4

Mechanisms of Organic Reactions

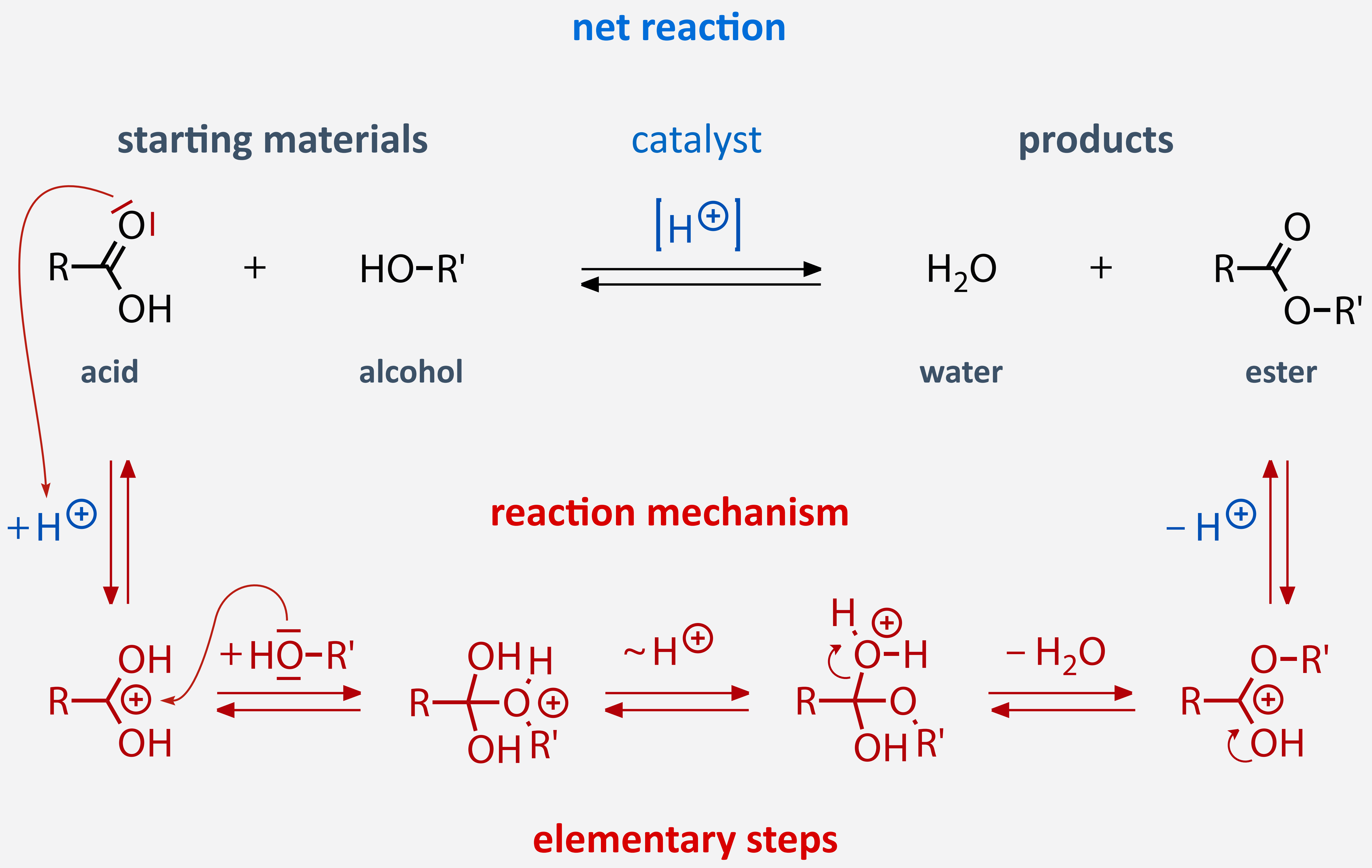
Table of Contents

Learning Goals and Reading Recommendations

- **thermodynamics concerned with the energy balance of reactions**
- **kinetics concerned with the rates of reactions**
- **identify nucleophilic centers, electrophilic centers, leaving groups**
  - compare nucleophilicity of different nucleophiles
  - estimate stabilization of electrophilic centers
  - estimate leaving group quality from the pKa values of the corresponding acids
- **formulate substitution, addition, elimination reactions**

4.1 Reaction Thermodynamics and Kinetics

Net Reaction versus Mechanism



net reaction

starting materials

catalyst

products

acid

alcohol

water

ester

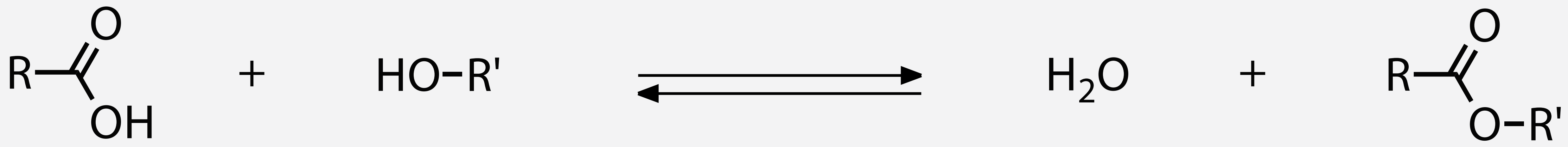
reaction mechanism

elementary steps

- **net reaction** describes the starting materials and the products of a reaction
- **reaction mechanisms** describes the individual **elementary steps** of the reaction
- **catalyst** takes part in the reaction mechanism but is retained unchanged

Thermodynamics of Chemical Reactions

- reaction thermodyamics are concerned with the overall energy balance of chemical reactions



$$\Delta G_R = \Delta G_R^\ominus + RT \ln \frac{[\text{R–COOR'}][\text{H}_2\text{O}]}{[\text{R–COOH}][\text{R'–OH}]}$$

$\Delta G_R > 0$ **endergonic reaction, runs from right to left**

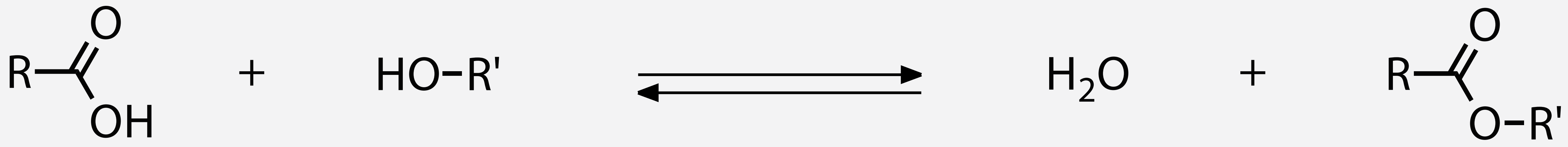
$\Delta G_R = 0$ **reaction is in equilibrium**

$\Delta G_R < 0$ **exergonic reaction, runs from left to right**

- **Gibbs' free reaction energy ΔG_R determines whether / in which direction the reaction runs**
- **standard Gibbs' free reaction energy $\Delta G°_R$ at standard conditions (1 bar, 25°C, 1 mol/L)**

The Chemical Equilibrium

- chemical reactions in a closed system progress until they reach thermodynamic equilibrium



$$\Delta G_R = \Delta G_R^\ominus + RT \ln \frac{[\text{R–COOR'}]_\text{eq}[\text{H}_2\text{O}]_\text{eq}}{[\text{R–COOH}]_\text{eq}[\text{R'–OH}]_\text{eq}} = 0$$

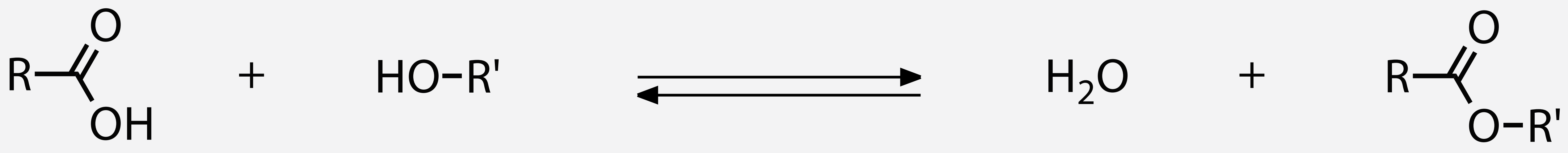
$$K_R = \frac{[\text{R–COOR'}]_\text{eq}[\text{H}_2\text{O}]_\text{eq}}{[\text{R–COOH}]_\text{eq}[\text{R'–OH}]_\text{eq}} \qquad pK_R = -\log K_R$$

$$\Delta G_R^\ominus = -RT \ln K_R \qquad pK_R \propto \frac{\Delta G_R^\ominus}{RT}$$

- **equilibrium constant *K*$_R$ is the ratio of reactant concentrations in equilibrium**
- **standard free reaction energy Δ*G*°$_R$ determines position of the equilibrium (at 25°C)**

Reaction Enthalpy and Entropy

- Gibbs-Helmholtz equation dissects free reaction energy into enthalpic/entropic contributions



$$\Delta G_R^{\ominus} = \Delta H_R^{\ominus} - T\Delta S_R^{\ominus}$$ **Gibbs-Helmholtz Equation**

$\Delta H_R^{\ominus} < 0$ **exothermic reactions, sum of all bond energy changes negative**

$\Delta H_R^{\ominus} > 0$ **endothermic reactions, sum of all bond energy changes positive**

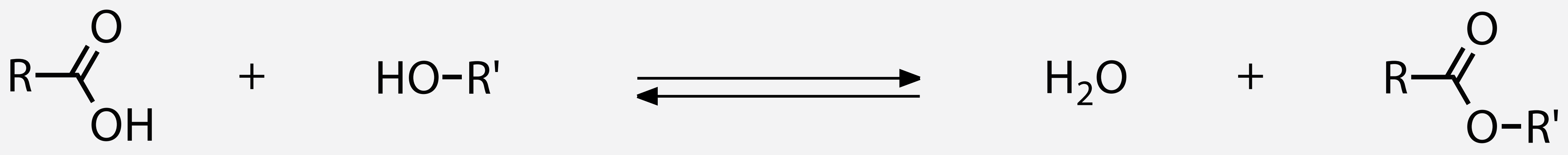
$\Delta S_R^{\ominus} < 0$ **exotropic reactions, disorder, degrees of freedom decrease**

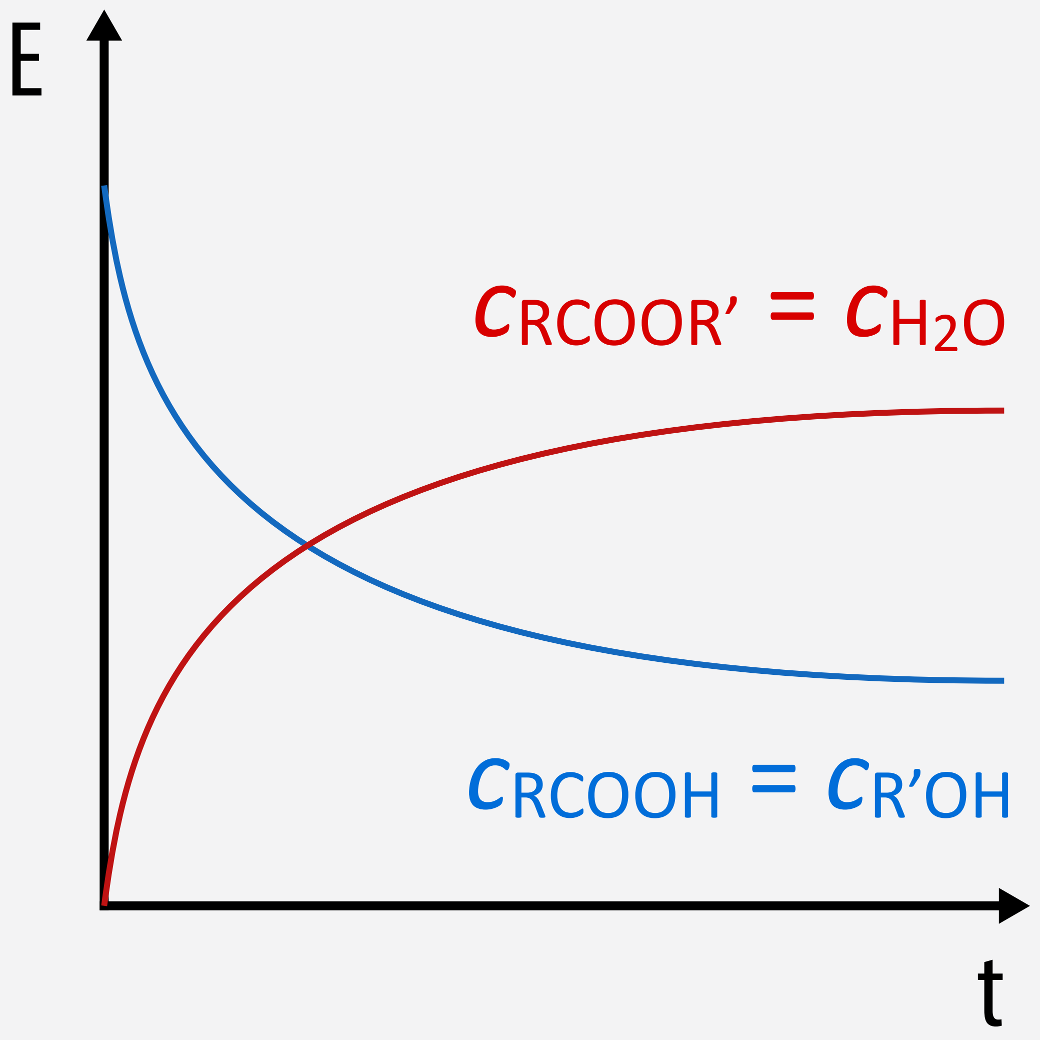
$\Delta S_R^{\ominus} > 0$ **endotropic reactions, disorder, degrees of freedom increase**

- **reaction enthalpy $\Delta H°_R$ is negative (favorable) if bond energies in products are higher**
- **reaction entropy $\Delta S°_R$ is positive (favorable) if the disorder within the system increases**

Kinetics of Chemical Reactions

- reaction kinetics describe “how fast” reactions proceed from initial state towards equilibrium





$$r = \frac{\mathrm{d}c(t)_{\mathrm{RCOOH}}}{\mathrm{d}t} = -k \cdot c(t)_{\mathrm{RCOOH}} \cdot c(t)_{\mathrm{ROH}} = -k \cdot c(t)^2_{\mathrm{RCOOH}}$$

$$r = \int \frac{\mathrm{d}c(t)_{\mathrm{RCOOH}}}{c(t)^2_{\mathrm{RCOOH}}} = -k \int \mathrm{d}t$$

$$c(t)_{\mathrm{RCOOH}} = \frac{1}{1 + kc(0)_{\mathrm{RCOOH}}t}$$

- **reaction rates $r = dc_i/dt$ describe the change of the concentrations c_i over time**
- **rate laws describe the relation between reaction rates r_i and substrate concentrations c_i**
- **rate laws are differential equations solved by integration, polynomial/exponential functions**

Reaction Order and Molecularity of Chemical Reactions

- reaction rates *r* proportional to reactant concentrations according to molecularity
- proportionality factor is called rate constant *k*

first order	**monomolecular**		**monomolecular**	**first order**
$r_{1\mathrm{f}} = k_{1\mathrm{f}} \cdot [A]$	A	$\rightleftharpoons$	B	$r_{1\mathrm{r}} = k_{1\mathrm{r}} \cdot [B]$
second order	**bimolecular**		**bimolecular**	**second order**
$r_{2\mathrm{f}} = k_{2\mathrm{f}} \cdot [A][B]$	A + B	$\rightleftharpoons$	C + D	$r_{2\mathrm{r}} = k_{2\mathrm{r}} \cdot [C][D]$
third order	**trimolecular**		**monomolecular**	**first order**
$r_{3\mathrm{f}} = k_{3\mathrm{f}} \cdot [A][B][C]$	A + B + C	$\rightleftharpoons$	D	$r_{3\mathrm{r}} = k_{3\mathrm{r}} \cdot [D]$
third order	**trimolecular**		**bimolecular**	**second order**
$r_{4\mathrm{f}} = k_{4\mathrm{f}} \cdot [A]^2[B]$	2 A + B	$\rightleftharpoons$	2 C	$r_{4\mathrm{r}} = k_{4\mathrm{r}} \cdot [C]^2$

- **molecularity is the number of molecules of each type involved in an elementary reaction**
- **reaction order is the sum of all exponents of the reactant concentrations in the rate law**
- **for simple, single-step reactions, the molecularity strictly determines the reaction order**

Relation of Reaction Thermodynamics and Kinetics

- **the thermodynamic equilibrium of a chemical reaction is a dynamic equilibrium**
  - once in equilibrium, concentrations of all reactants / products do not change anymore
  - forward and reverse reaction still proceed, but their rates must be equal

$$r_{2\mathrm{f}} = k_{2\mathrm{f}} \cdot [A][B] \qquad \mathrm{A + B} \rightleftharpoons \mathrm{C + D} \qquad r_{2\mathrm{r}} = k_{2\mathrm{r}} \cdot [C][D]$$

$$r_{2\mathrm{f}} = r_{2\mathrm{r}}$$

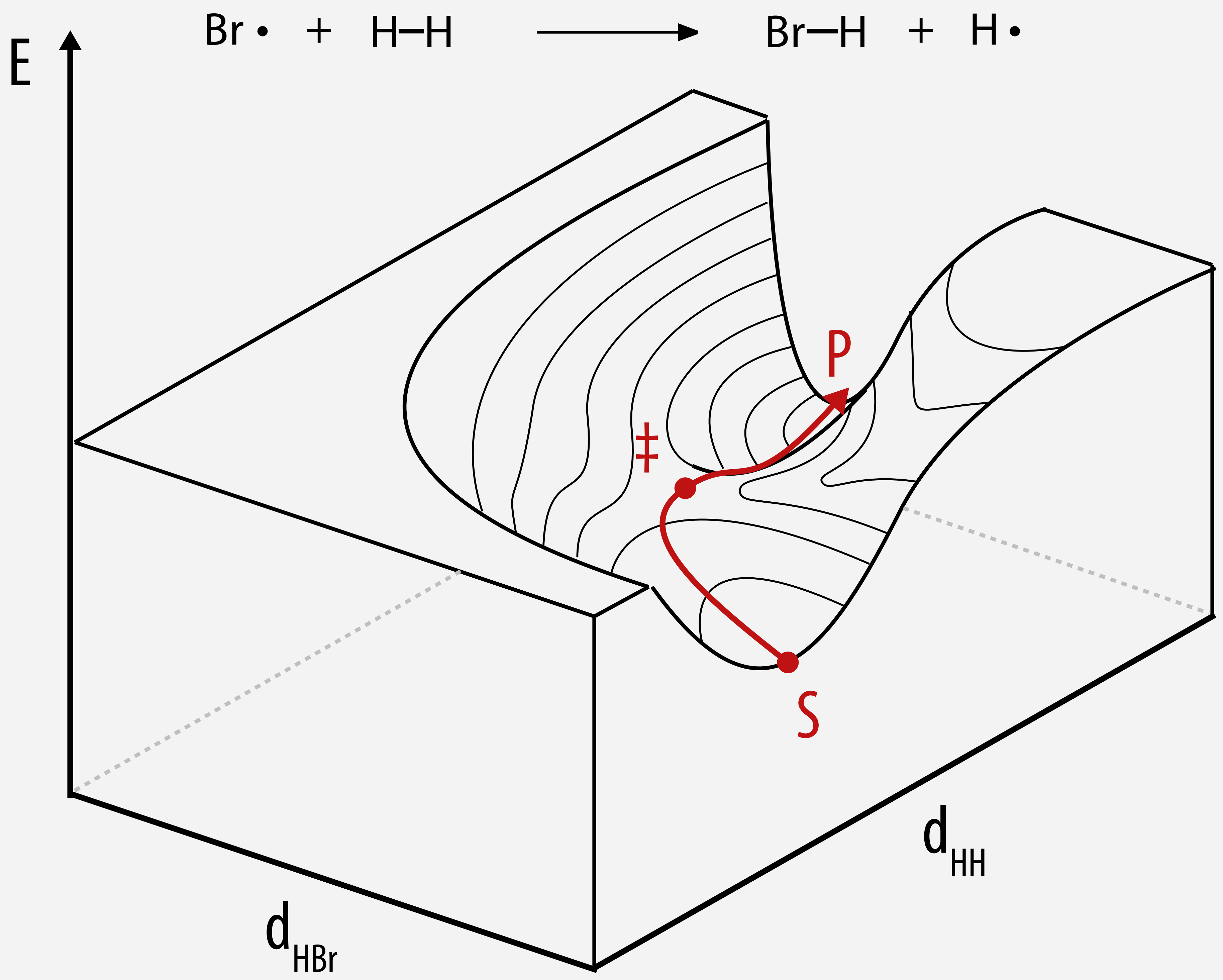
$$k_{2\mathrm{f}} \cdot [A][B] = k_{2\mathrm{r}} \cdot [C][D]$$

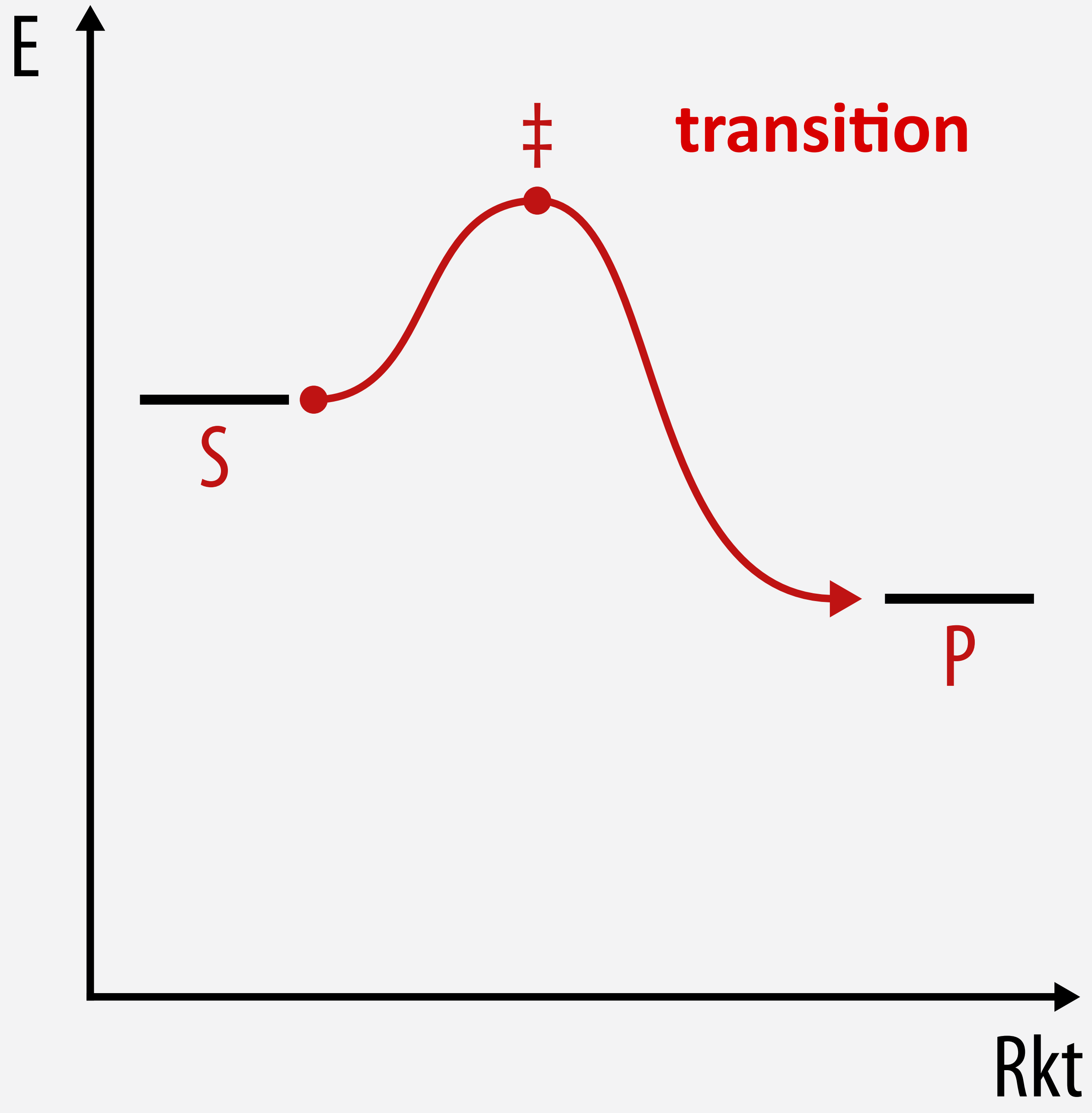
$$\frac{k_{2\mathrm{f}}}{k_{2\mathrm{r}}} = \frac{[C][D]}{[A][B]} = K$$

- **ratio of rate constants of forward and reverse reactions determines equilbrium constant K**
- **the higher the rate constant of the forward relative to the reverse reaction, the larger is K**

Simplified Reaction Profiles

- reaction profiles are simplified diagrams describing the energy profile of chemical reactions
- follow the lowest energy path from starting materials to products in the energy hypersurface

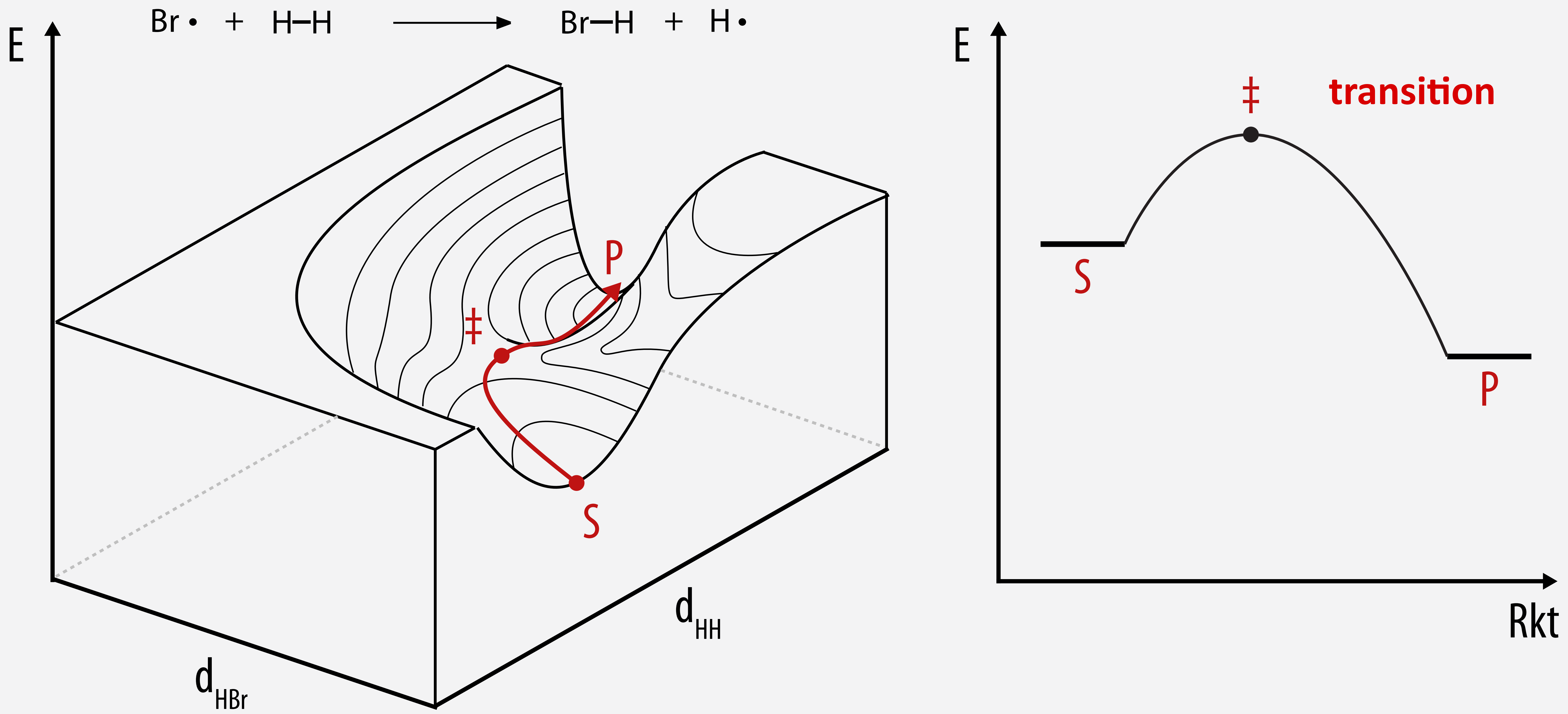




- **starting materials (S) and products (P) are stable compounds, i.e., local energetic minima**
- **transition states (‡) are saddle points (energy hypersurface), local maxima (reaction profile)**

Simplified Reaction Profiles

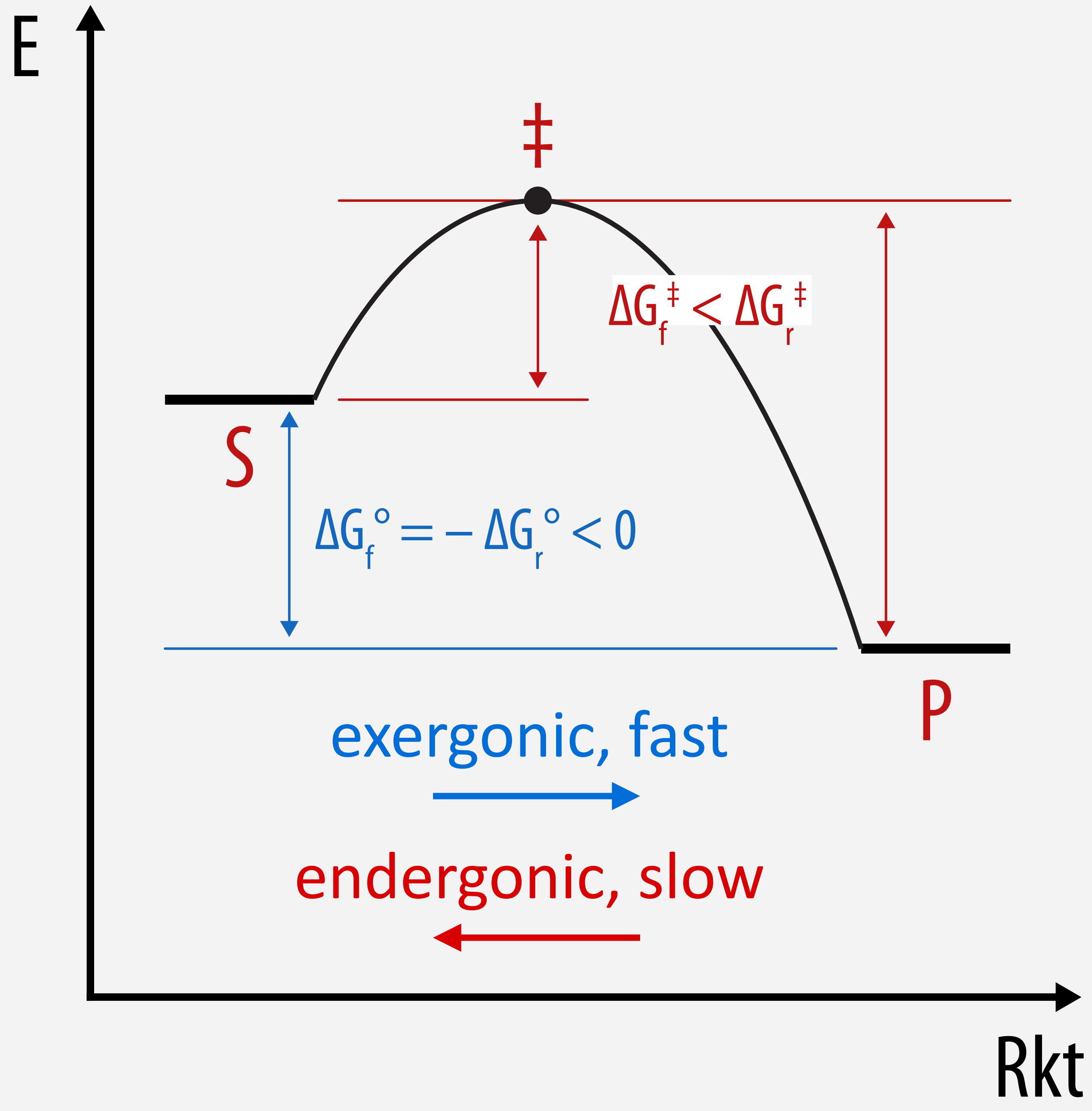
- reaction profiles are simplified diagrams describing the energy profile of chemical reactions,
- follow the lowest energy path from starting materials to products in the energy hypersurface



- **starting materials (S) and products (P) are stable compounds, i.e., local energetic minima**
- **transition states (‡) are saddle points (energy hypersurface), local maxima (reaction profile)**

Relation of Reaction Profiles, Thermodynamics, and Kinetics

- reaction profiles illustrate both thermodynamics and kinetics of chemical reactions



$$\Delta G_R^\ominus = -RT \ln K_R$$

$$\Delta G_R^\ominus = \Delta G_f^\ddagger - \Delta G_r^\ddagger$$

$$K_R = \frac{k_f}{k_r}$$

$$E_{A,r} \approx \Delta G_r^\ddagger = -RT \ln k_r$$

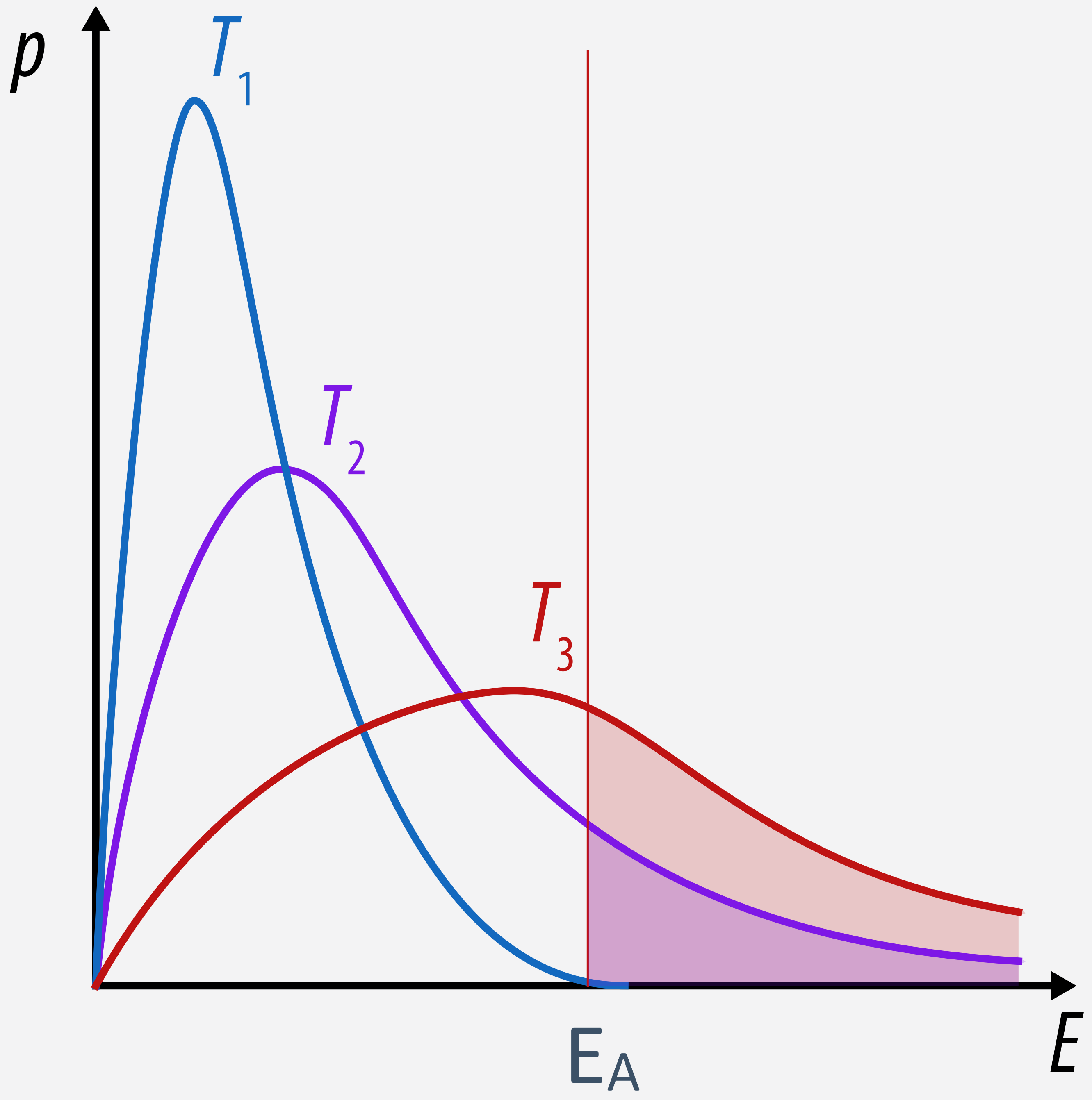
$$E_{A,f} \approx \Delta G_f^\ddagger = -RT \ln k_f$$

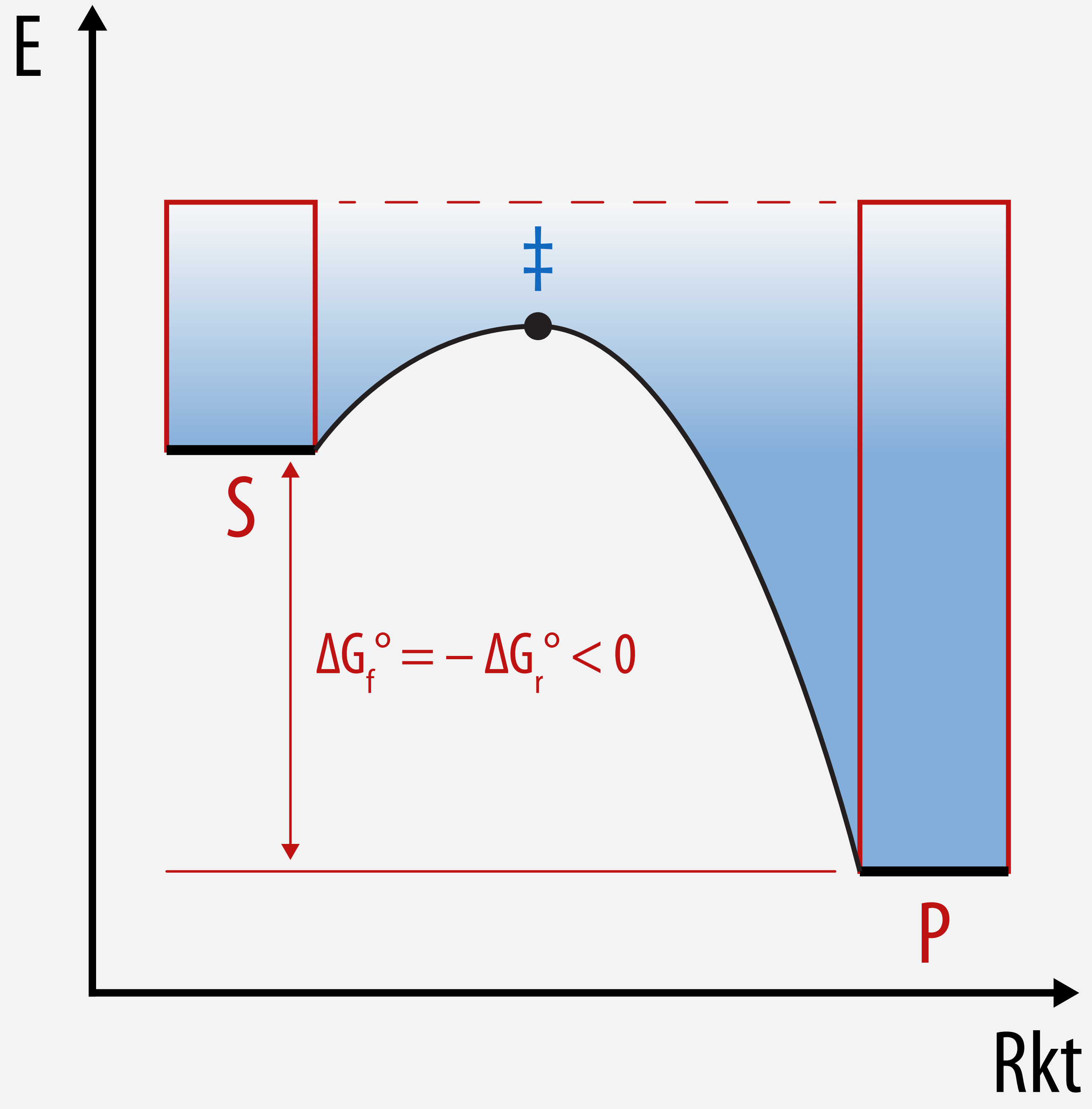
- **standard free reaction energy Δ*G*° is difference between (S) and (P) energies**
- **Δ*G*° is also the difference between free transition energies Δ*G*‡ of forward/reverse reactions**
- **reaction rates *k* depend on activation energies E_A ≈ Δ*G*‡ of chemical reactions**

Reaction Kinetics and Thermal Energy

- molecules have energies according to the Boltzmann probability distribution *p*

$$p(E) = \left(\frac{8}{kT}\right)^{3/2} \left(\frac{E}{\pi}\right)^{1/2} \exp\left(\frac{-E}{kT}\right)$$



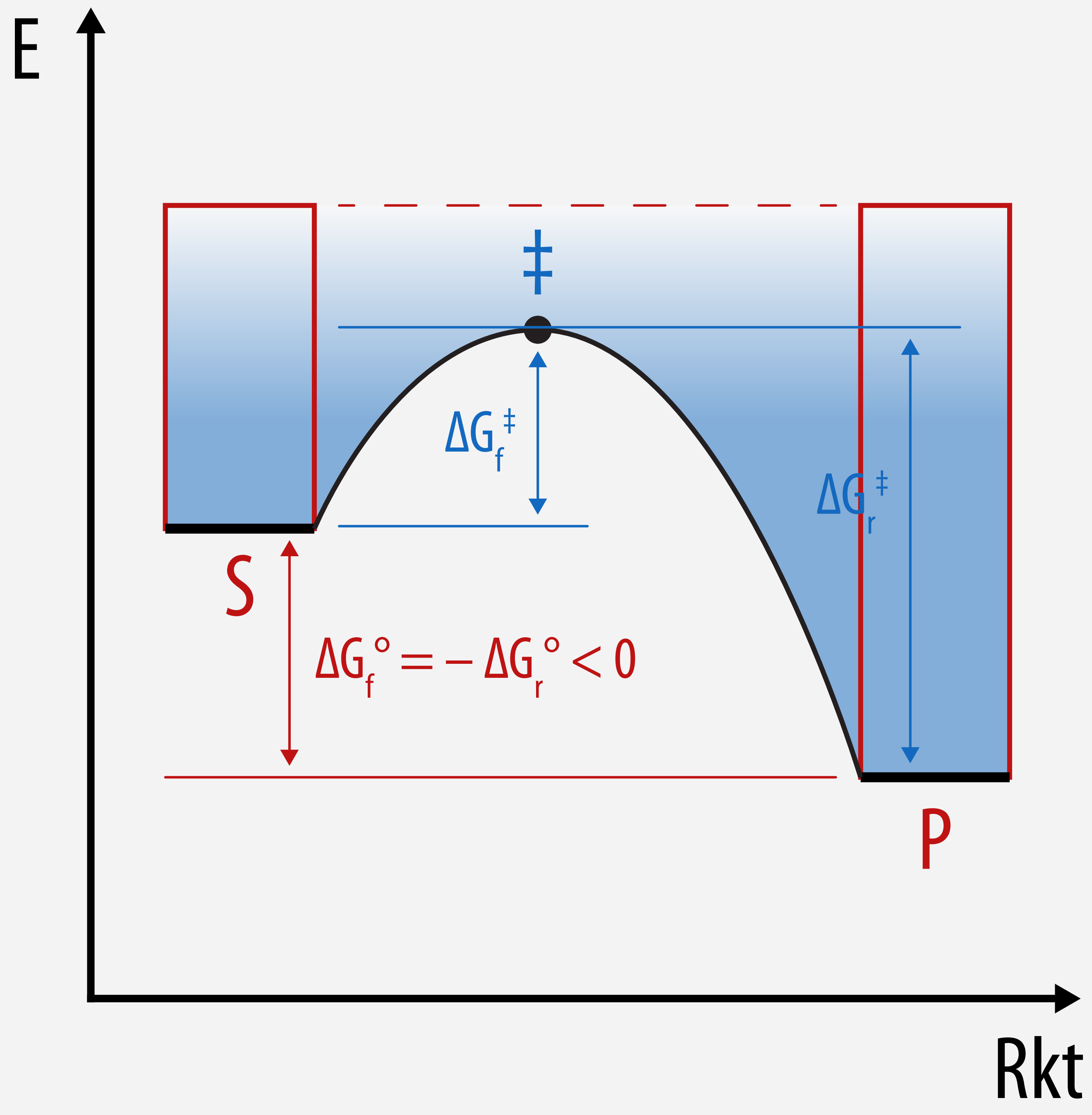


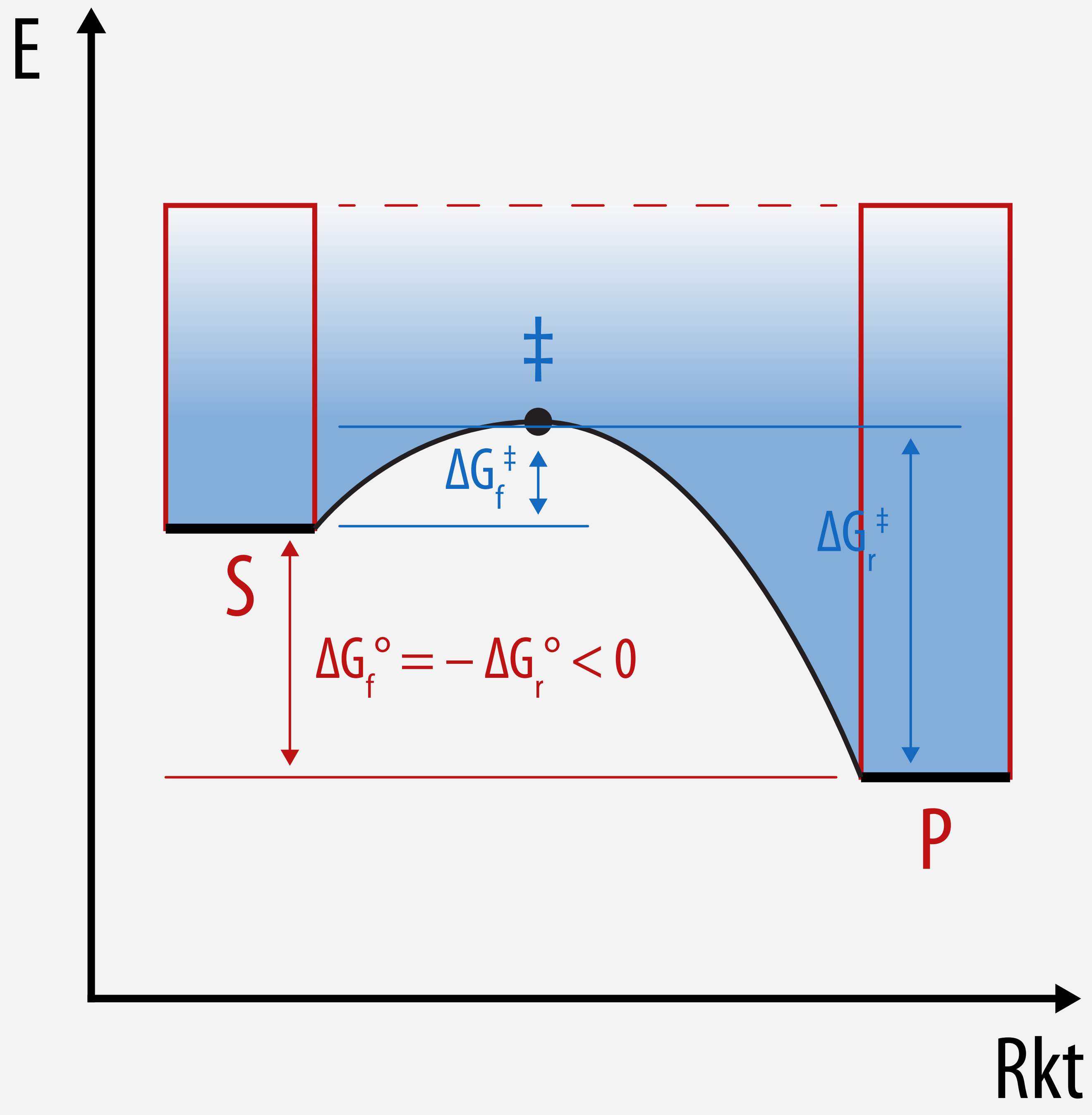
- **at higher temperatures, a larger fraction of molecules overcomes activation energy *E*$_A$**
- **both forward and reverse reaction are accelerated**

Reaction Profiles: Thermodynamics and Kinetics

- a change in the overall activation barrier will affect the reaction rates but not the equilibrium

$$\Delta G_f^\ddagger = -RT\ln k_f \quad \text{and} \quad \Delta G_r^\ddagger = -RT\ln k_r$$



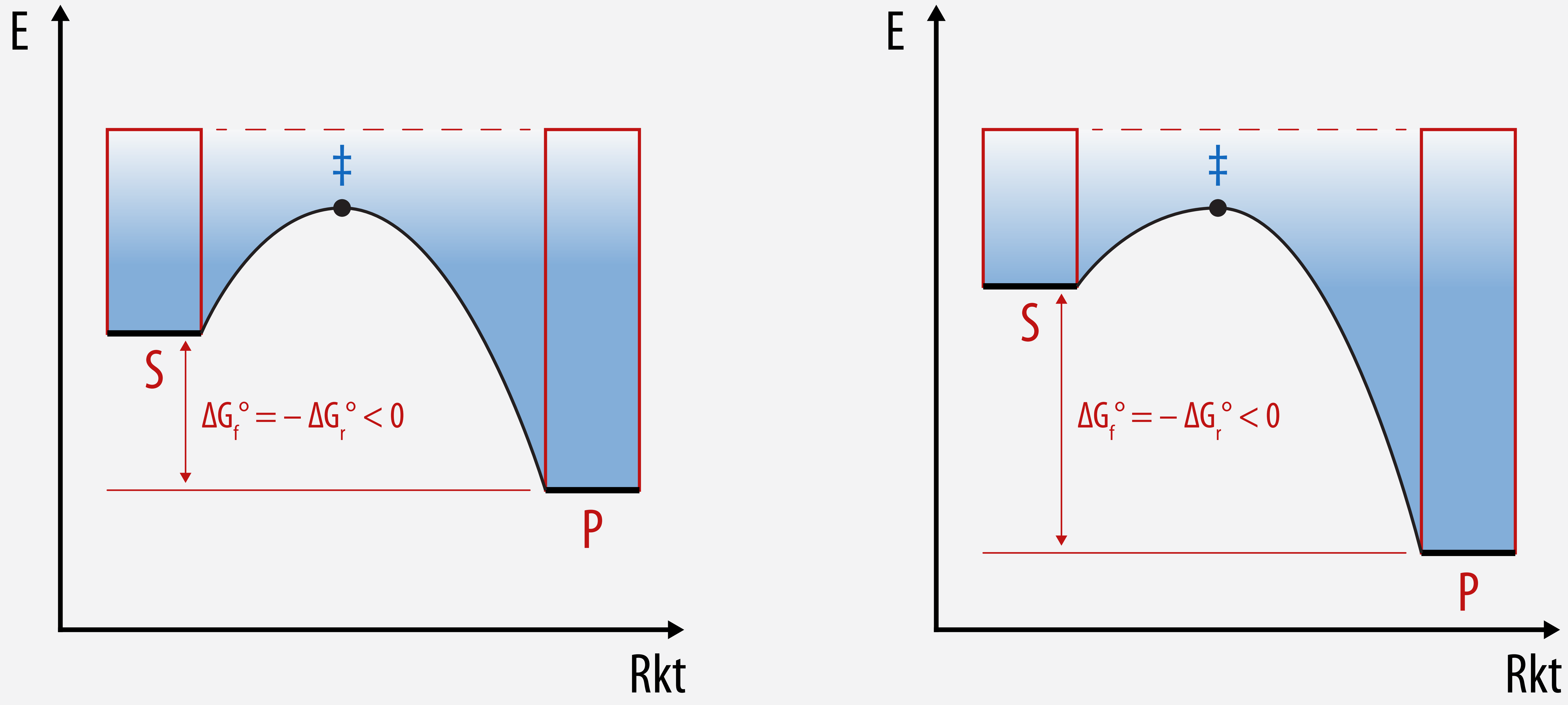


- **at a lower activation barrier, forward/reverse reaction both accelerated by same ratio**
- **catalyst provides new reaction pathway with lower activation barrier (same equilibrium)**

Kinetic Interpretation of the Equilibrium

- a more exergonic reaction will be more shifted towards the product side

$$\Delta G_R^\ominus = -RT \ln K_R$$



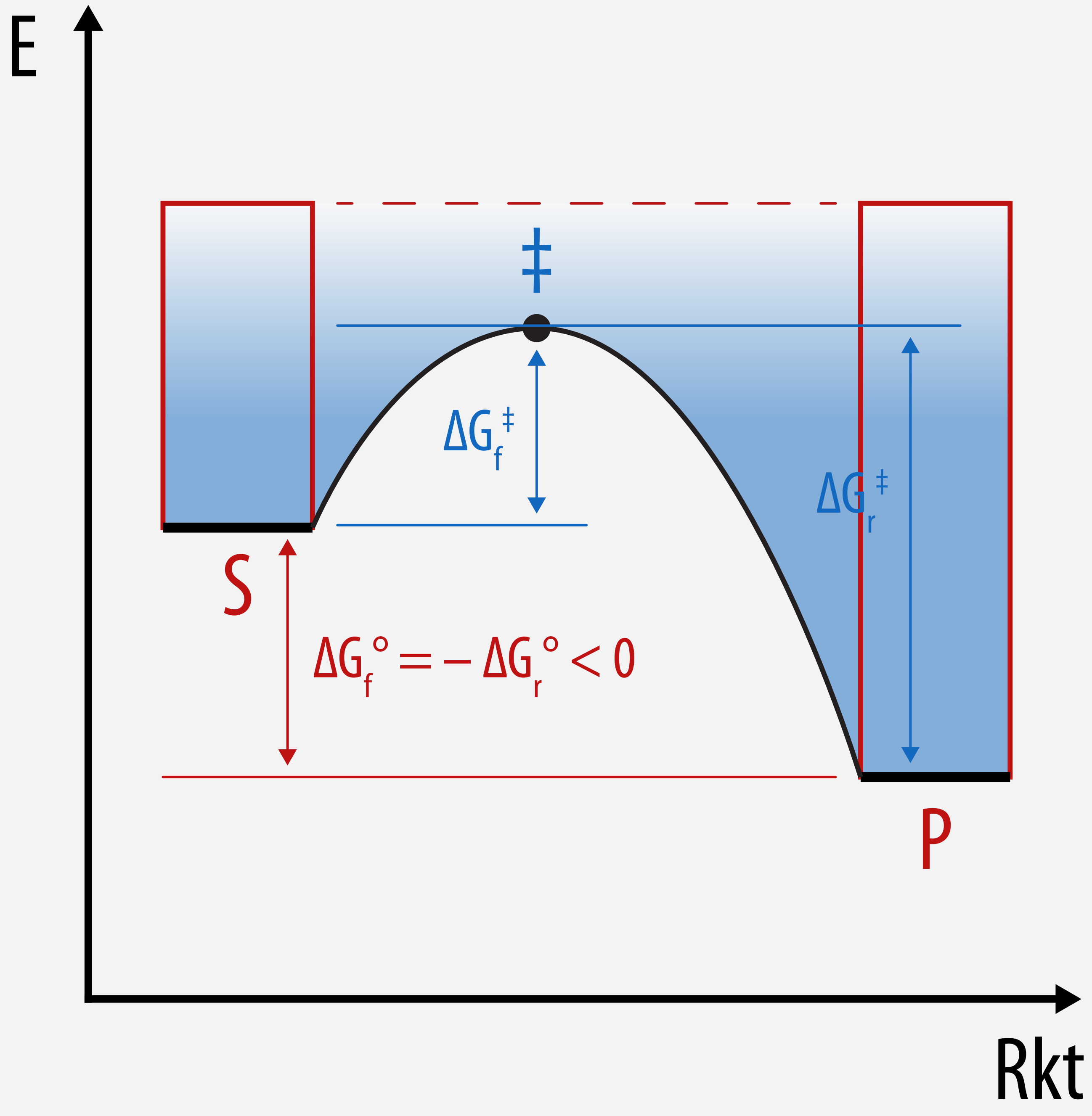
- **forward reaction accelerated, reverse reaction decelerated**
- **ratio of activation energies and hence equilibrium constant *K* changes,**

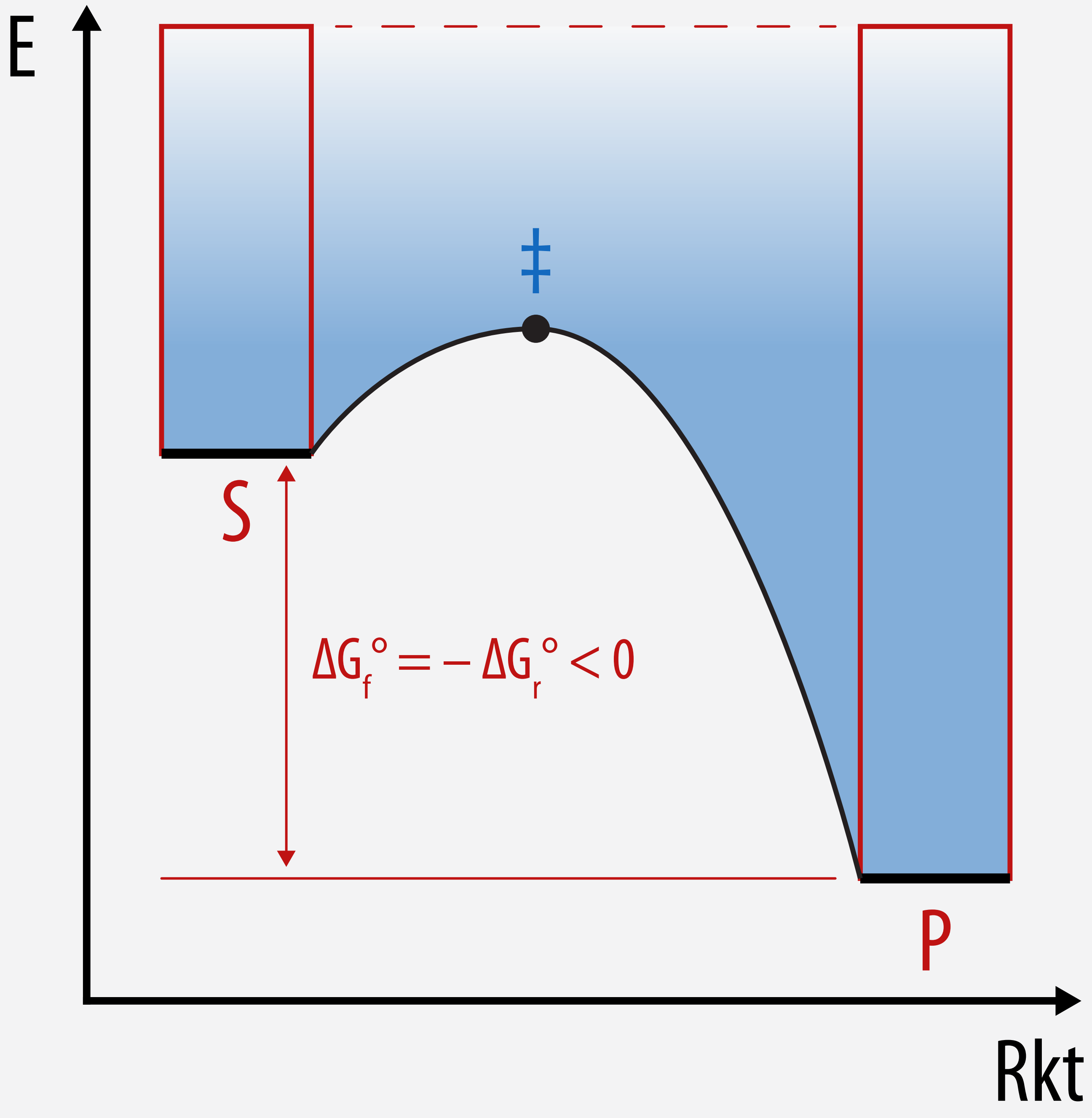
Reactions at Different Temperatures

- change in temperature will both change kinetics and thermodynamics

$$\Delta G_R^\ominus = \Delta H_R^\ominus - T\Delta S_R^\ominus \quad \text{and} \quad \Delta G_R^\ominus = -RT\ln K_R$$

$$\Delta G_f^\ddagger = -RT\ln k_f \quad \text{and} \quad \Delta G_r^\ddagger = -RT\ln k_r$$



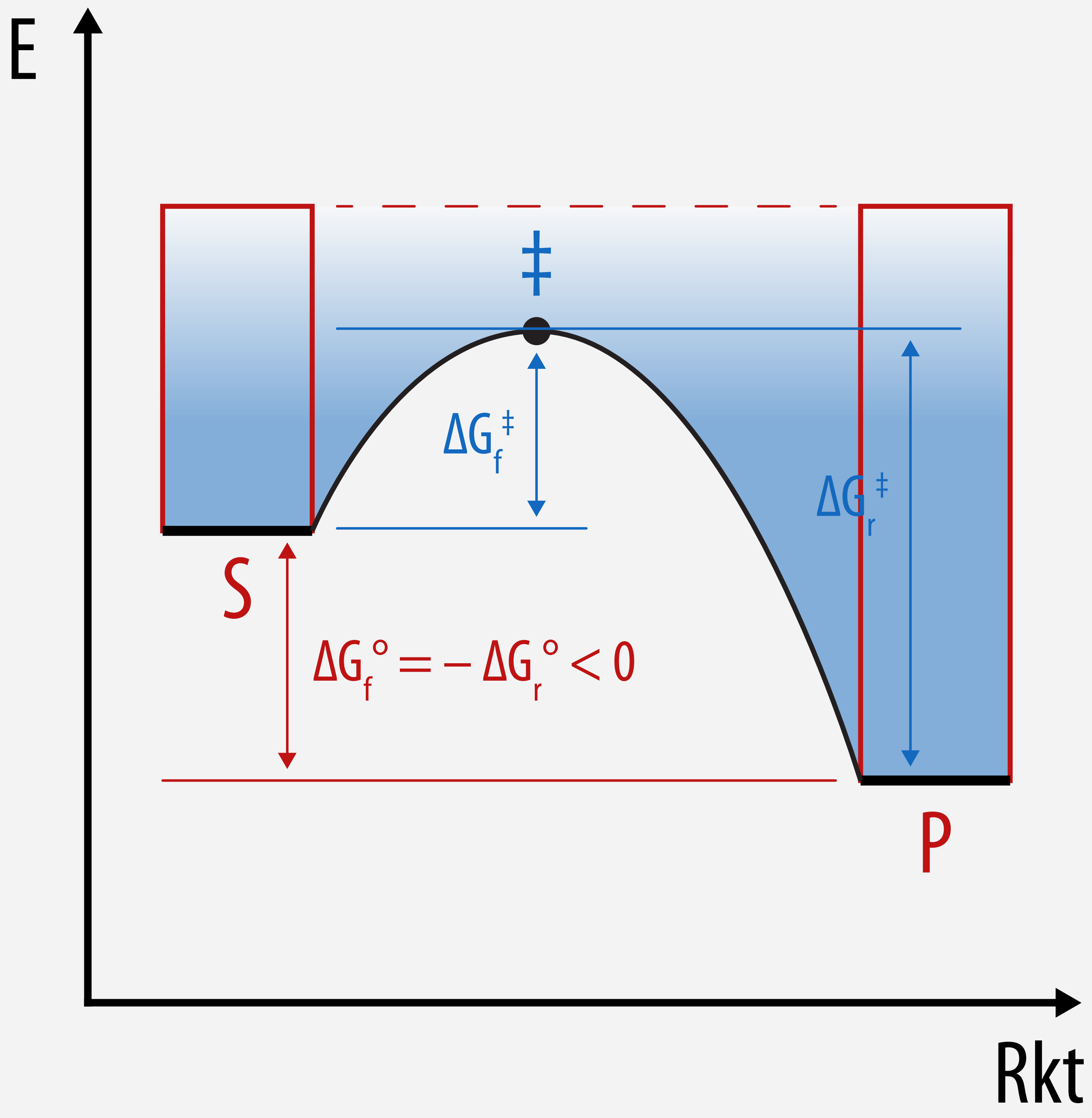


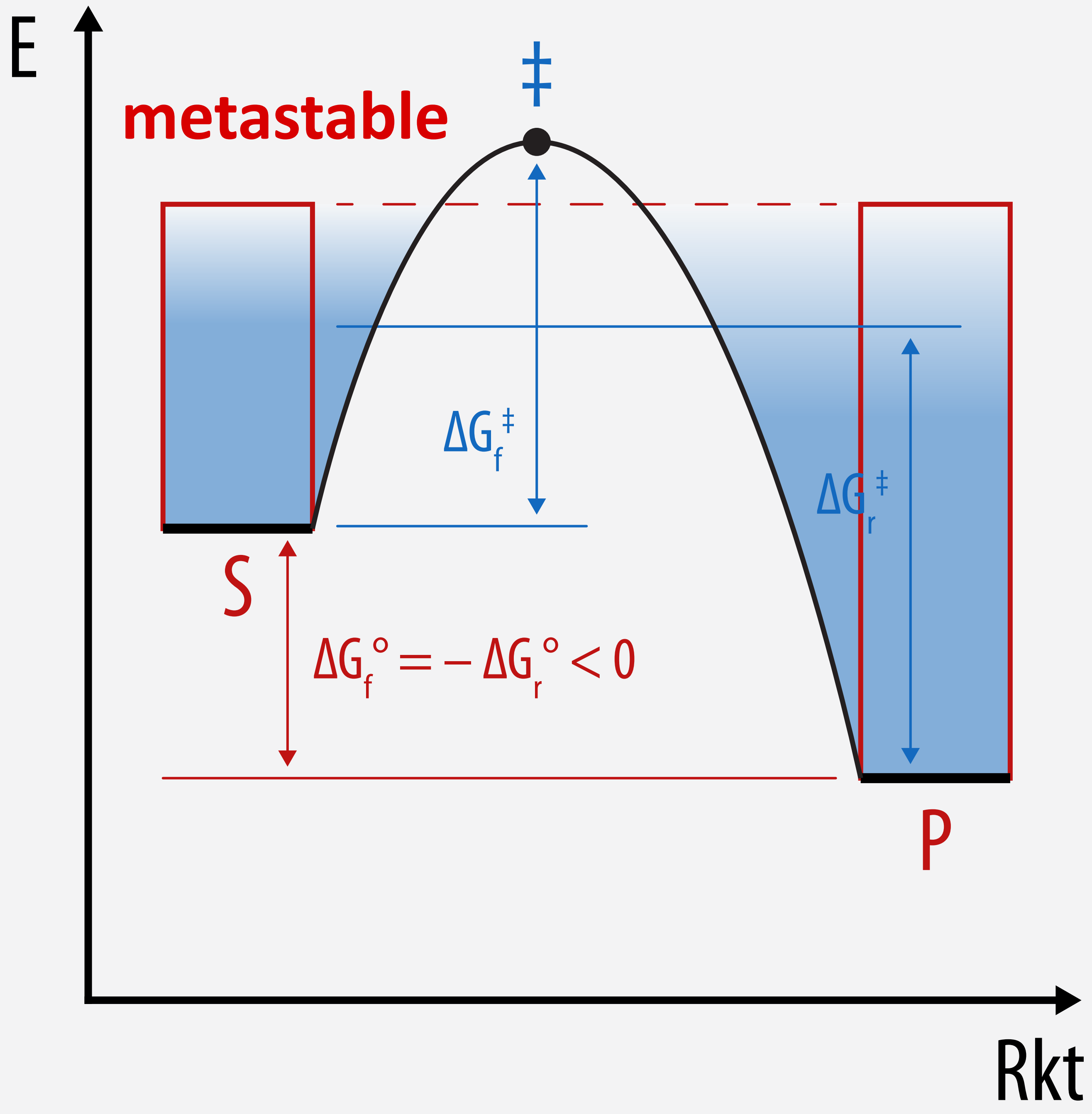
- **temperature change affects equilibrium itself (Gibbs / Gibbs-Helmholtz equations)**
- **change in temperature also changes relative reaction rates (Maxwell distribution)**

Metastable States

- if the activation barrier is far above the thermal energy, the equilibrium cannot be established

$$\Delta G_f^{\ddagger} = -RT \ln k_f \quad \text{and} \quad \Delta G_r^{\ddagger} = -RT \ln k_r$$





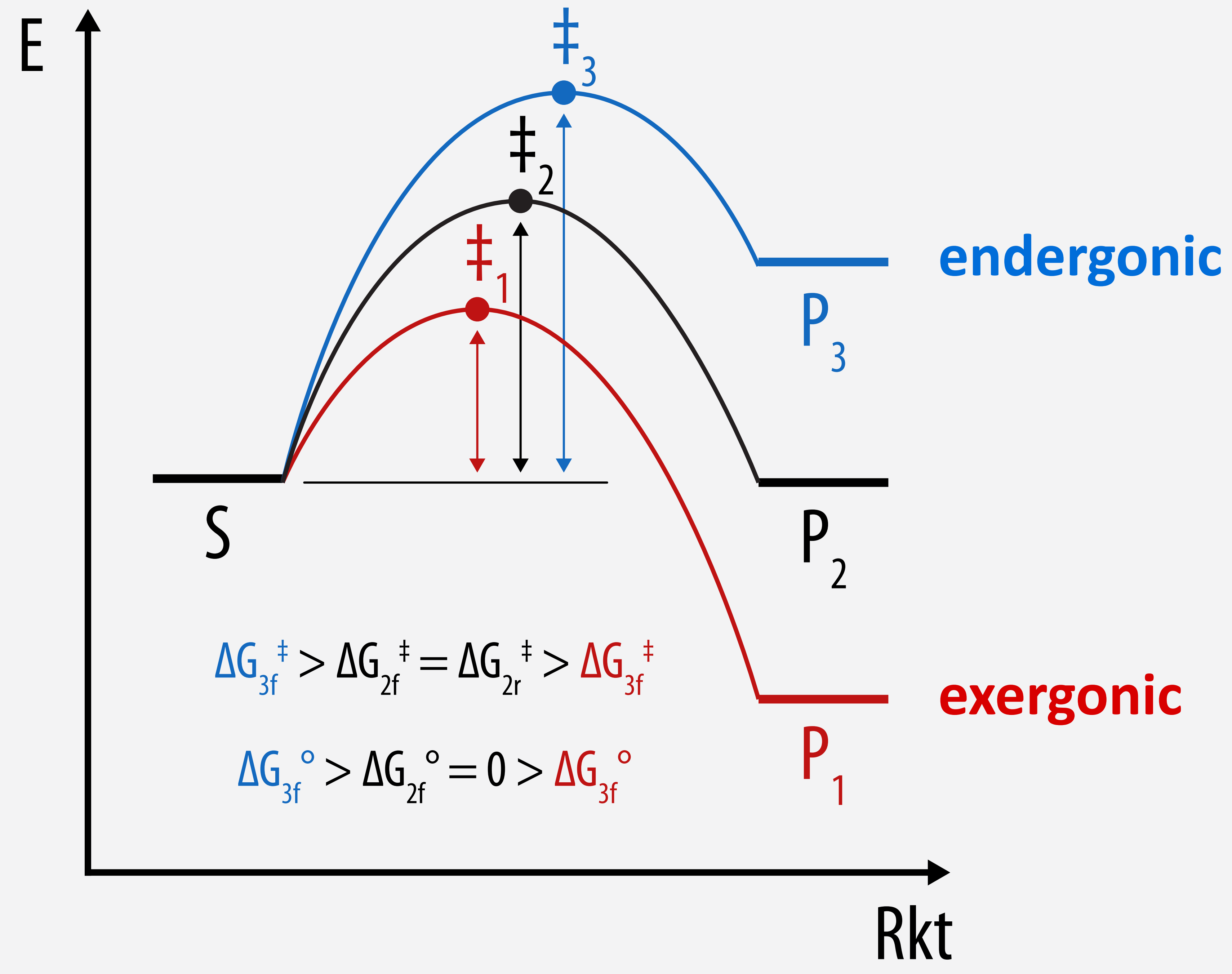
- **for “very high” activation barriers, forward and reverse reaction become “infinitely slow”**
- **even “high-energy reactants” are “kinetically stable”, “kinetically trapped”, “metastable”**

Hammond Postulate and Polanyi Principle

- Polanyi Principle and Hammond Postulate for mechanistically similar, single-step reactions

“late” transition state
higher activation energy

“early” transition state
lower activation energy



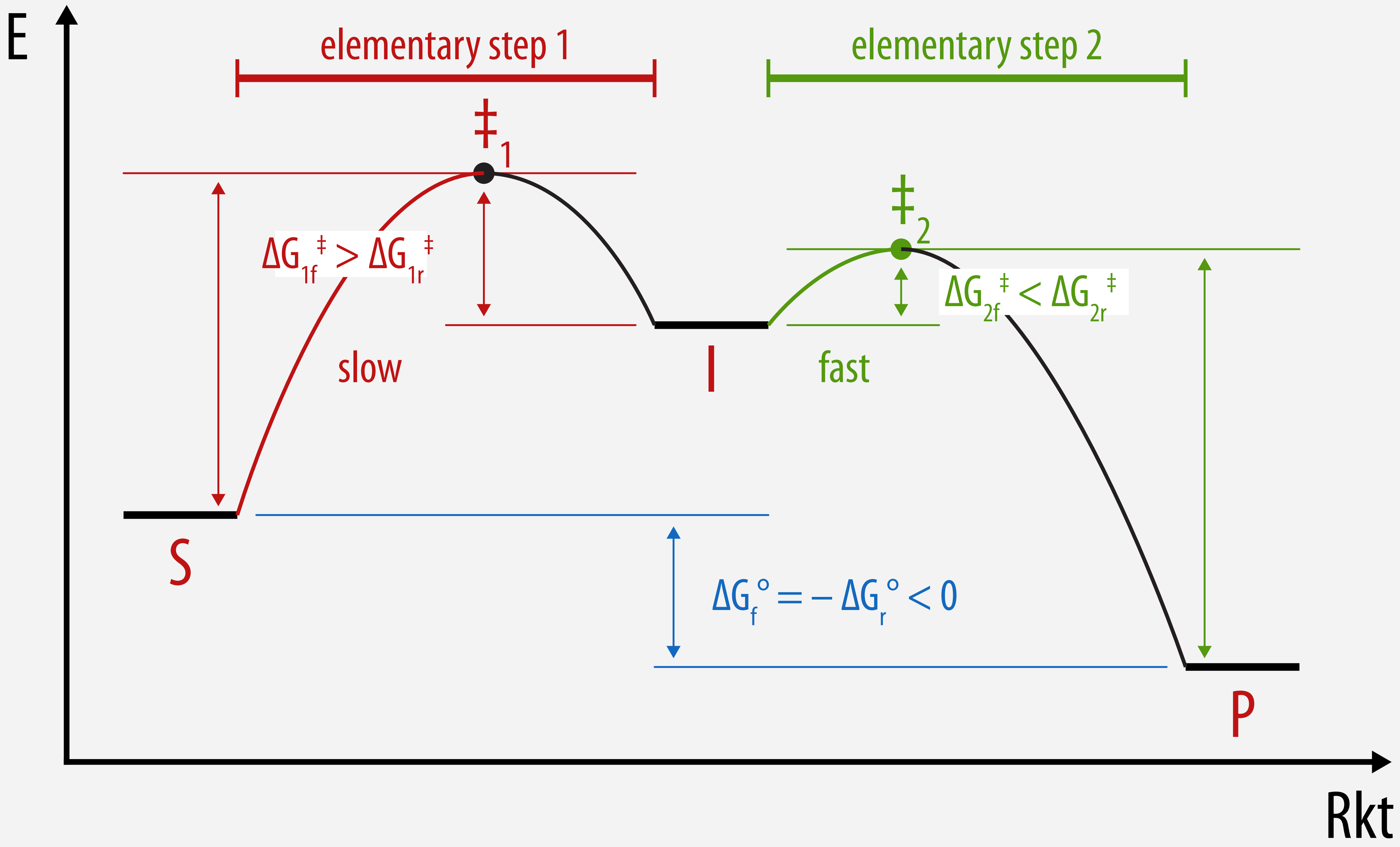
$$\Delta G_{3f}^{\ddagger} > \Delta G_{2f}^{\ddagger} = \Delta G_{2r}^{\ddagger} > \Delta G_{3f}^{\ddagger}$$

$$\Delta G_{3f}^{\circ} > \Delta G_{2f}^{\circ} = 0 > \Delta G_{3f}^{\circ}$$

- **the difference in standard Gibbs’ free energies develops propostionally to reaction progress**
- **activation energies of comparable reactions proportional to difference in Gibbs’ free energies**
- **Hammond Postulate: energetically more similar states are also geometrically more similar**

Multistep Reactions

- elementary reactions are steps between individual local minima in the reaction profile
- starting materials (S) to intermediates (I) and products (P) separated by transition states (‡)



- **overall reaction rate controlled by slowest, rate-determining step**
- **overall reaction order controlled by molecularity of the slowest, rate-determining step**
- **typically, the generation of the reactive intermediate is the rate-determining step (Polanyi)**
- **intermediate is approximation for transition state of the rate-determining step (Hammond)**

Learning Outcome

- **reaction thermodynamics concerned with the energy balance of reactions**
  - Gibbs free energy decides whether / in which sense a reaction proceeds
  - standard Gibbs free energy gives inherent energetics of a reaction
  - Gibbs-Helmholtz equation describes contribution of enthalpy & entropy
  - enthalpy represents sum of bond formations and cleavages
  - entropy represents changes in the degrees of freedom
- **reaction kinetics concerned with the rates of reactions**
  - relation of reaction order and molecularity in the rate-determining step
  - the lower the activation energy, the faster the reaction
- **Polanyi principle and Hammond postulate**