C7790 Introduction to Molecular Modelling

TSM Modelling Molecular Structures

C9087 Computational Chemistry for Structural Biology

Lesson 21

Kinetic Isotope Effect (KIE)

JS/2022 Distant Form of Teaching: Rev2

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Context

macroworld **microworld**

states

(thermodynamic properties, G, T,...)

phenomenological thermodynamics

equilibrium (equilibrium constant)

kinetics (rate constant)

free energy
(Gibbs/Helmholtz)

partition function

statistical thermodynamics

microstates

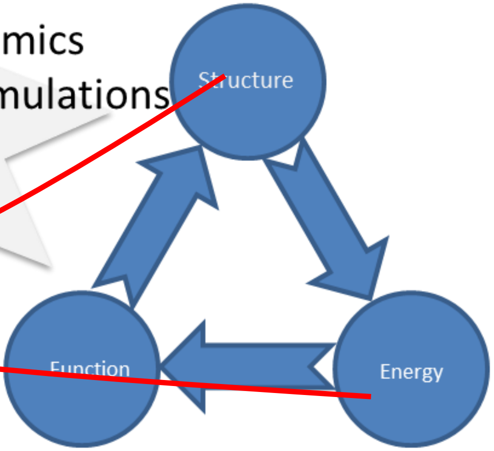
(mechanical properties, E)

Description levels (model chemistry):

- quantum mechanics
  - semiempirical methods
  - ab initio methods
  - post-HF methods
  - DFT methods
- molecular mechanics
- coarse-grained mechanics

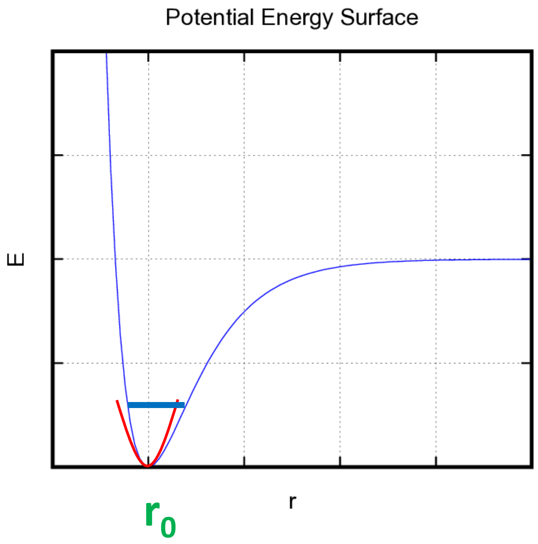
Simulations:

- molecular dynamics
- Monte Carlo simulations
- docking
- ...



microstate ≠ microworld

Revision

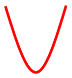


To characterize a quantum state:

$$E = E(r_o) + E_{VRT}$$

a) we need to find
a potential energy minimum

b) we can further evaluate vibrations
from **the PES curvature at the minimum**

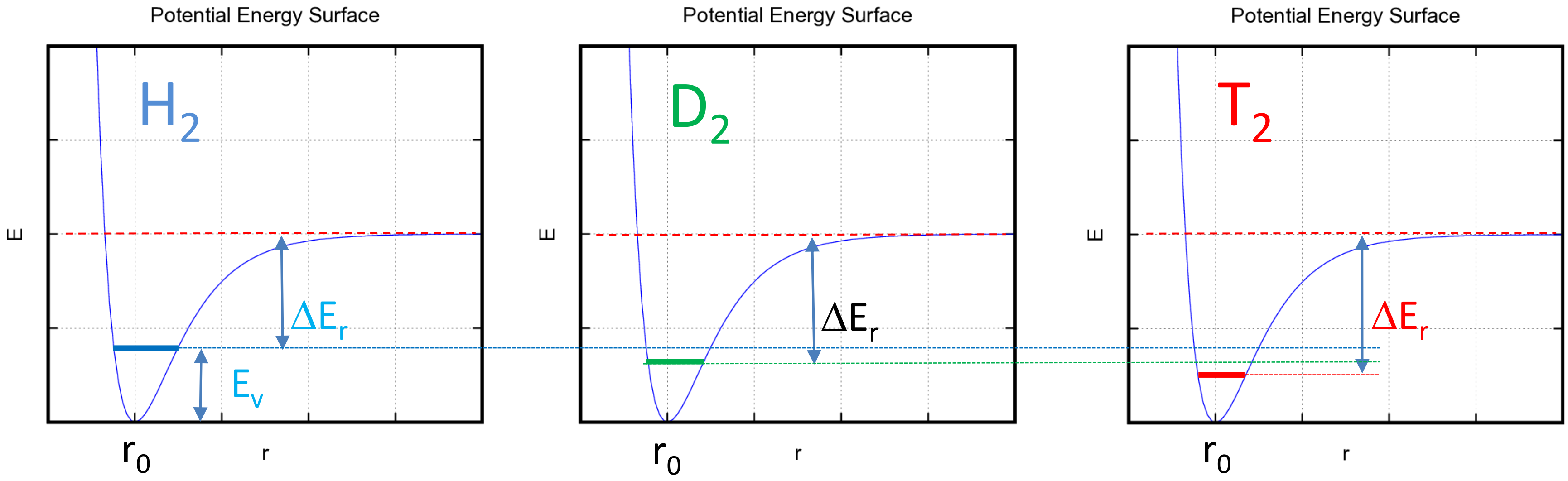


(too difficult to calculate, thus it is usually neglected)

Remember:

- PES cannot describe mass effect of nuclei; it only describes electronic effects.

Revision: H_2, D_2, T_2



!! not in scale !!

$|\Delta E_r| < |\Delta E_r| < |\Delta E_r|$

$r_0 = r_0 = r_0$

$r_e \sim r_e \sim r_e$ observable equilibrium bond lengths impact of anharmonicity and QM character of vibrations

$$E_V = \left(v + \frac{1}{2}\right) h\nu$$

$$\nu = \frac{1}{2\pi}\sqrt{\frac{K}{\mu}}$$

the same for all systems due to the same PES

different: bigger mass -> smaller frequency -> lower energy

Kinetic Isotope Effect

Kinetic Isotope Effect

The **kinetic isotope effect** (KIE) is the change in the reaction rate of a chemical reaction when one of the atoms in the reactants is replaced by one of its isotopes:

$$KIE = \frac{k_{light}}{k_{heavy}}$$

Example:

$$\mathrm{CN^- + {}^{12}CH_3{-}Br \xrightarrow{k_{12}} {}^{12}CH_3{-}CN + Br^-}$$
$$\mathrm{CN^- + {}^{13}CH_3{-}Br \xrightarrow{k_{13}} {}^{13}CH_3{-}CN + Br^-}$$

$$\mathrm{KIE} = \frac{k_{12}}{k_{13}} = 1.082 \pm 0.008$$

The major contributing factor is the change in ZPVE (zero-point vibrational energy).

However, other factors can also be involved including:

- breaking symmetry (entropic factor)
- changes in rotation and/or translational energies
- tunneling

https://en.wikipedia.org/wiki/Kinetic_isotope_effect

Activation Energy

Eyring equation

$$k = \kappa \frac{k_B T}{h} e^{-\frac{\Delta G^{\neq}}{RT}}$$

Assume the following approximation:

$$\Delta G^{\neq} \approx \Delta E^{\neq} = E_{TS} - E_R$$

transition state (activated complex)

reactants

$$E_{TS} = E(\boldsymbol{R}_{TS}) + \sum_{k=1}^{3N-6} E_{V(TS),k}$$

$$E_R = E(\boldsymbol{R}_R) + \sum_{k=1}^{3N-6} E_{V(R),k}$$

potential energy

zero-point vibrational energy

3N-6 degrees of freedom (N - number of atoms)
= number of normal vibrational modes

Activation Energy, cont.

Assume the following approximation:

$$\Delta G^{\neq} \approx \Delta E^{\neq} = E_{TS} - E_R$$

3N-6 degrees of freedom (N - number of atoms)
= number of normal vibrational modes

$$E_{TS} = E(\boldsymbol{R}_{TS}) + \sum_{k=1}^{3N-6} E_{V(TS),k}$$

$$E_R = E(\boldsymbol{R}_R) + \sum_{k=1}^{3N-6} E_{V(R),k}$$

consider two similar vibrational modes in R and TS, which mainly include atoms involved in creating/breaking bonds

$$E_R = E(\boldsymbol{R}_R) + E_{V(R),1} + E_{V(R),2} + \cdots + E_{V(R),3N-7} + E_{V(R),3N-6}$$

$$E_{TS} = E(\boldsymbol{R}_{TS}) + E_{V(TS),1} + E_{V(TS),2} + \cdots + E_{V(TS),3N-7} + \cancel{E_{V(TS),3N-6}}$$

imaginary vibration,
it does not contribute to the total energy

Activation Energy, cont.

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imaginary vibration,
it does not contribute to the total energy

First consequence:

$$E(\boldsymbol{R}_{TS}) - E(\boldsymbol{R}_R) > E_{TS} - E_R$$

REMEMBER: neglecting ZPVE has a greater impact on calculated activation energy than on reaction energy because of one imaginary vibrational mode in TS

Activation Energy, cont.

Assume the following approximation:

$$\Delta G^{\neq} \approx \Delta E^{\neq} = E_{TS} - E_{R}$$

3N-6 degrees of freedom (N - number of atoms)
= number of normal vibrational modes

Second consequence:

The isotope substitution dominantly influences only on ONE state, which is the reactant. As a result, the activation barrier is changed.

consider two similar vibrational modes in R and TS, which mainly include atoms involved in creating/breaking bonds

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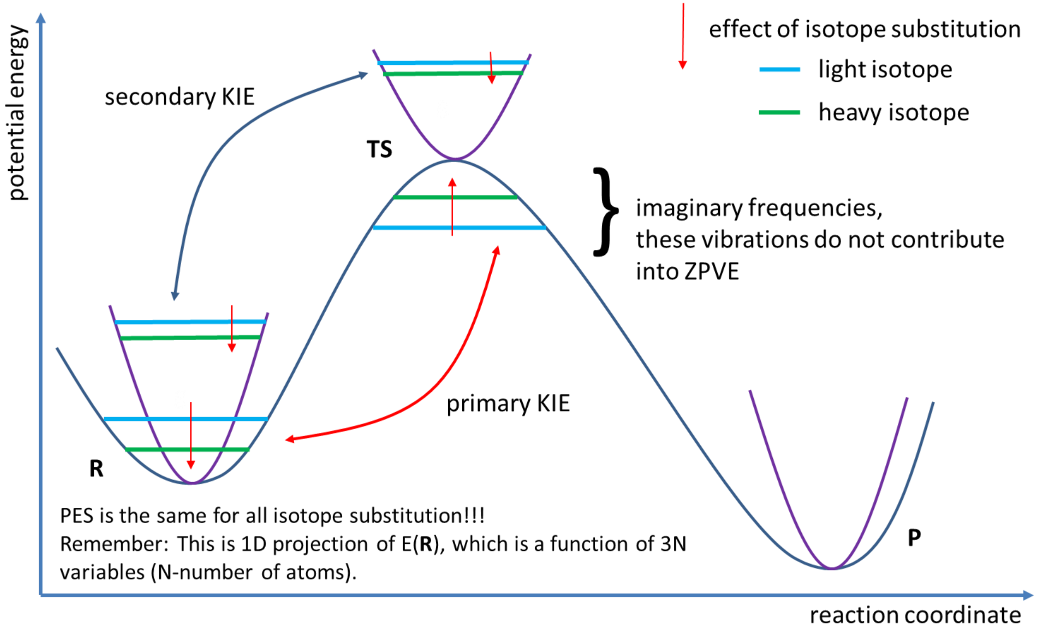
Types of KIE

$$E_R = E(\boldsymbol{R}_R) + E_{V(R),1} + E_{V(R),2} + \cdots + E_{V(R),3N-7} + E_{V(R),3N-6}$$

$$E_{TS} = E(\boldsymbol{R}_{TS}) + E_{V(TS),1} + E_{V(TS),2} + \cdots + E_{V(TS),3N-7} + E_{V(\xcancel{TS}),3N-6}$$

secondary KIE

primary KIE



imaginary frequencies, these vibrations do not contribute into ZPVE

PES is the same for all isotope substitution!!!
Remember: This is 1D projection of E(**R**), which is a function of 3N variables (N-number of atoms).

Main conclusion:
heavier isotopes makes the reaction slower*

$$KIE = \frac{k_{light}}{k_{heavy}} > 1$$

*) there are certain exceptions, see for the inverse kinetic isotope effect

Types of KIE

$$E_R = E(\boldsymbol{R}_R) + E_{V(R),1} + E_{V(R),2} + \cdots + E_{V(R),3N-7} + E_{V(R),3N-6}$$

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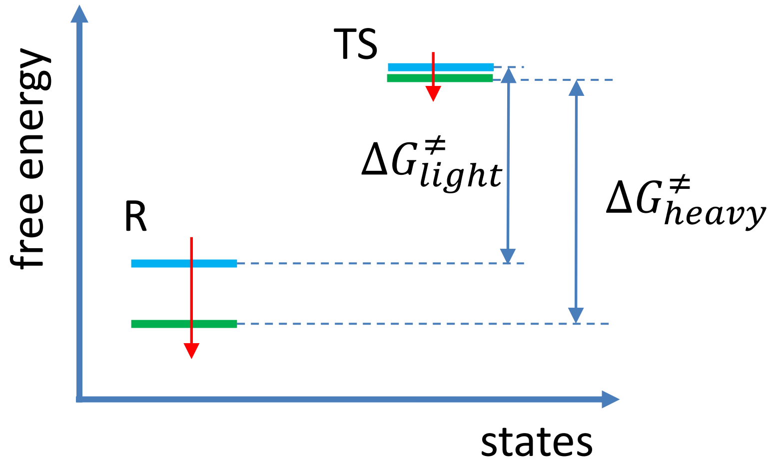
secondary KIE

primary KIE



↓ effect of isotope substitution

🟦 light isotope

🟩 heavy isotope

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$$E_{TS} = E(\boldsymbol{R}_{TS}) + E_{V(TS),1} + E_{V(TS),2} + \cdots + E_{V(TS),3N-7} + E_{V(\cancel{TS}),3N-6}$$

secondary KIE < primary KIE

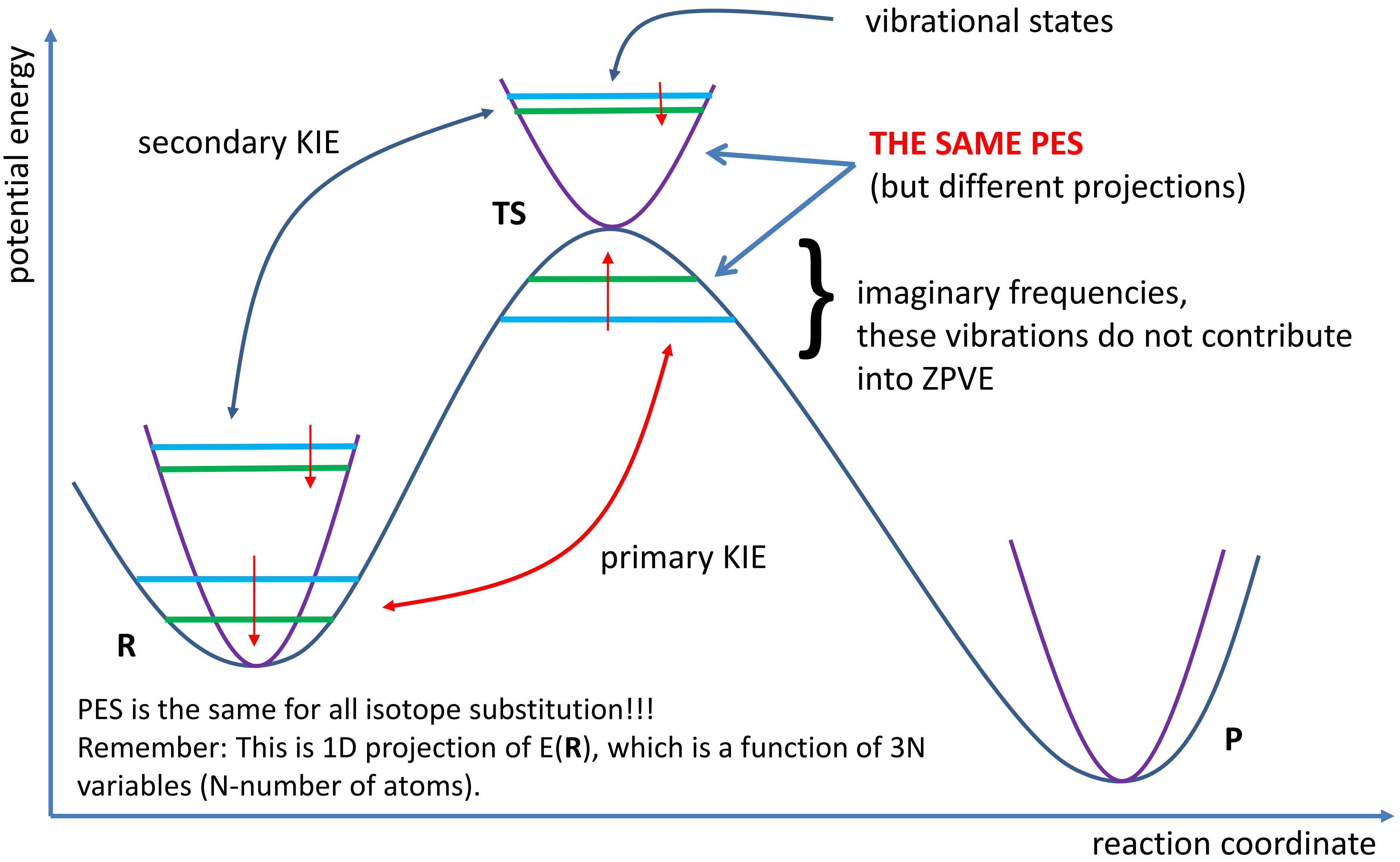
isotope substitution takes place nearby the reaction center
since ALL atoms are involved in ALL normal mode vibrations, the isotope effect is different for both states

isotope substitution takes place in the reaction center (substituted atom is involved in forming/breaking bonds)

Typical use of KIE:

- KIE is employed in experimental validation of reaction mechanisms

ZPVE as Major Contributor to KIE



vibrational states

secondary KIE

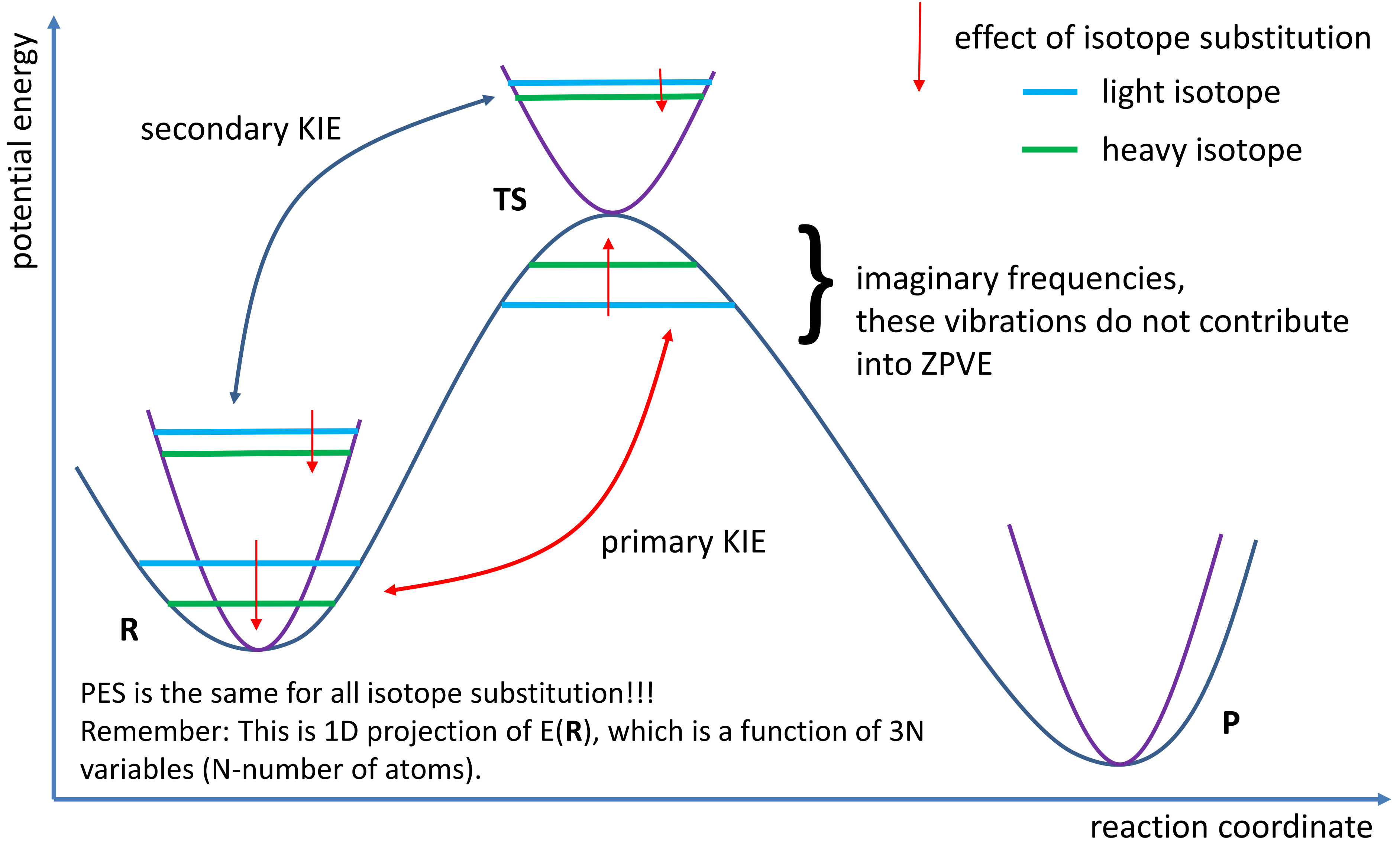
THE SAME PES
(but different projections)

imaginary frequencies,
these vibrations do not contribute
into ZPVE

primary KIE

PES is the same for all isotope substitution!!!
Remember: This is 1D projection of E(**R**), which is a function of 3N variables (N-number of atoms).

ZPVE as Major Contributor to KIE



secondary KIE

primary KIE

imaginary frequencies, these vibrations do not contribute into ZPVE

PES is the same for all isotope substitution!!!
Remember: This is 1D projection of E(**R**), which is a function of 3N variables (N-number of atoms).

Summary

- KIE is an experimental method important for studying reaction mechanisms.
- KIE is a consequence of quantum behavior of molecular vibrations, which due to Heisenberg principle of uncertainty cannot posses zero energy.
- In general, neglecting ZPVE in calculations of activation energies can introduce non-negligible error.
- ZPVE cannot be modelled by methods employing classical physical laws (molecular dynamics, Monte-Carlo simulations). It is necessary to use special techniques such as the path integral molecular dynamics, which can describe these quantum effects even when employing non-QM potentials such as molecular mechanics.
- Very accurate QM calculations are required to predict/quantify KIE. In many cases, calculations will not be accurate enough to predict KIE.
- Instead, the modelling can provide supplementary data such as suggesting suitable atoms for isotope substitutions based on analysis of molecular vibrations.

Homework

Homework

- Find some experimental study employing KIE.
  - Can be KIE used for studying mechanisms of enzymatic reactions?
- What is the largest KIE observed so far. What is the reason for such high value?
- What is the change of the activation free energy responsible for KIE from two previous points?