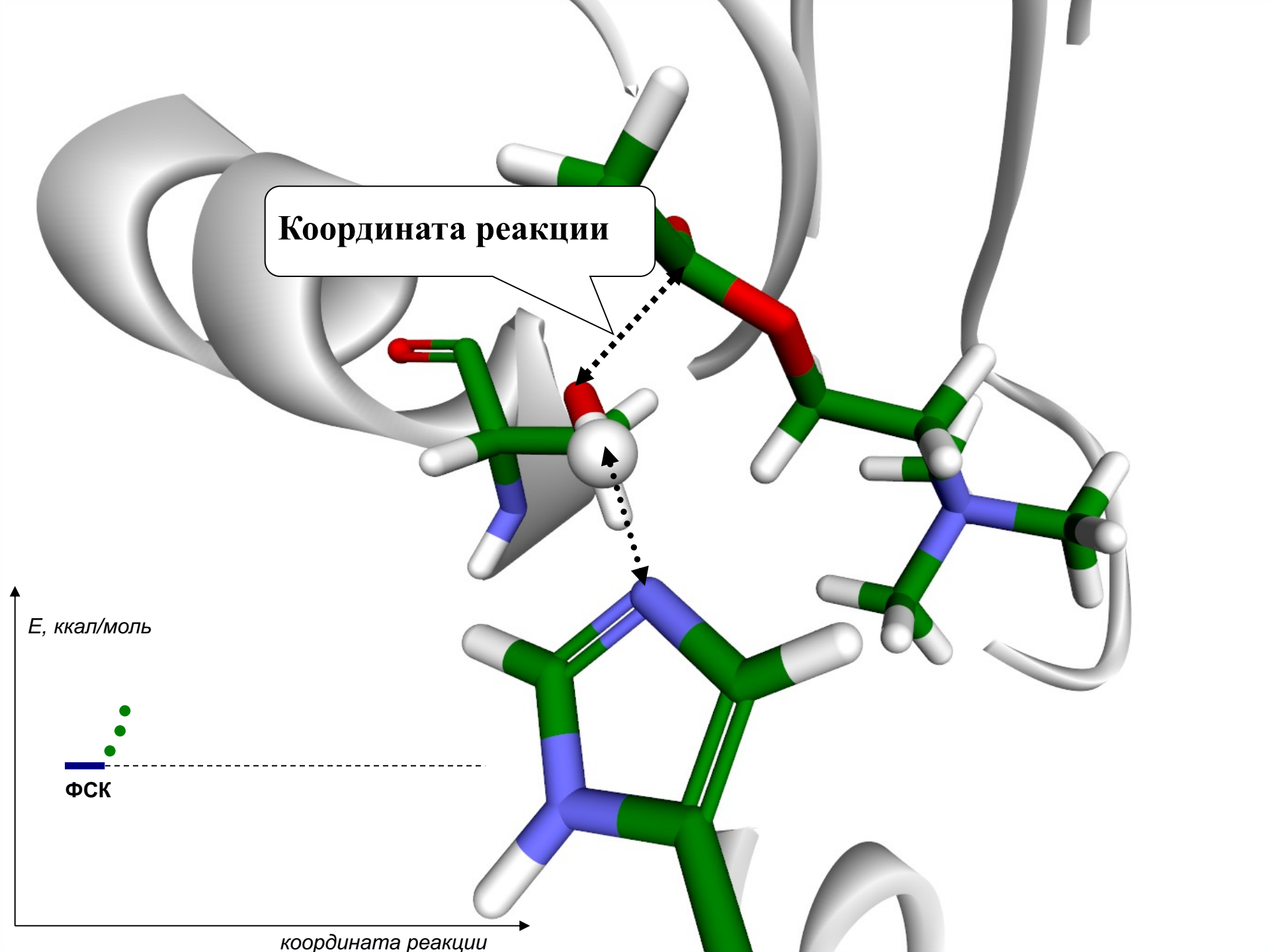


Координата реакции

E , ккал/моль

ФСК

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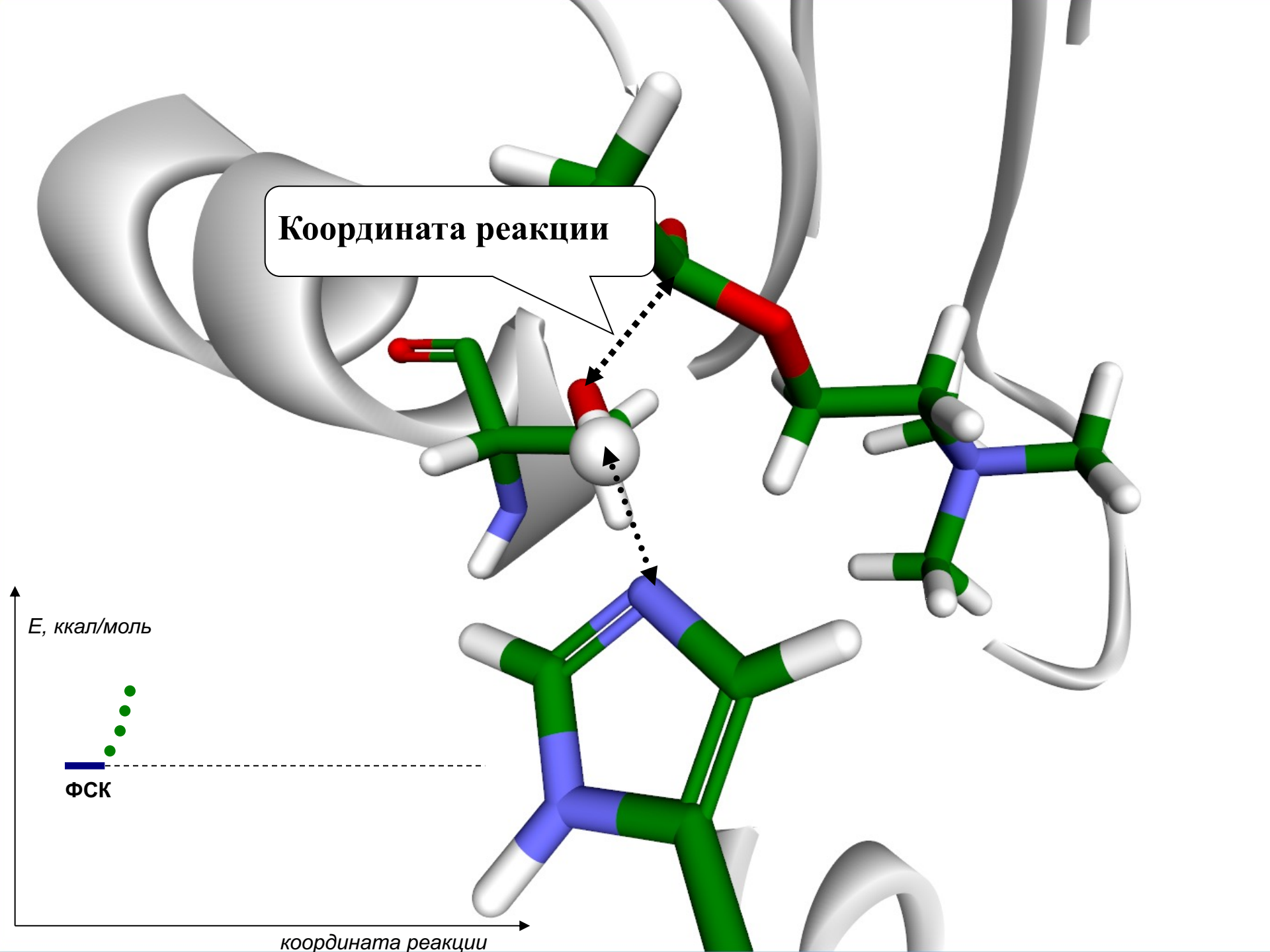


Координата реакции

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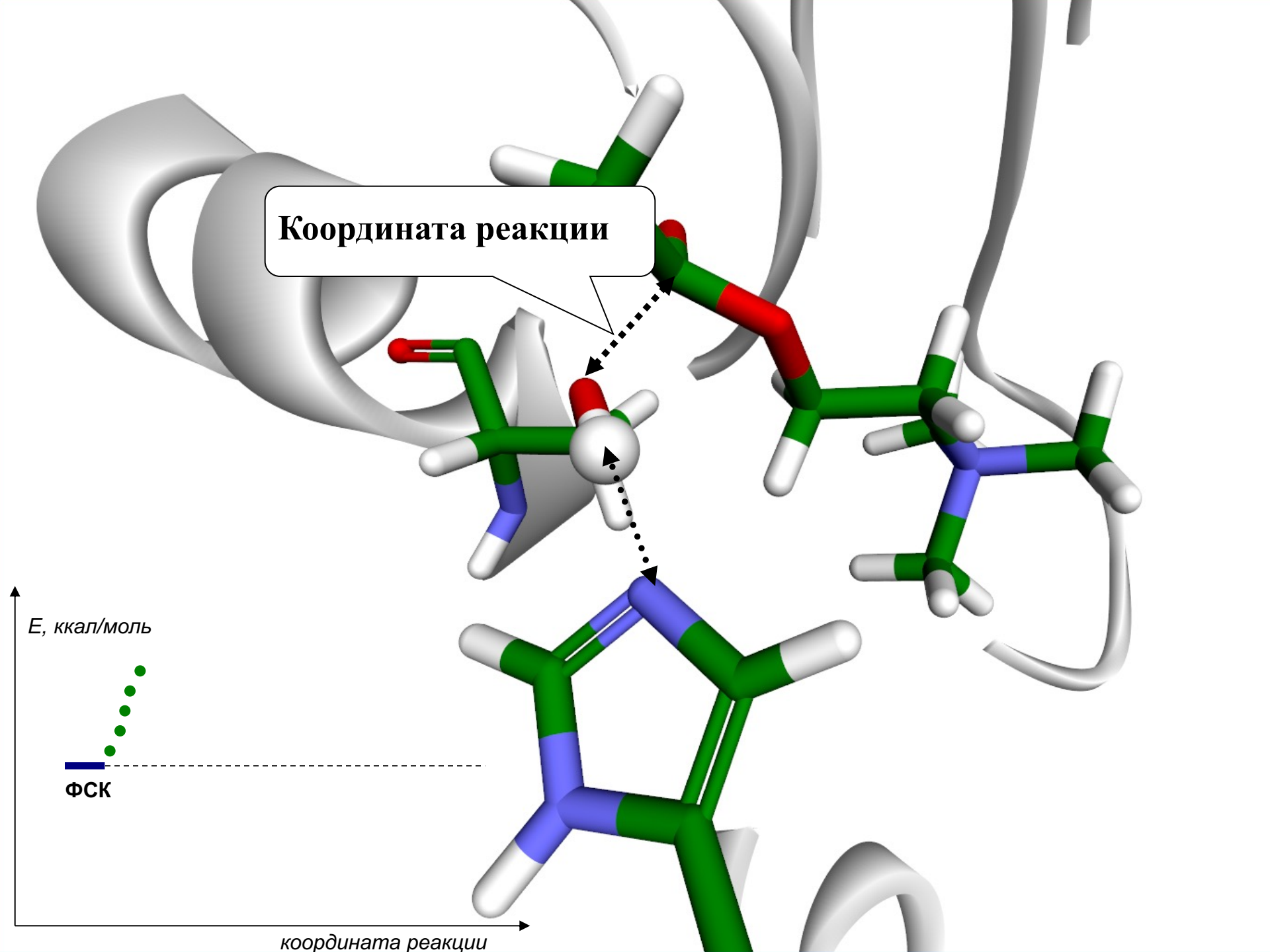


Координата реакции

E , ккал/моль

ФСК

координата реакции



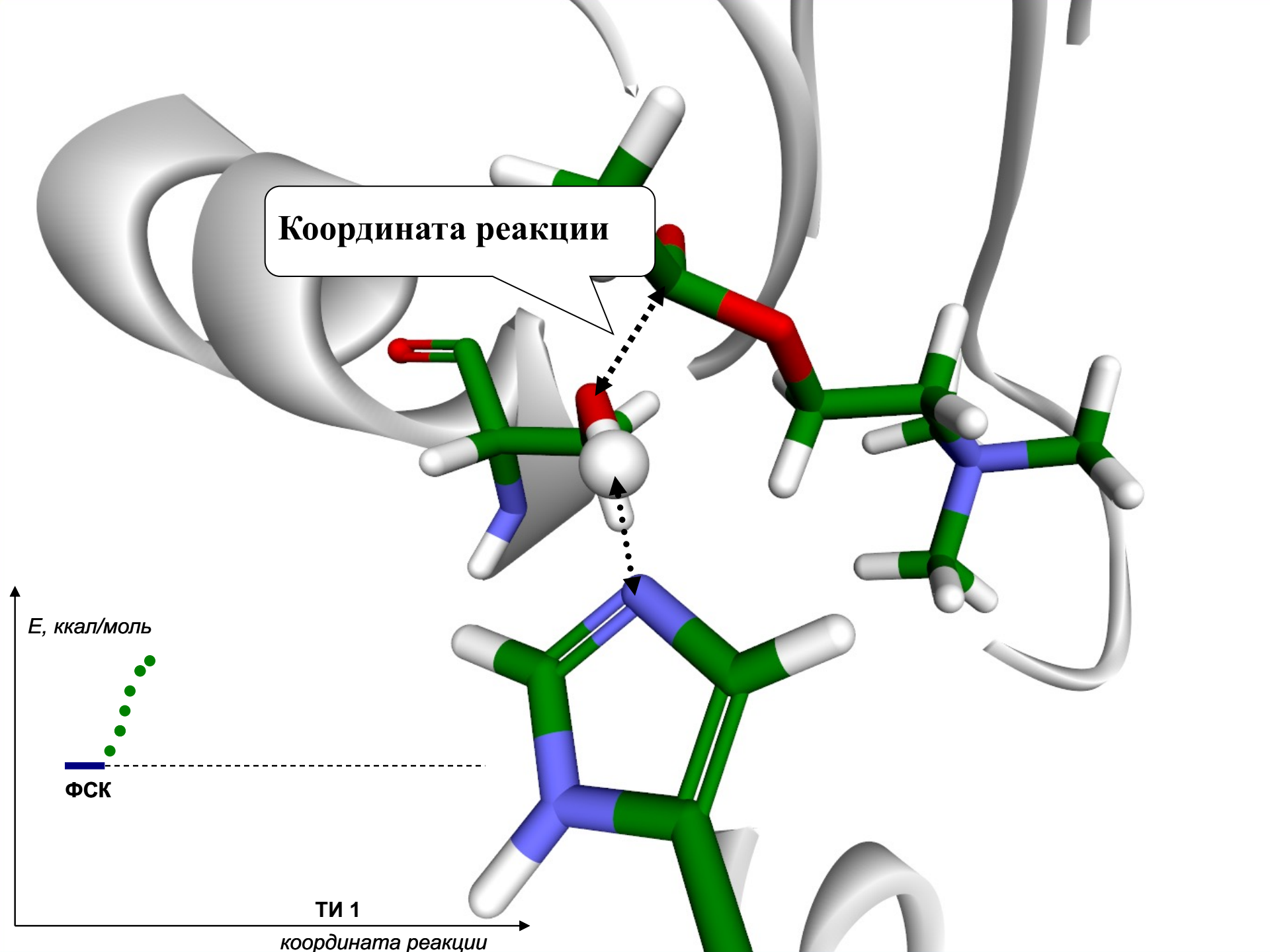
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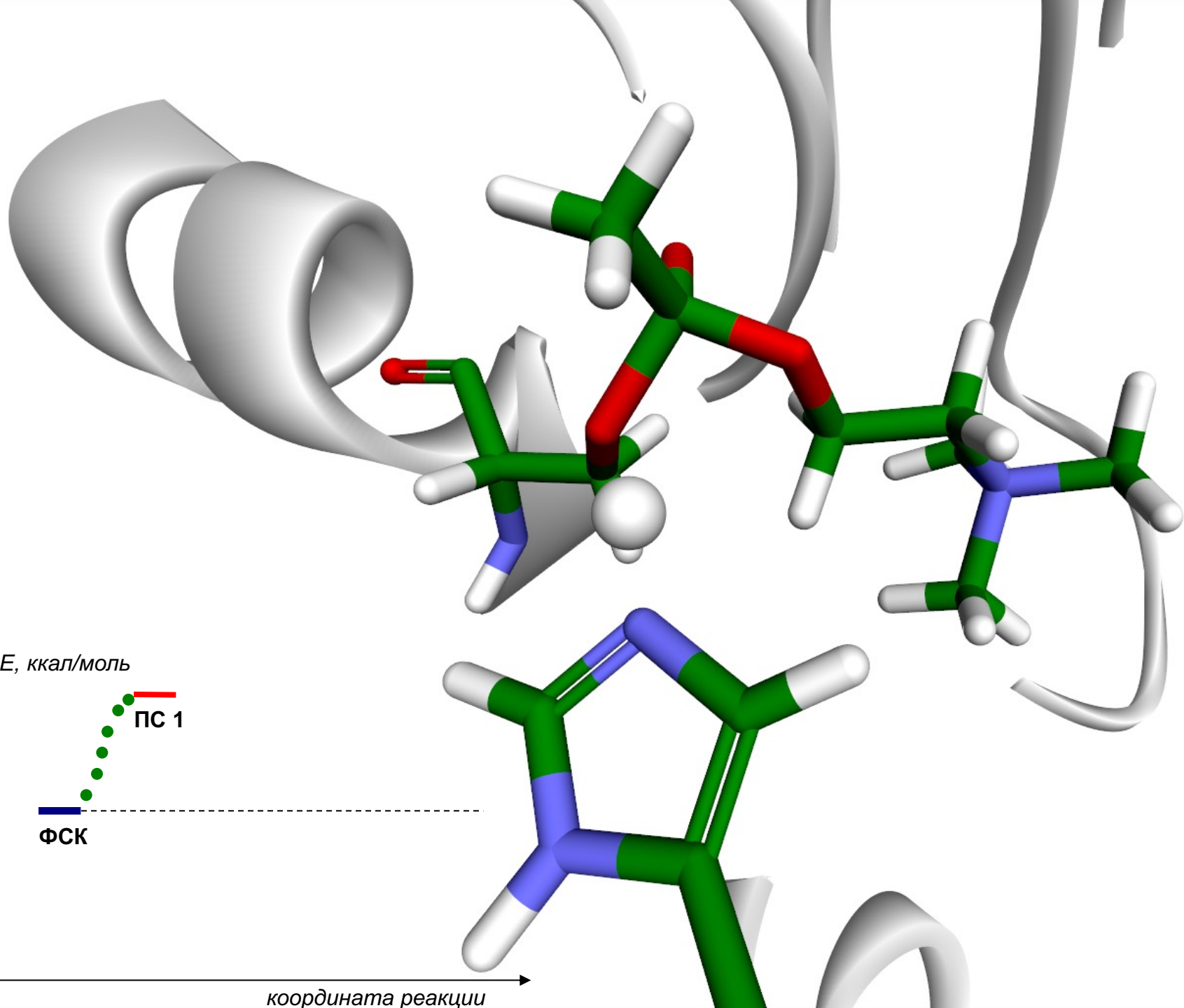
E , ккал/моль

ФСК

ТИ 1

координата реакции



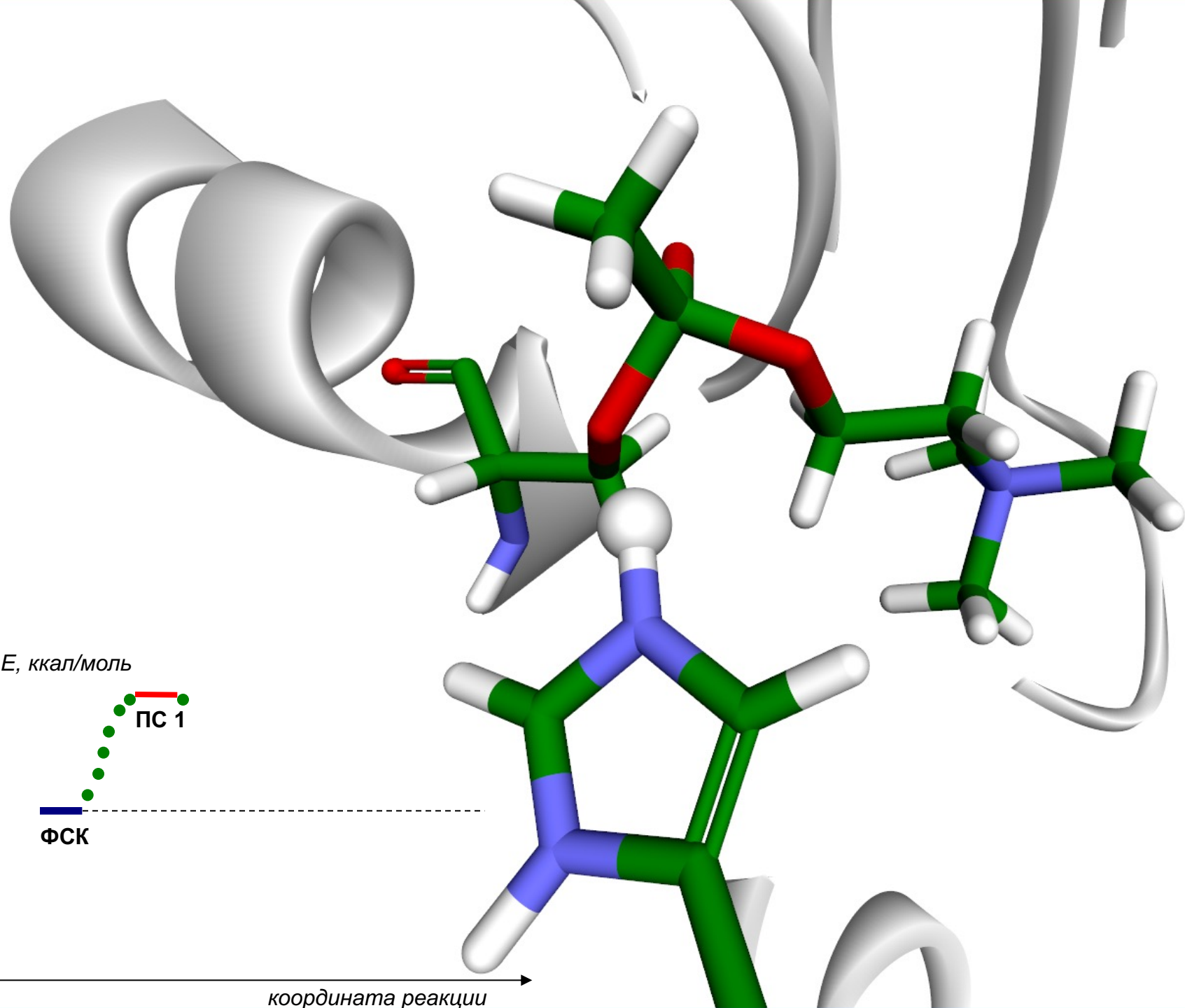


E , ккал/моль

ПС 1

ФСК

координата реакции

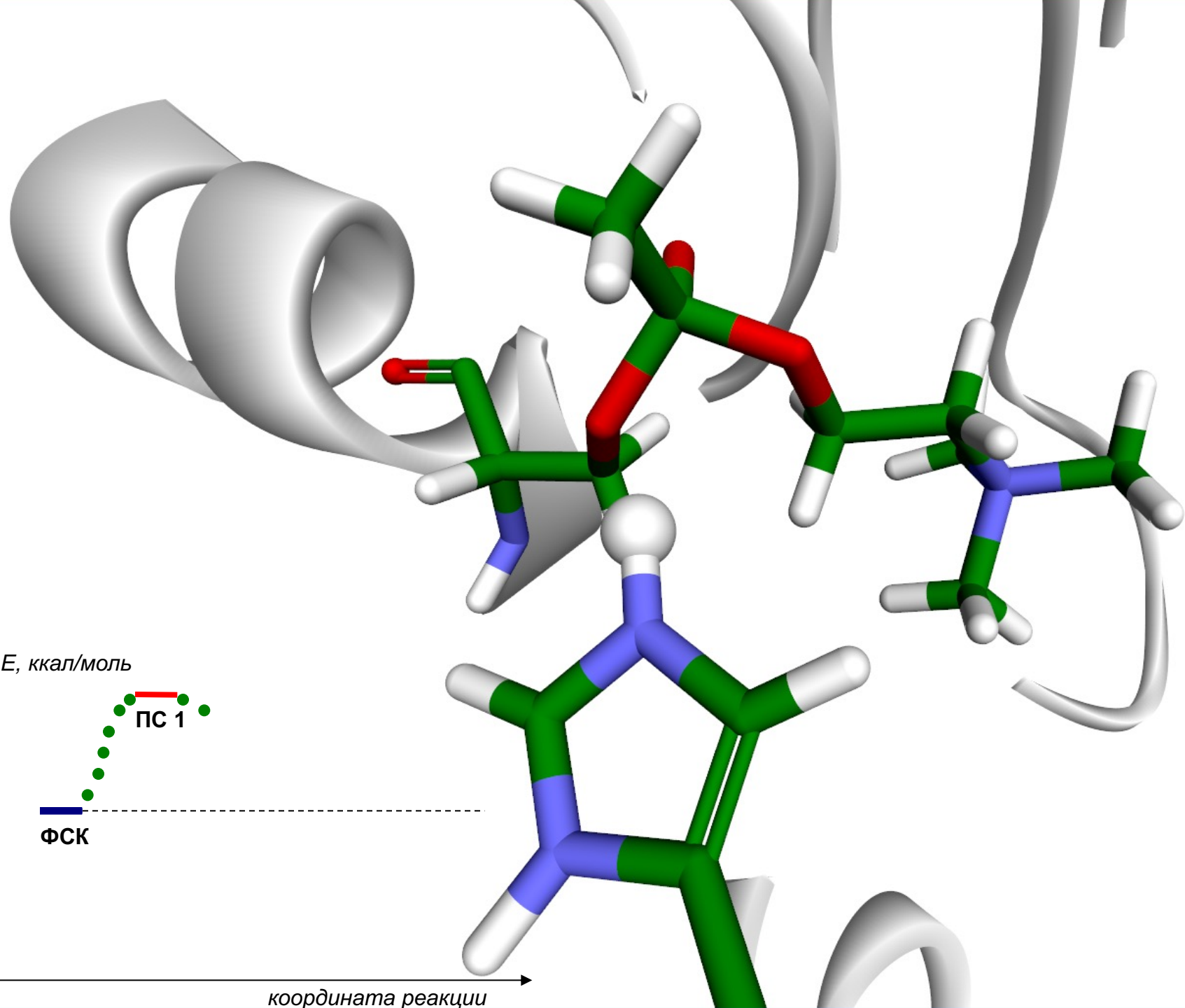


E , ккал/моль

ПС 1

ФСК

координата реакции

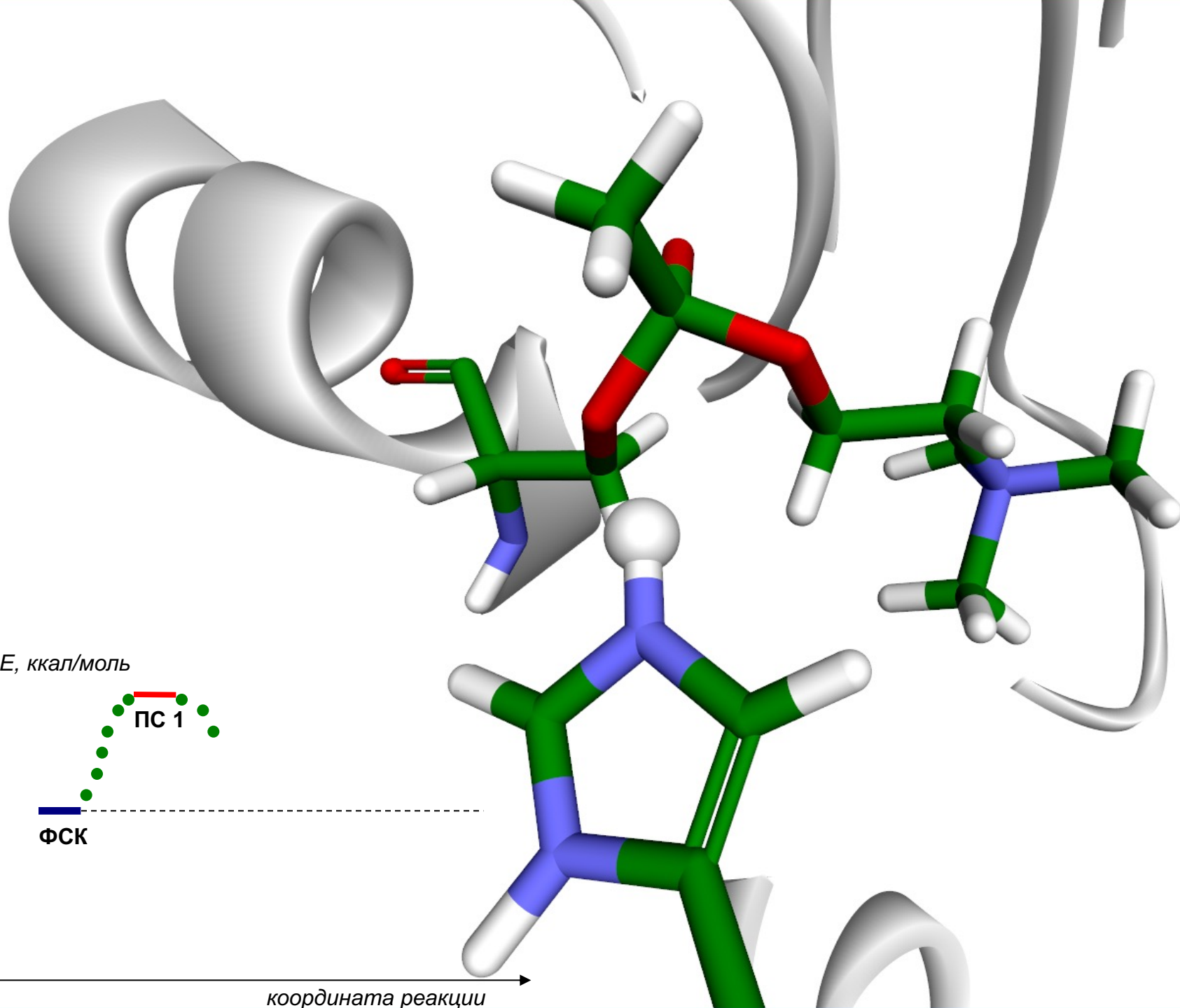


E , ккал/моль

ПС 1

ФСК

координата реакции

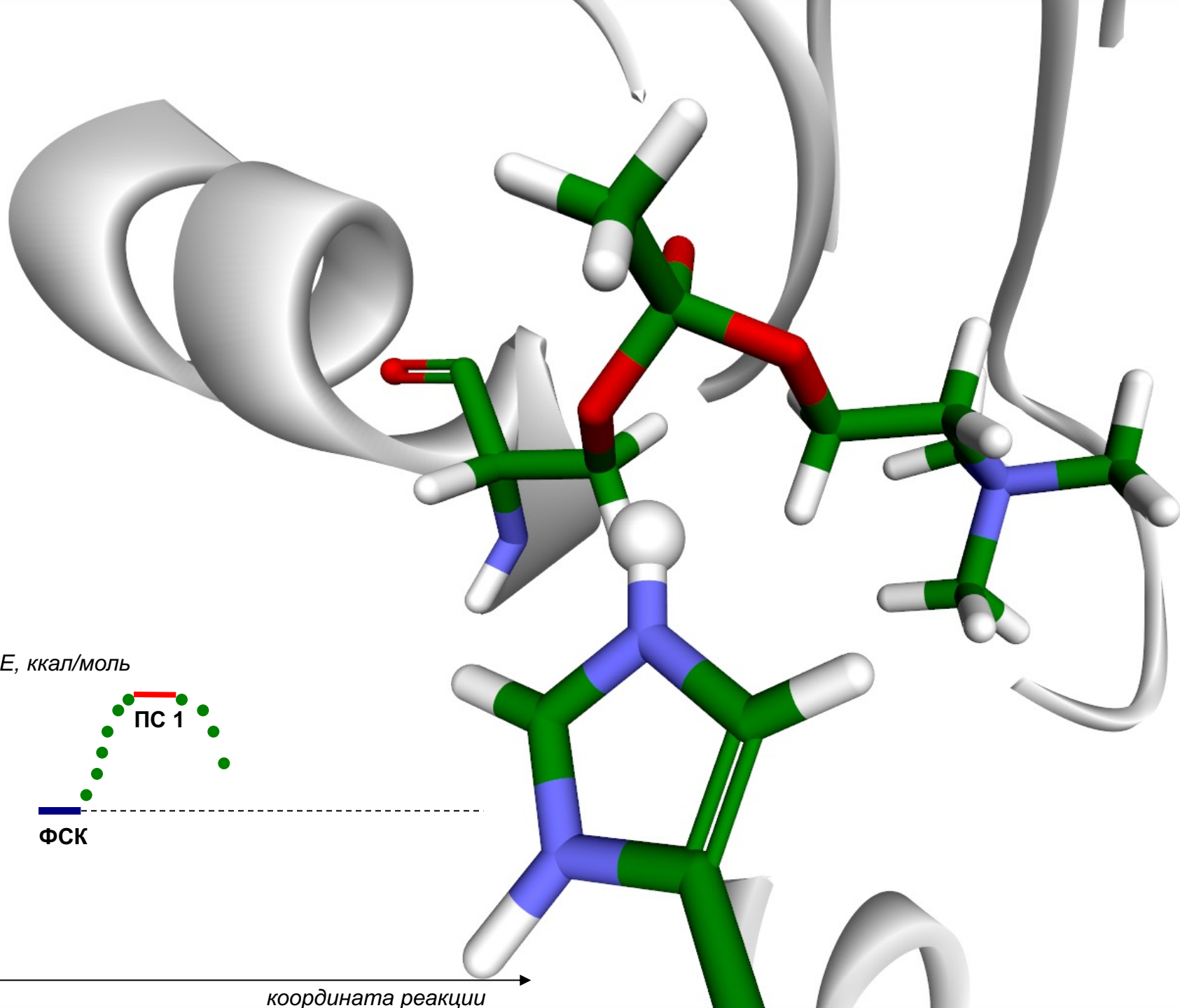


E , ккал/моль

ПС 1

ФСК

координата реакции

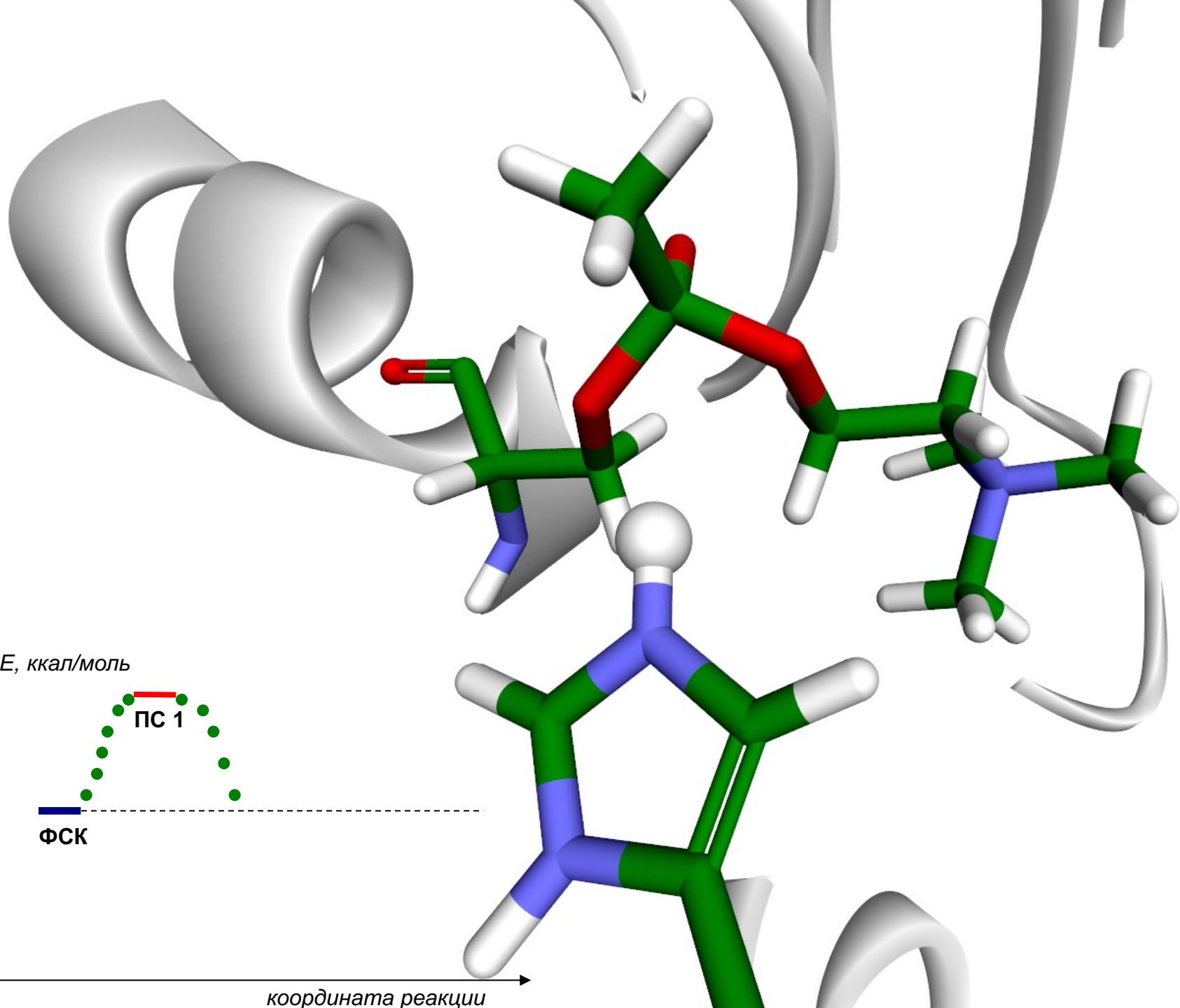


E , ккал/моль

ПС 1

ФСК

координата реакции

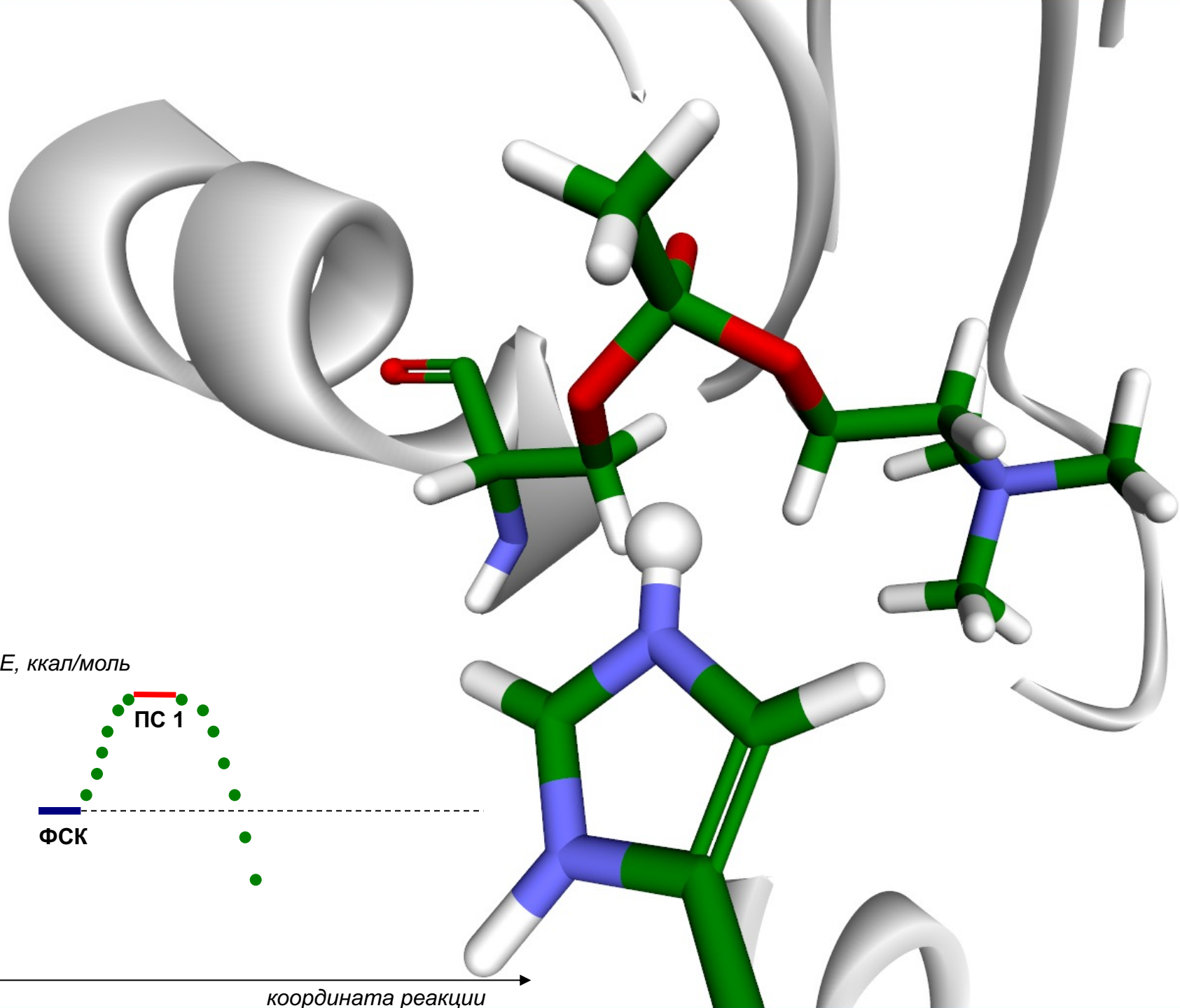


E , ккал/моль

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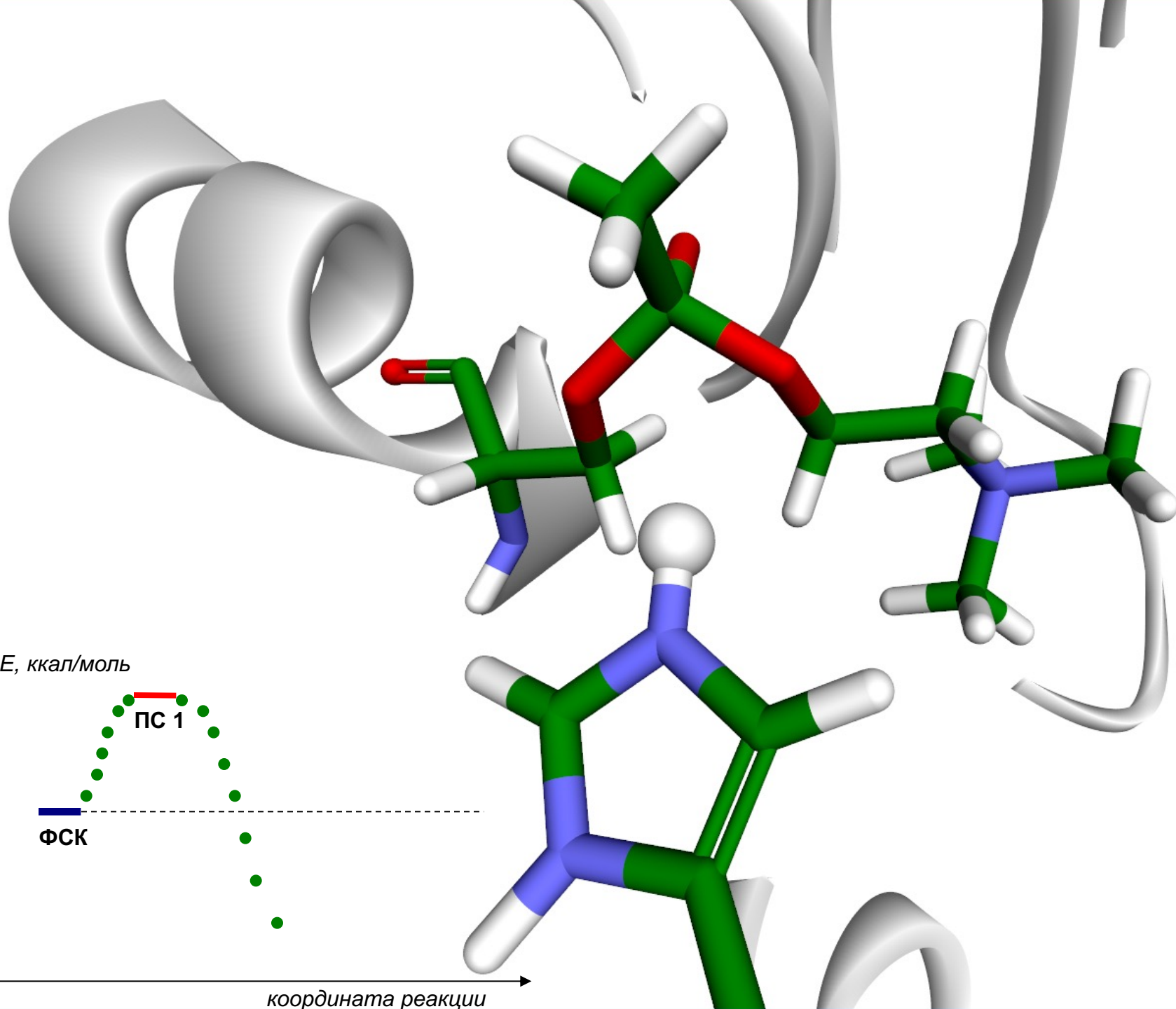


E , ккал/моль

ПС 1

ФСК

координата реакции

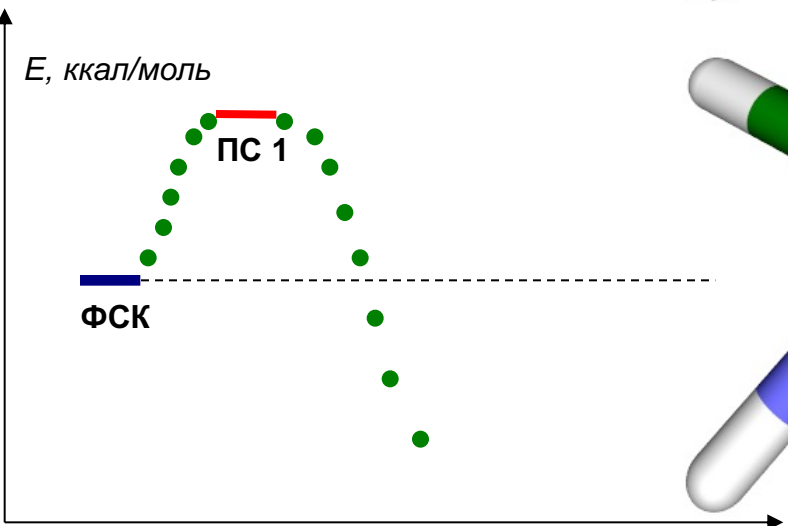


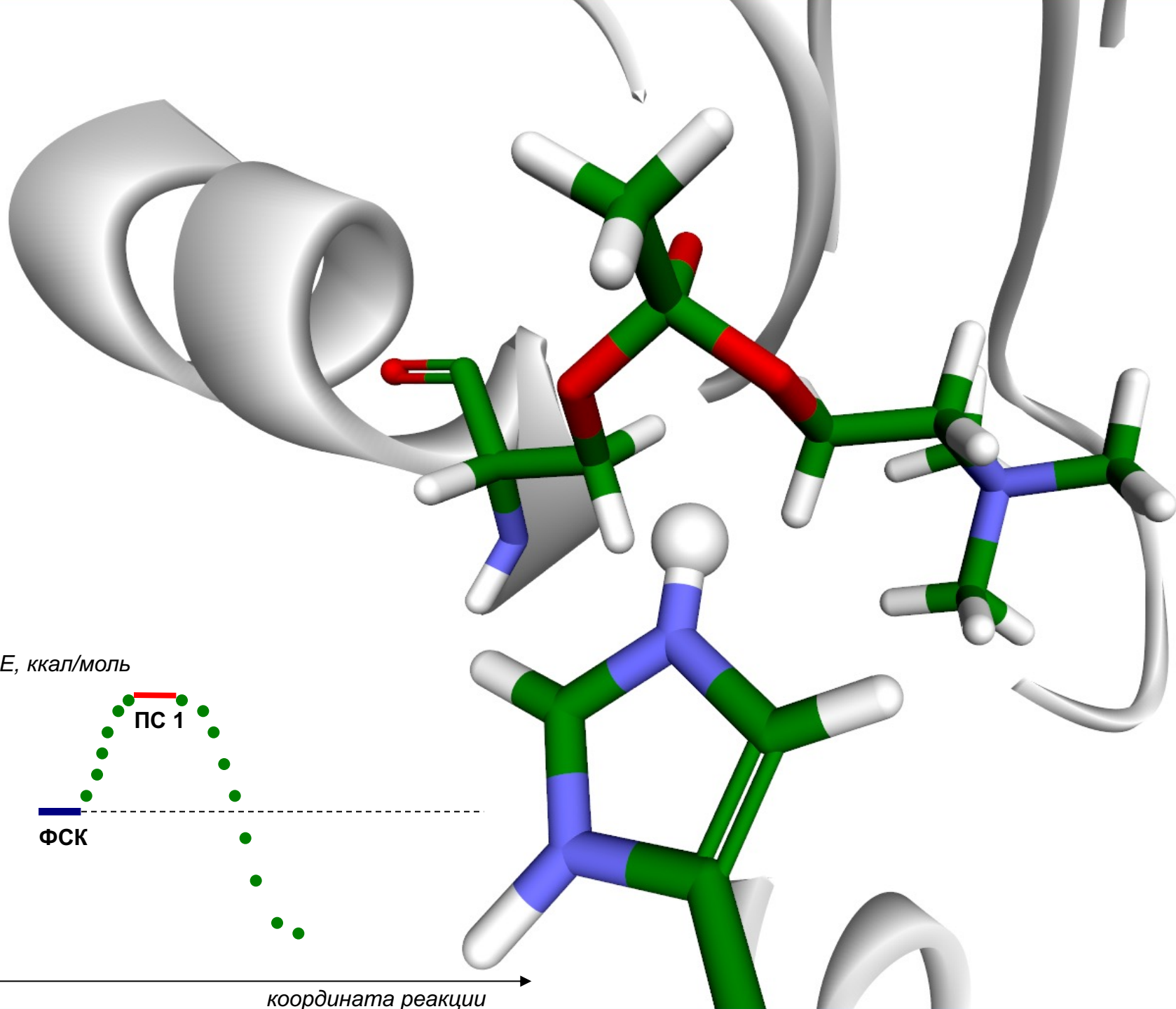
E , ккал/моль

ПС 1

ФСК

координата реакции



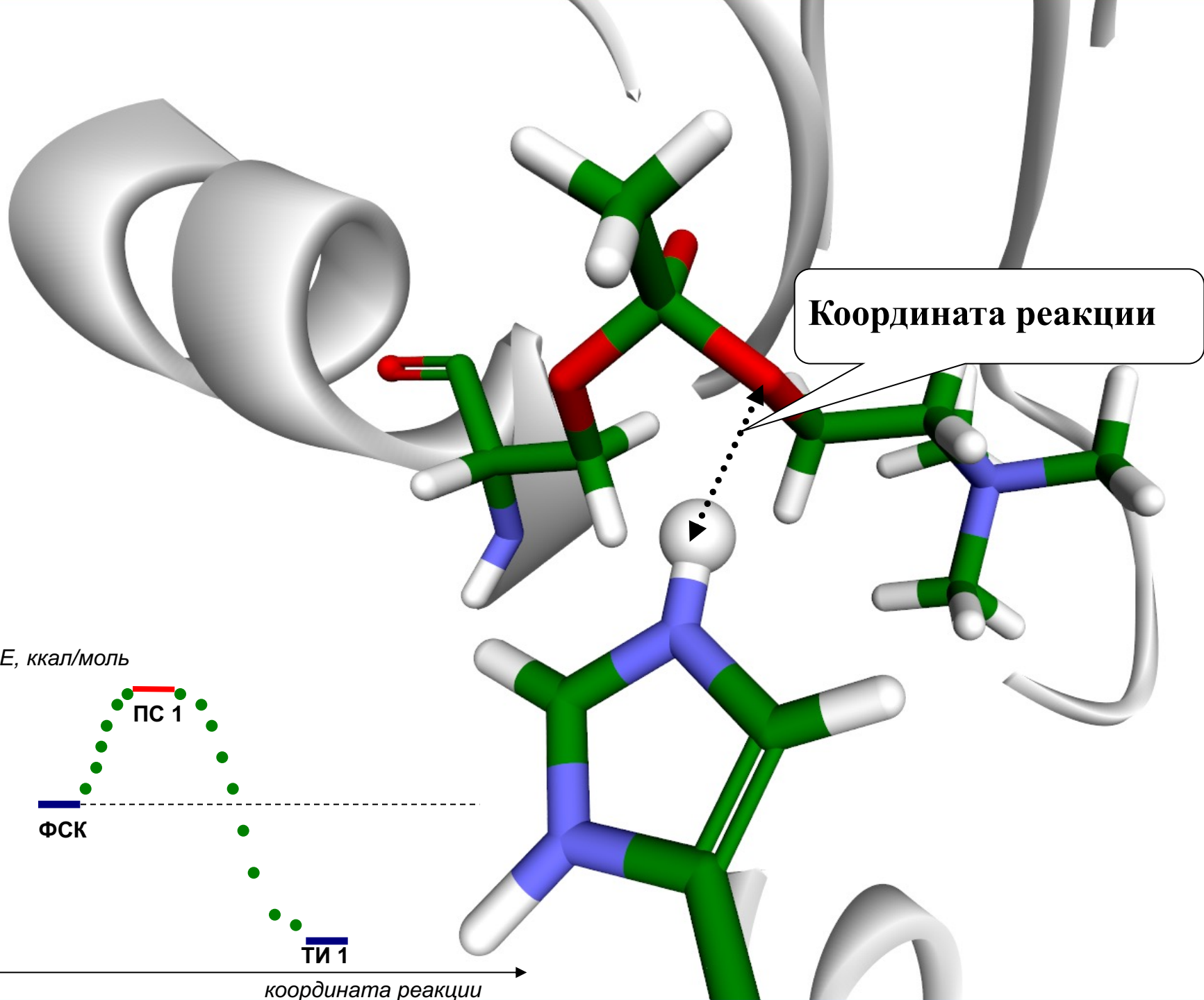


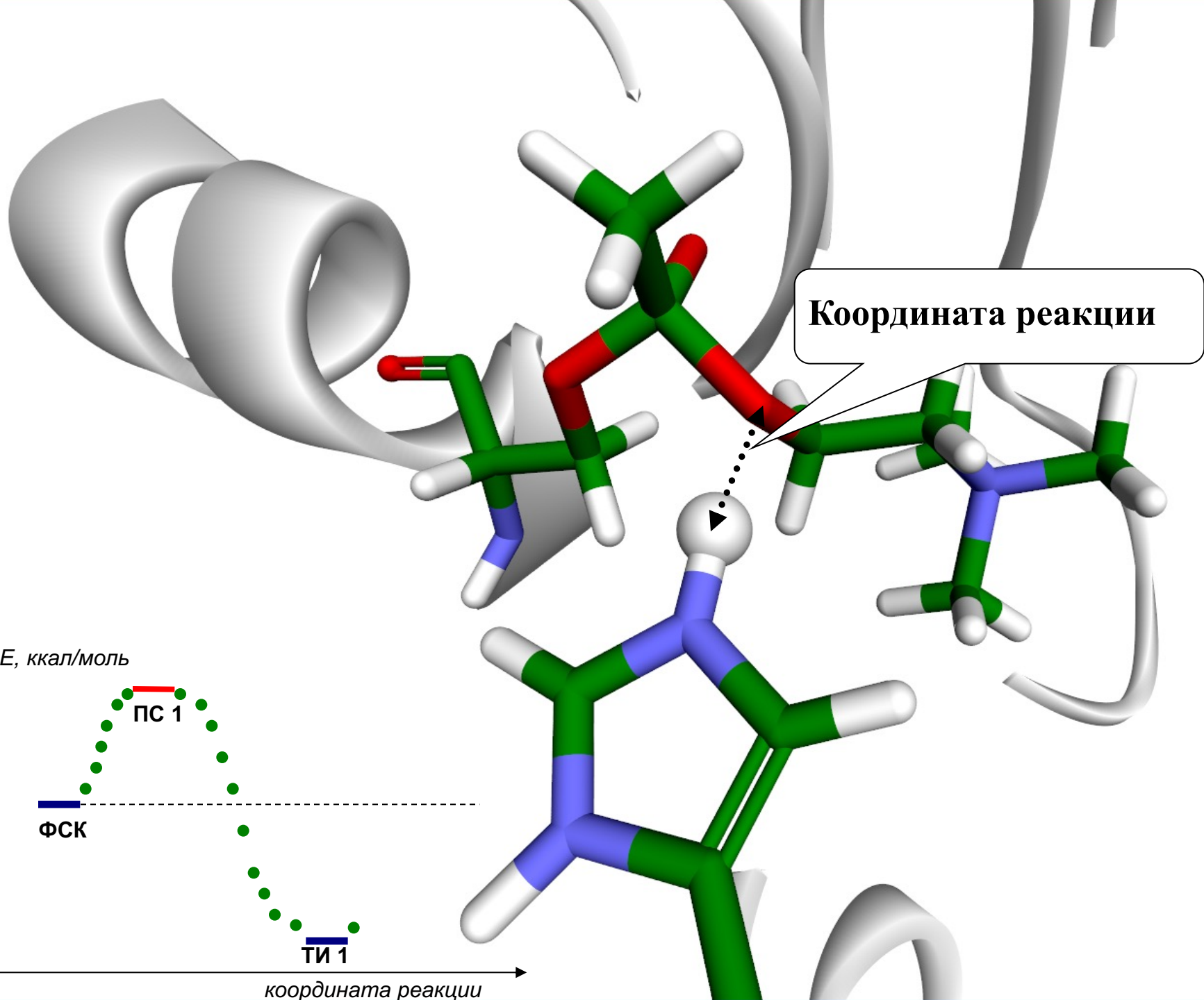
E , ккал/моль

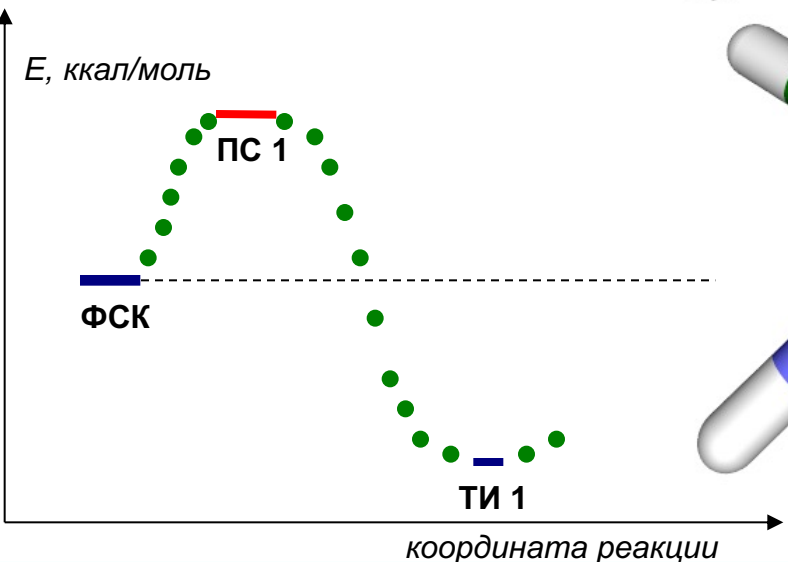
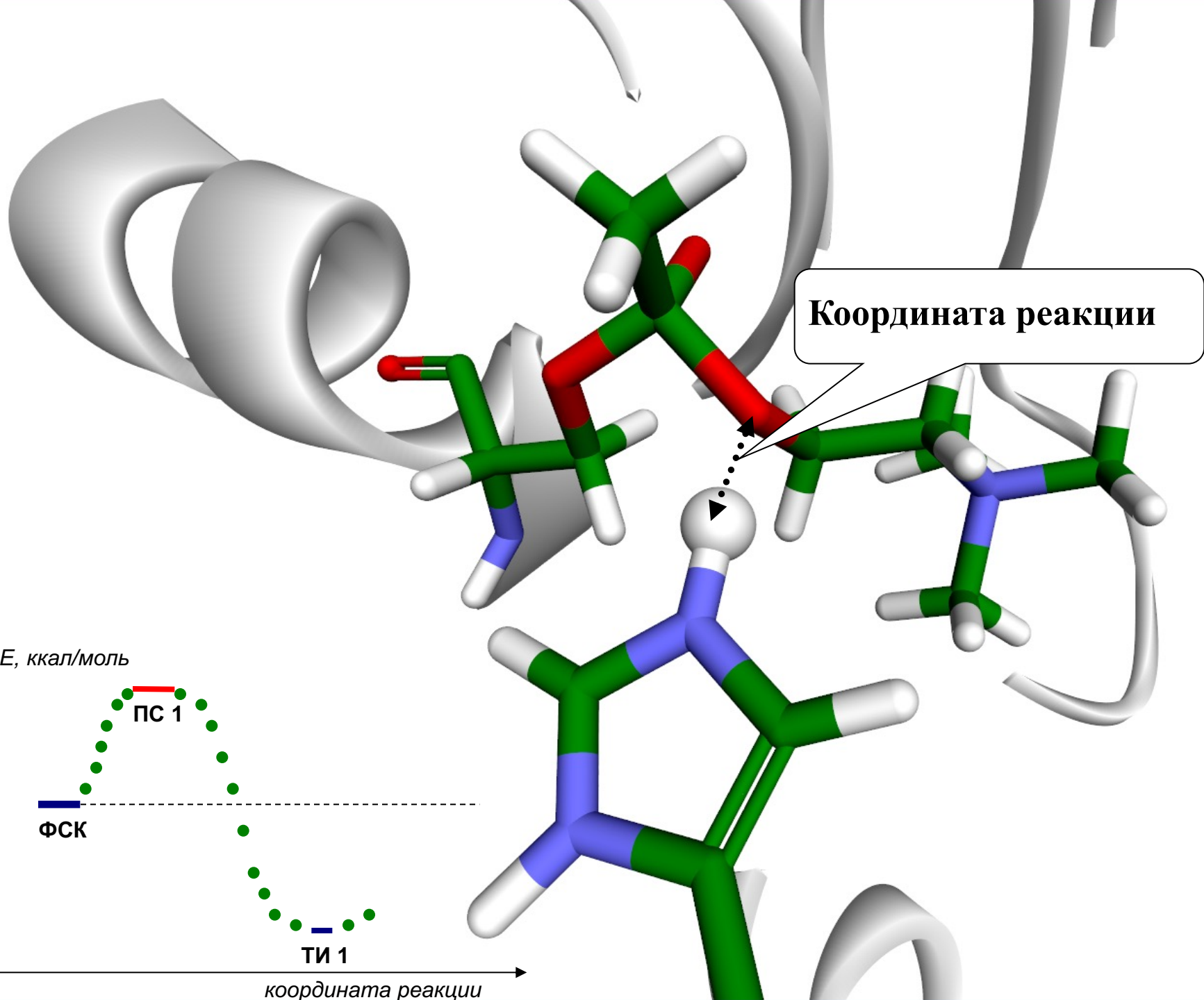
ПС 1

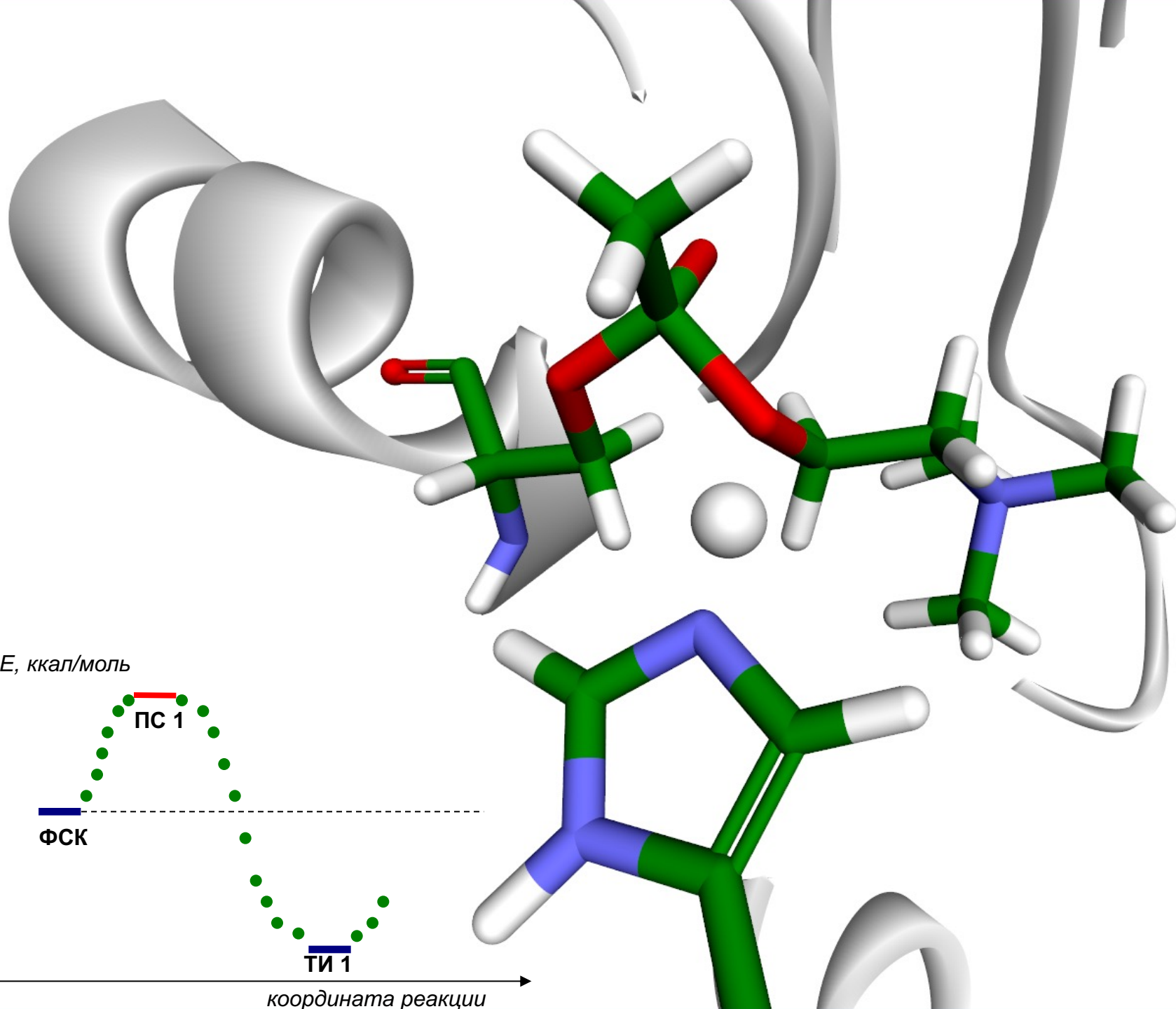
ФСК

координата реакции









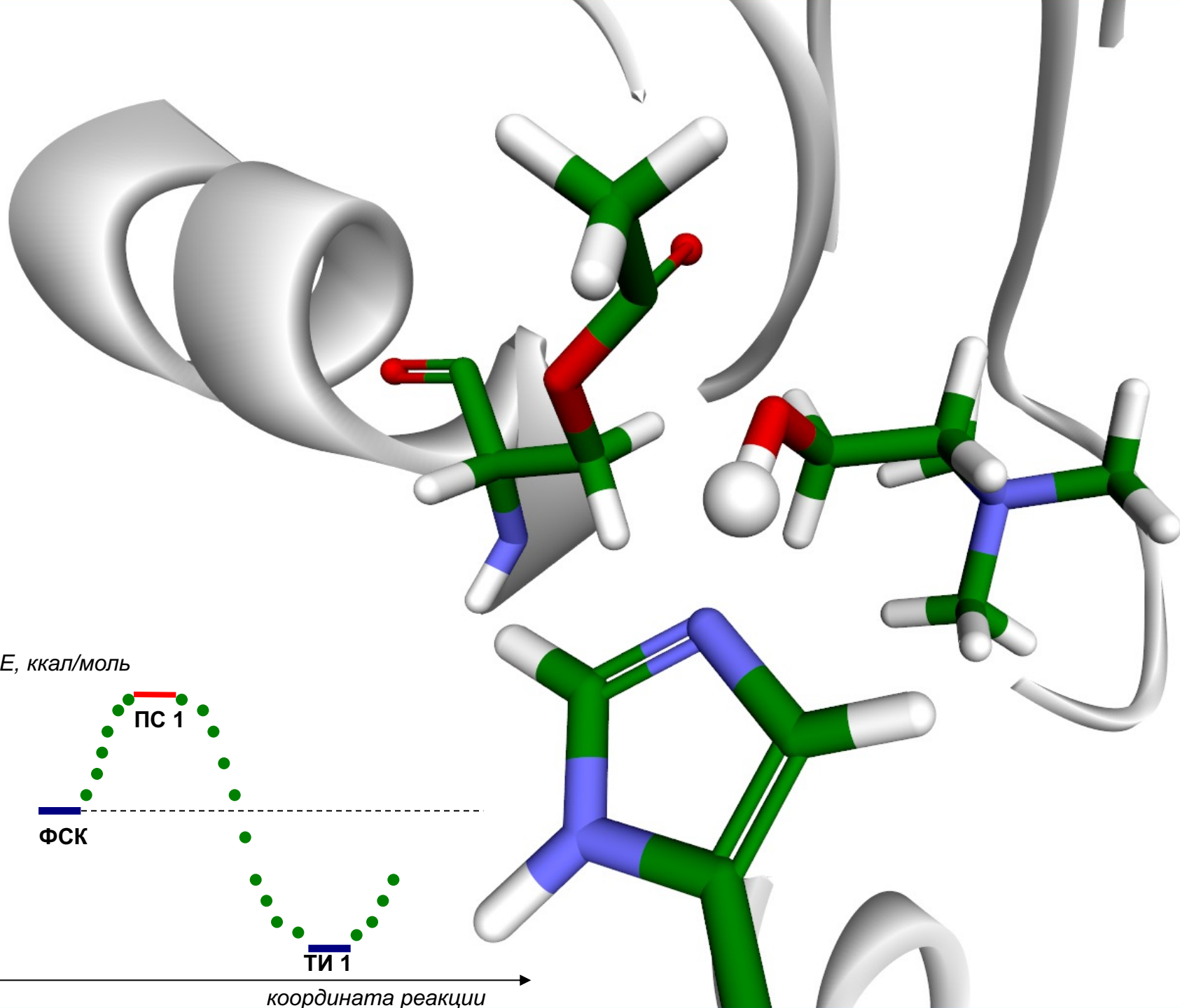
E , ккал/моль

ПС 1

ФСК

ТИ 1

координата реакции



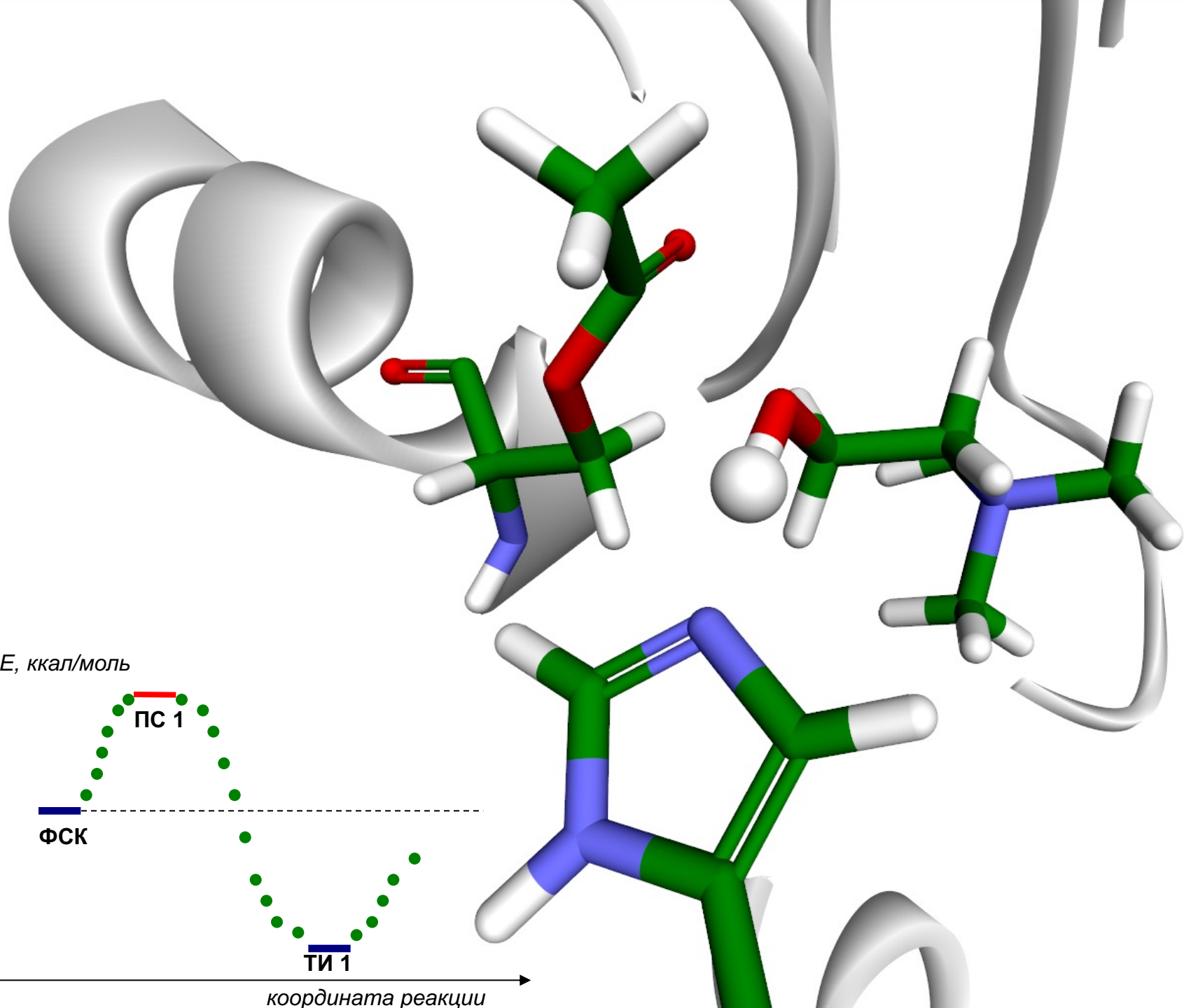
E , ккал/моль

ПС 1

ФСК

ТИ 1

координата реакции



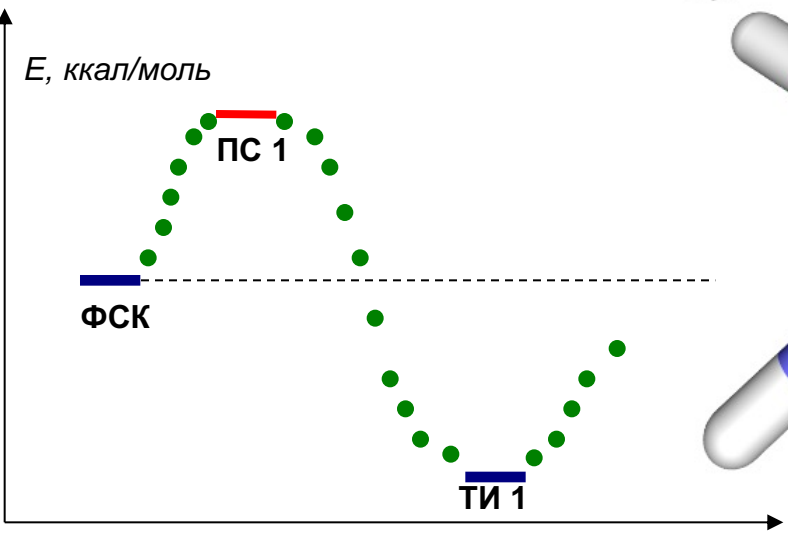
E , ккал/моль

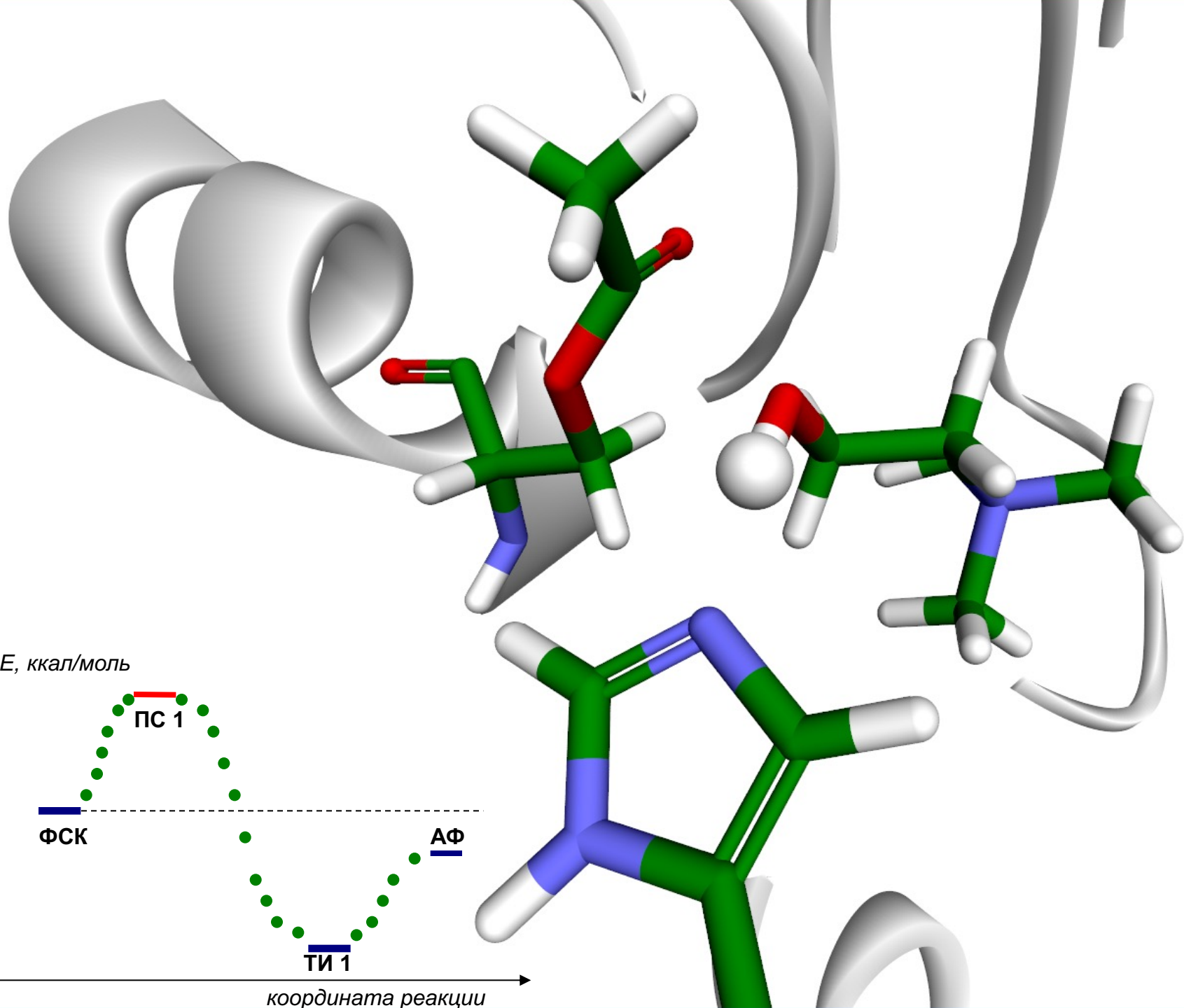
ПС 1

ФСК

ТИ 1

координата реакции





E , ккал/моль

ПС 1

ФСК

АФ

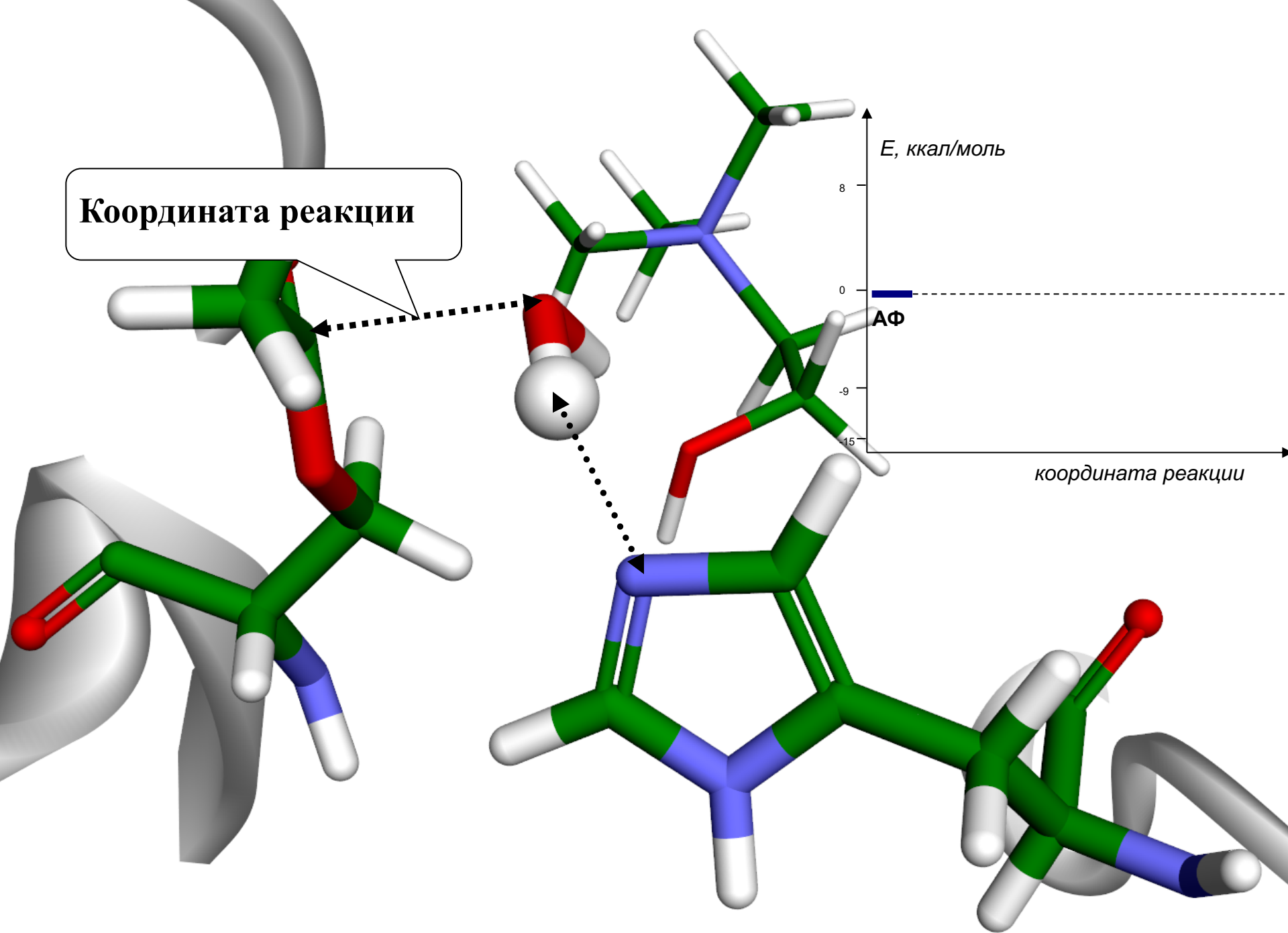
ТИ 1

координата реакции

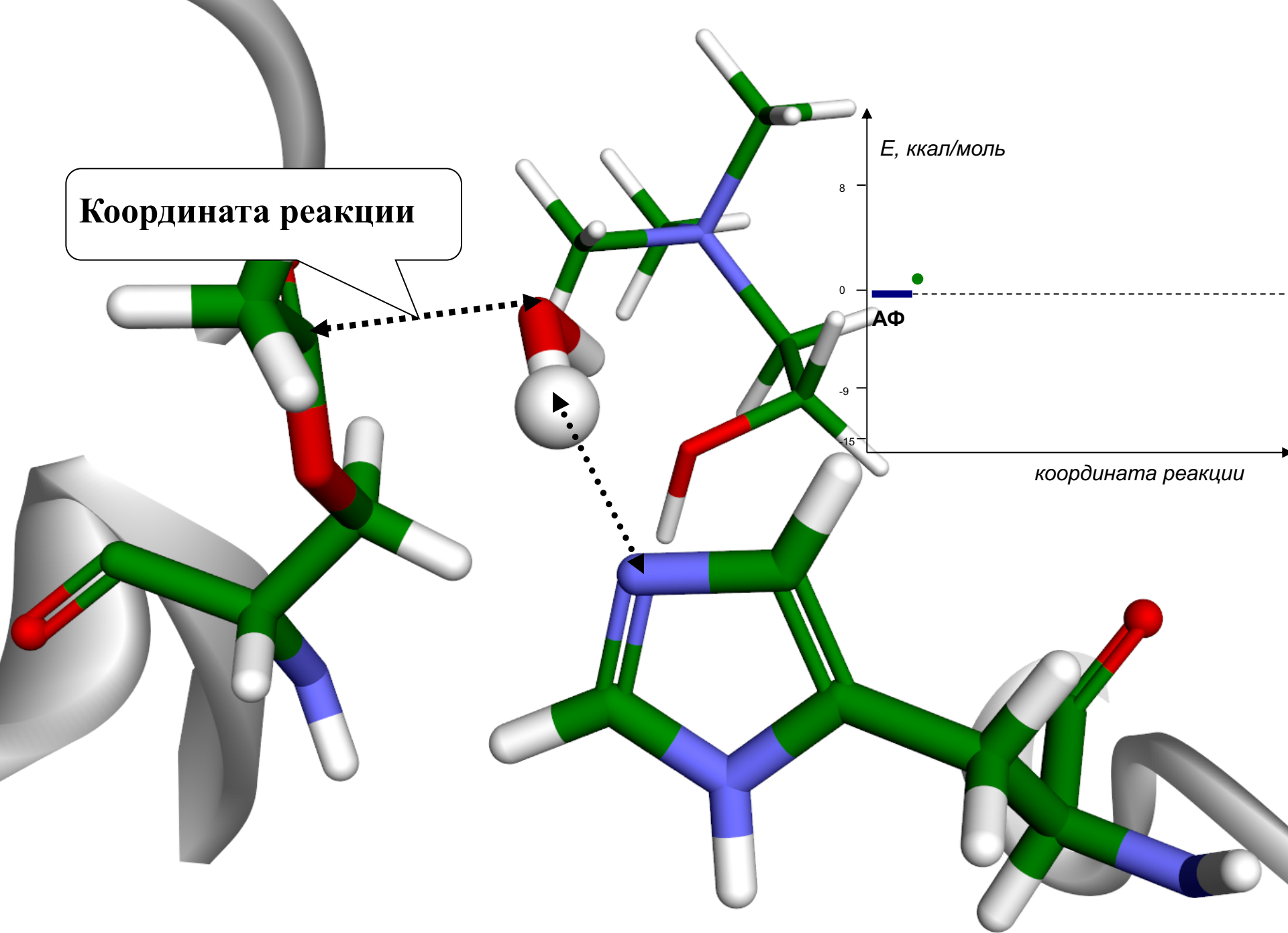


Deacylation step

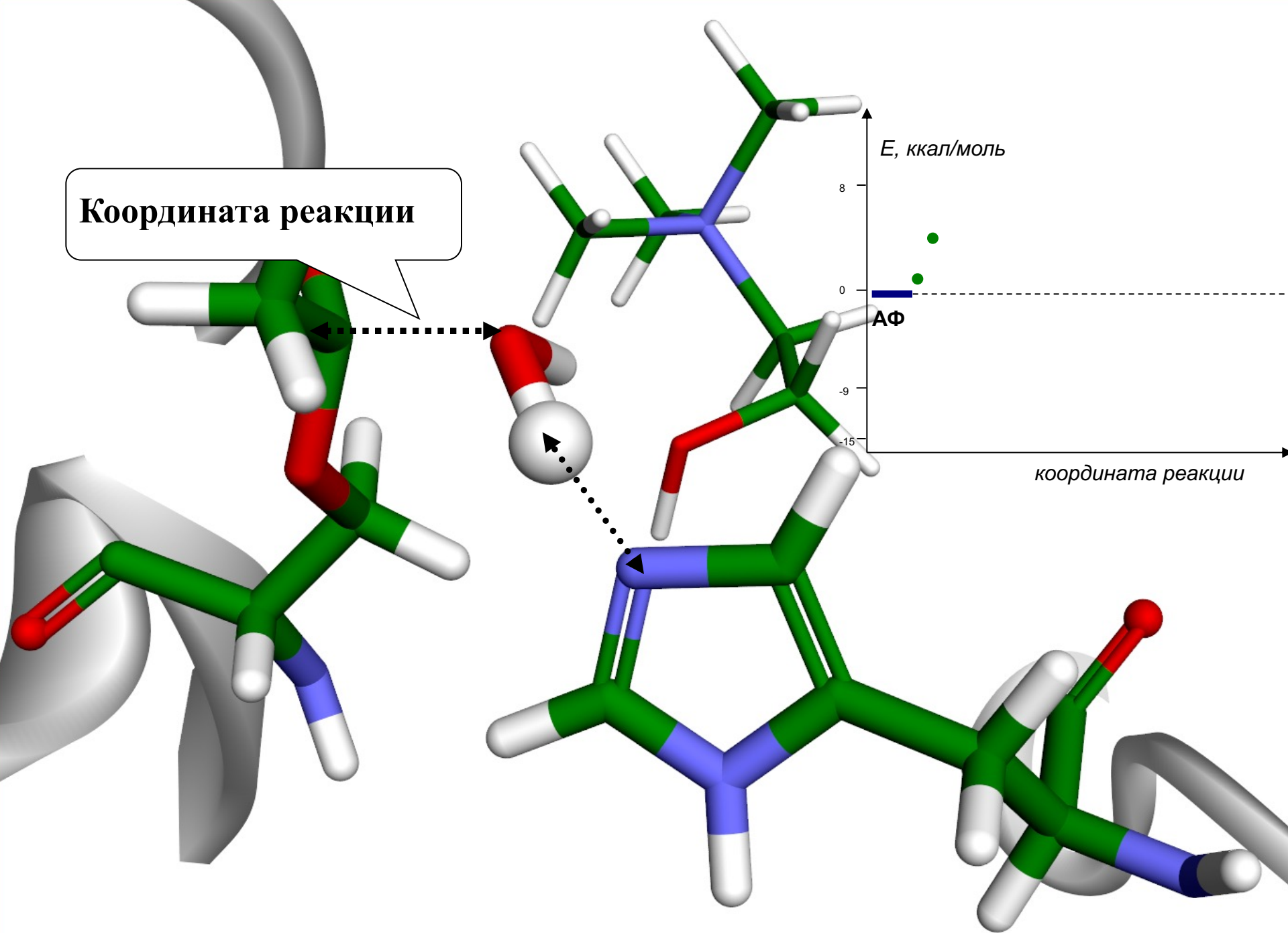
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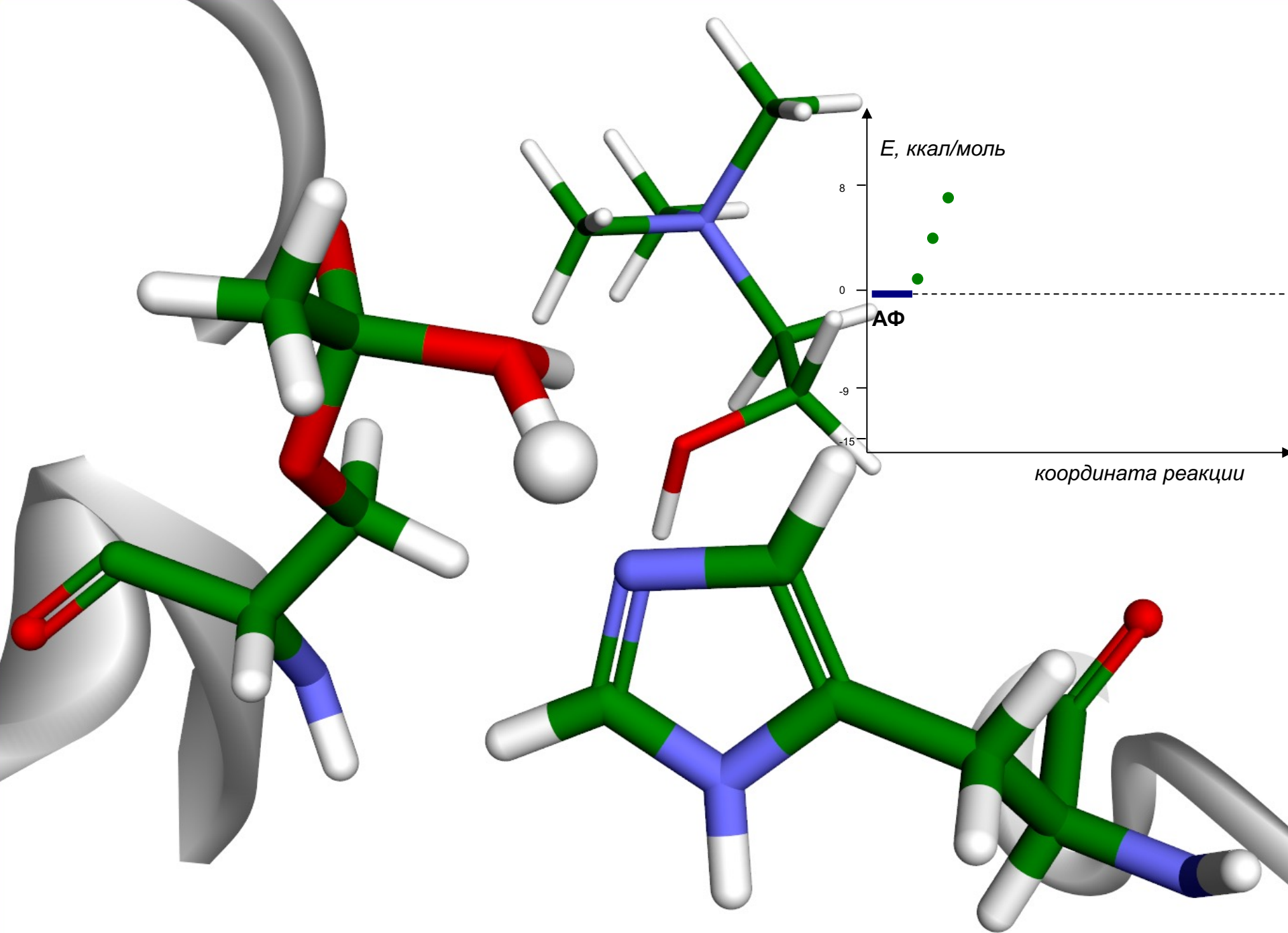


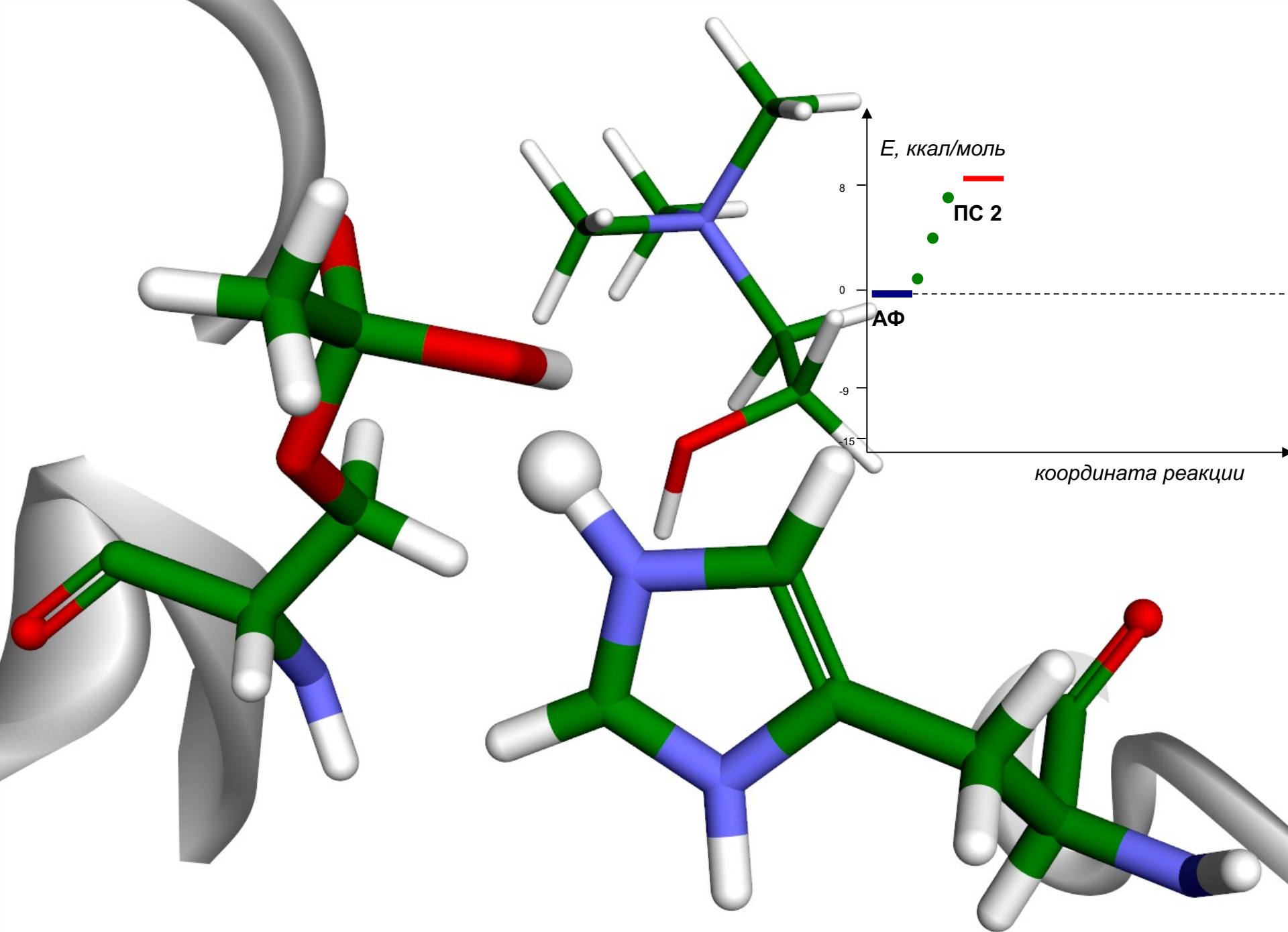
Координата реакции

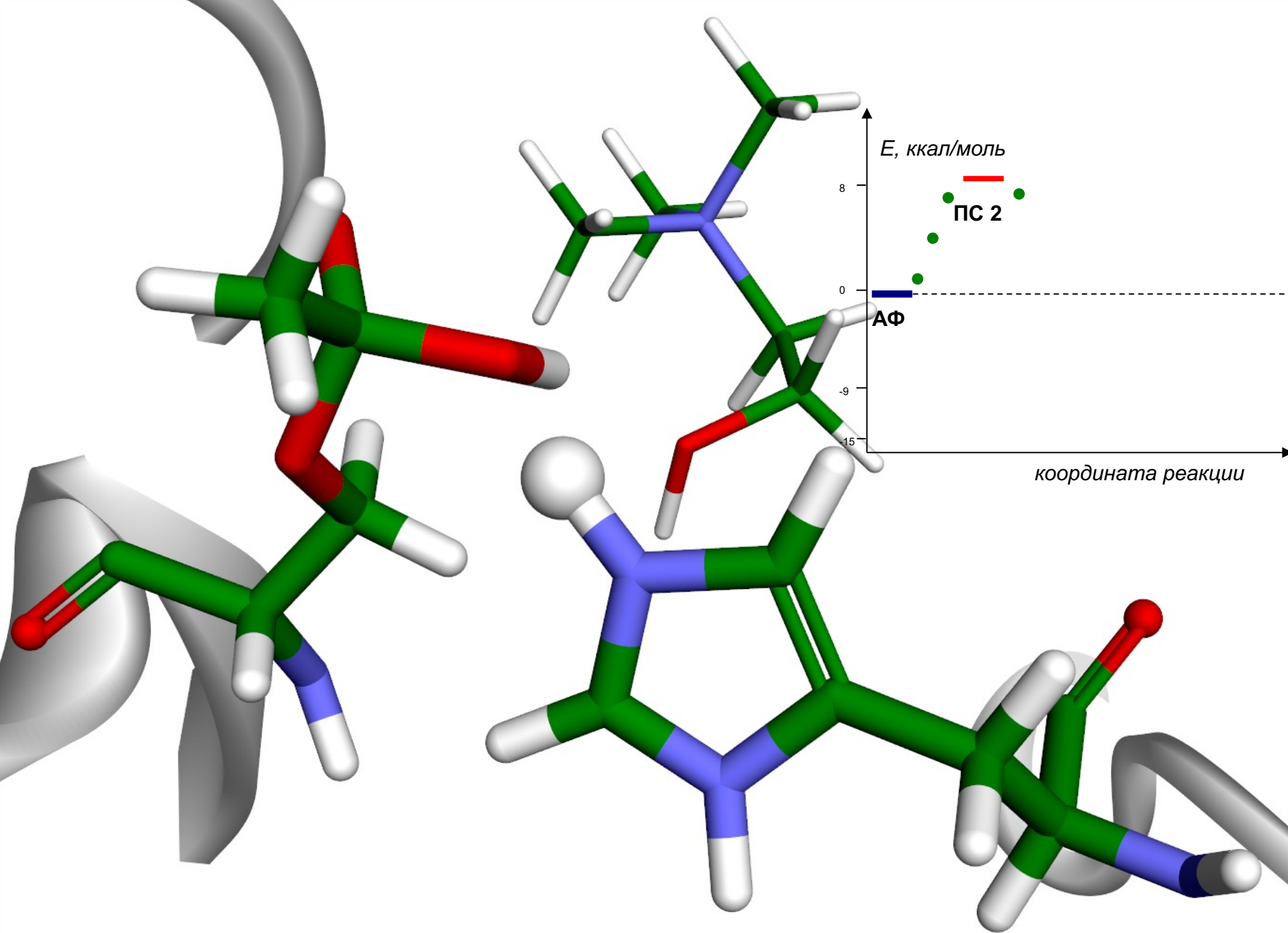


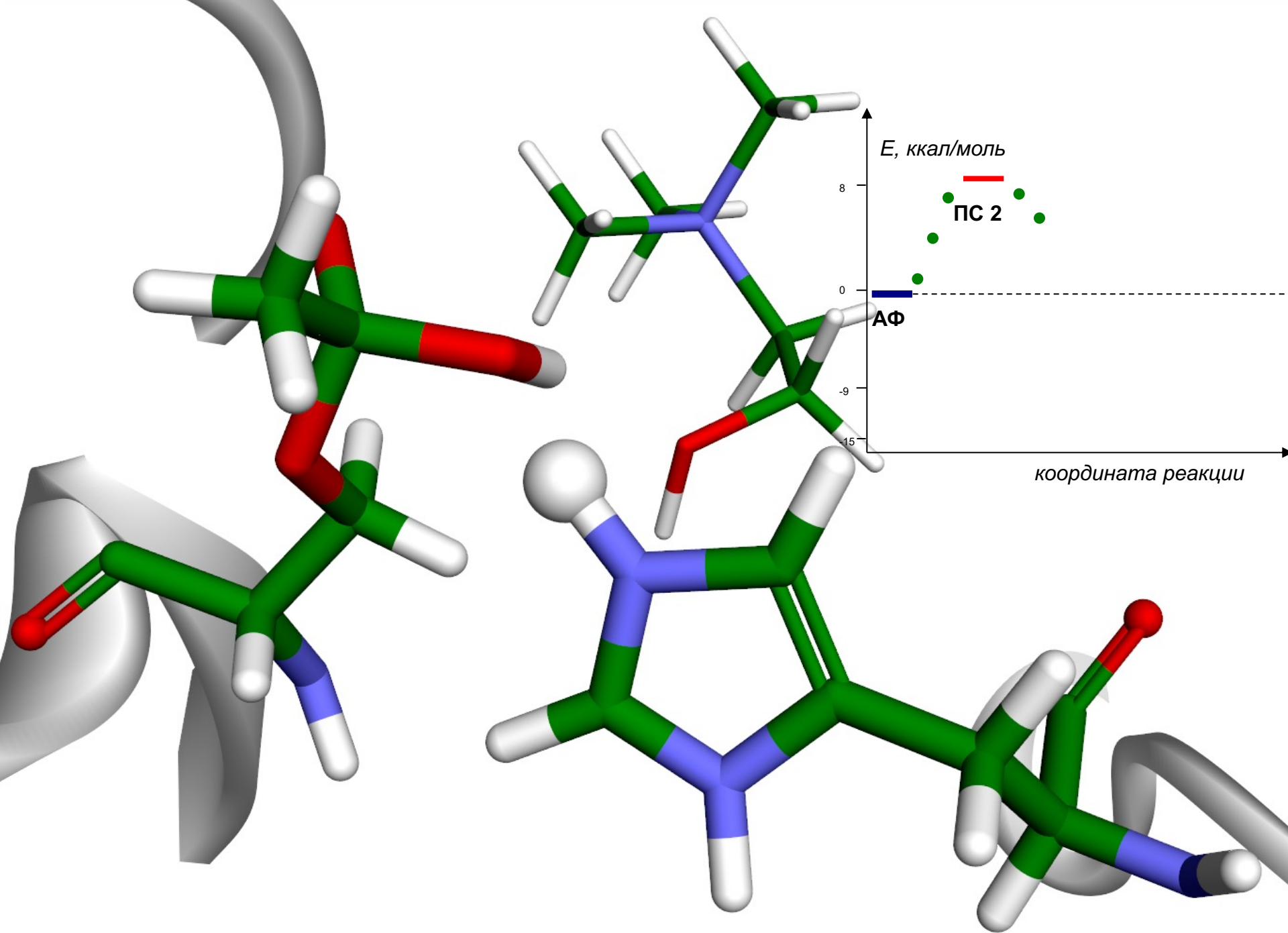
Координата реакции

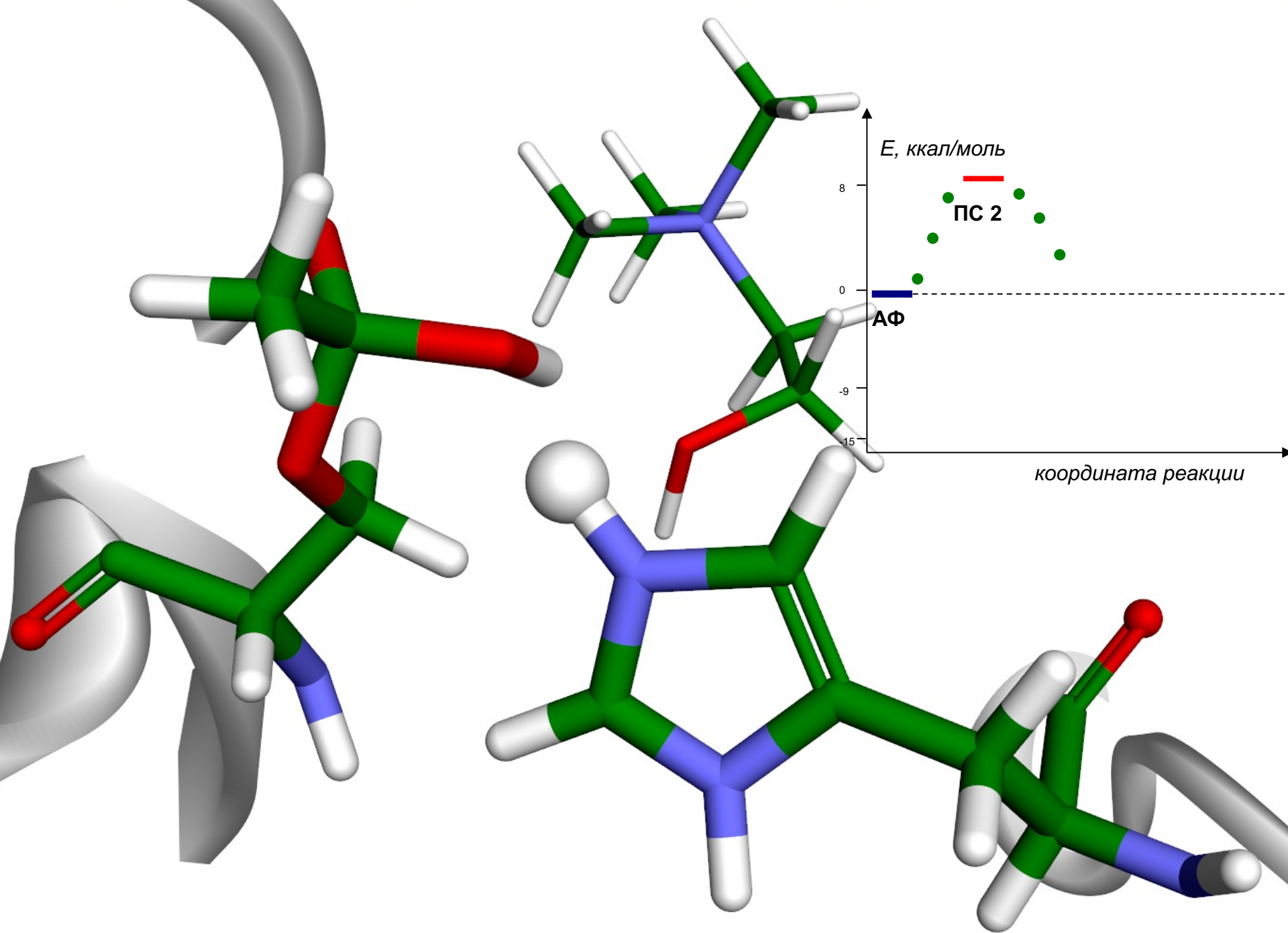


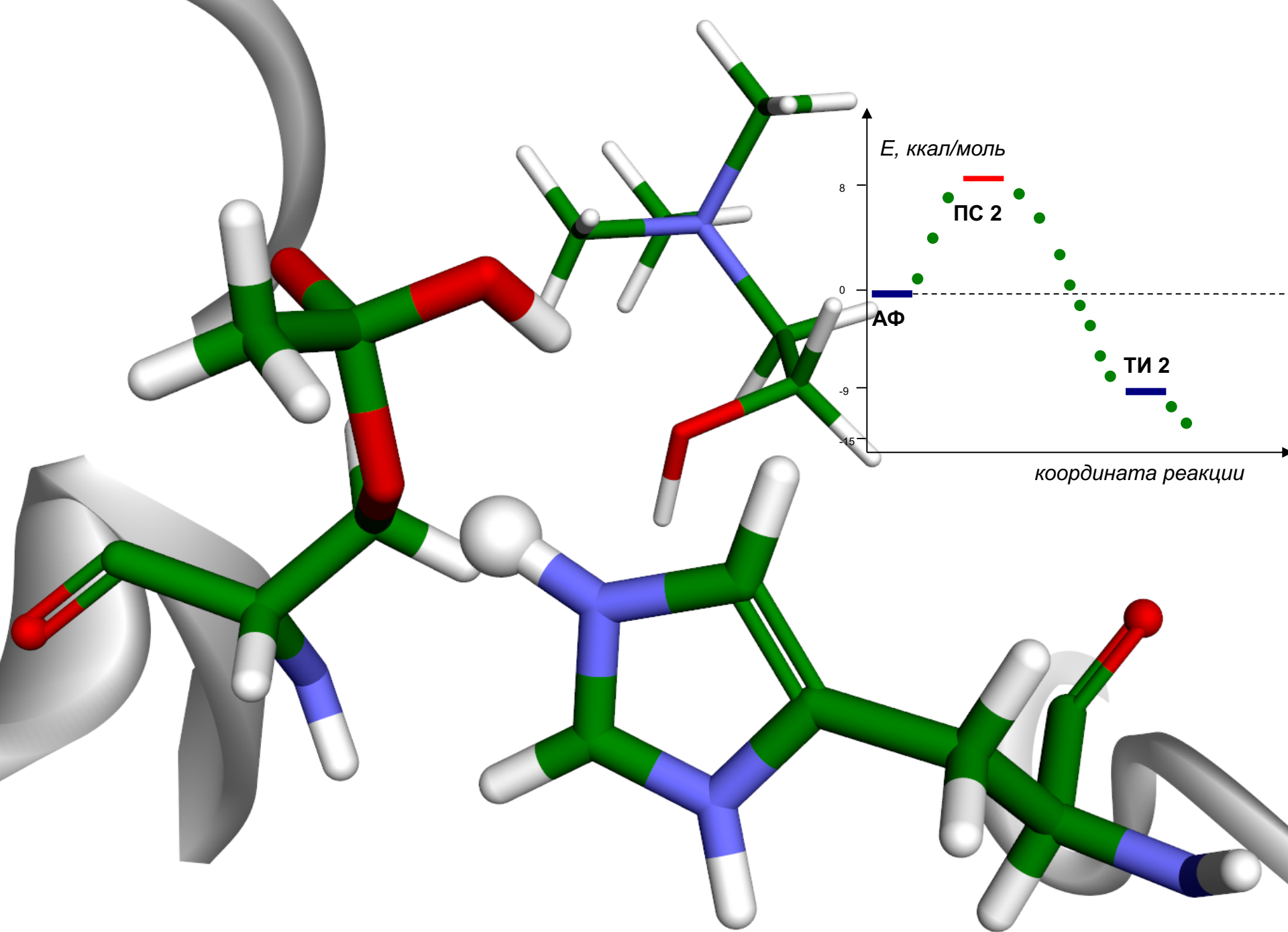


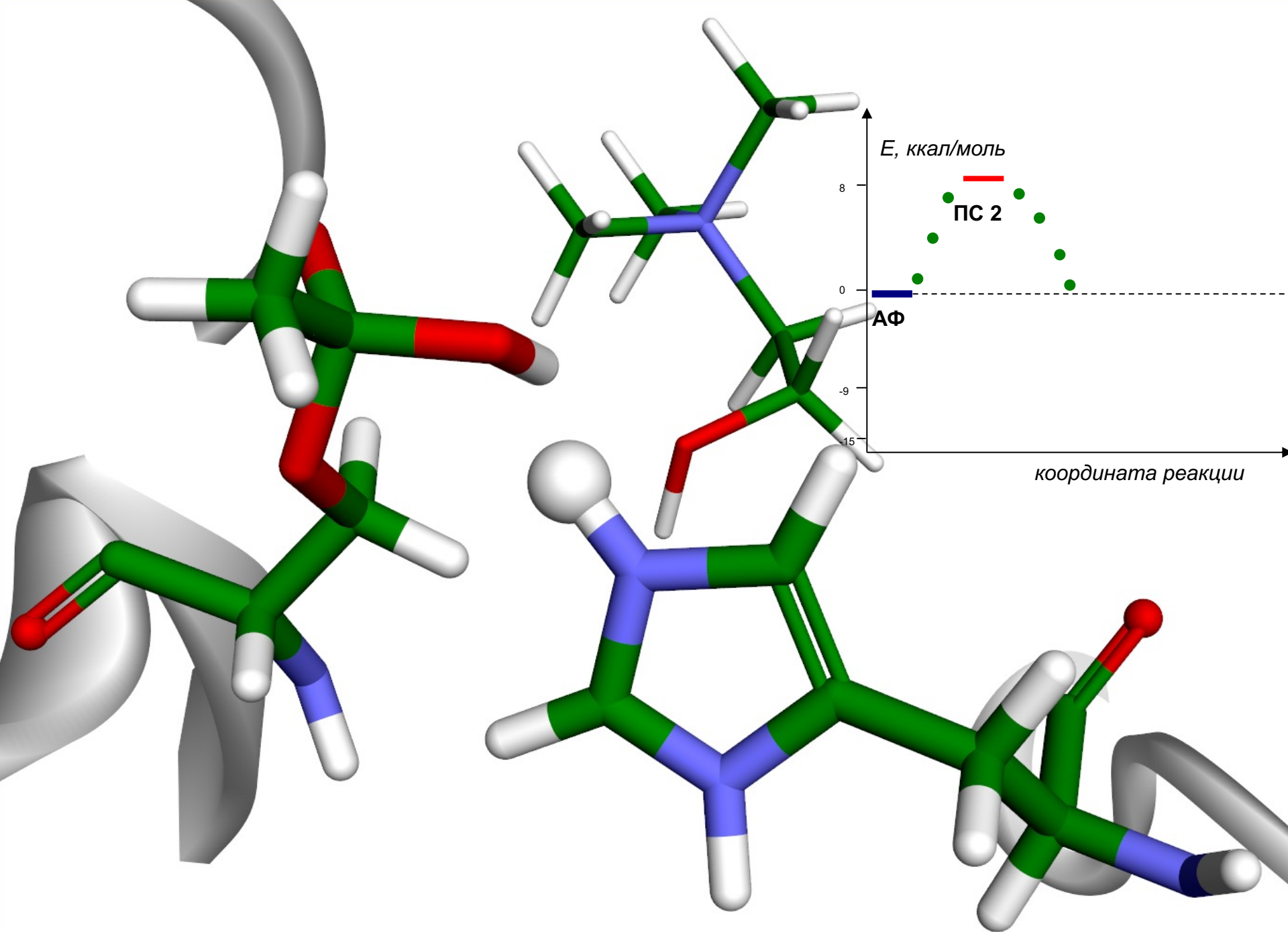












E , ккал/моль

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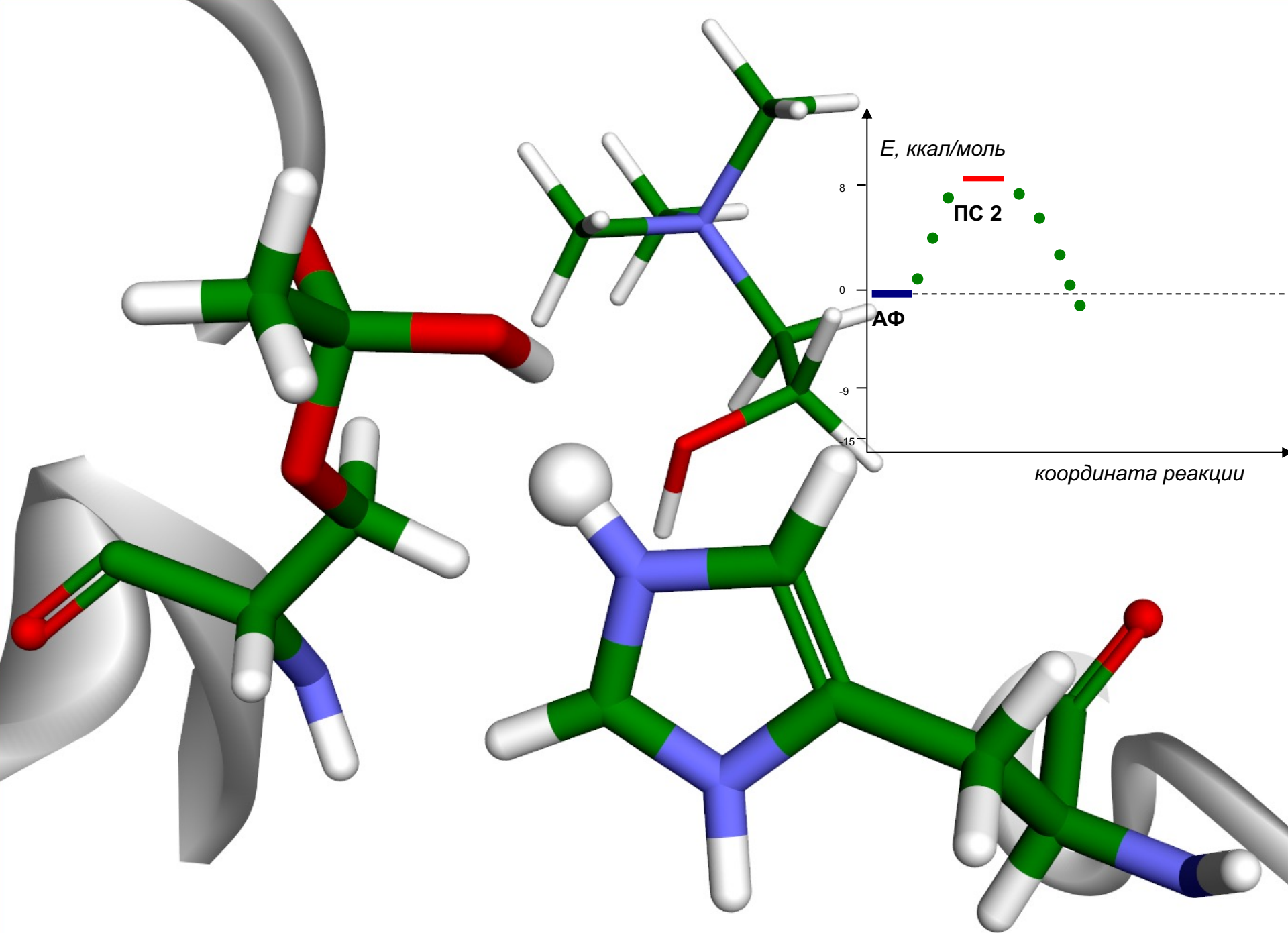
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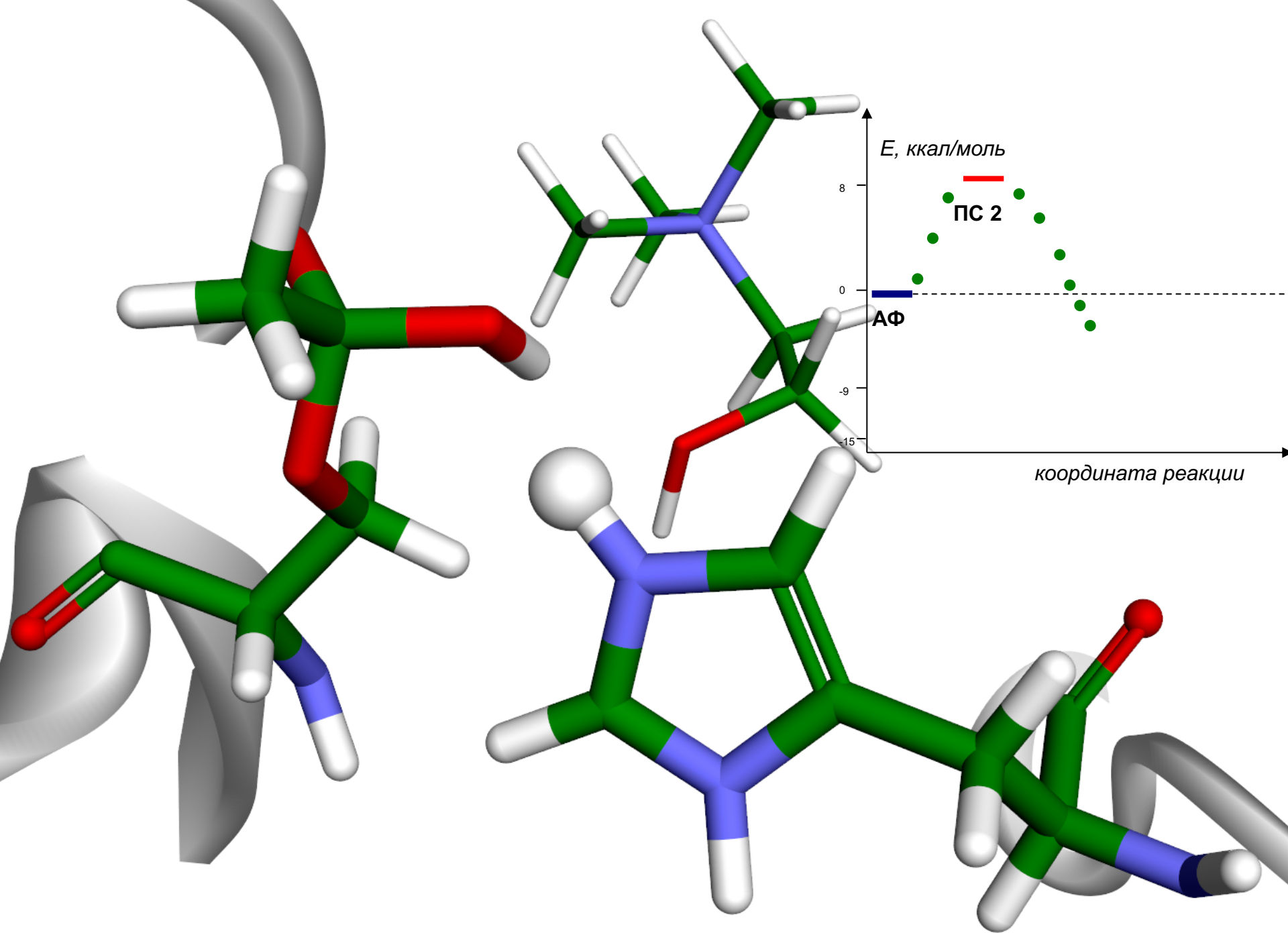
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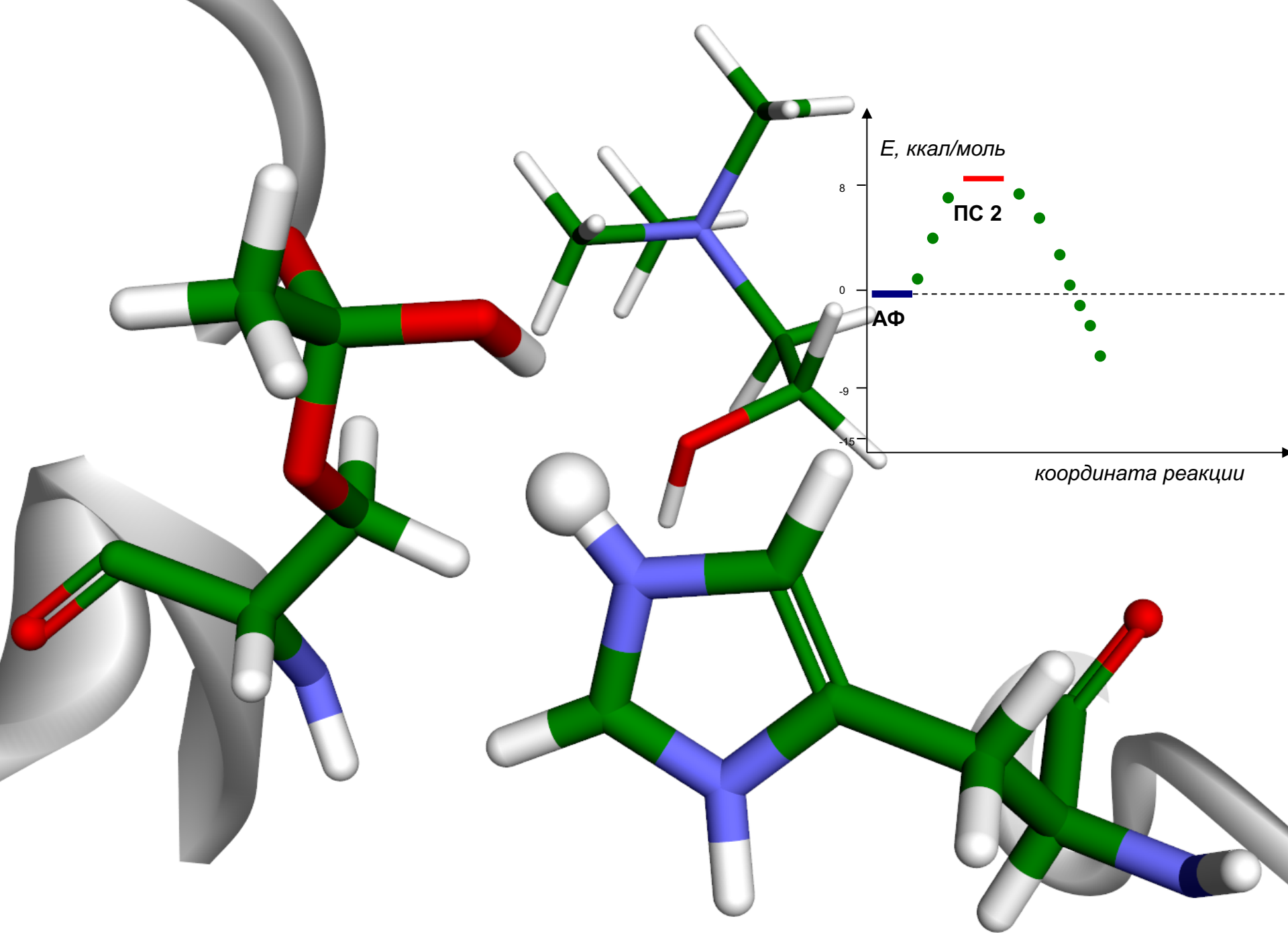
ПС 2

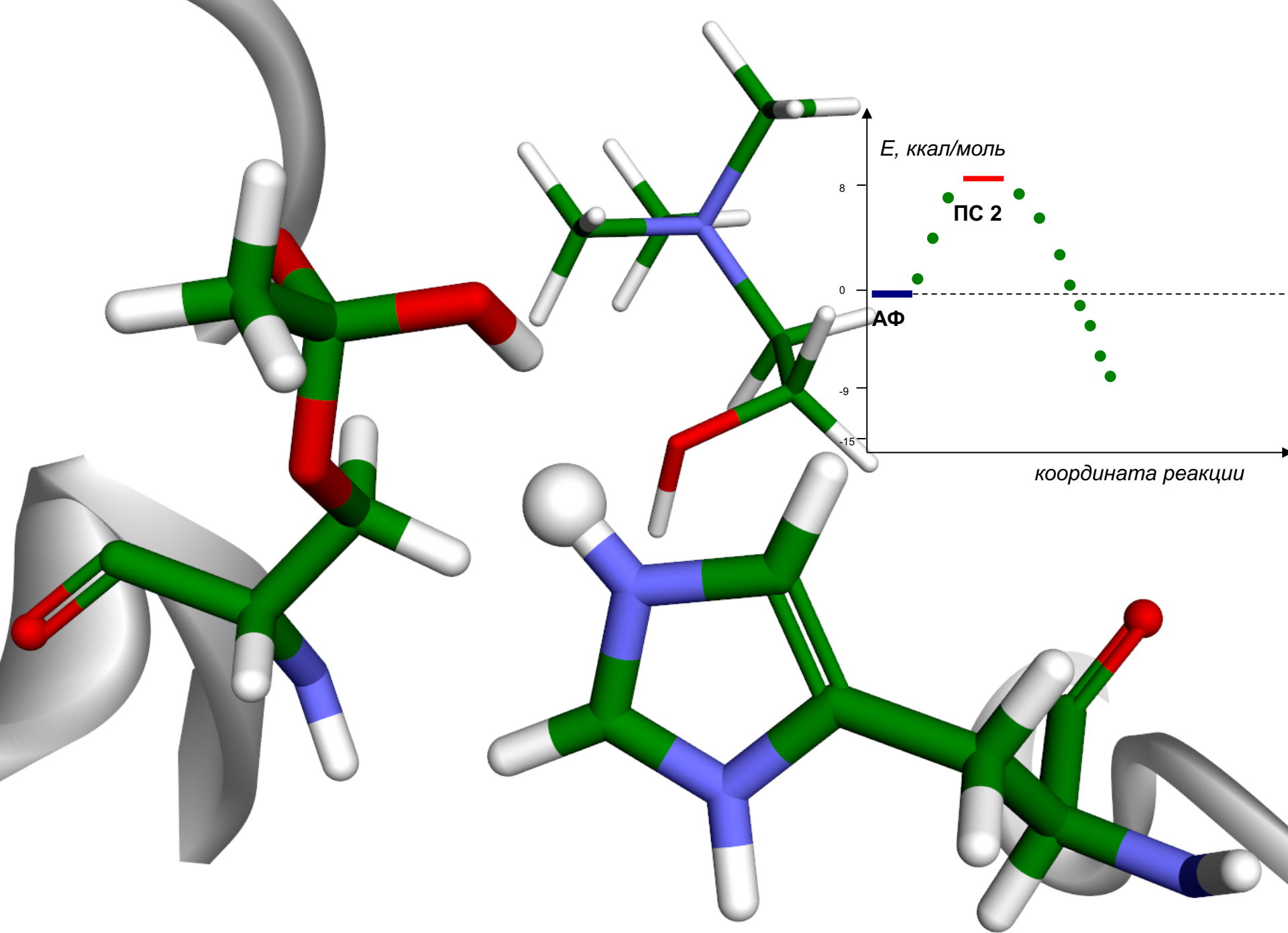
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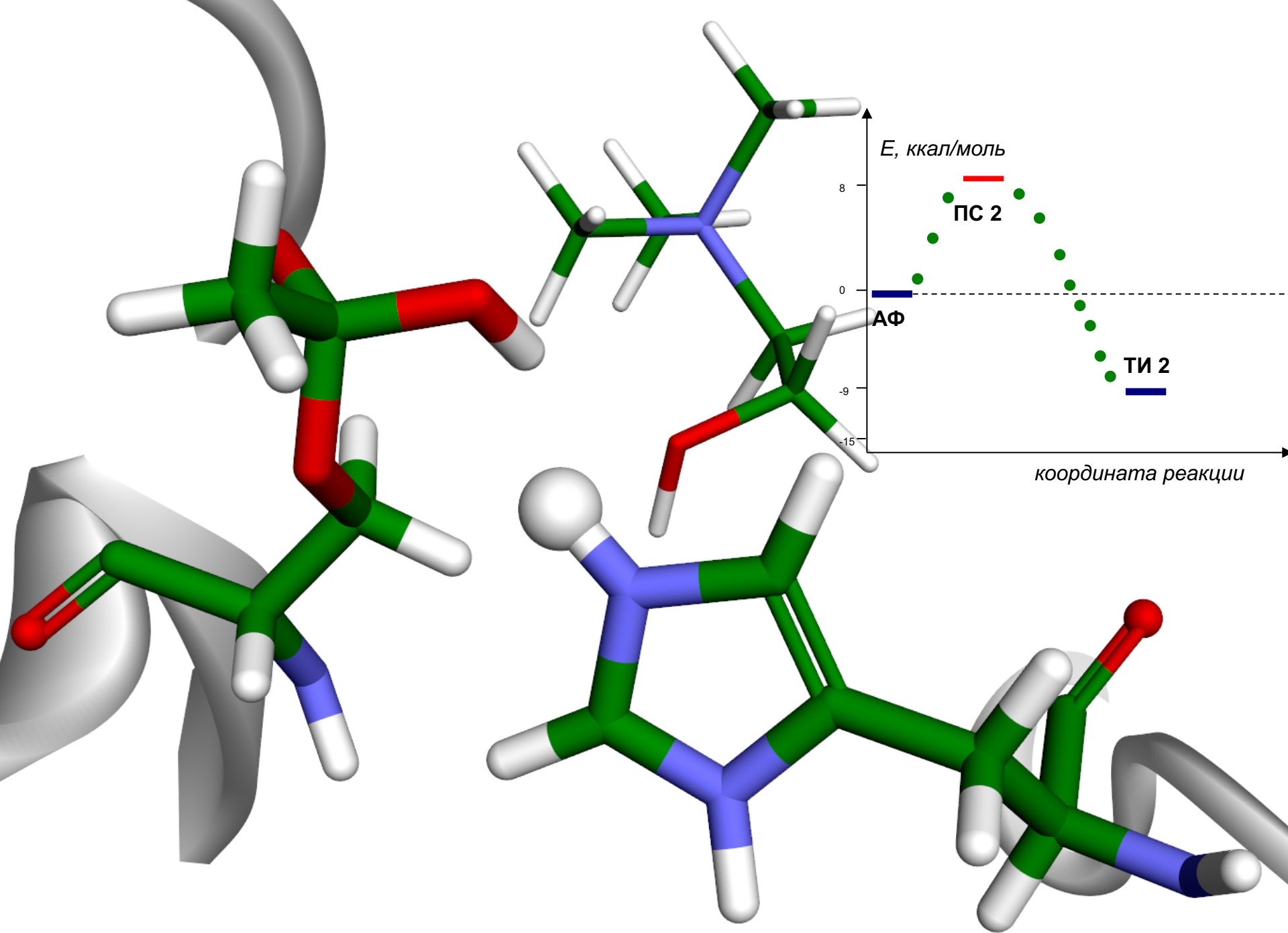
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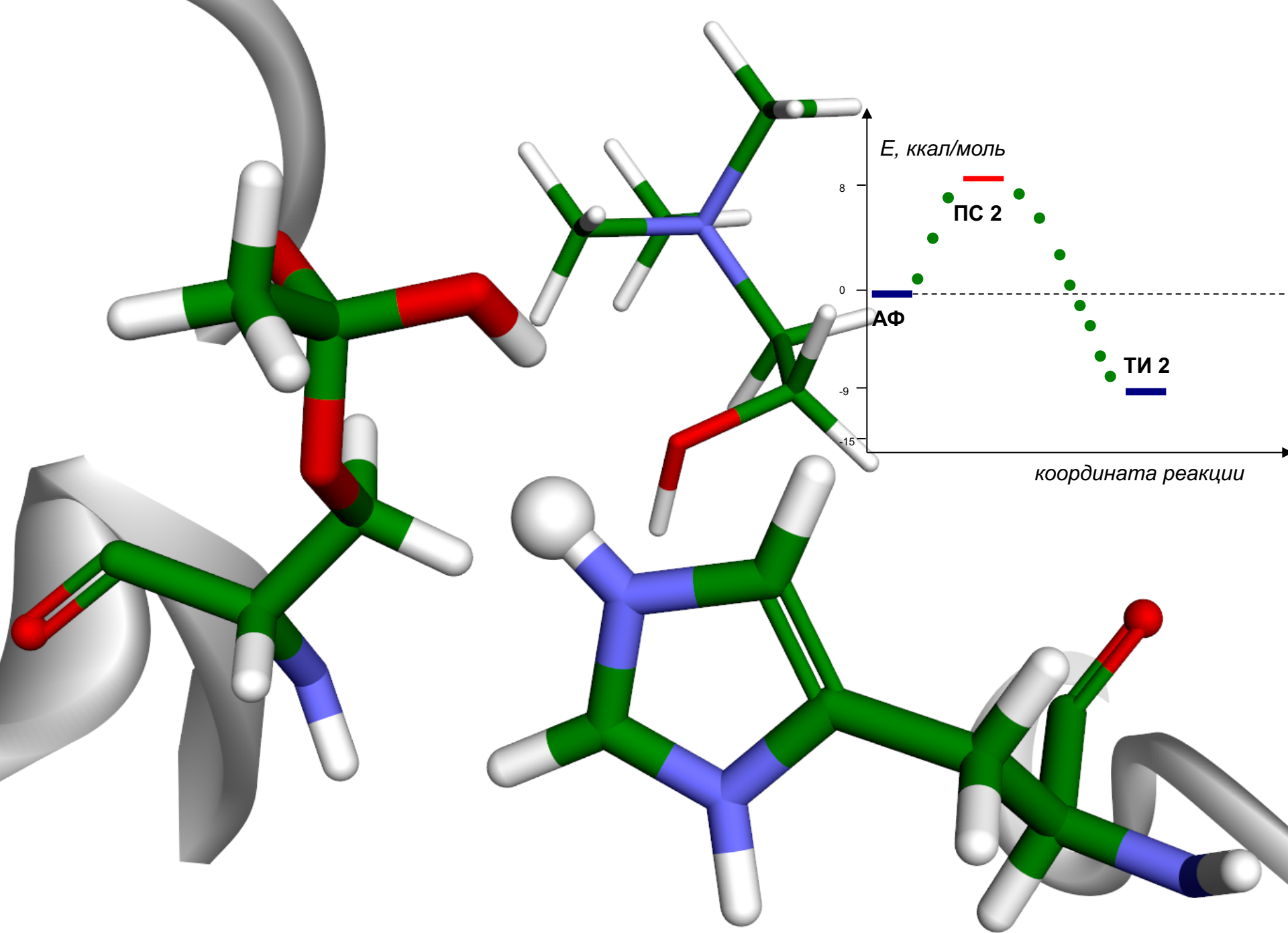


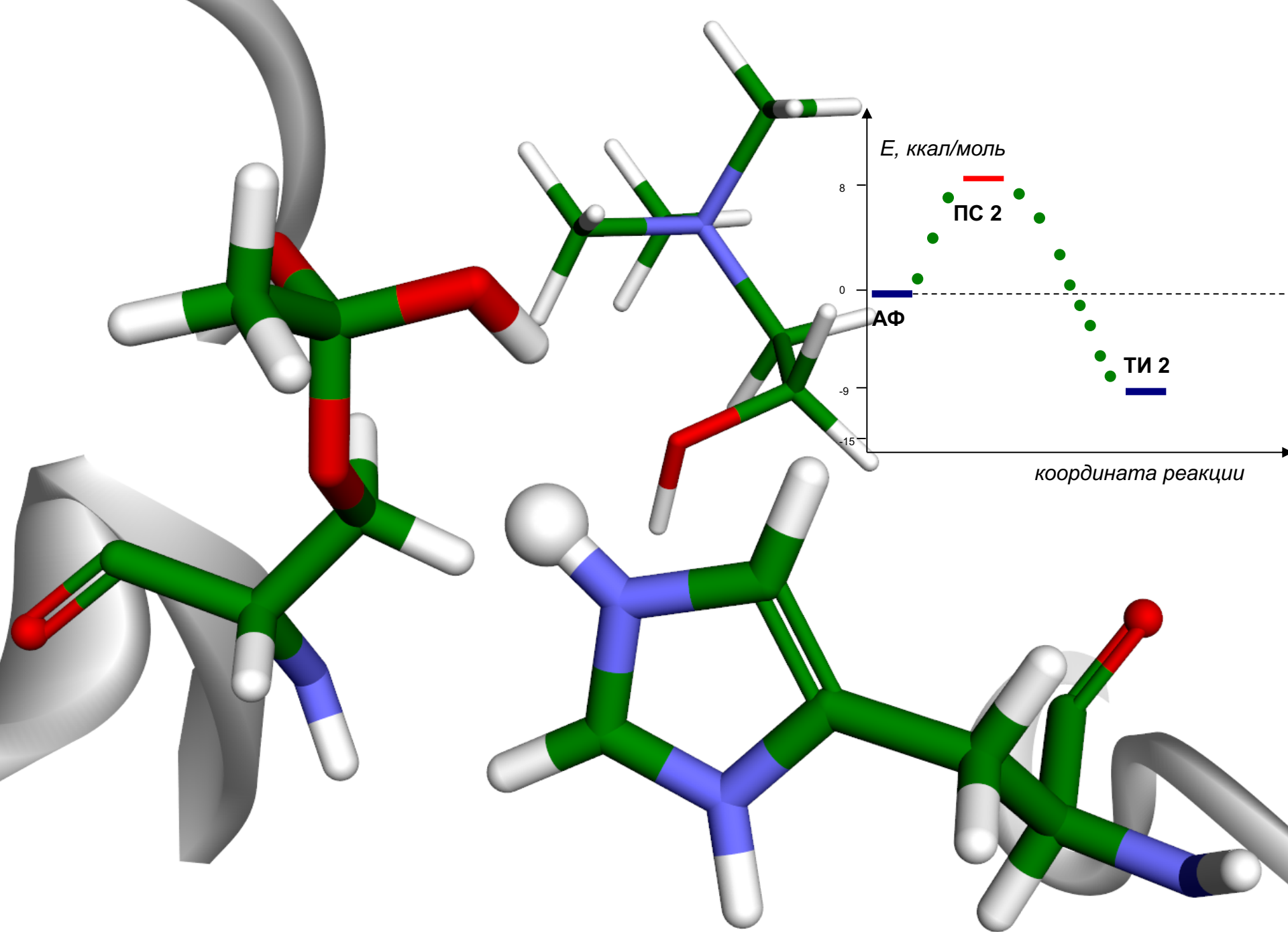












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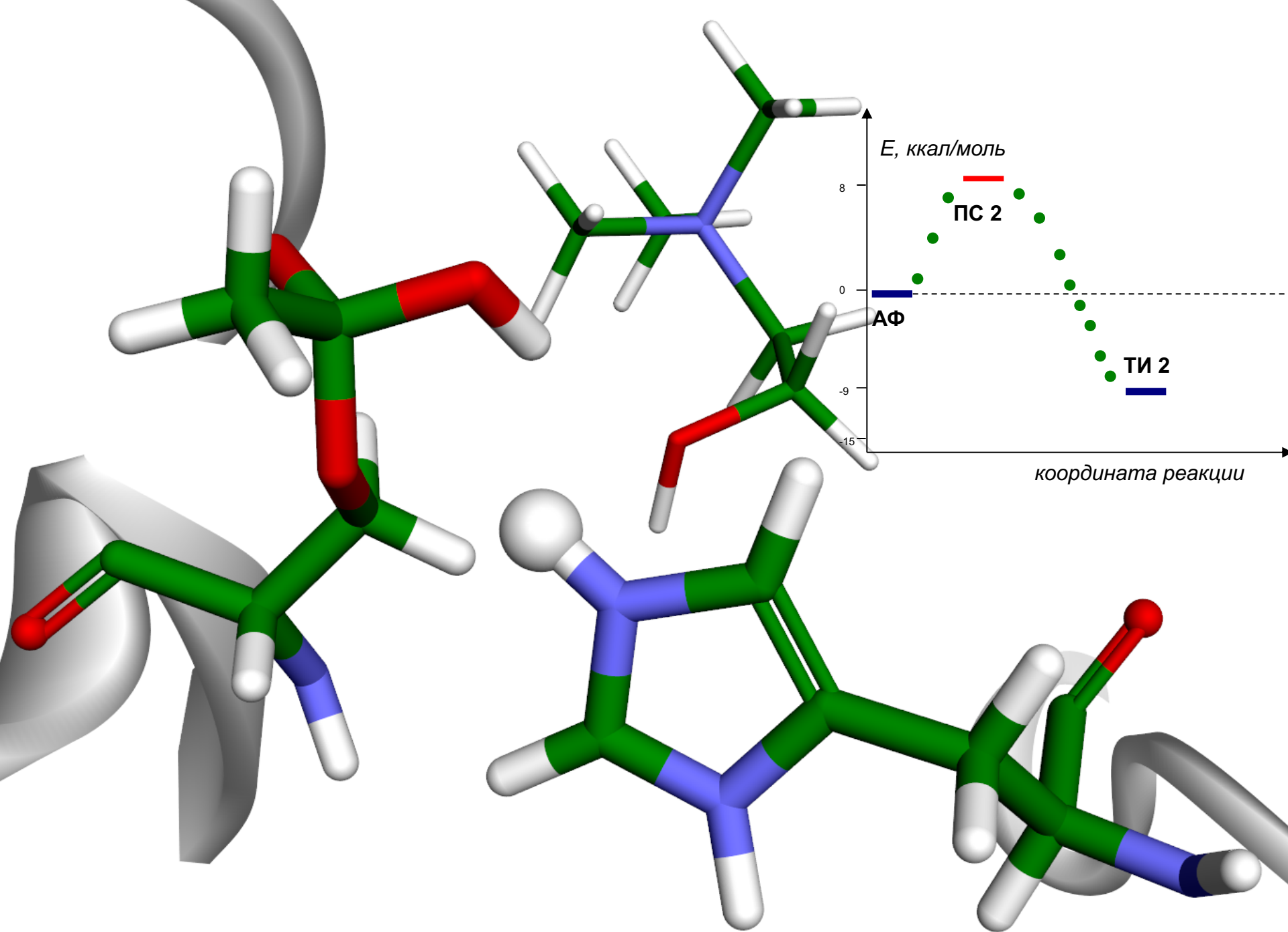
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ТС 2

АФ

ТИ 2

координата реакции



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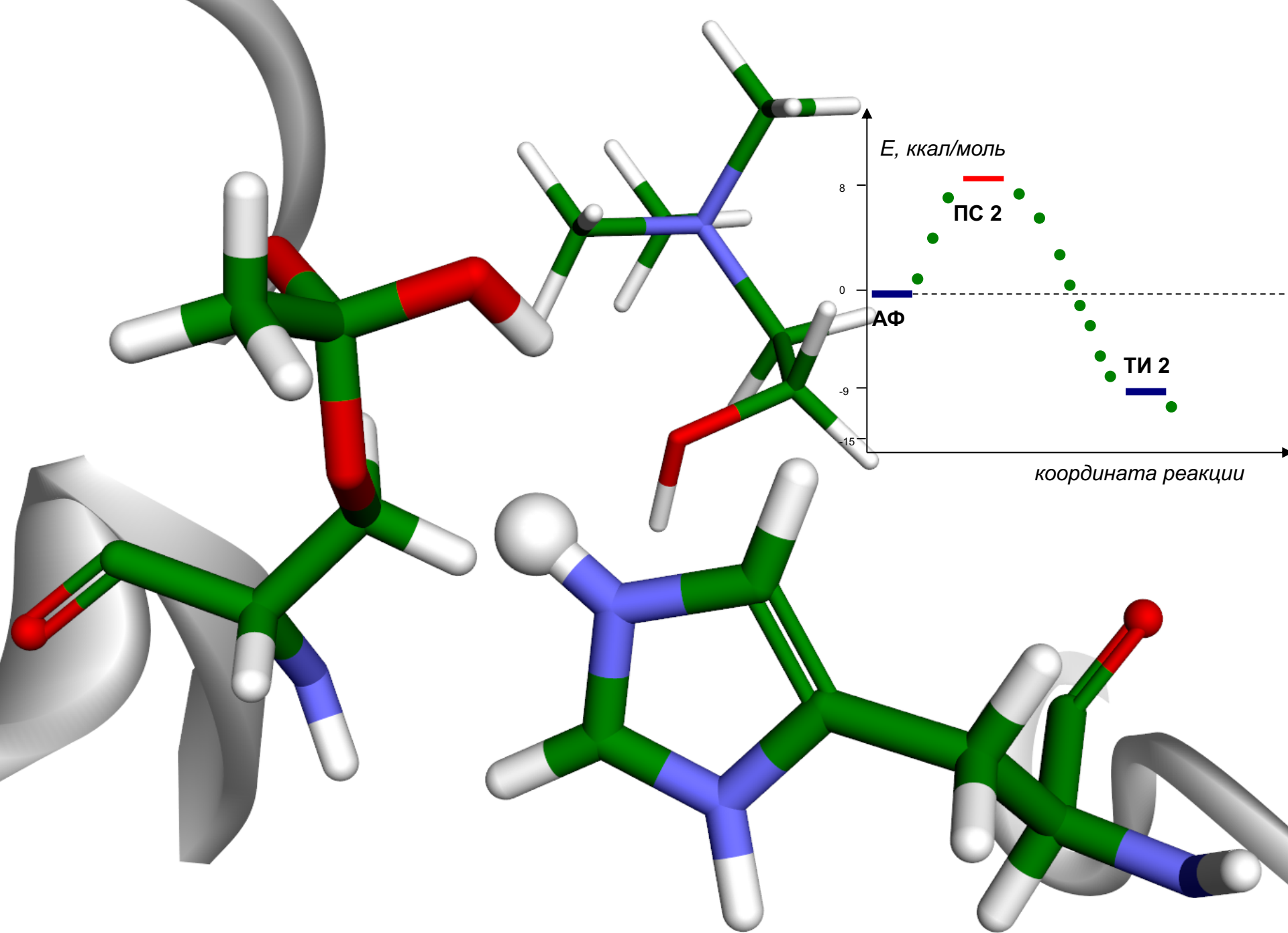
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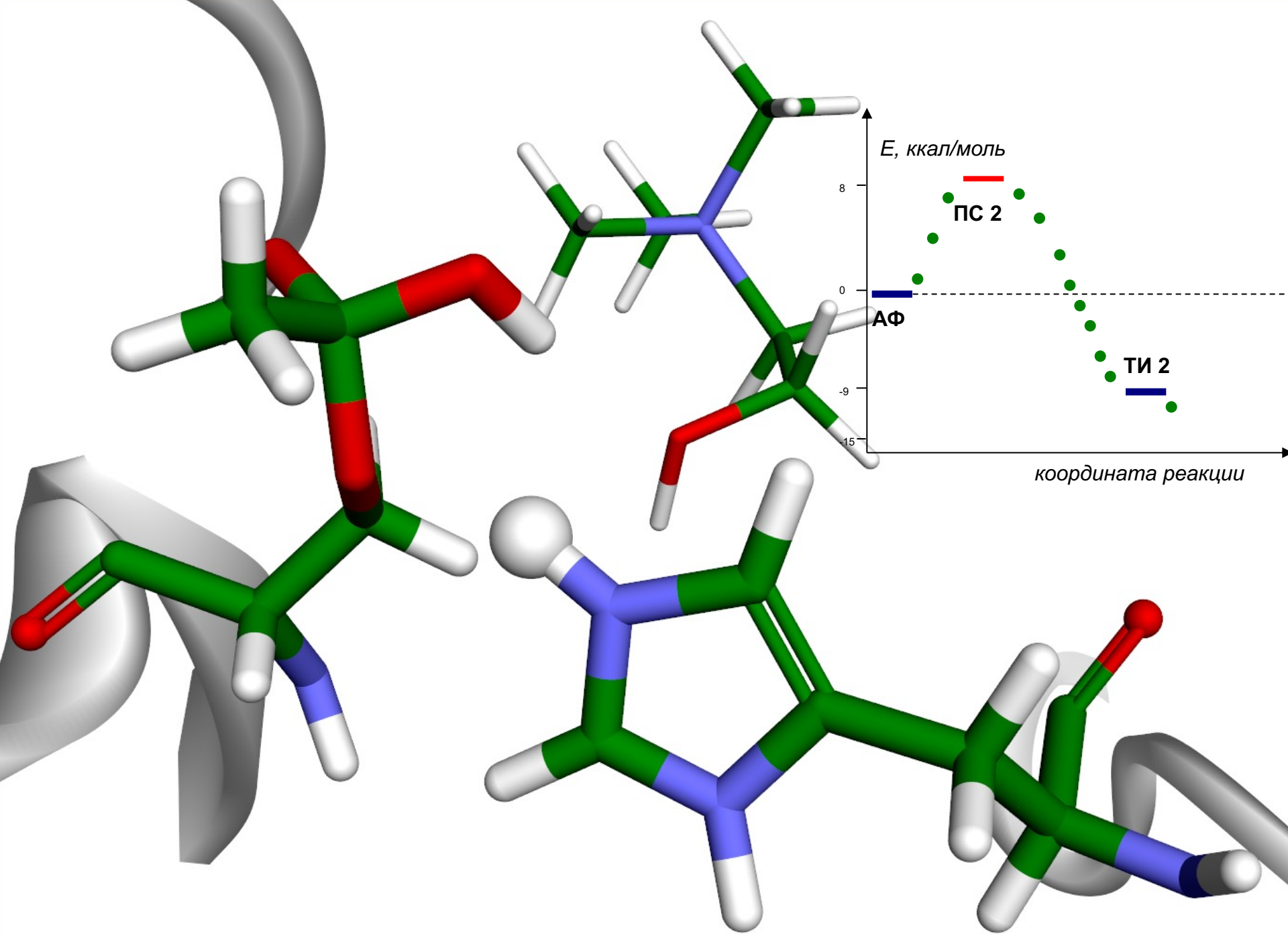
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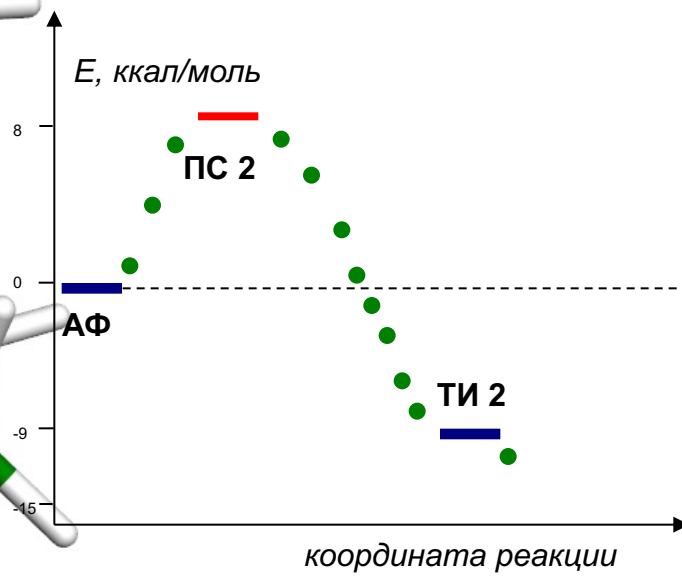
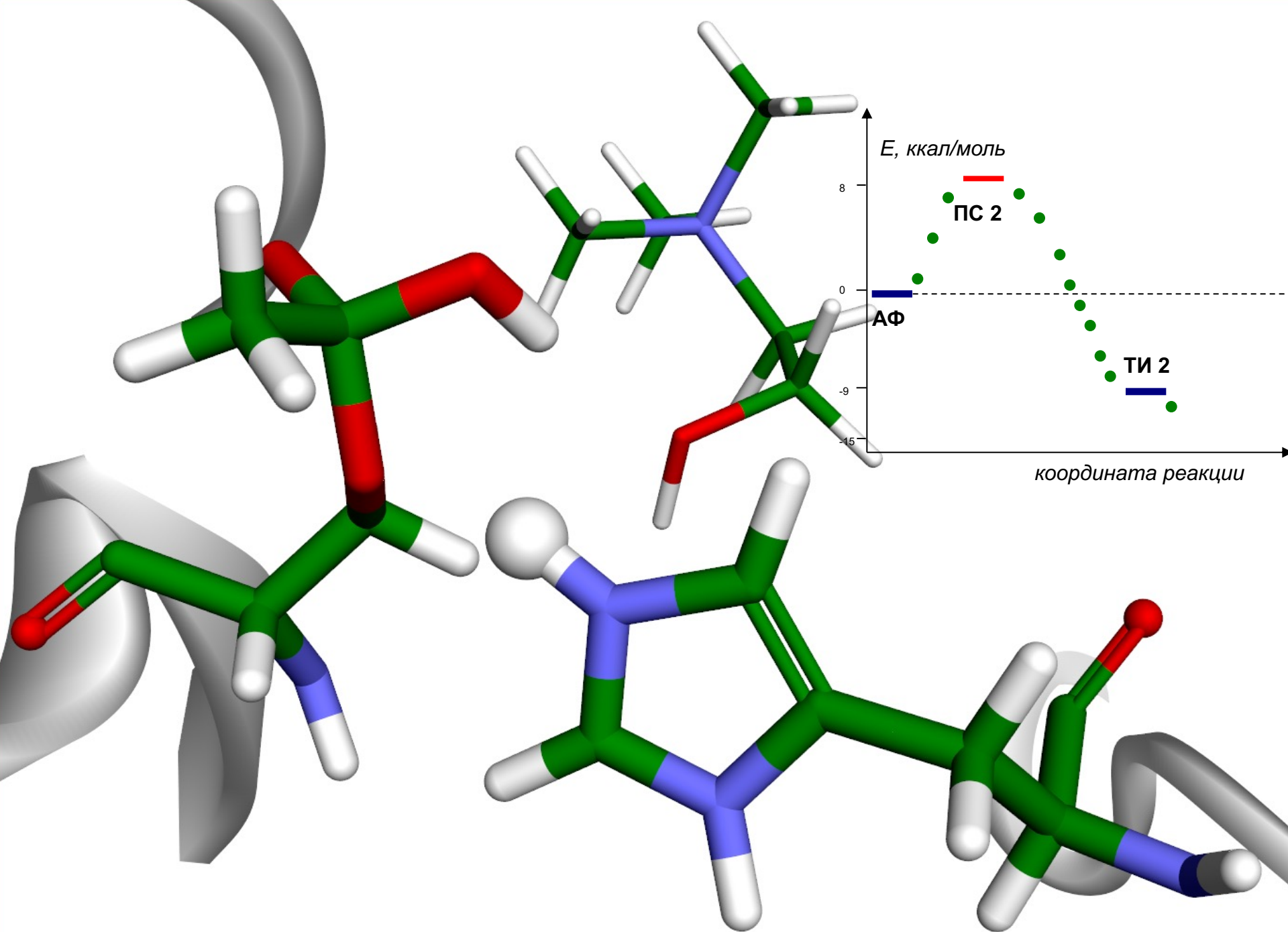
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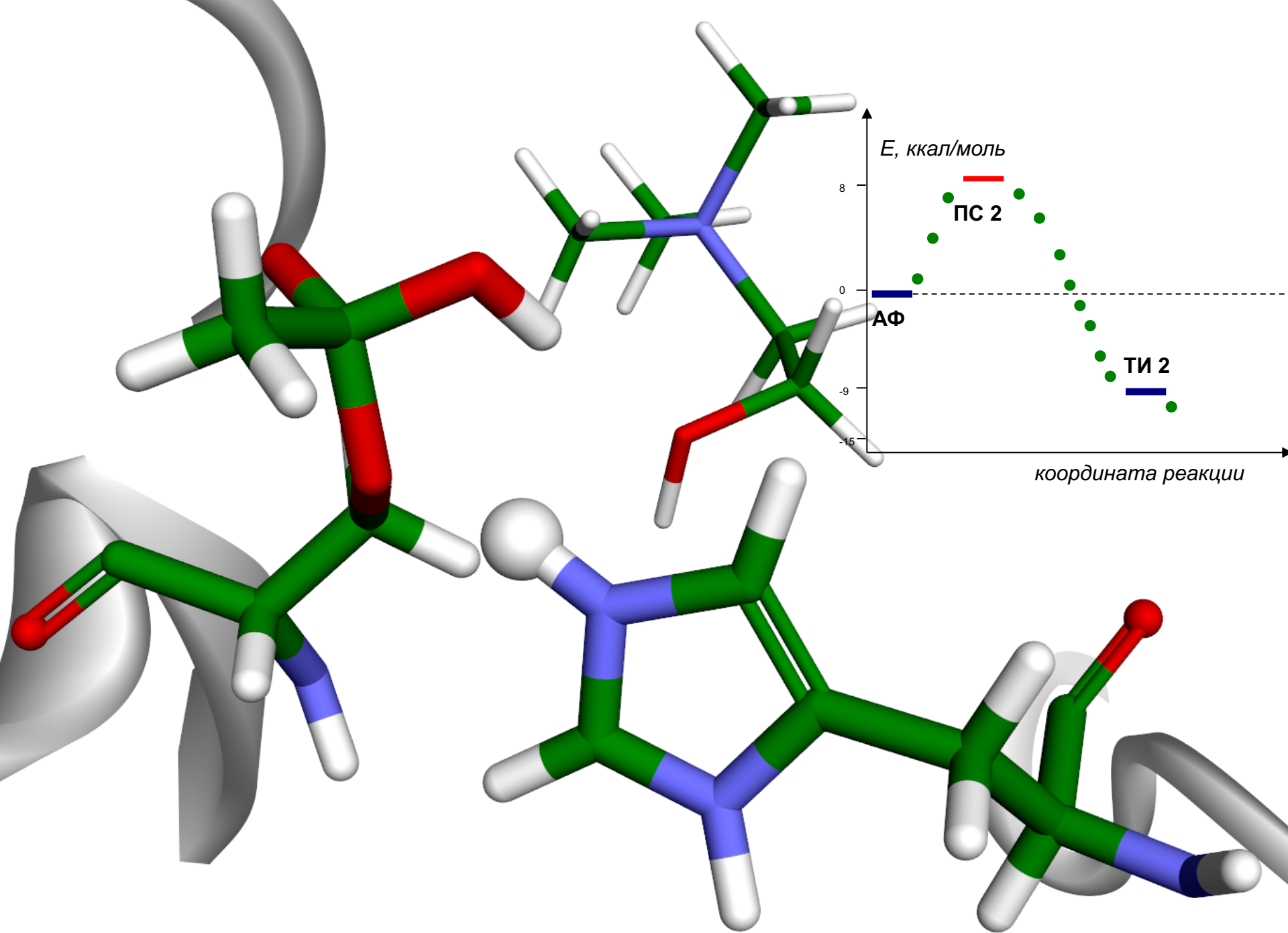
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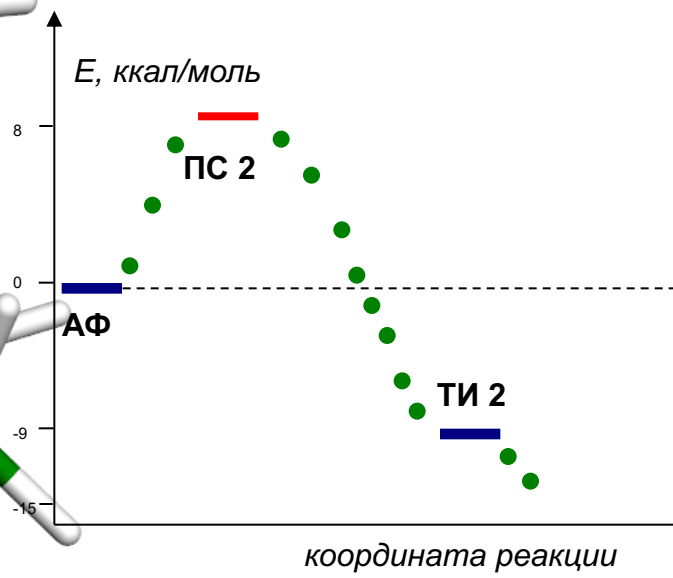
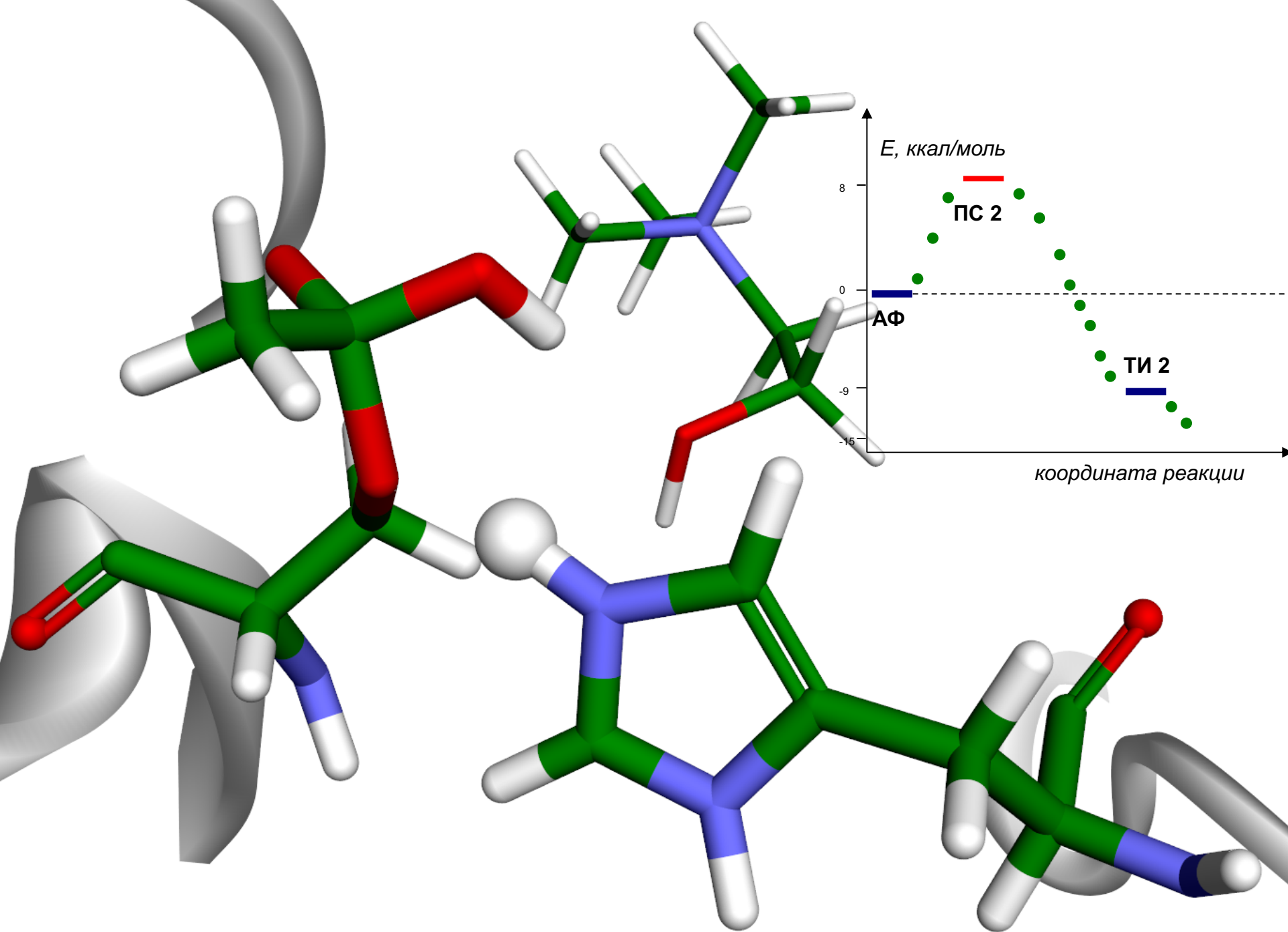
координата реакции

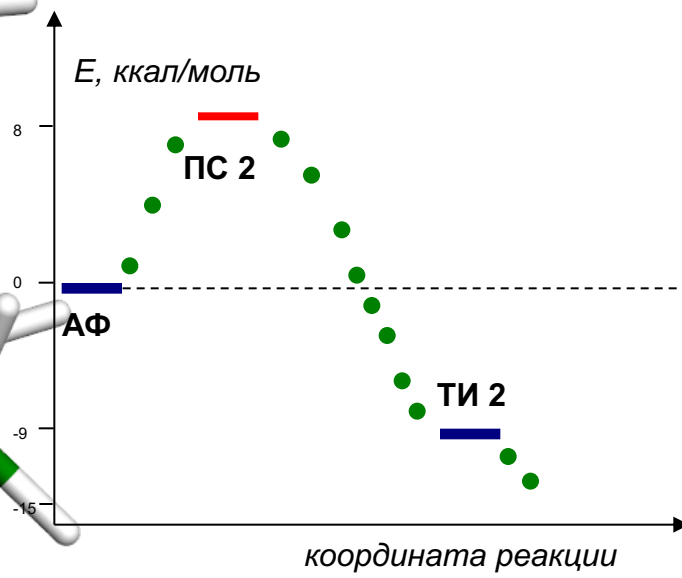
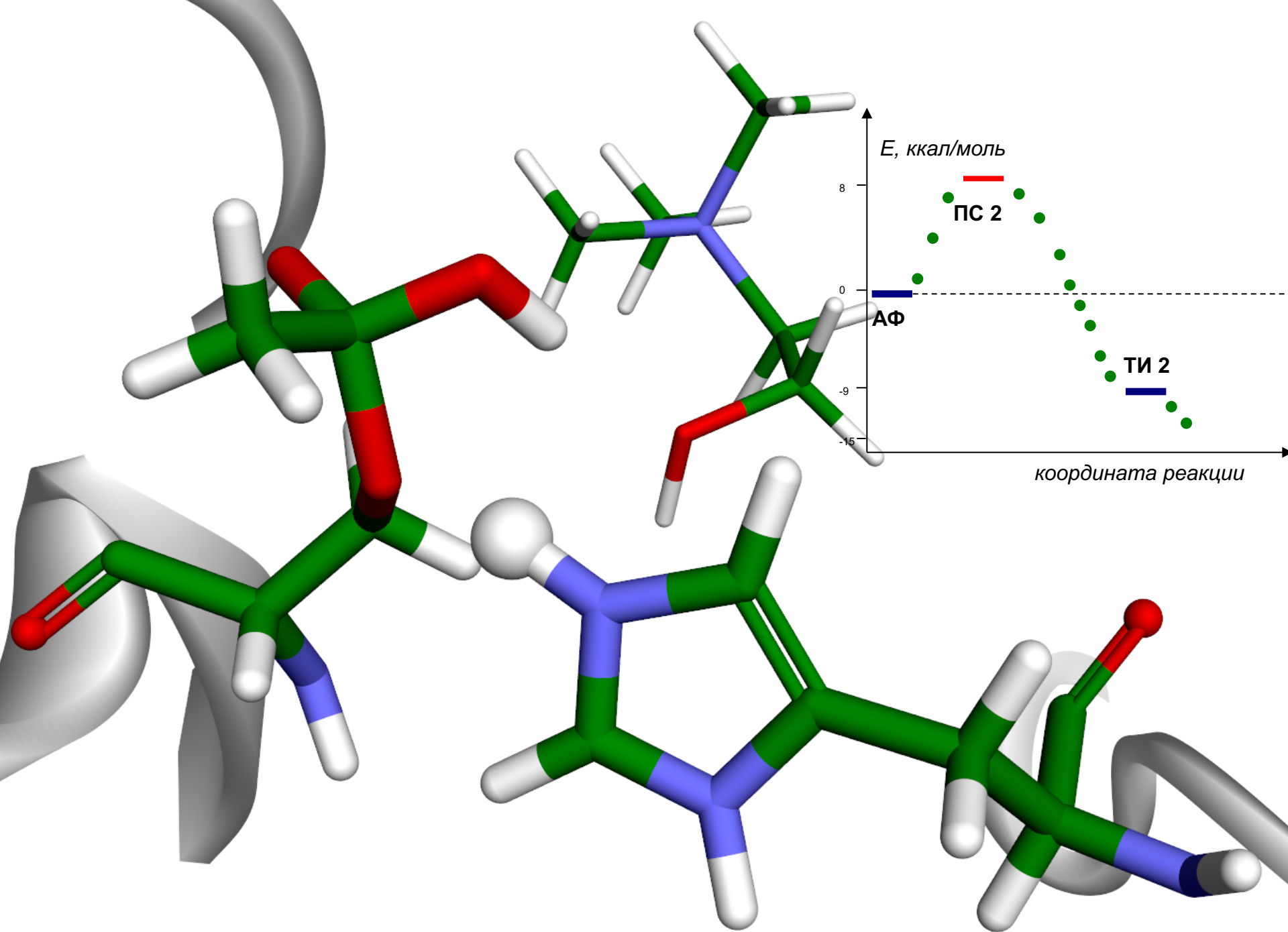


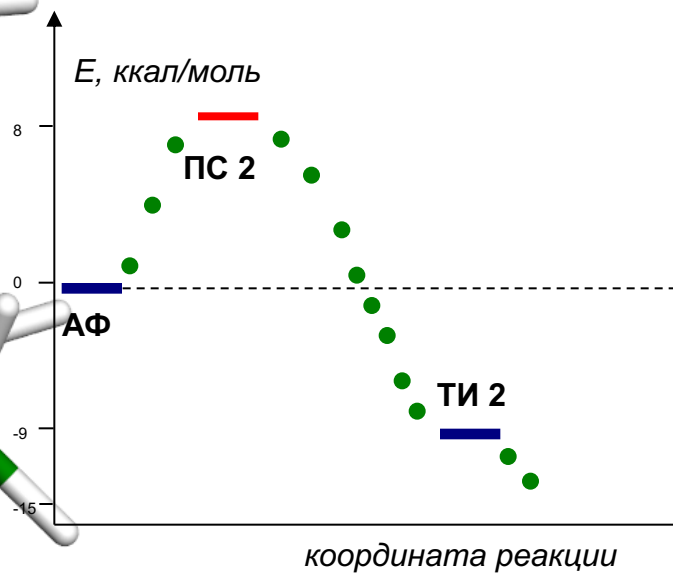
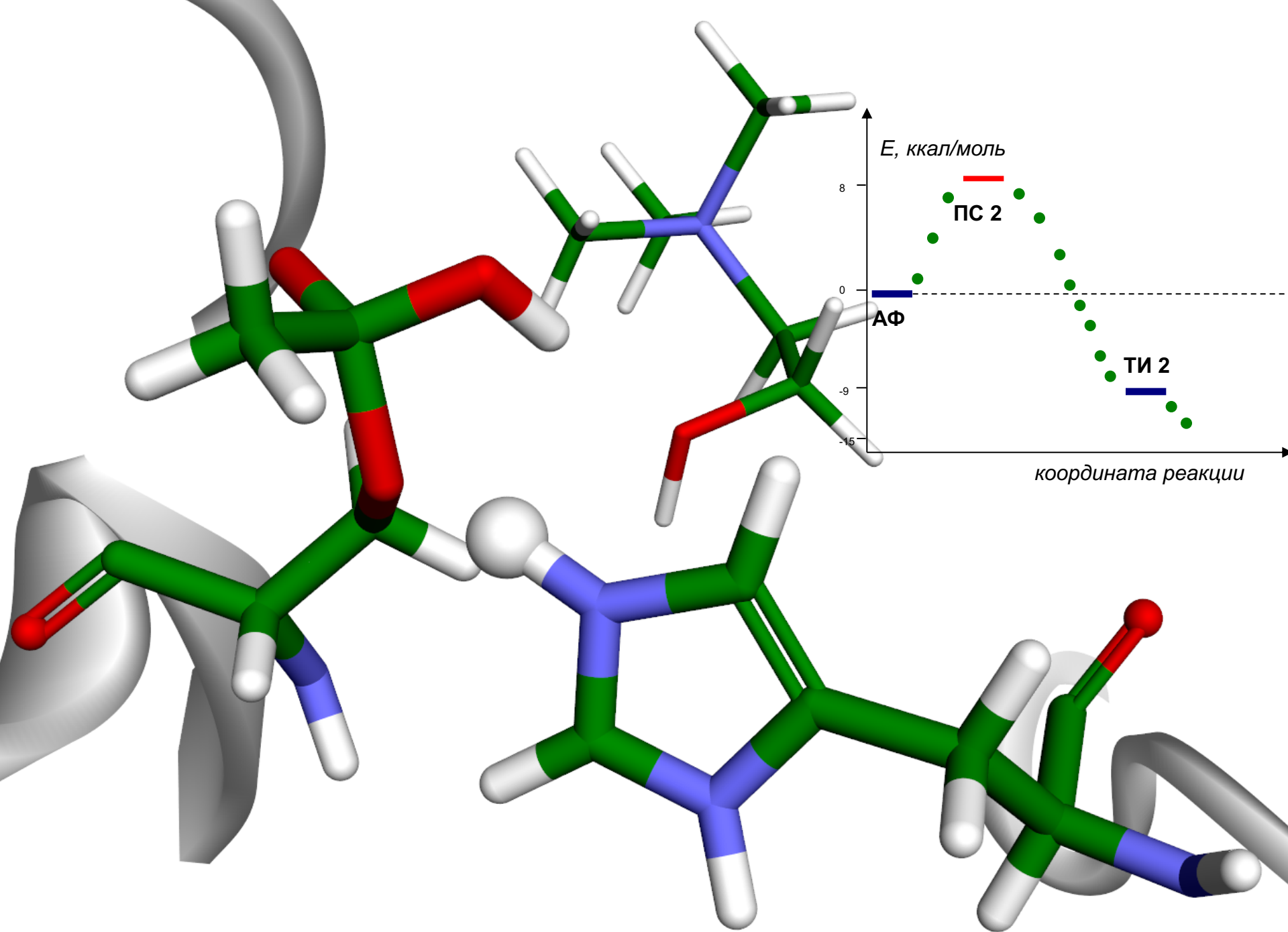


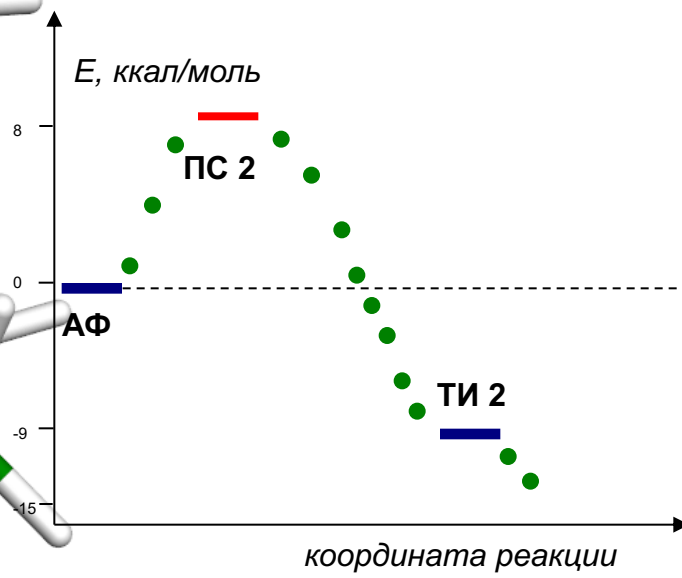
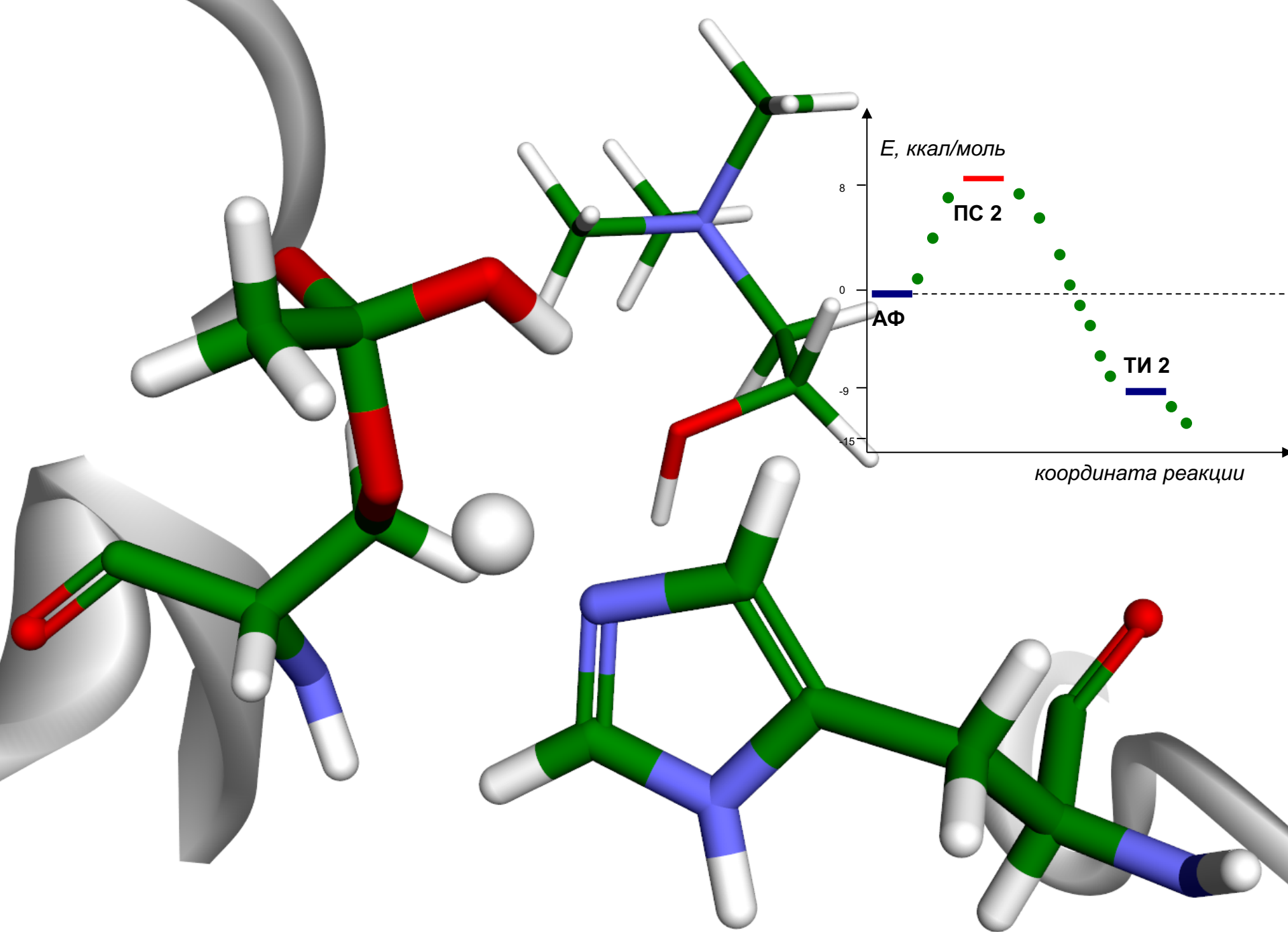


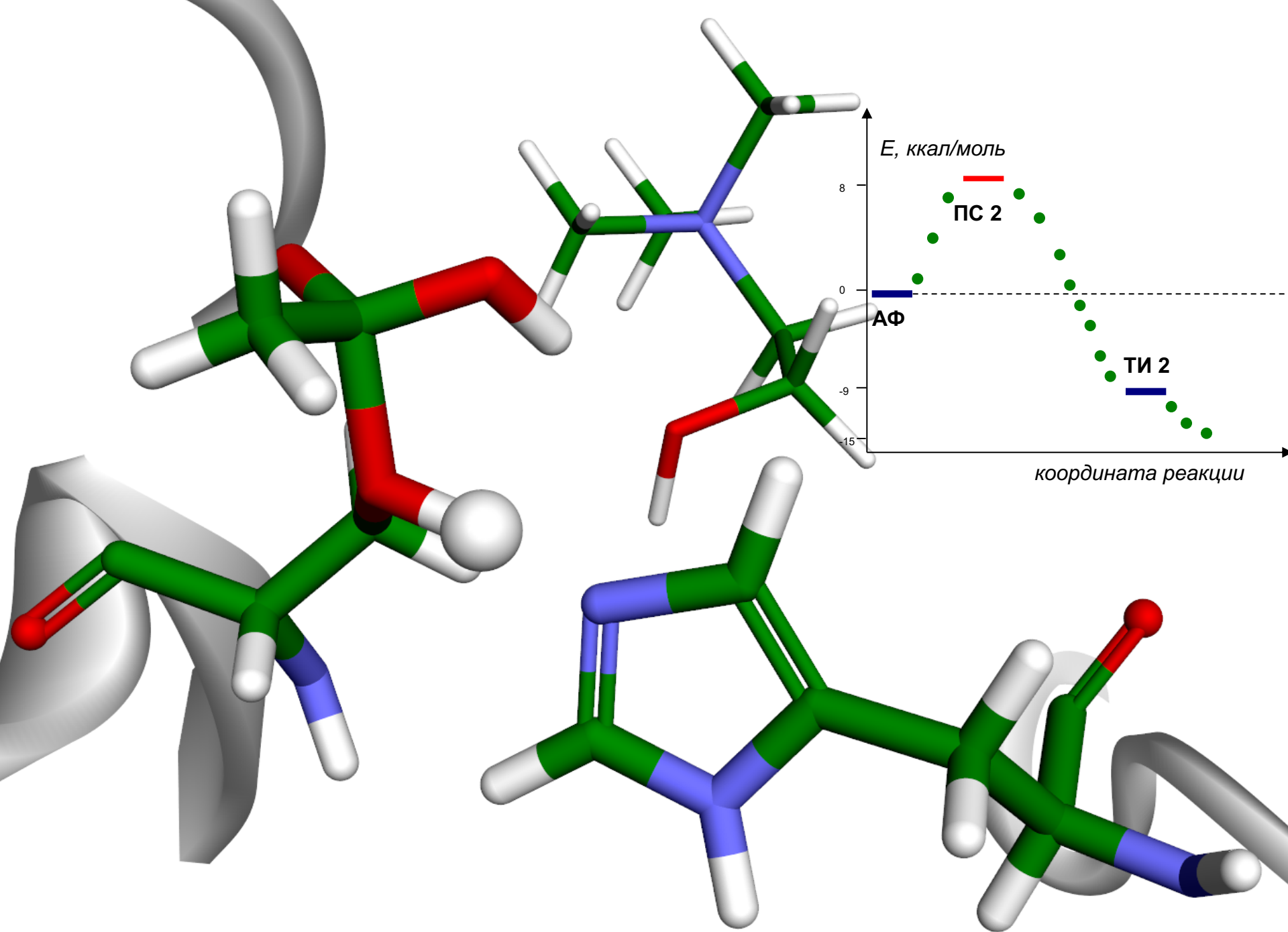












E , ккал/моль

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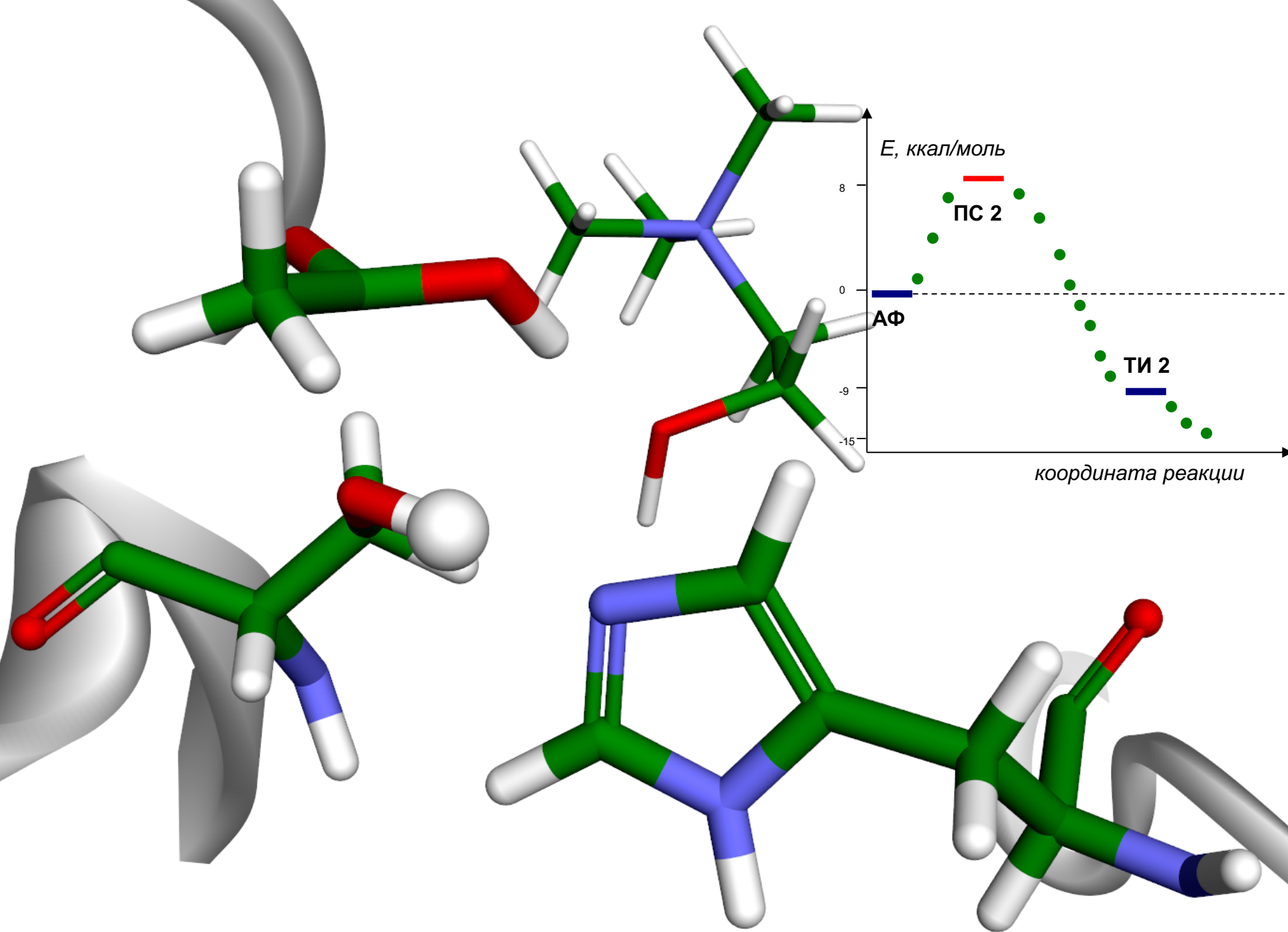
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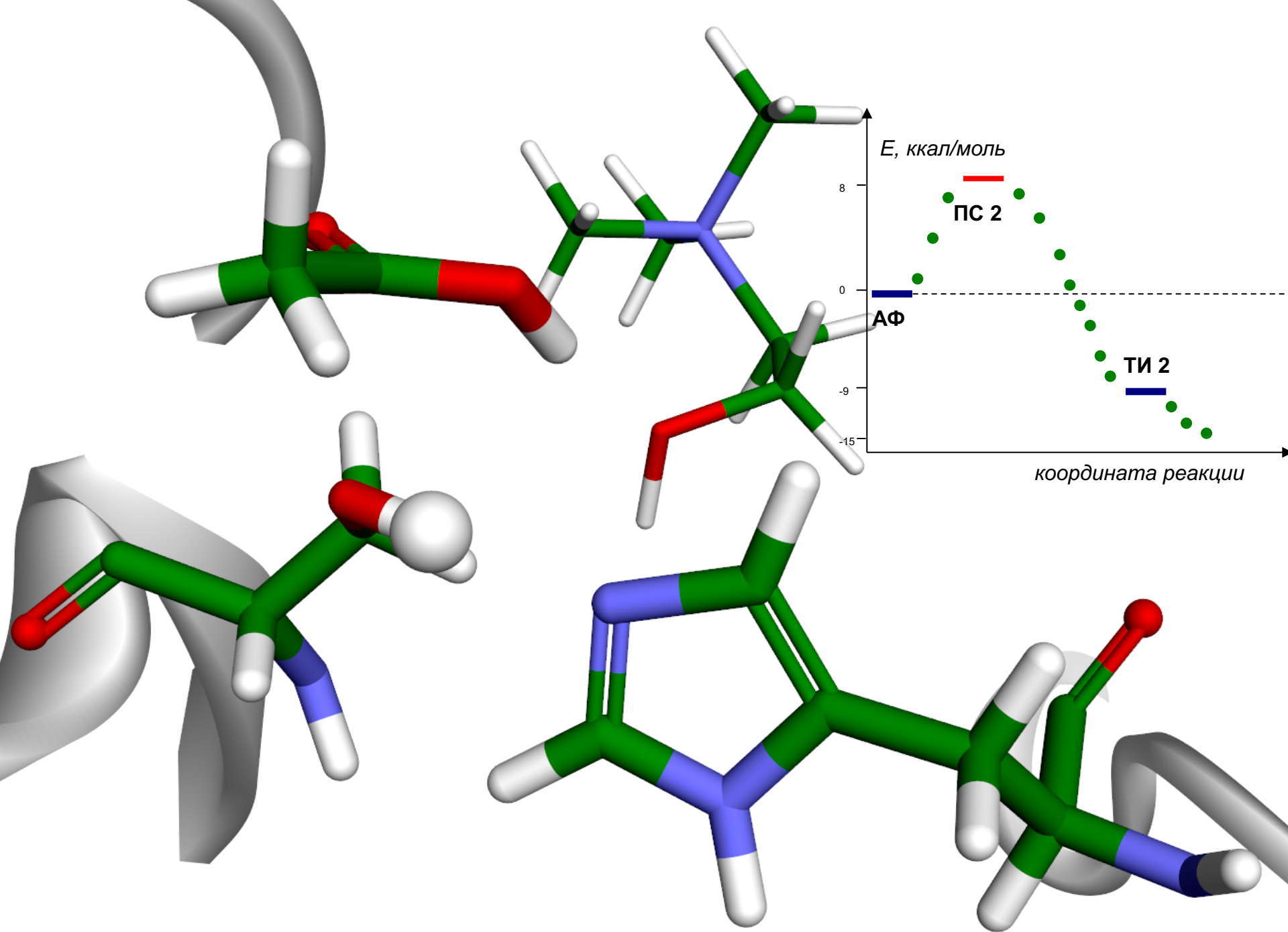
ПС 2

АФ

ТС 2

координата реакции





E , ккал/моль

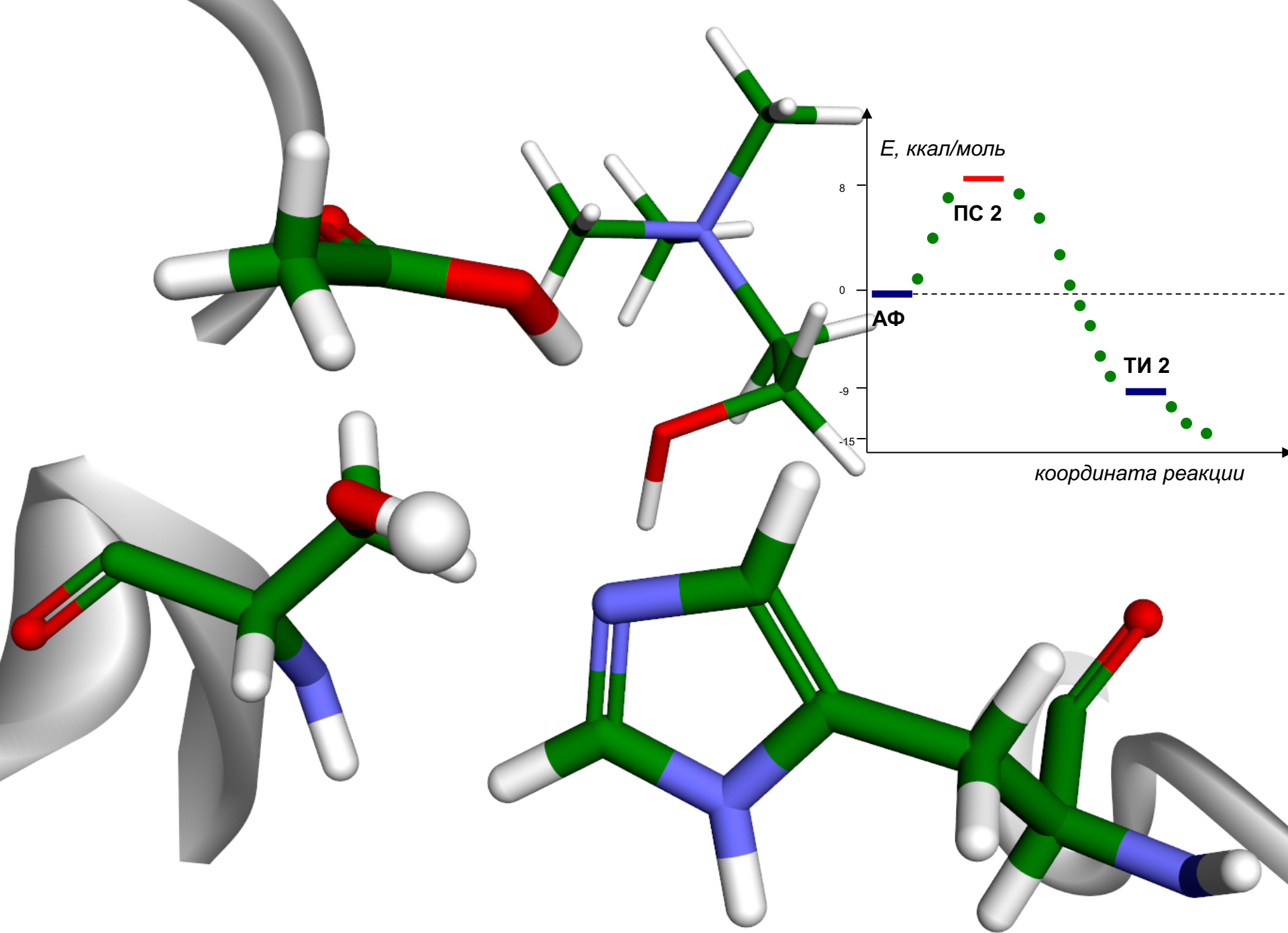
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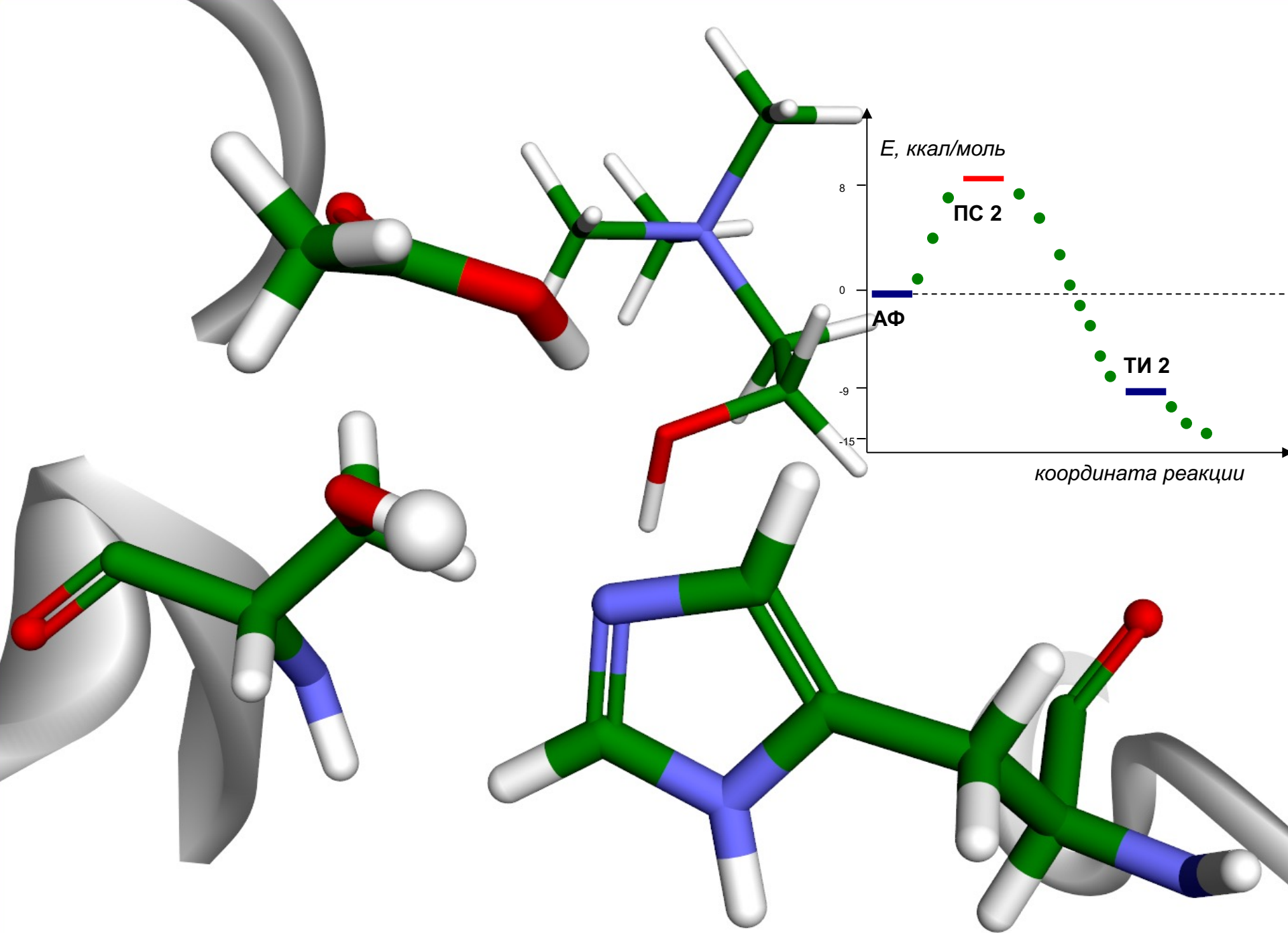
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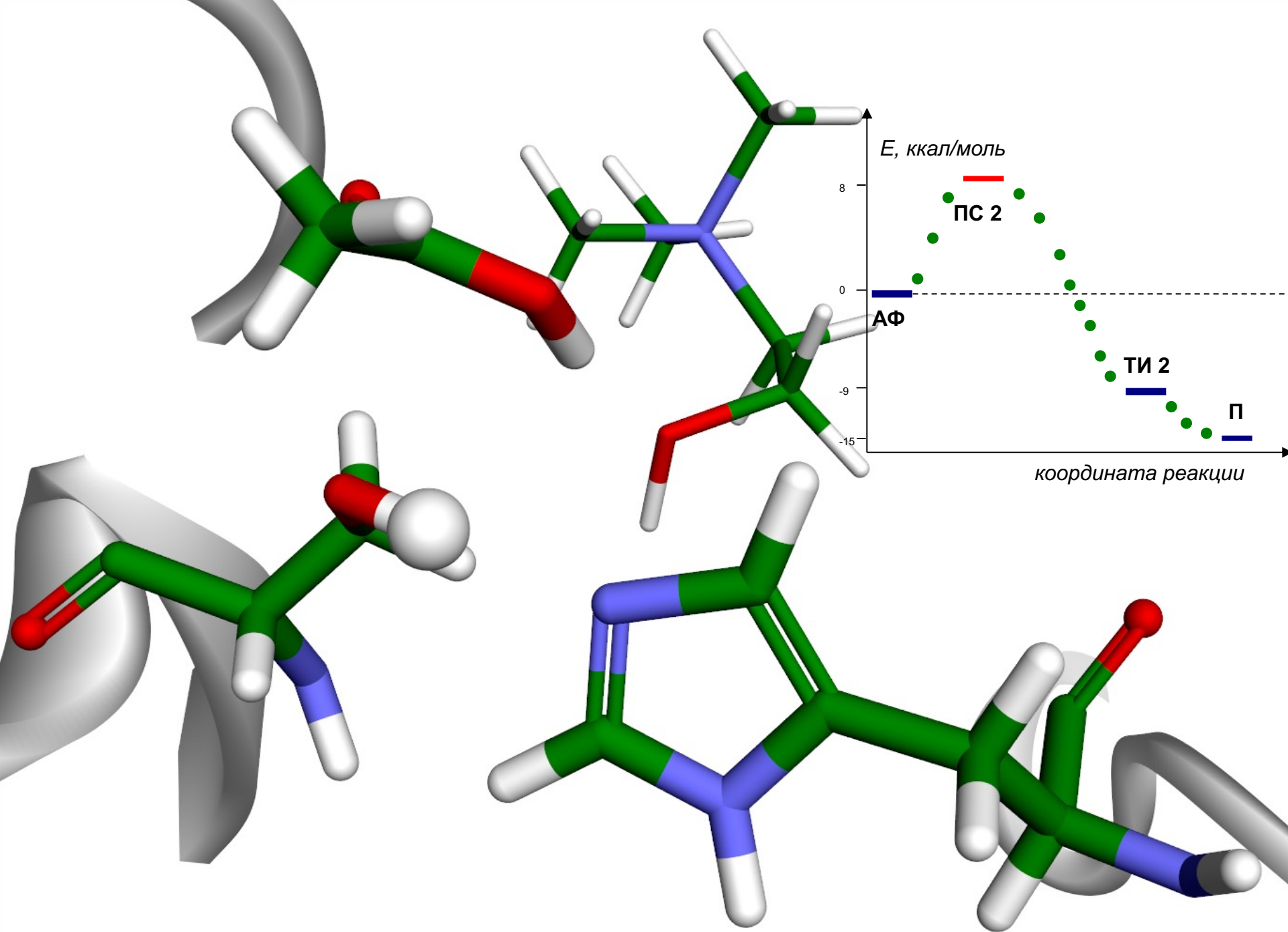
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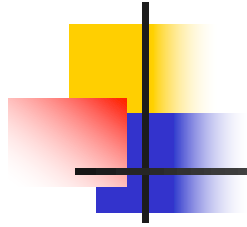
ТИ 2

координата реакции



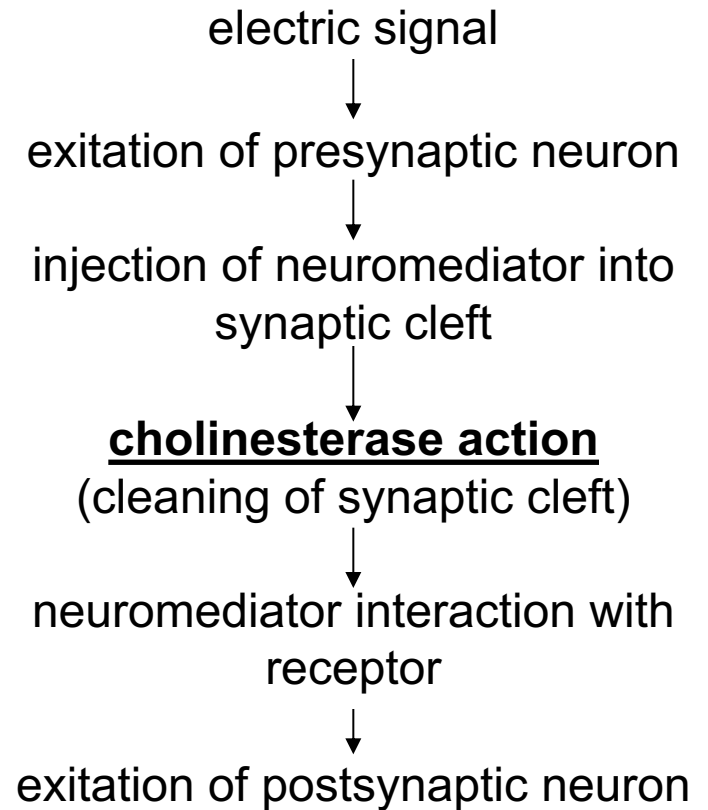
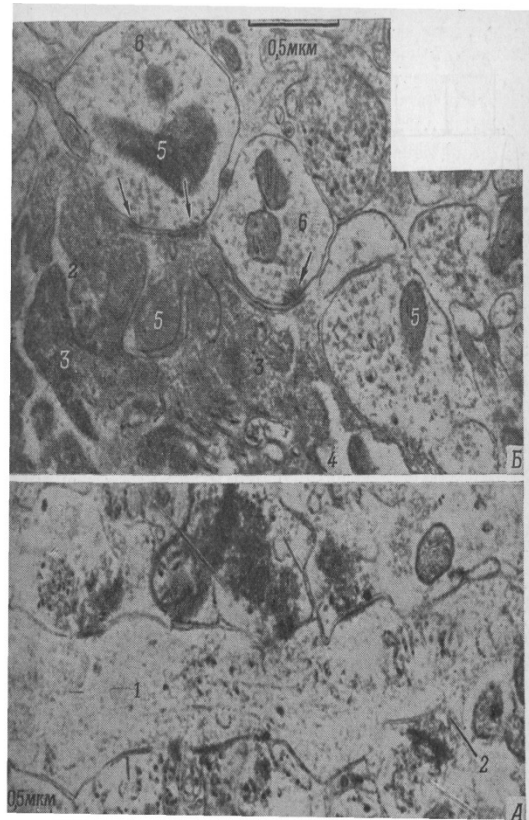
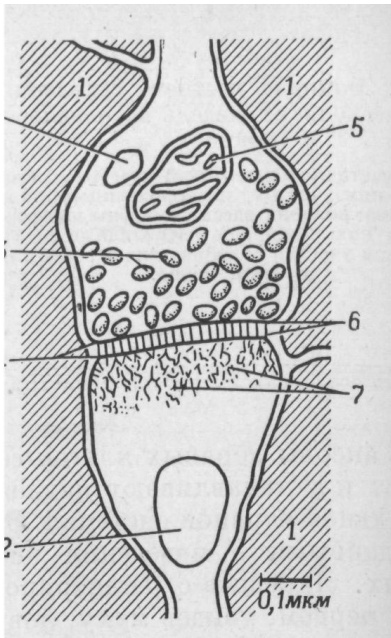




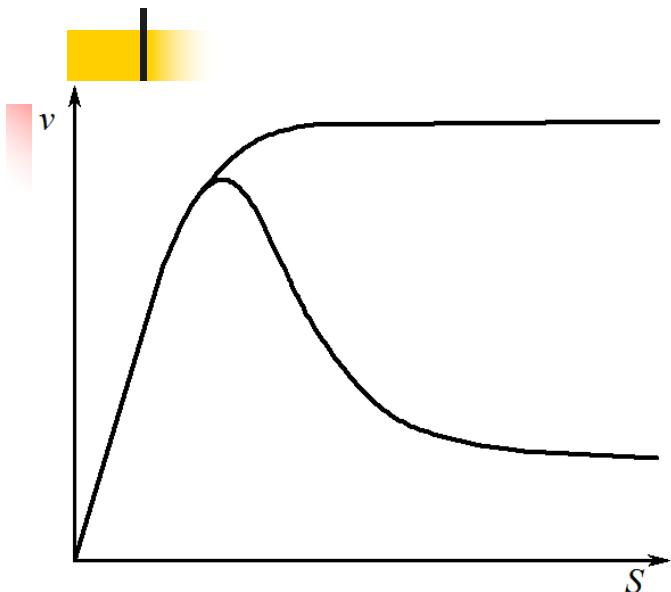


How Matter Becomes Consciousness

Synapse – “Chemical Semiconductor” in Neuronet



Protonic (H⁺) mechanism of synapse conductivity fixation in memory process



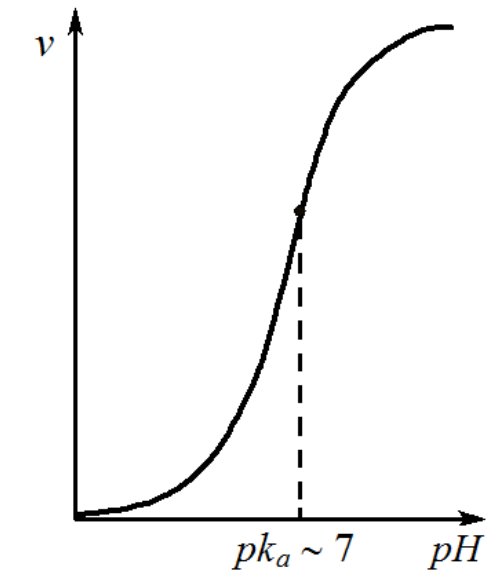
$$v([S]) = \frac{V_m[S]}{K_m + [S]}$$

Kinetics of acetylcholinesterase catalysis

$$v([S]) = \frac{V_m[S]}{K_m + [S] + [S]^2 / K_i}$$

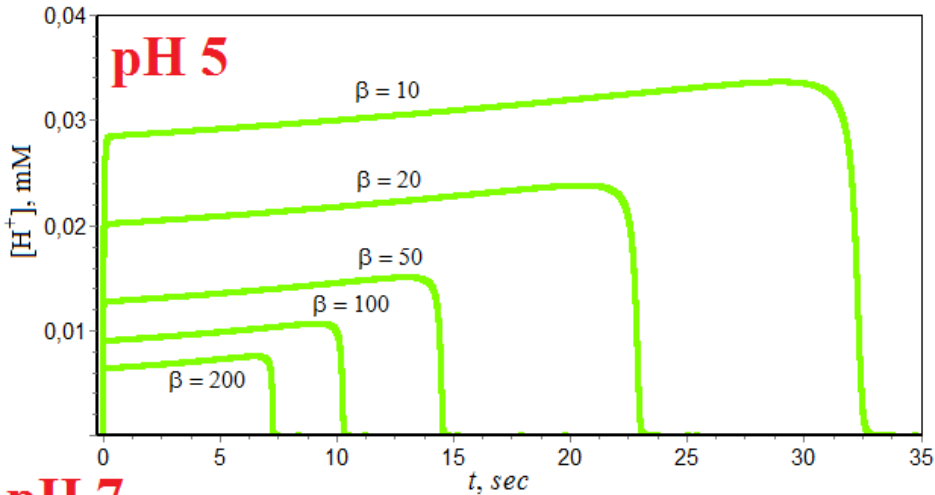
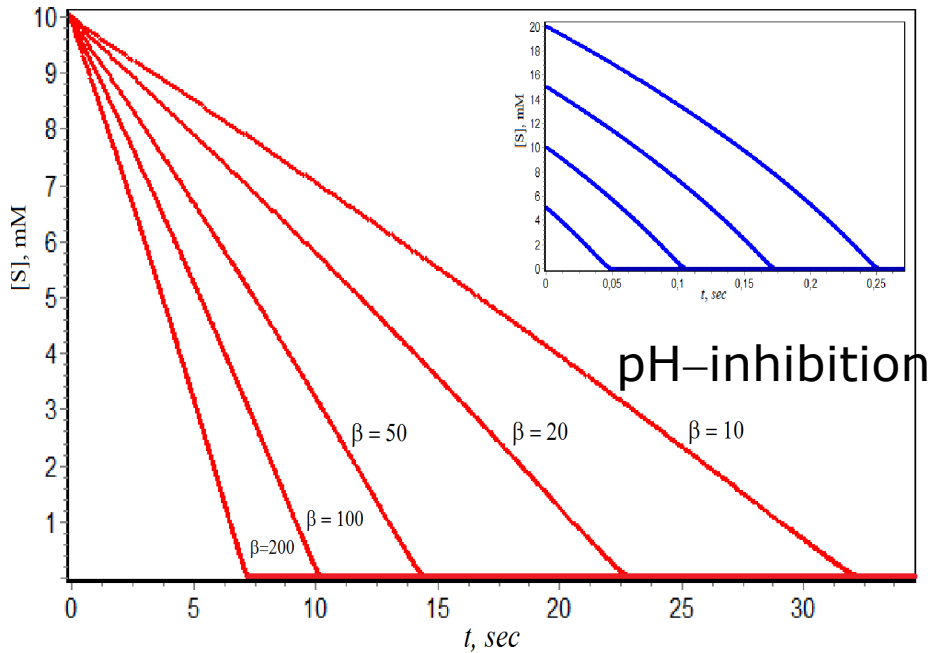
$$v([S]) = \frac{V_m[S]}{\left(1 + \frac{H^+}{K_a}\right) \left(K_m + [S] + [S]^2 / K_i\right)}$$

pH 7,5 → pH 4



Blocking of catalytic activity

pH-jump in acetylcholinesterase memory synapse

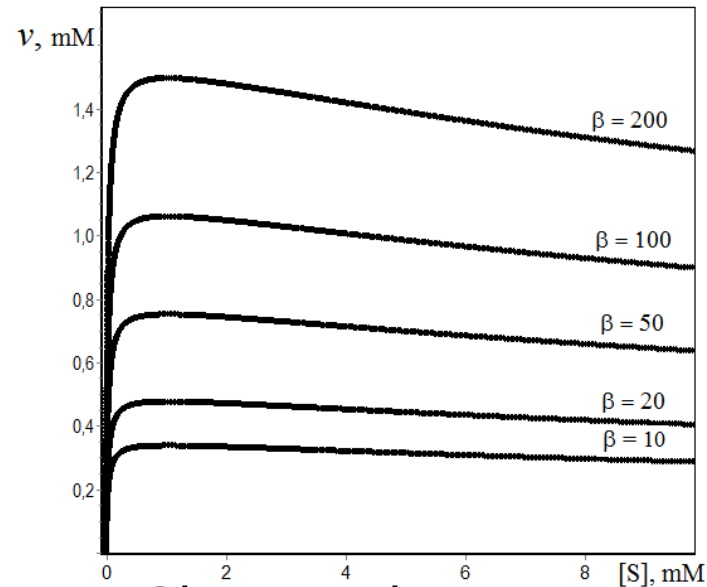


pH 7

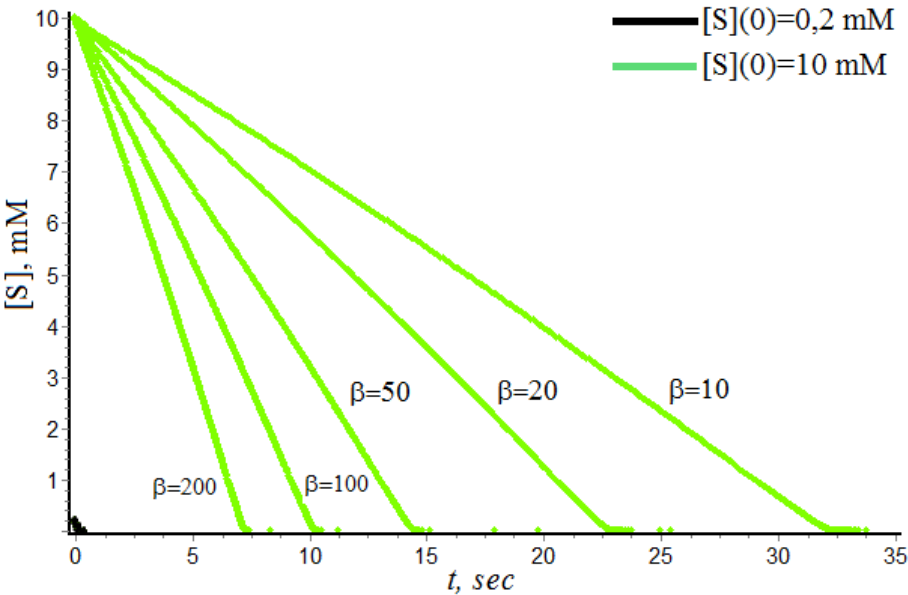
$$v([S],[H^+]) = \frac{V_m[S]}{\left(1 + \frac{[H^+]}{K_a}\right) \left(K_m + [S] + [S]^2 / K_i\right)}$$

$$\frac{d[S]}{dt} = -v([S],[H^+]),$$

$$\frac{d[H^+]}{dt} = v([S],[H^+]) - \beta \cdot [H^+].$$



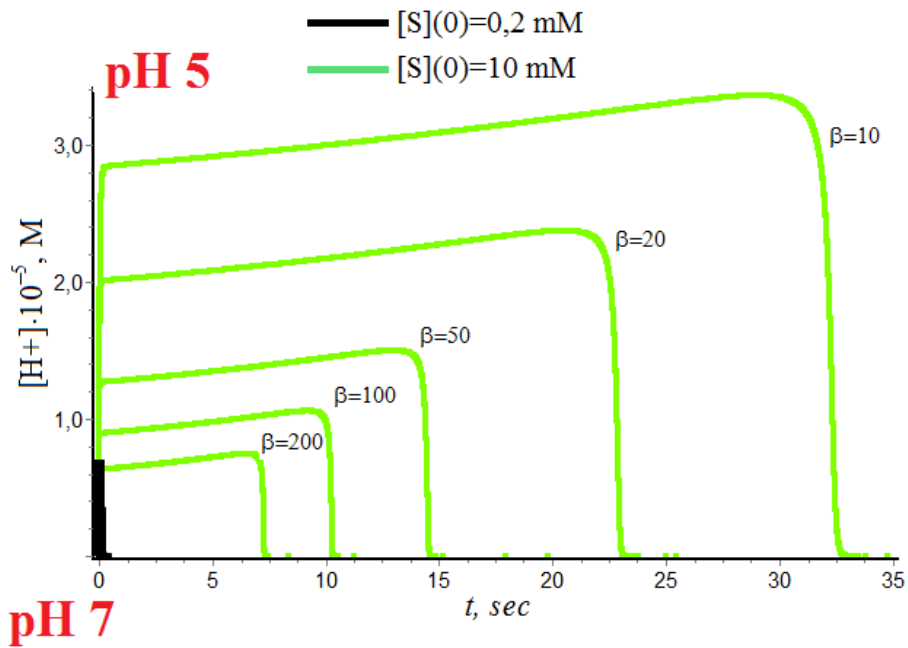
pH-jump in acetylcholinesterase memory synapse



$$v([S],[H^+]) = \frac{V_m[S]}{\left(1 + \frac{[H^+]}{K_a}\right)(K_m + [S] + [S]^2/K_i)}$$

$$\frac{d[S]}{dt} = -v([S],[H^+]),$$

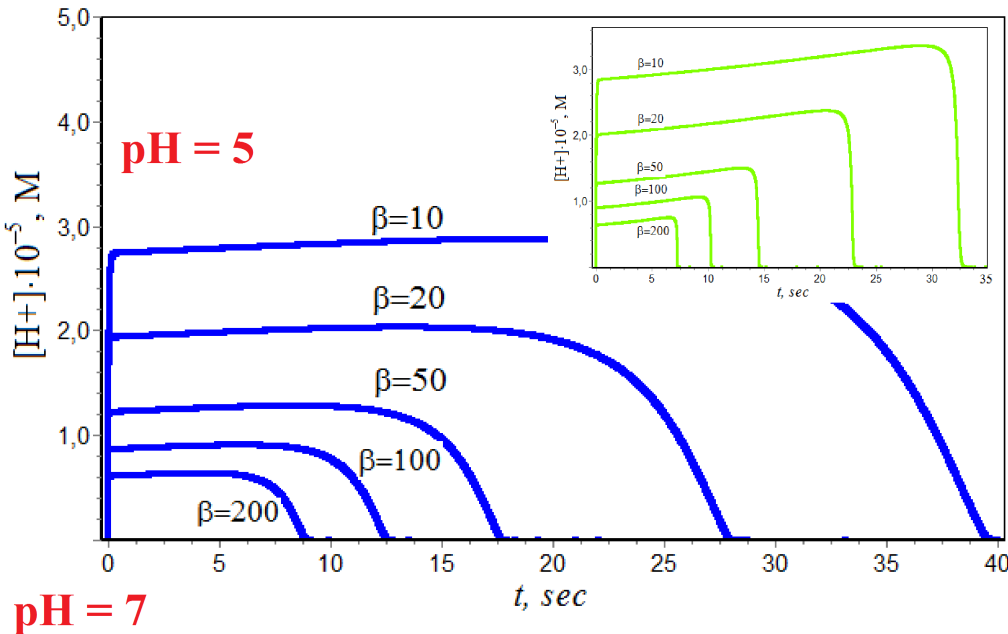
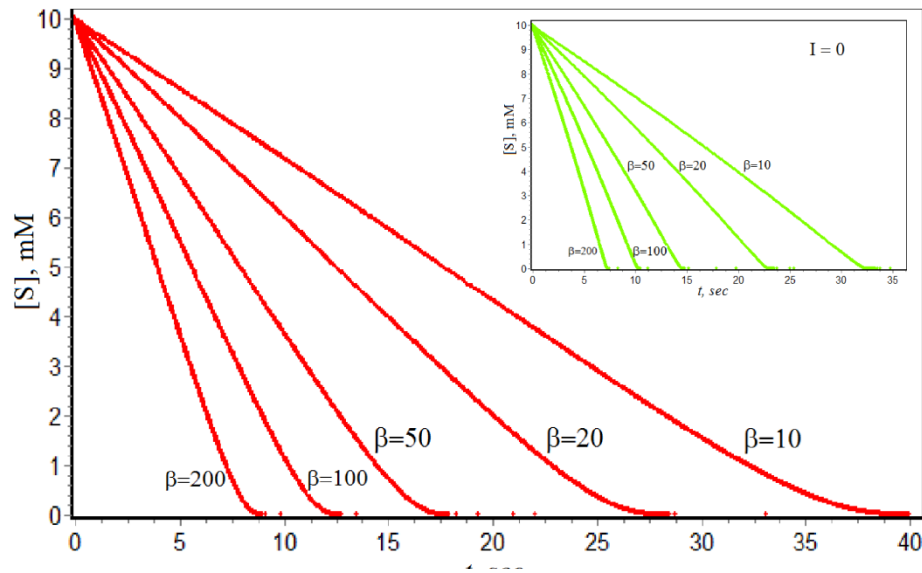
$$\frac{d[H^+]}{dt} = v([S],[H^+]) - \beta \cdot [H^+].$$



S. D. Varfolomeev, V.I. Bykov,
S.B. Tsybenova

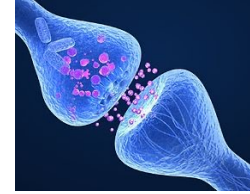
Rivastigmine prolongs acetylcholine in synaptic cleft

$$v([S],[H^+]) = \frac{V_m[S]}{\left(1 + \frac{[H^+]}{K_a}\right) \cdot \left(K_m \left(1 + \frac{I}{K'_I}\right) + [S] + [S]^2 / K_i\right)}$$



S. D. Varfolomeev, V.I. Bykov,
S.B. Tsybenova

Nerve agents and antidotes



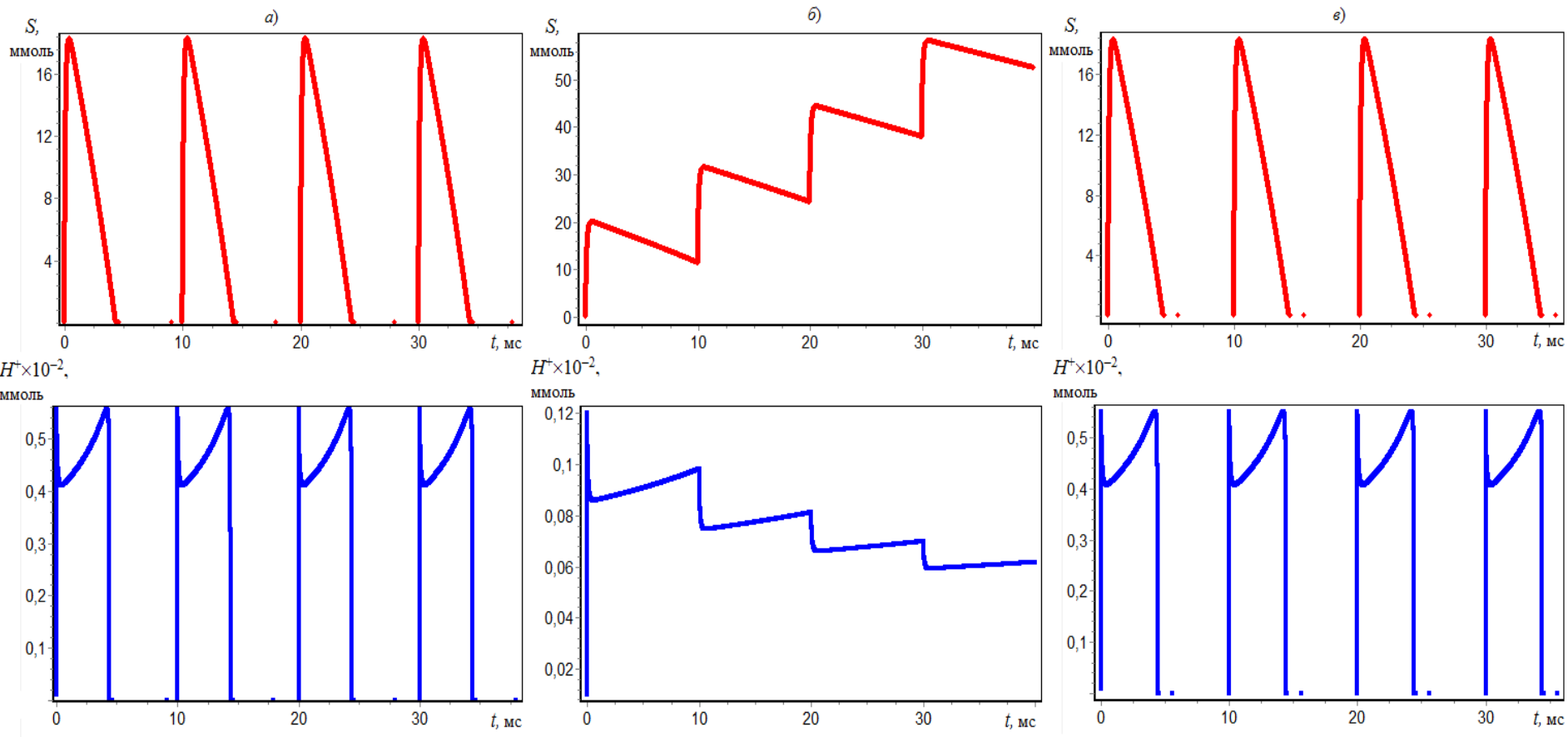
The cholinergic synapse.
Mechanisms of functioning
and control methods

(sarin, soman, VX, pesticides)

(atropine, oximes)

$$E(t) = E_0 e^{-t/\tau_{in}},$$

$$E(t) = E_0 (1 - e^{-t/\tau_r}),$$

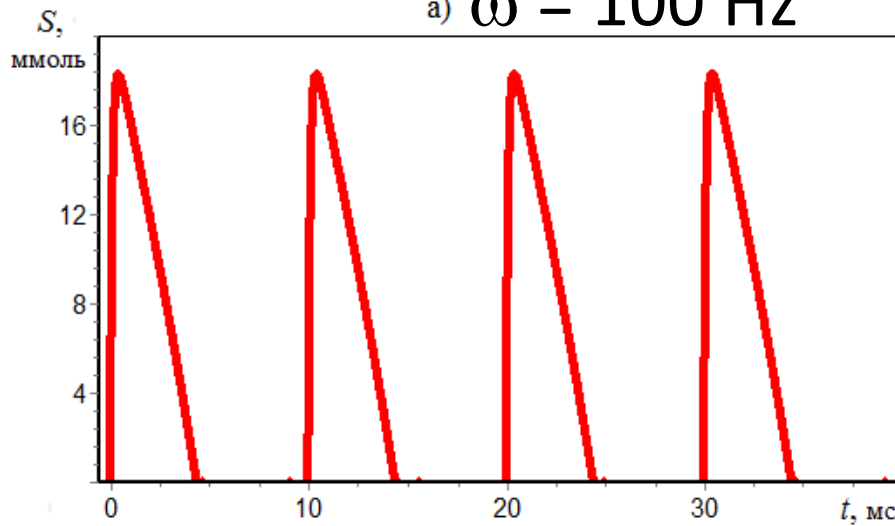


STROKE. Neuromuscular paralysis

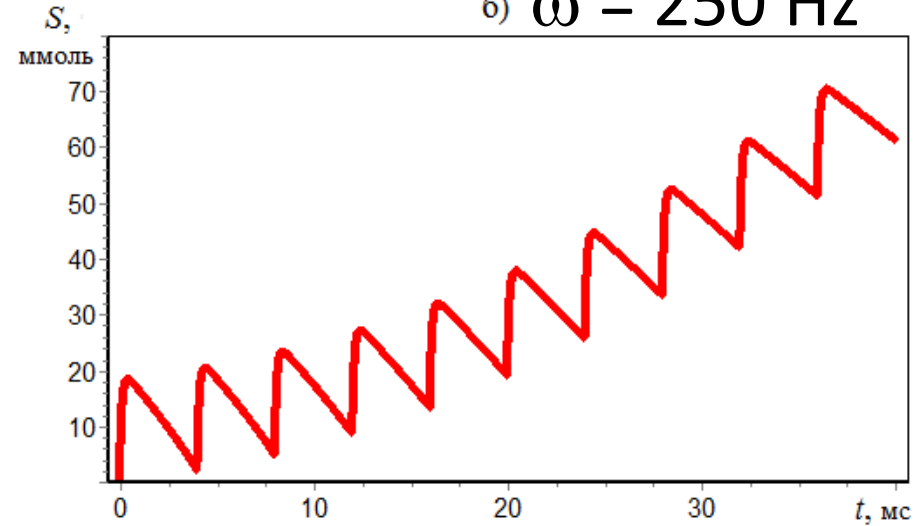


The cholinergic synapse.
Mechanisms of functioning
and control methods

a) $\omega = 100$ Hz

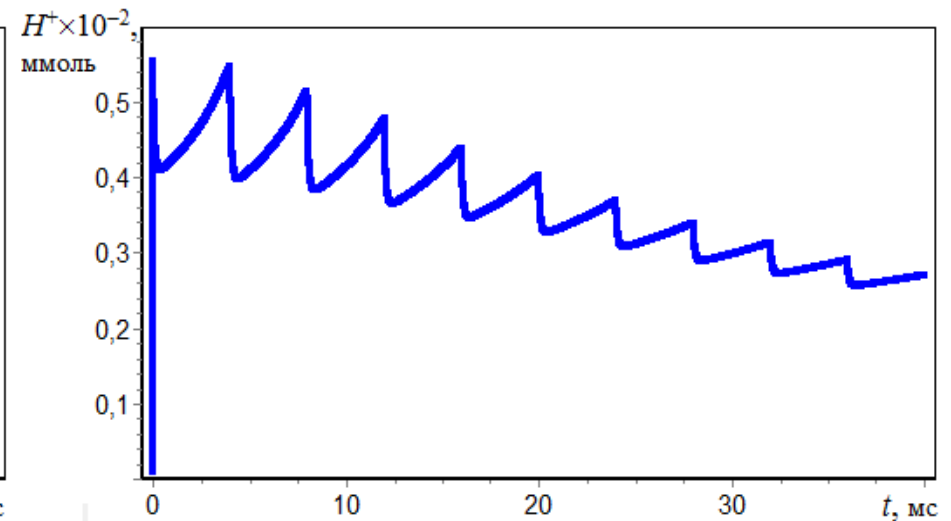
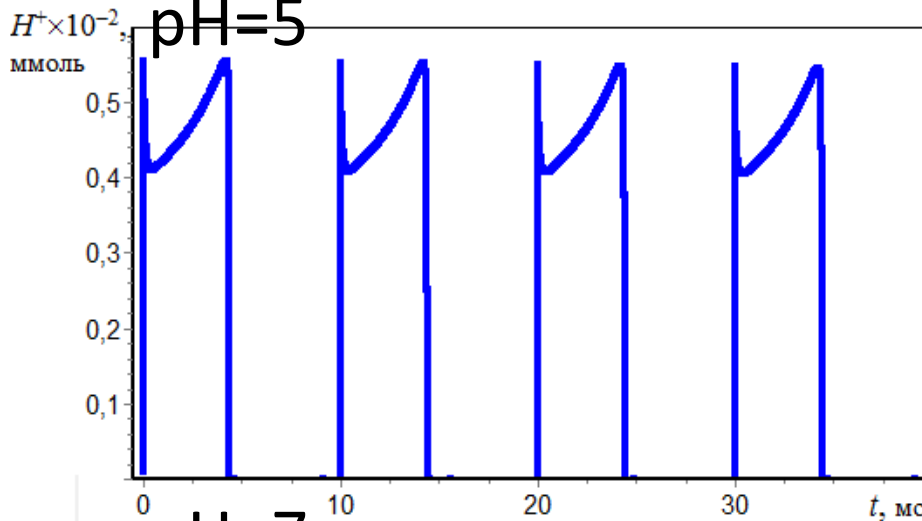


b) $\omega = 250$ Hz

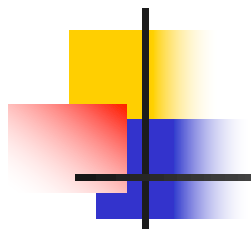


$H^+ \times 10^{-2}$
mmol

pH=5

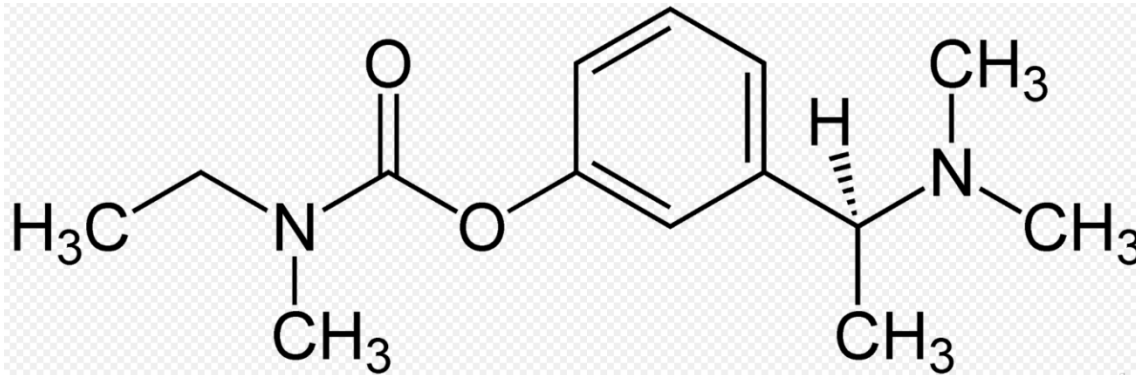


pH=7



Alzheimer disease

Substrates-inhibitors – drugs against Alzheimer disease



Inhibition of acetylcholine
esterase

Increasing of
acetylcholine
level

Increasing of
cognitive ability

Nature of neurological memory

Neuron-Synaps System Theory

Synaps-

“chemical semiconductor”,

shut or **open** state

Real volume of memory

$I = 10 \exp 9$ bites

Volume of memory

$I = \log N$, N-number of possible states of system, m-number of neurons, n-number of synapses per neuron

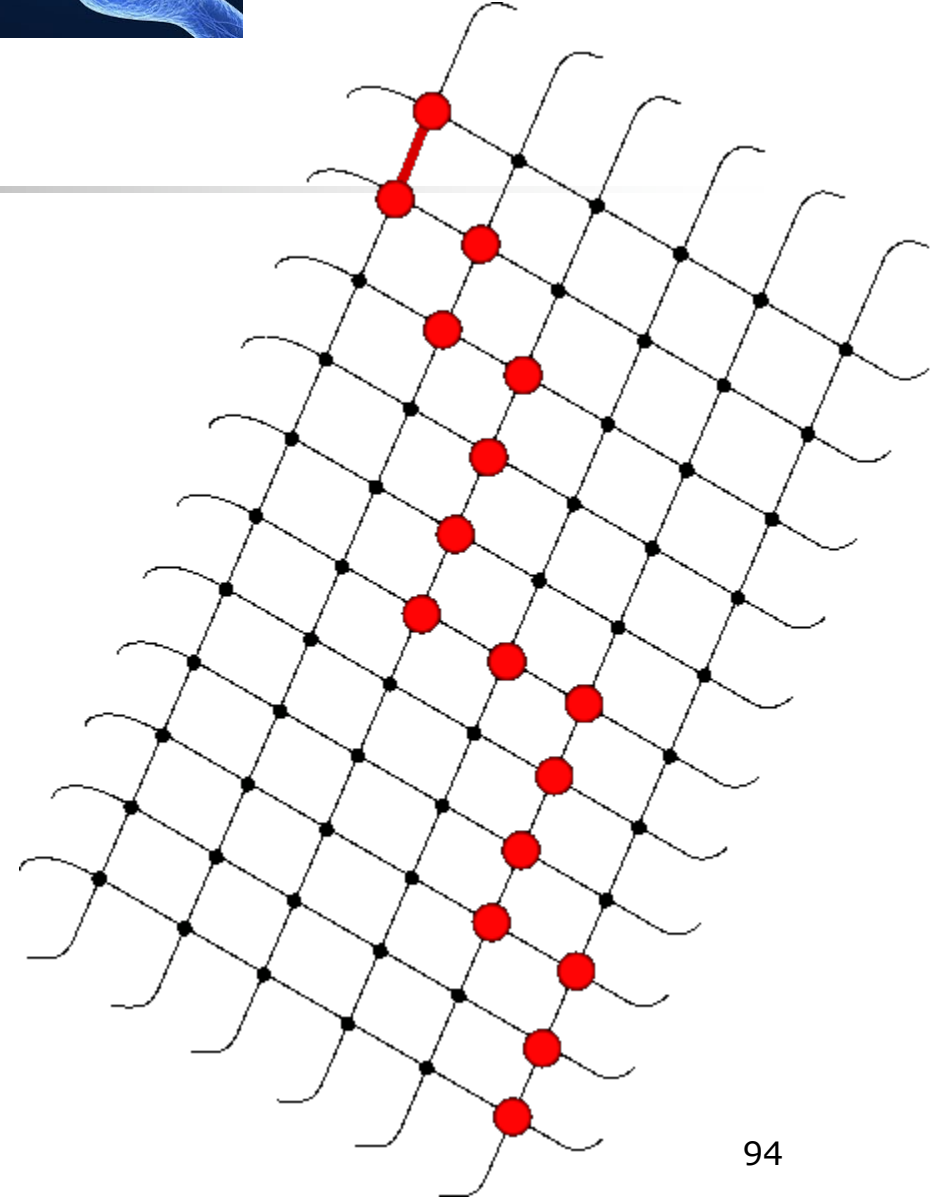
$I = \log n \exp m = 10 \exp 10$ bites

Memory reflex in the brain – three dimension “tree” of connected **shut** and **open** synapses, the way of memory signal transfer, the “tree” of excited neurons

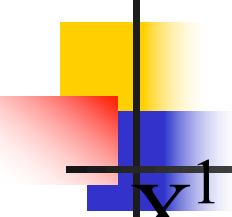
Neurological memory. Proton mechanism of information recording and storage



The cholinergic synapse.
Mechanisms of functioning
and control methods



Neurological memory



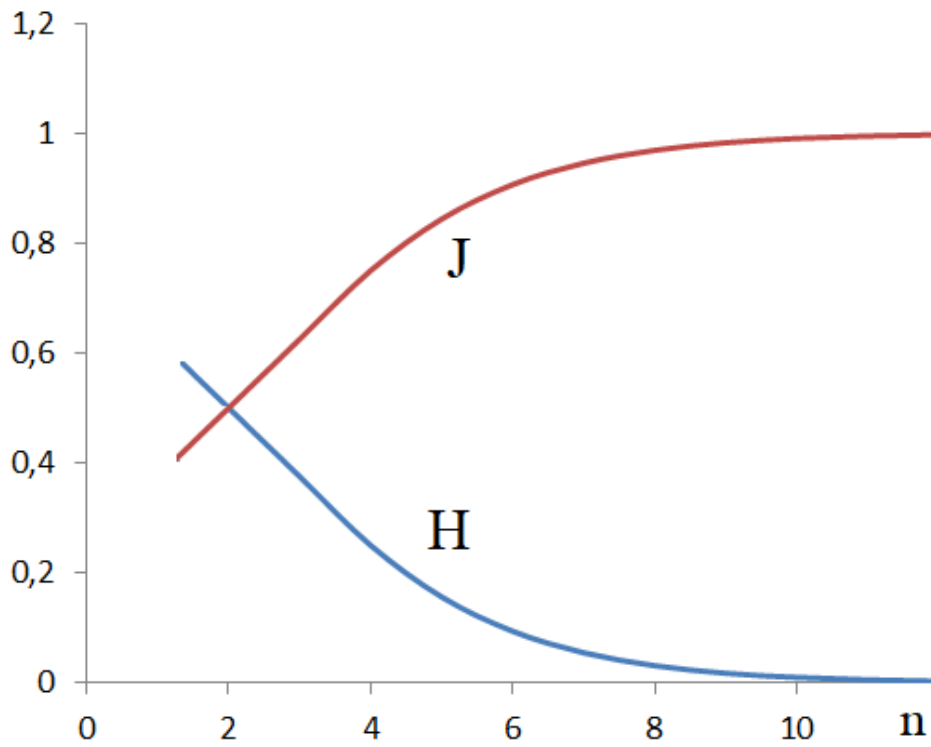
$X_1^1 X_2^0 X_3^0 X_4^1 \dots$

X_i^1 – signal conducting synapse (proton-blocking of acetylcholinesterase in the synaptic cleft)

X_j^0 – signal non-conductive synapse (active acetylcholinesterase in the synaptic cleft)

Neurological memory

Volumes of information recording:
the capabilities of signal conducting synaptic
circuits of different lengths(n)

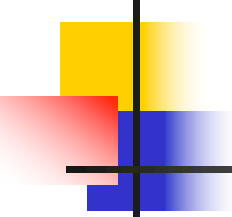


To record 1 bit of information, it is enough a signal conducting synaptic circuit with a length of 8-10 synapses



Consciousness:

sensory signals – sensory information
processing – neuromemory – learning
– cognitive functions – idea generation



Система глутаматных
синапсов-молекулярная основа
возбуждения, процессинга
информации, участник всех
нейропатологий

Глутамат–NAAG синапс

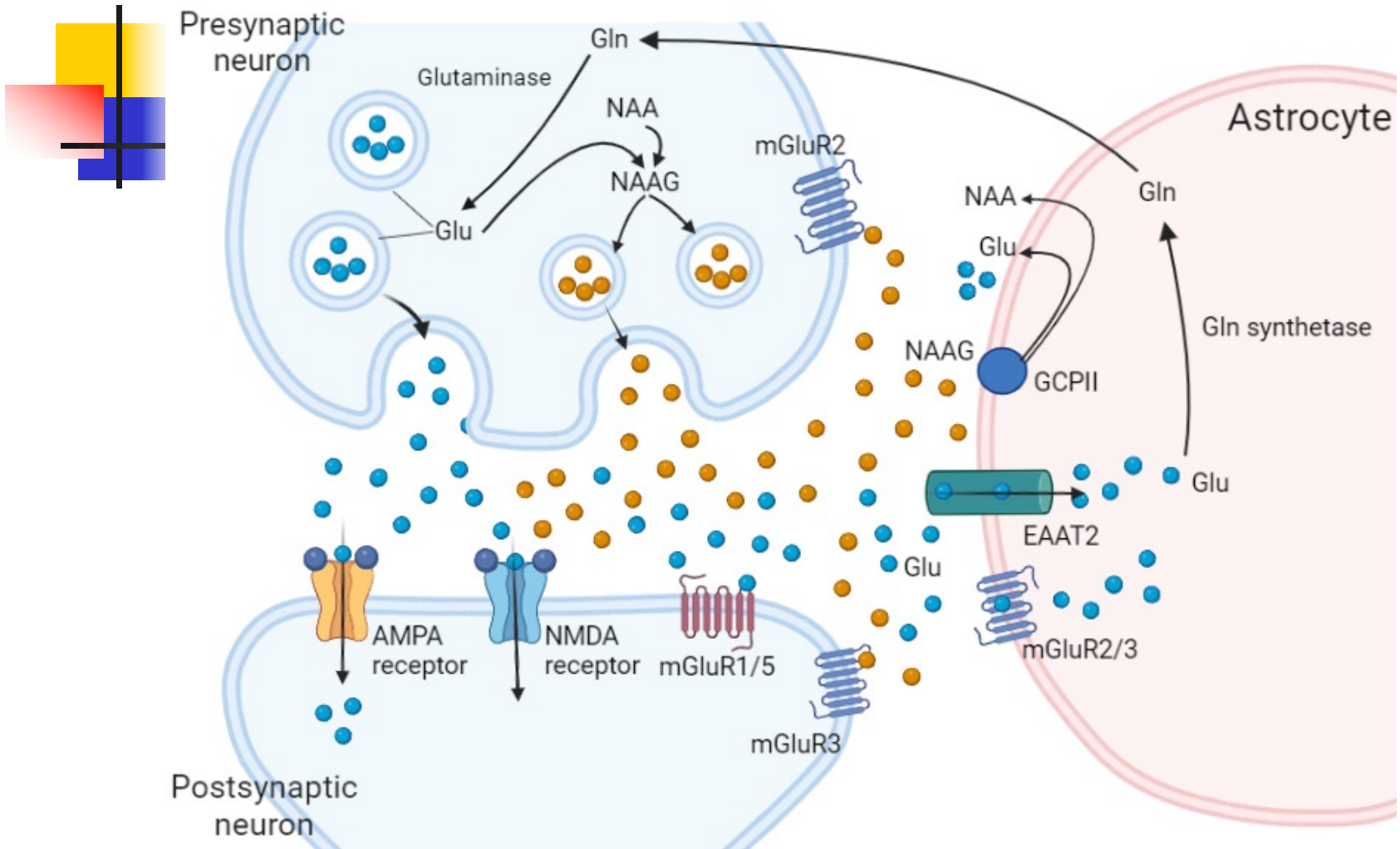


Схема функционирования глутамат-астроцитарной системы

Кинетическая модель

$$\frac{d\text{Glu}}{dt} = \left(a_1(\text{Glu}_0) \cdot e^{-\alpha_1 t} - \beta \cdot \text{Glu} + \frac{V_m \text{NAAG}}{K_m + \text{NAAG}} + \chi_1 \cdot D \right) \cdot N. \quad (1)$$

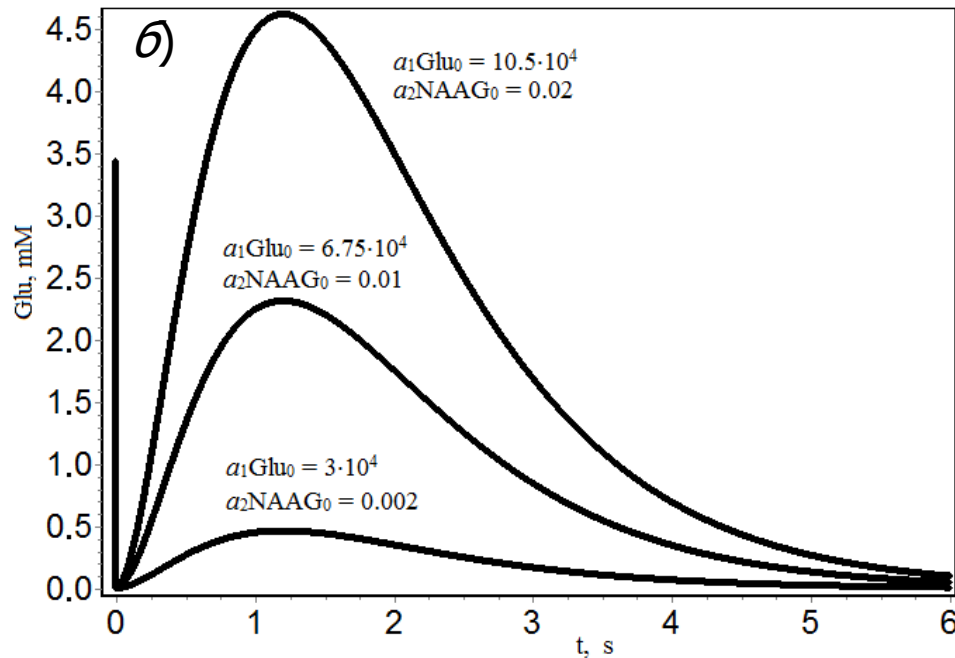
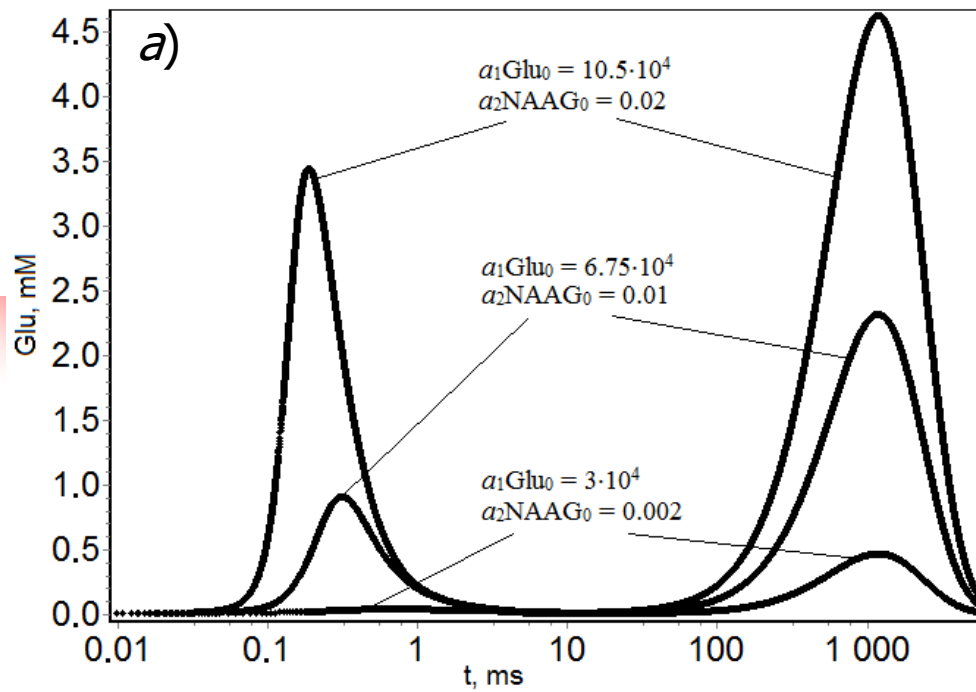
$$\frac{d\text{NAAG}}{dt} = a_2(\text{NAAG}_0) \cdot e^{-\alpha_2 t} - \delta \text{NAAG} - \frac{V_m \text{NAAG}}{K_m + \text{NAAG}} + \omega \cdot \text{Glu}. \quad (2)$$

$$\frac{dD}{dt} = \xi \frac{R_2 \text{NAAG}}{K_2 + \text{NAAG}} - \lambda D. \quad (3)$$

$$N = \varphi \text{Glu} + \chi_2 \text{NAAG}. \quad (4)$$

$$\frac{d\text{NAA}}{dt} = v + \frac{V_m \text{NAAG}}{K_m + \text{NAAG}} - \frac{V_{ma} (\text{NAA})^3}{K_{ma} + (\text{NAA})^4} - \rho \cdot \text{NAA}; \quad (5)$$

Glu – концентрация глутаминовой кислоты, NAAG – концентрация нейротрансмиттера NAAG, NAA - концентрация N-ацетиласпарагиновой кислоты, D – концентрация продуктов функционирования метаболитных рецепторов, N – число возбужденных (проводящих сигнал) нейронов



Двухфазный характер ответа, система амплификации возбуждения

Рис.2. Двухфазный характер функционирования глутаматергической нейронально-астроцитарной системы (1)–(5).

a) – логарифмическая шкала в миллисекундах

б) – арифметическая шкала в секундах

Механизмы управления когнитивностью

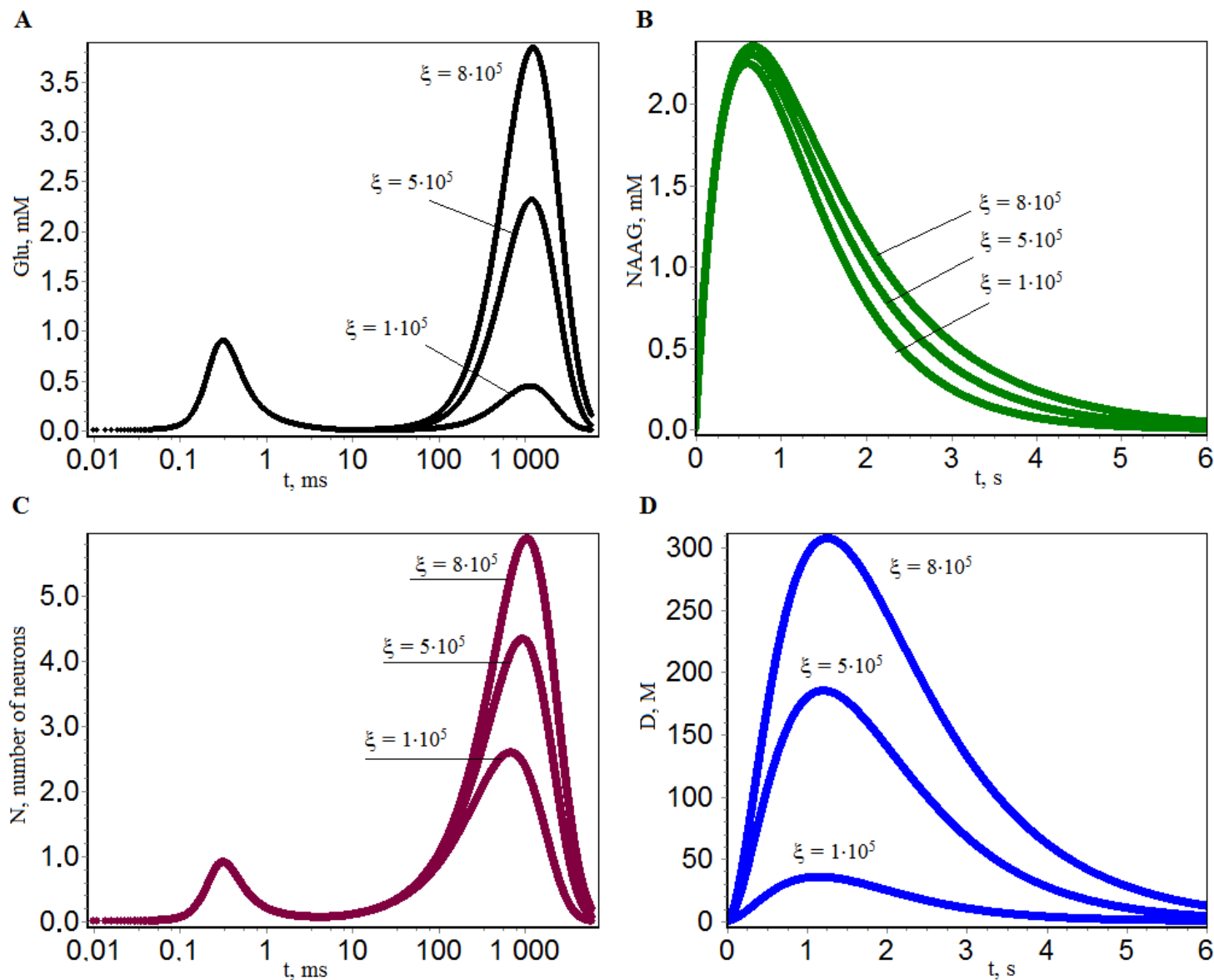


Рис. 3. Динамический ответ системы по Glu (A), NAAG (B), D (D) и числа возбужденных клеток N (C) при вариации параметра ξ , характеризующего эффективность действия метаботропного рецептора mGluR3.

Управление процессом гидролиза NAAG

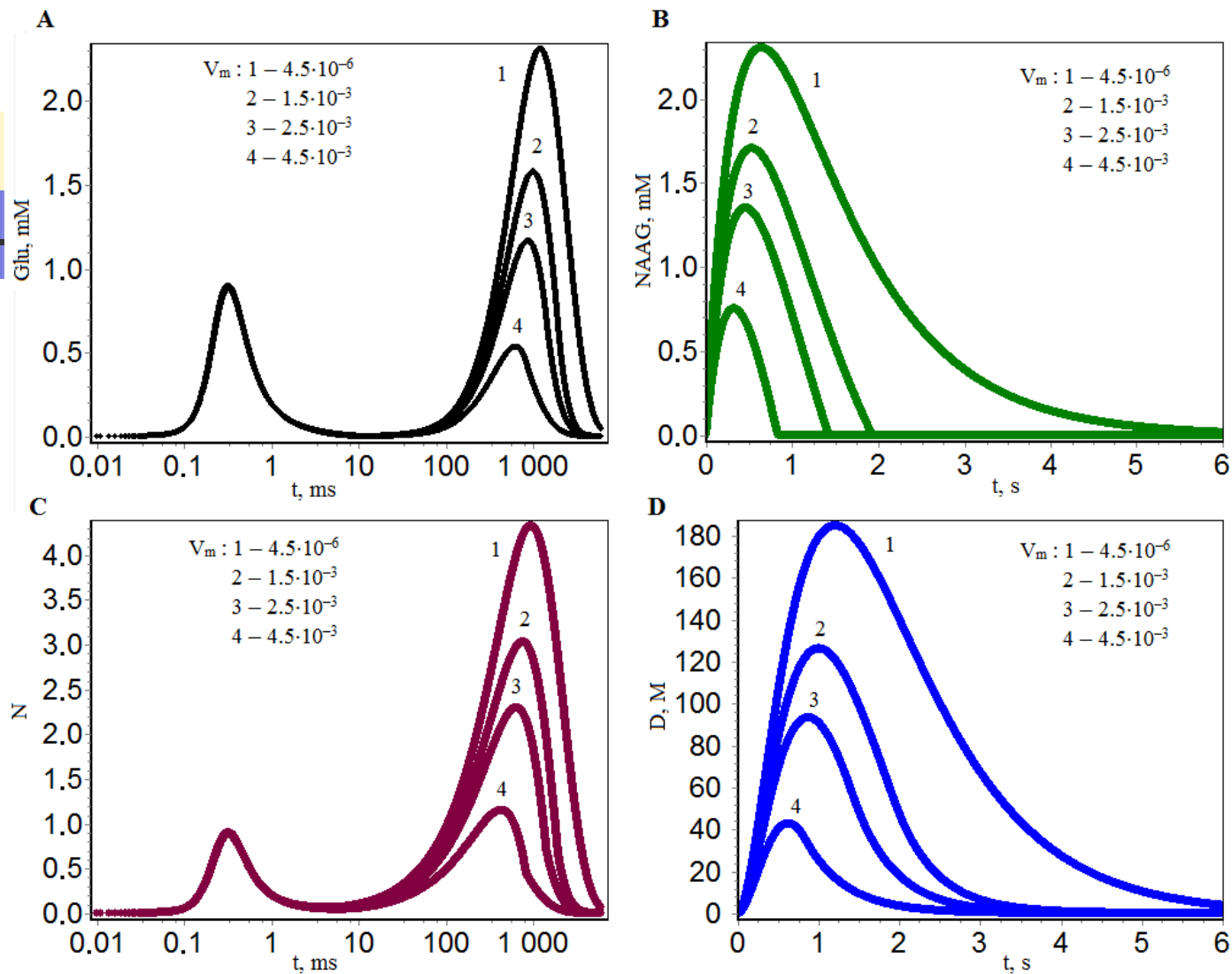
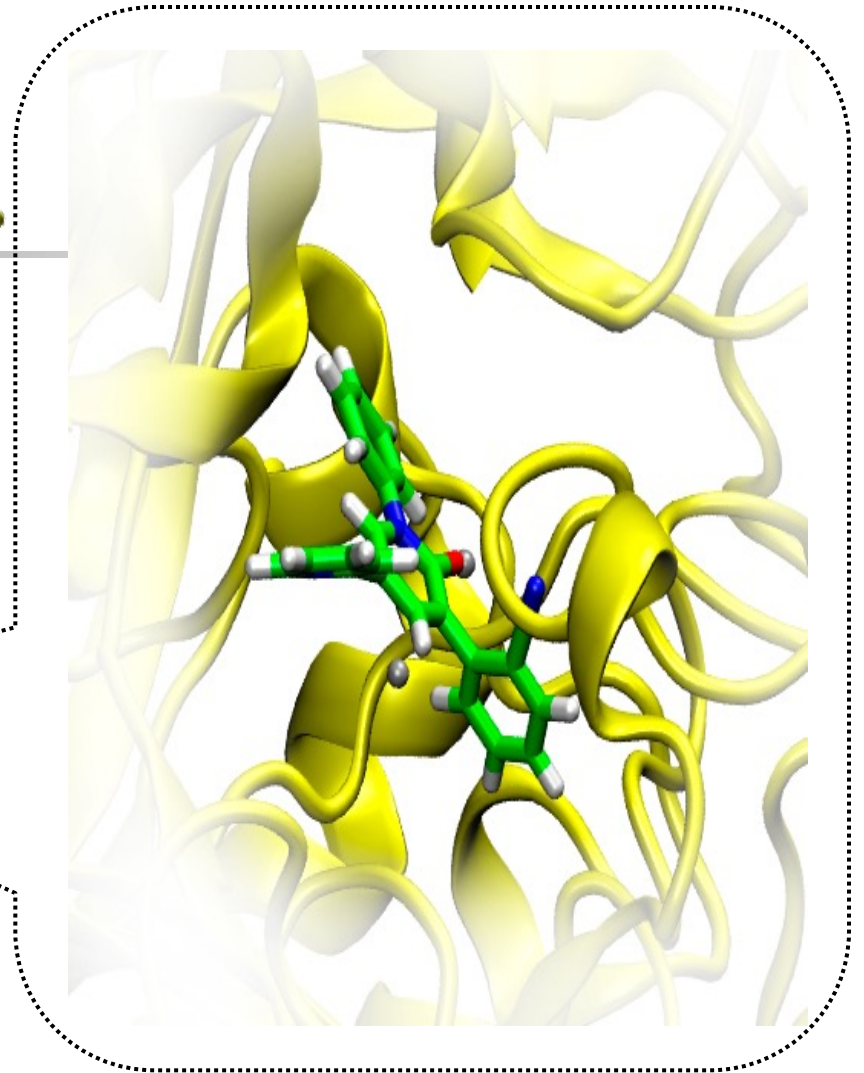
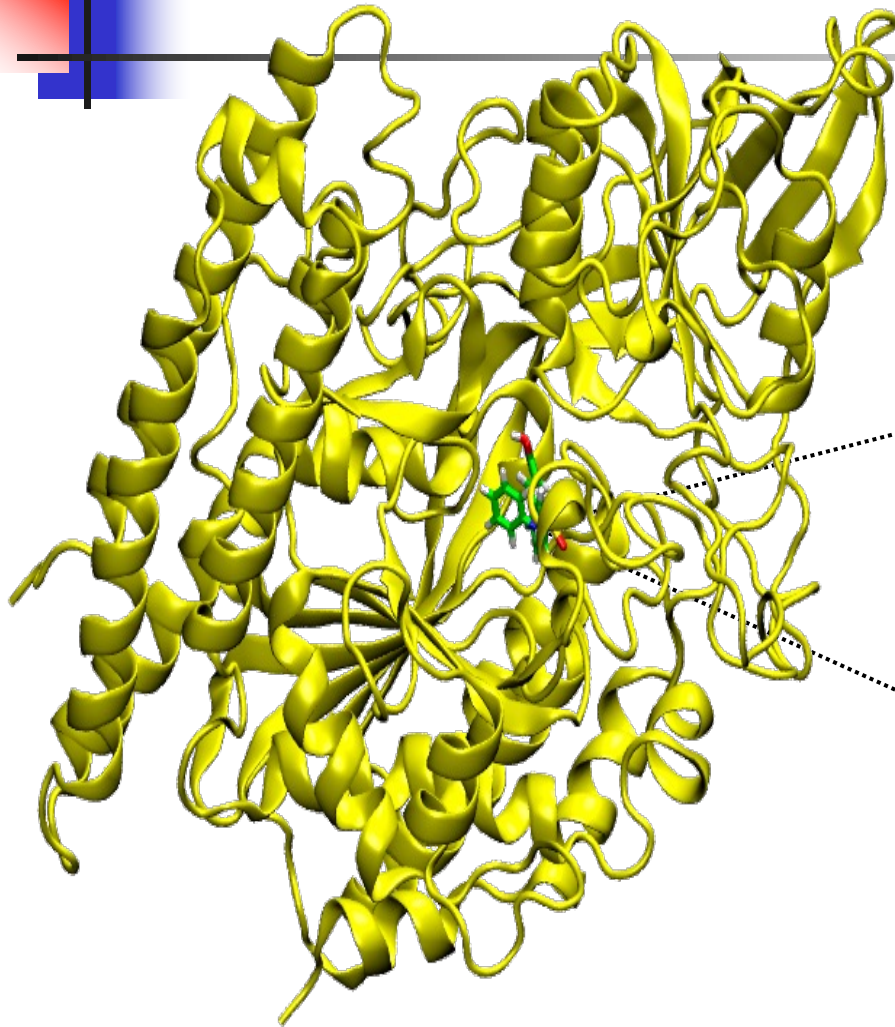
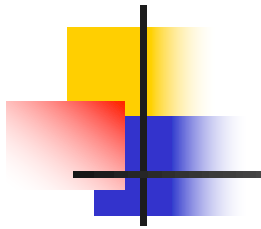
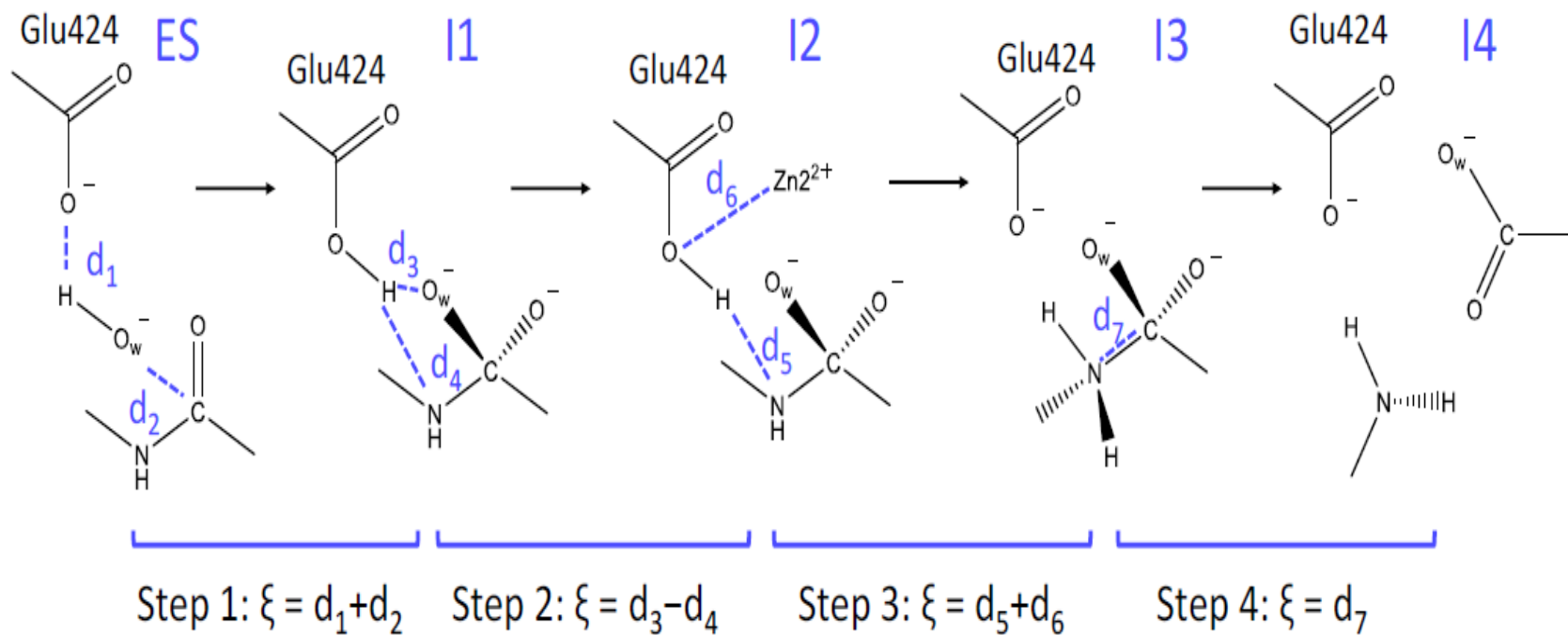
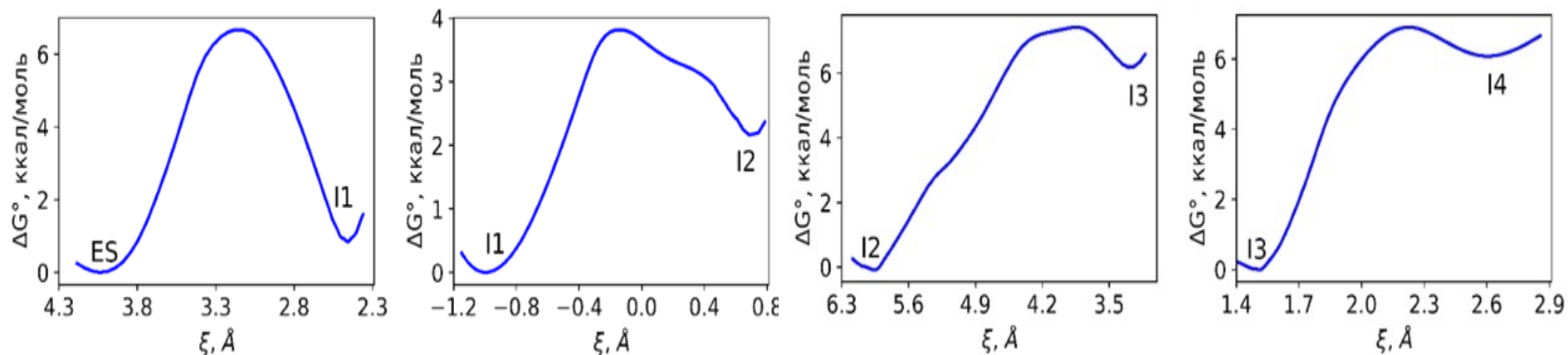


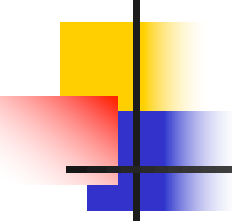
Рис.4. Влияние активности GCPII на динамические ответы глутаматергической системы. **При варьировании максимальной скорости гидролиза (V_m) NAAG под действием GCPII может быть реализовано за счет ингибирования фермента или уровня его экспрессии.**

GCPII

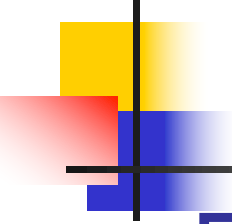


Механизм гидролиза НААГ





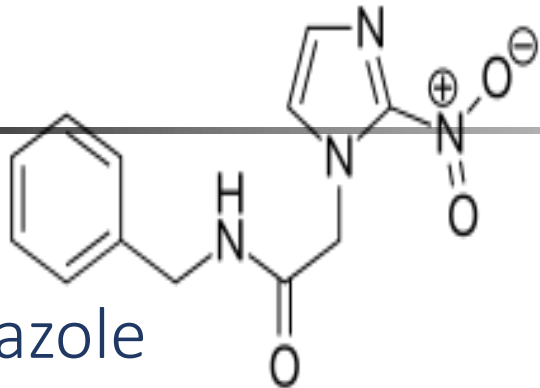
Ингибиторы
глутаматкарбоксипептидазы
мозга – стимуляторы
КОГНИТИВНЫХ функций



Докинг и молекулярная
динамика всех применяемых в
мире лекарств как
потенциальных ингибиторов
глутаматкарбоксипептидазы
мозга человека

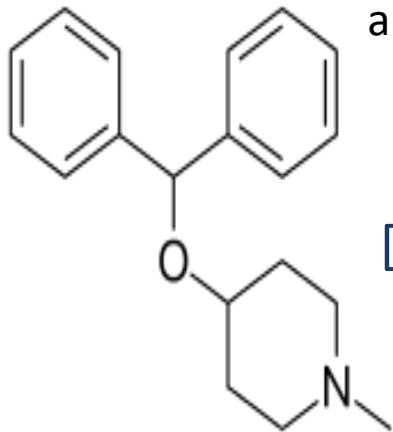
Предполагаемые ингибиторы

Лекарственные препараты одобренные FDA на 2016 год



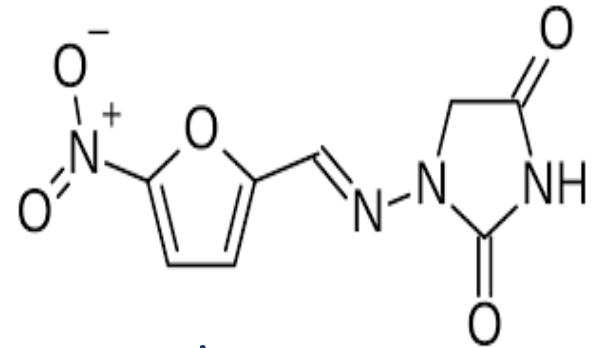
Benznidazole

Противопаразитарное лекарство, используемое при лечении болезни Шагаса. Трипаноцидный агент.



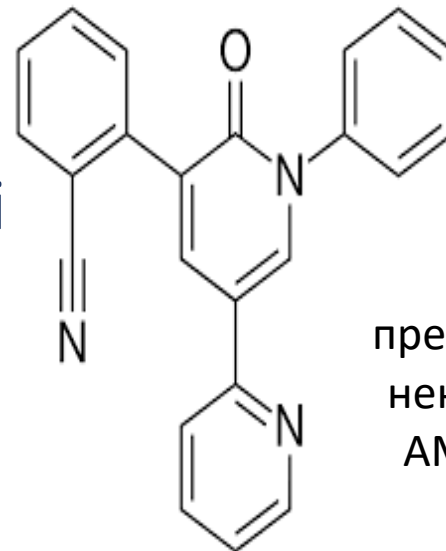
Diphenylpyrali

Представляет собой антигистаминный препарат первого поколения с антихолинергическими



Nitrofurantoin

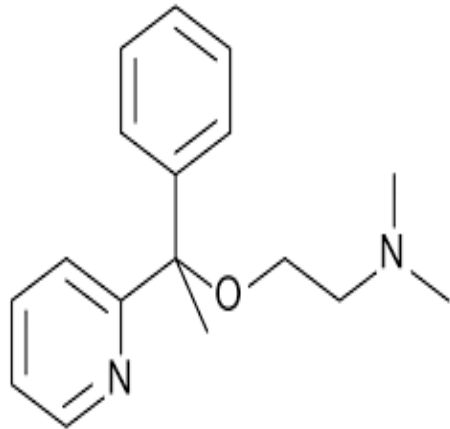
Противомикробное действие, производное нитрофуранов. Нарушает синтез ДНК и РНК, белков, в бактериях и в клеточной мембраны.



Perampanel

Противоэпилептический препарат, является селективным неконкурентным антагонистом AMPA-рецепторов, основного подтипа ионотропных глутаматных рецепторов.

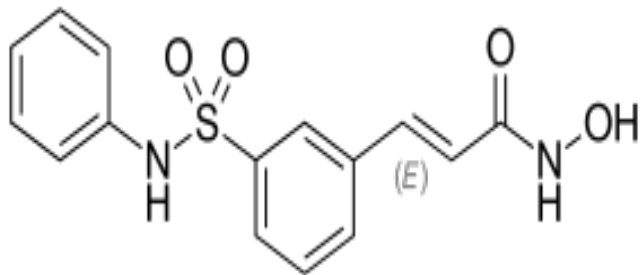
Doxylamine



Седативный антигистаминный препарат, обладающий сильным холинолитическим действием. Блокирует H1-гистаминовые рецепторы,

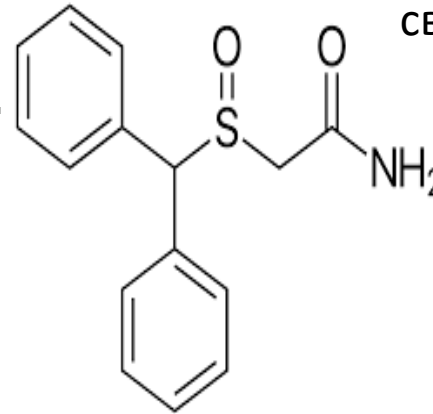
оказывает м-холиноблокирующее действие.

Belinostat



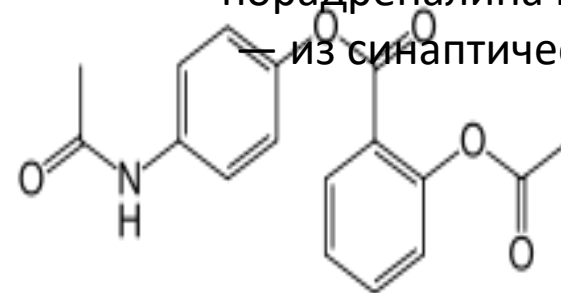
Лекарственный препарат, предназначенный для лечения периферической Т-клеточной лимфомы. Ингибирует

Modafinil




Аналептик, применяется для лечения сонливости, связанной с нарколепсией. Точный механизм или комплекс механизмов взаимодействия остаётся неясным. Вероятно, модафинил, подобно другим стимуляторам, увеличивает выброс

Benorilate



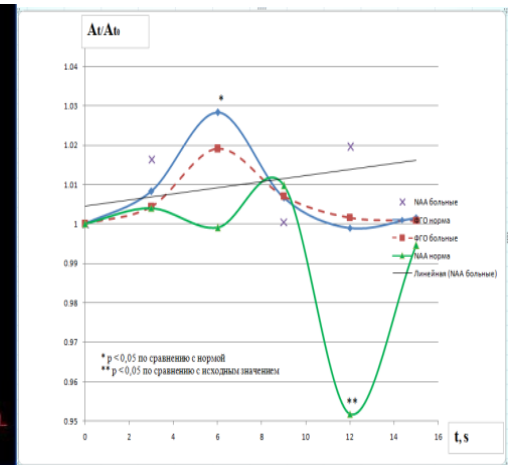
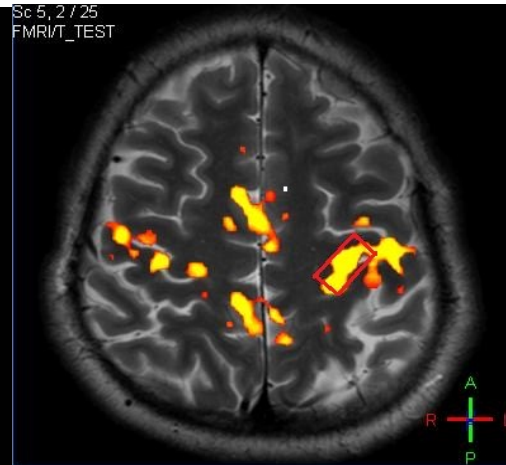
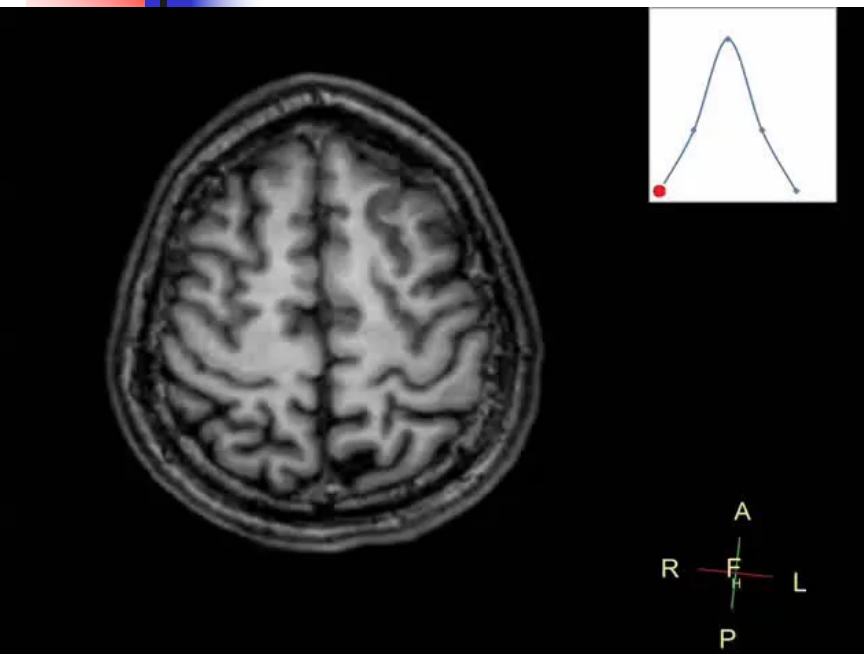
моноаминов — особенно, катехоламинов норадреналина и дофамина — из синаптических щелей.

Используется как противовоспалительное и жаропонижающее средство. Блокируют синтез простагландинов путем ингибирования циклооксигеназы, которая превращает арахидоновую кислоту в циклические



Энергообеспечение мозга как
компьютера –
нейроваскулярное сопряжение
– расширение
микрокапилляров зоны
возбуждения в ответ на
внешний сигнал

Functional magnet resonance tomography and spectroscopy

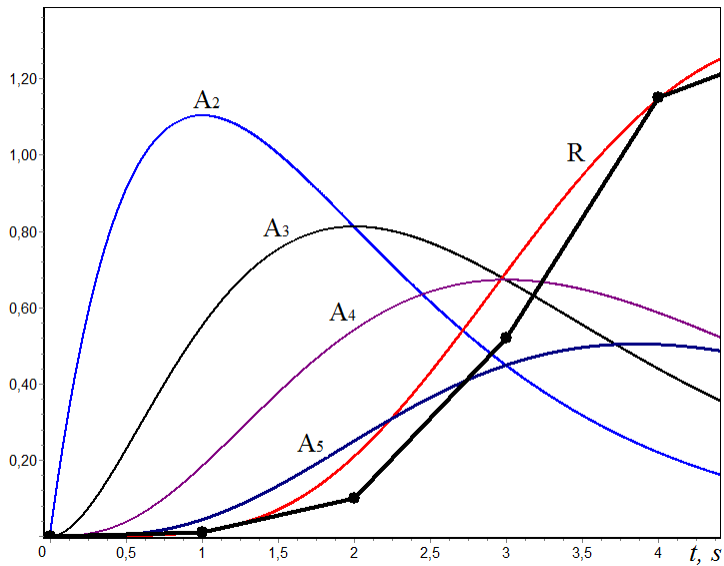
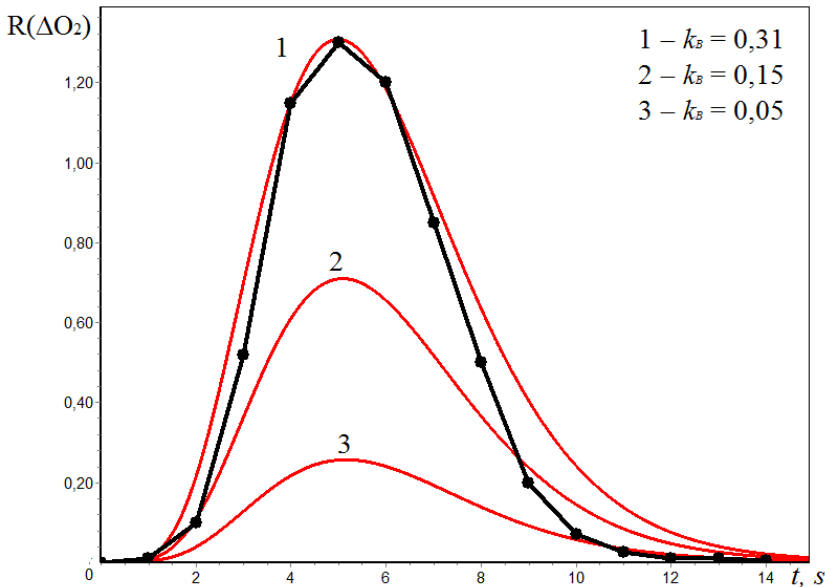


The activation zone in the premotor cortex, where metabolism was studied by 1H NMR in vivo, is marked with a red rectangle

Time dependences of $[NAA]$ in the premotor cortex in normal and schizophrenic patients and the hemodynamic response function (HFR) to the presented stimulus.

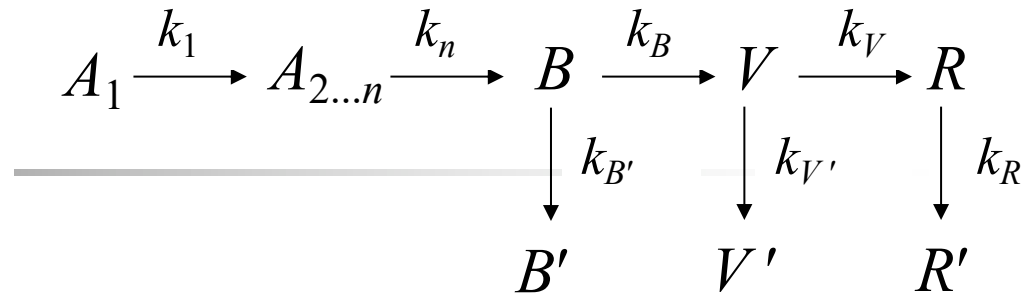
Assignment: in response to the sound signal, press the button with the index finger of the right hand.

Experimental and calculated dynamics



Dynamics of A_i

BOLD-effect



A_i –receptor chemical signal ,
 V –vasodilatator,
 R – experimentally detected ΔO_2

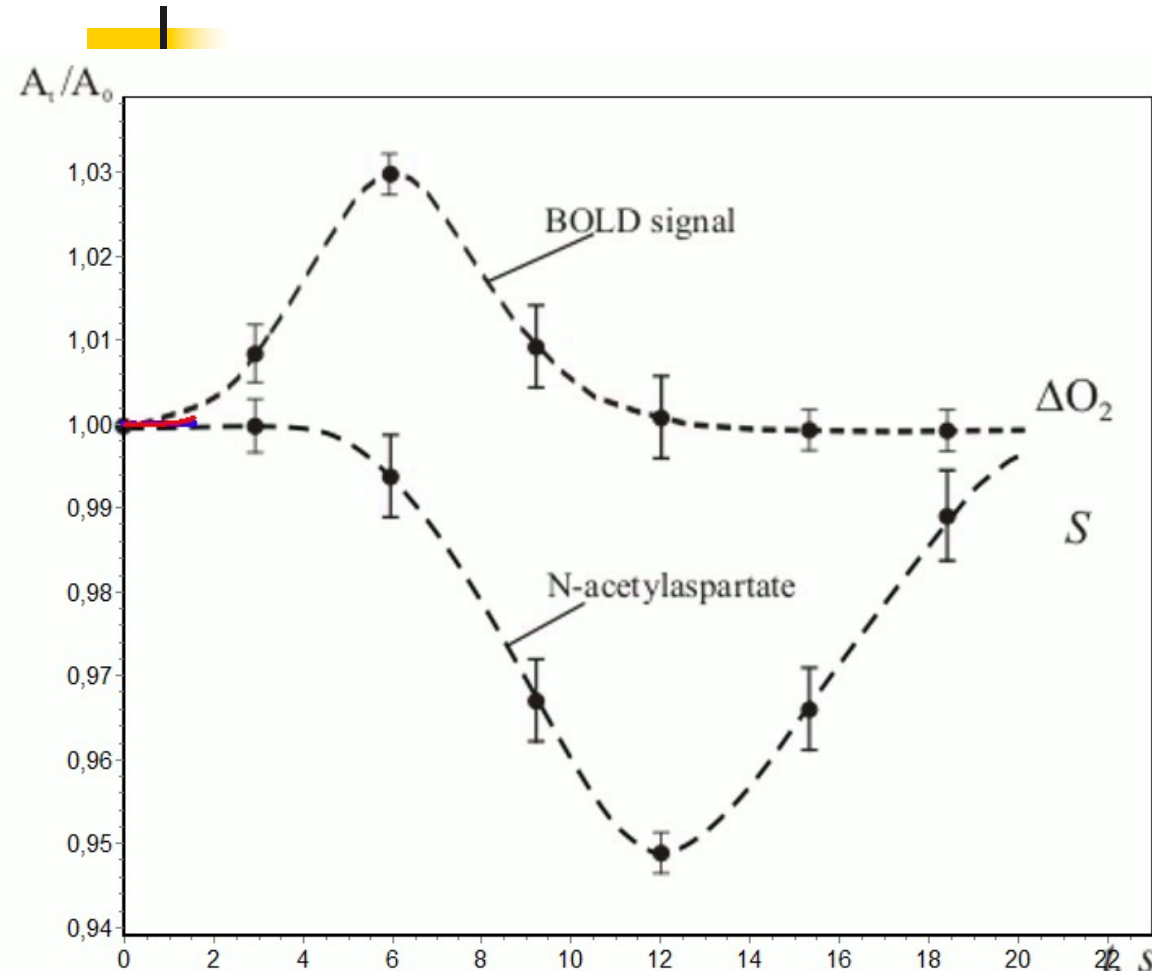
$$\frac{dA_i}{dt} = k_{i-1}A_{i-1} - k_iA_i,$$

$$\frac{dB}{dt} = k_nA_n - (k_B + k_{B'})B,$$

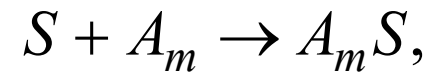
$$\frac{dV}{dt} = k_B B - (k_V + k_{V'})V,$$

$$\frac{dR}{dt} = k_V V - k_R R.$$

Experiment and theory



$$\Delta O_2(A/A_0) = A \cdot t^n \cdot \exp(-\xi t)$$



A_1, \dots, A_m – intermediates

Kinetic model

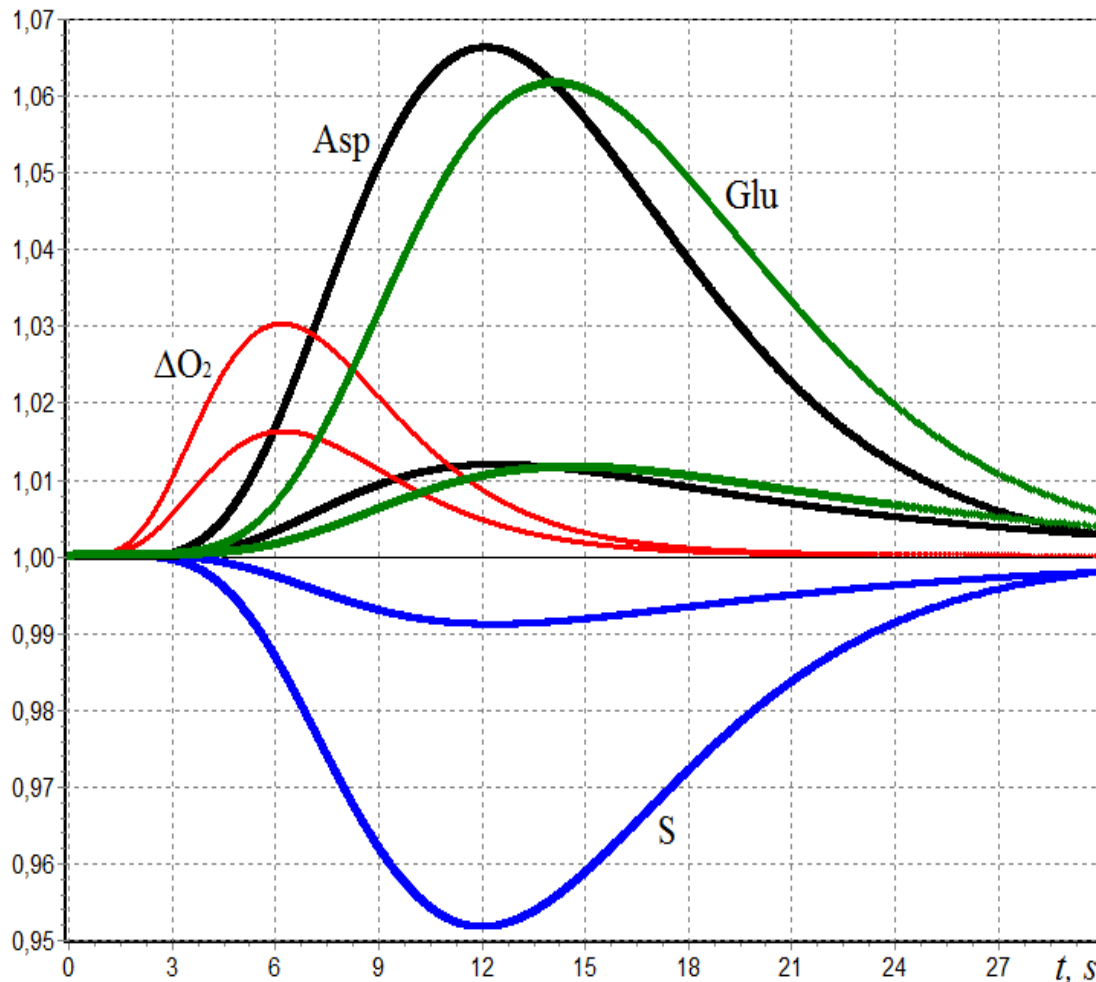
$$\frac{dA_1}{dt} = -k_1 \Delta O_2 A_1,$$

$$\frac{dA_2}{dt} = k_1 \Delta O_2 \cdot A_1 - k_2 A_2,$$

$$\frac{dA_3}{dt} = k_2 A_2 - k_3 A_3 S,$$

$$\frac{dS}{dt} = \alpha(S_0 - S) - \beta w(S) - k_3 A_3 S,$$

BOLD-signal initiates the hydrolysis of N-acetyl-aspartate (**experiment**) and injection into neuron aspartic, acetic, glutamic acids (**calculated**)



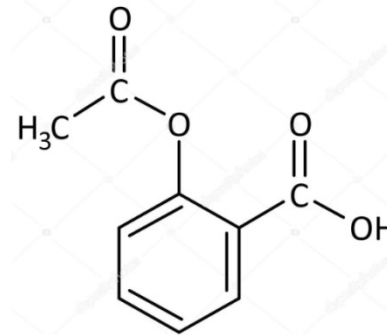
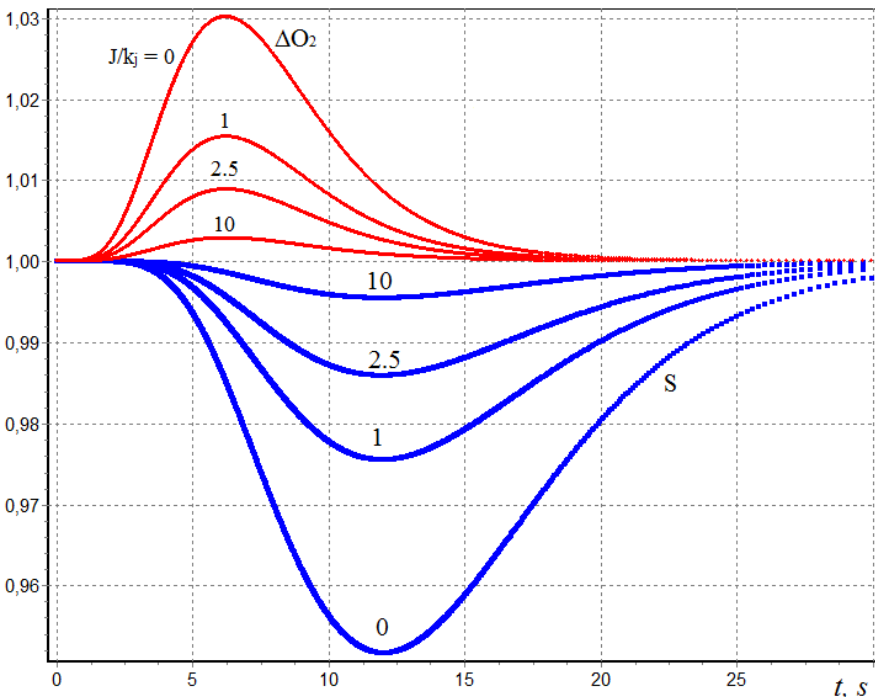
$$w(S) = f\left(\frac{S^3}{S^4}\right)$$

Inhibition by substrate-non-linear factor-provides the trigger behavior

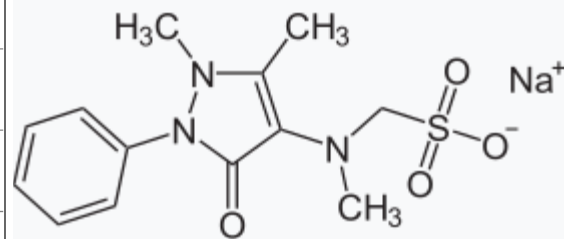
BOLD-effect

Inhibition of BOLD-effect by non-steroid anty-inflammetory drugs (aspirin, analgin, ibuprofen, voltaren and others)

$$w = \frac{w_0}{1 + J/k_i}$$

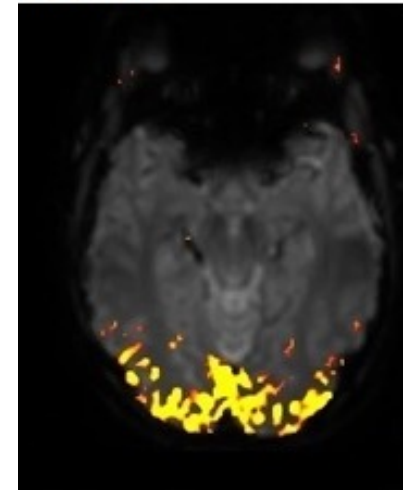


Aspirin

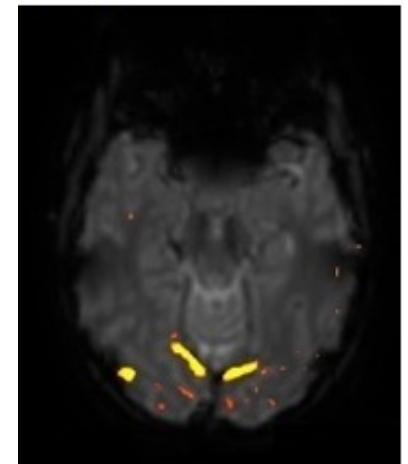


Analgin

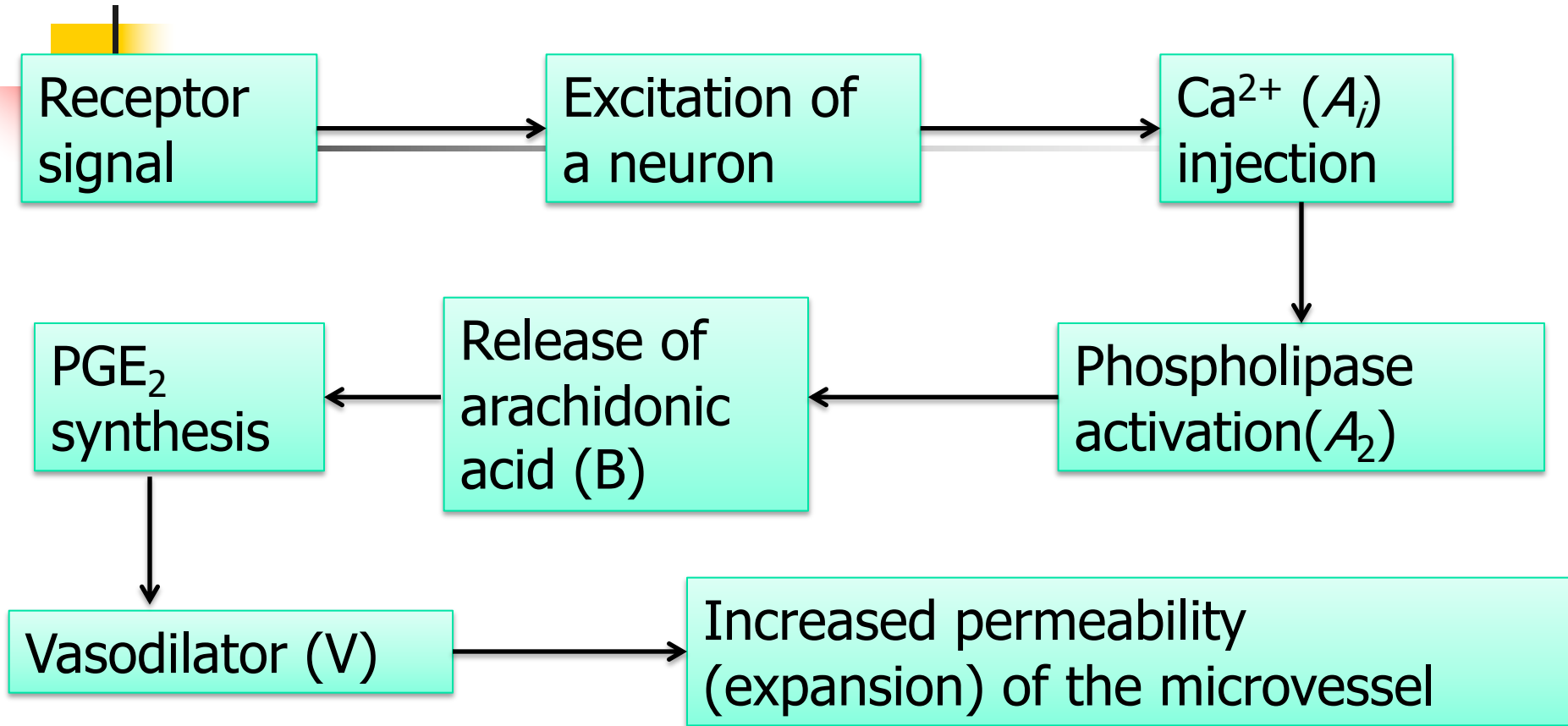
Before



After



BOLD-effect



Experimental confirmation - inhibition of PGH-synthetase, limiting the enzyme of prostaglandin synthesis.



Supercomputer technologies ,dynamic models/molecular basis of intelligence

Sergey Varfolomeyev

Institute of Biochemical Physics,Russian Academy of Sciences

Moscow State University