4 Mechanisms of Organic Reactions

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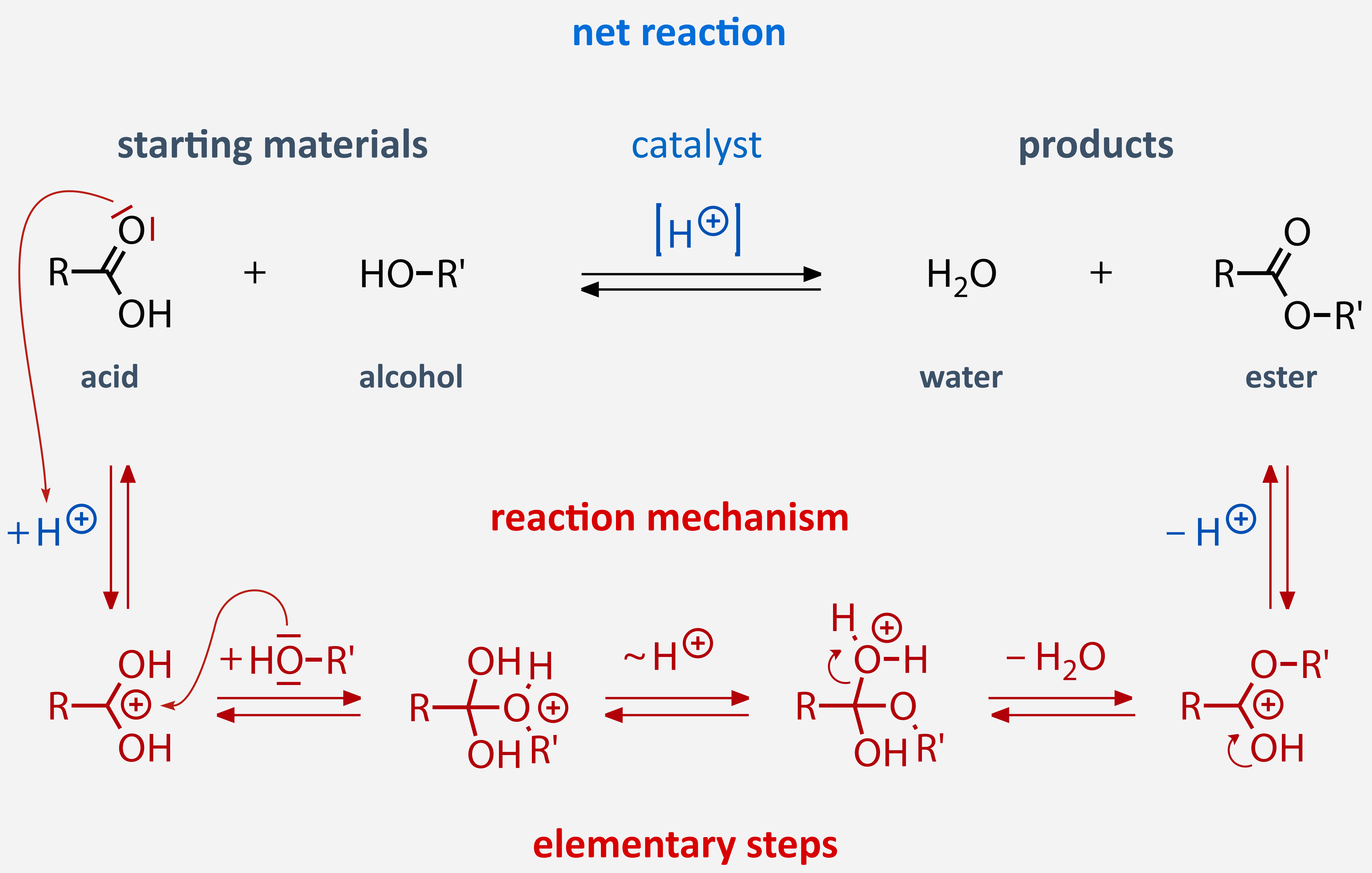
Learning Goals and Reading Recommendations

- **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

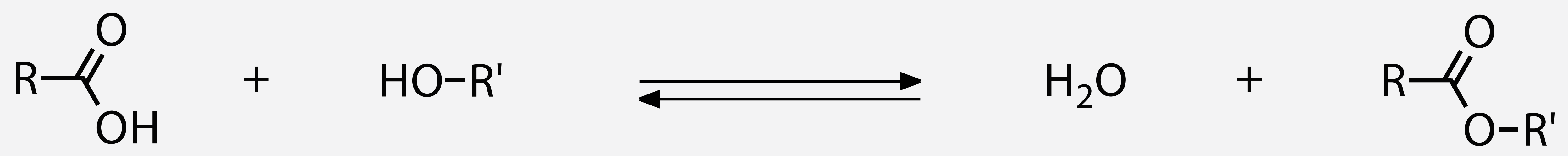
Net Reaction versus Mechanism



- **net reaction** 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**

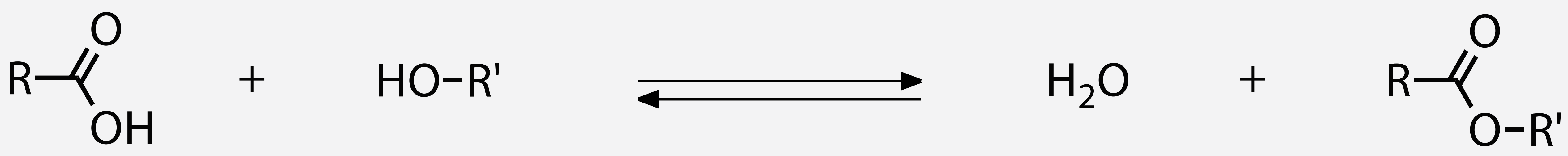
$\Delta G_R = 0$ **reaction is in equilibrium**

$\Delta G_R < 0$ **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



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

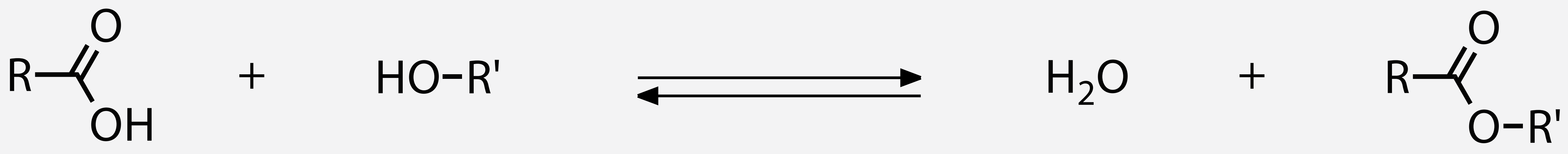
$$K_R = \frac{[\text{R–COOR'}]_{\text{eq}}[\text{H}_2\text{O}]_{\text{eq}}}{[\text{R–COOH}]_{\text{eq}}[\text{R'–OH}]_{\text{eq}}} \qquad pK_R = -\log K_R$$

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

- **equilibrium constant K_R is the ratio of reactant concentrations in equilibrium**
- **standard free reaction energy $\Delta G°_R$ 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**

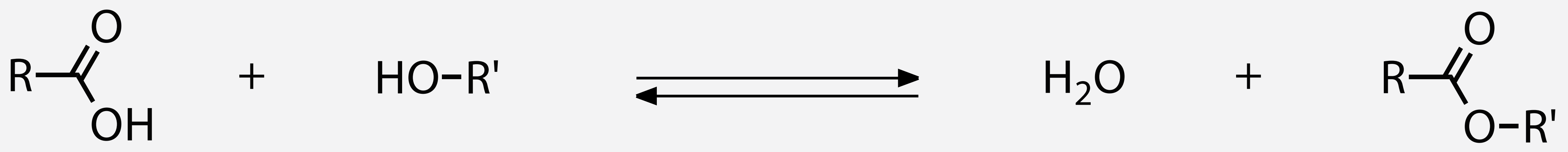
$\Delta S_R^\ominus < 0$ **exotropic reactions, disorder, degrees of freedom decrease**

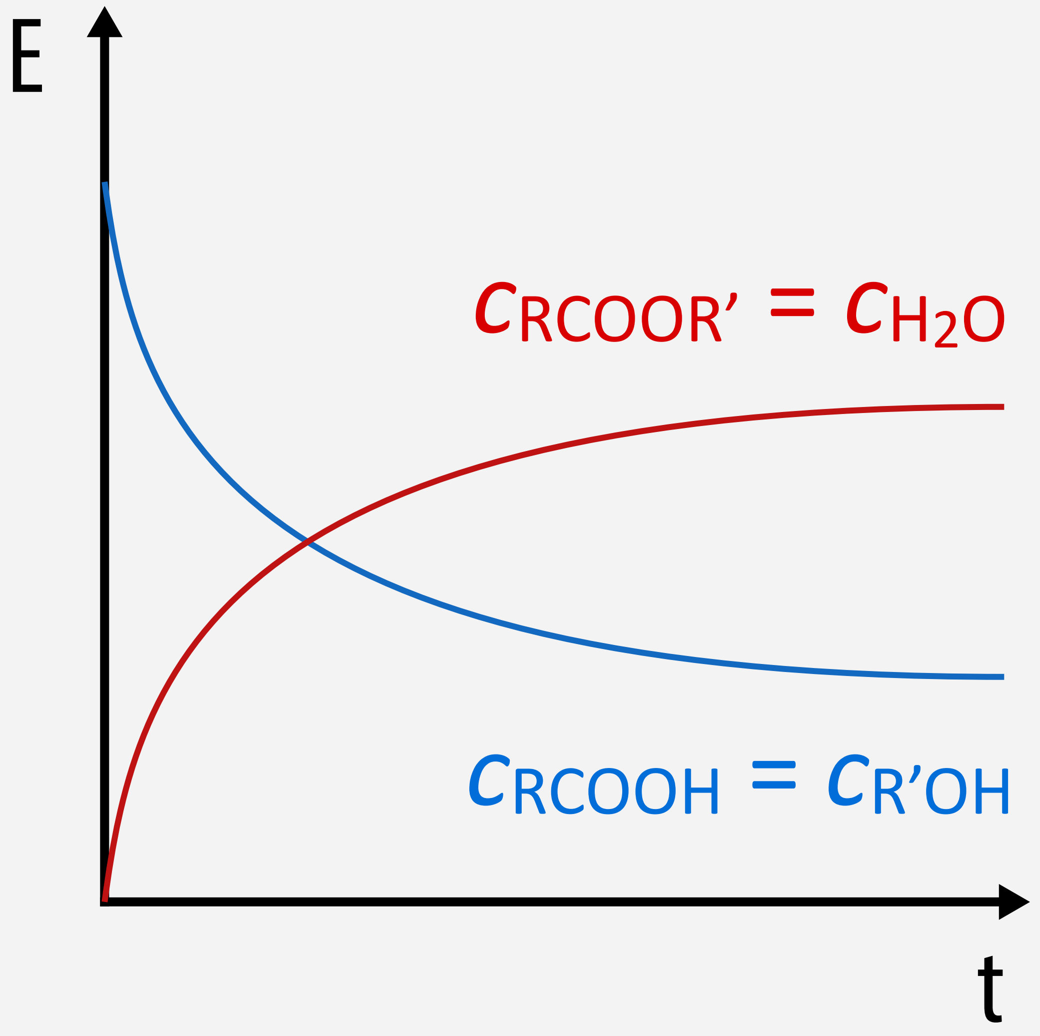
$\Delta S_R^\ominus > 0$ **endotropic reactions, disorder, degrees of freedom increase**

- **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 $r = \mathrm{d}c_i/\mathrm{d}t$ 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

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

- **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**

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

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

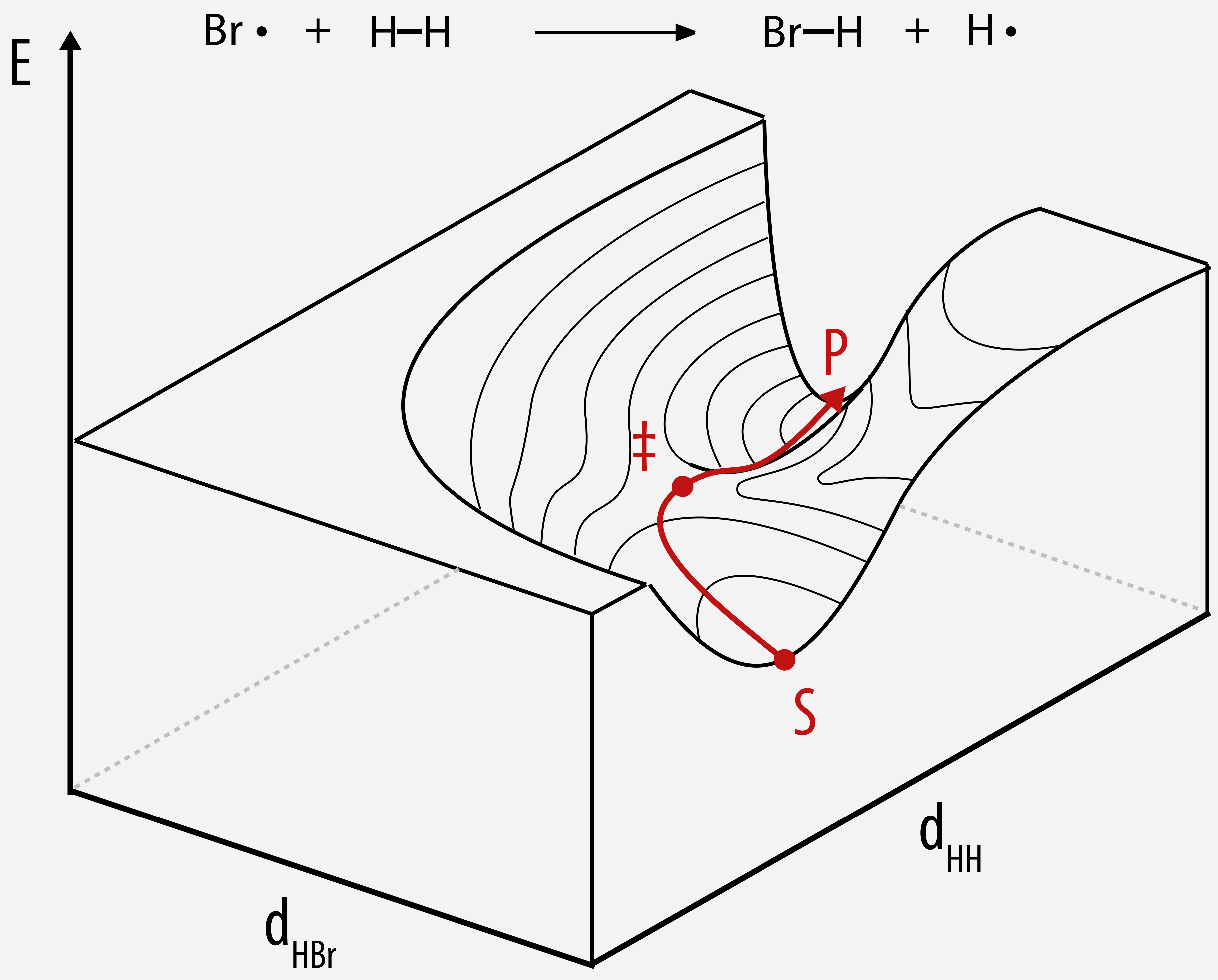
$$k_{2f} \cdot [A][B] = k_{2r} \cdot [C][D]$$

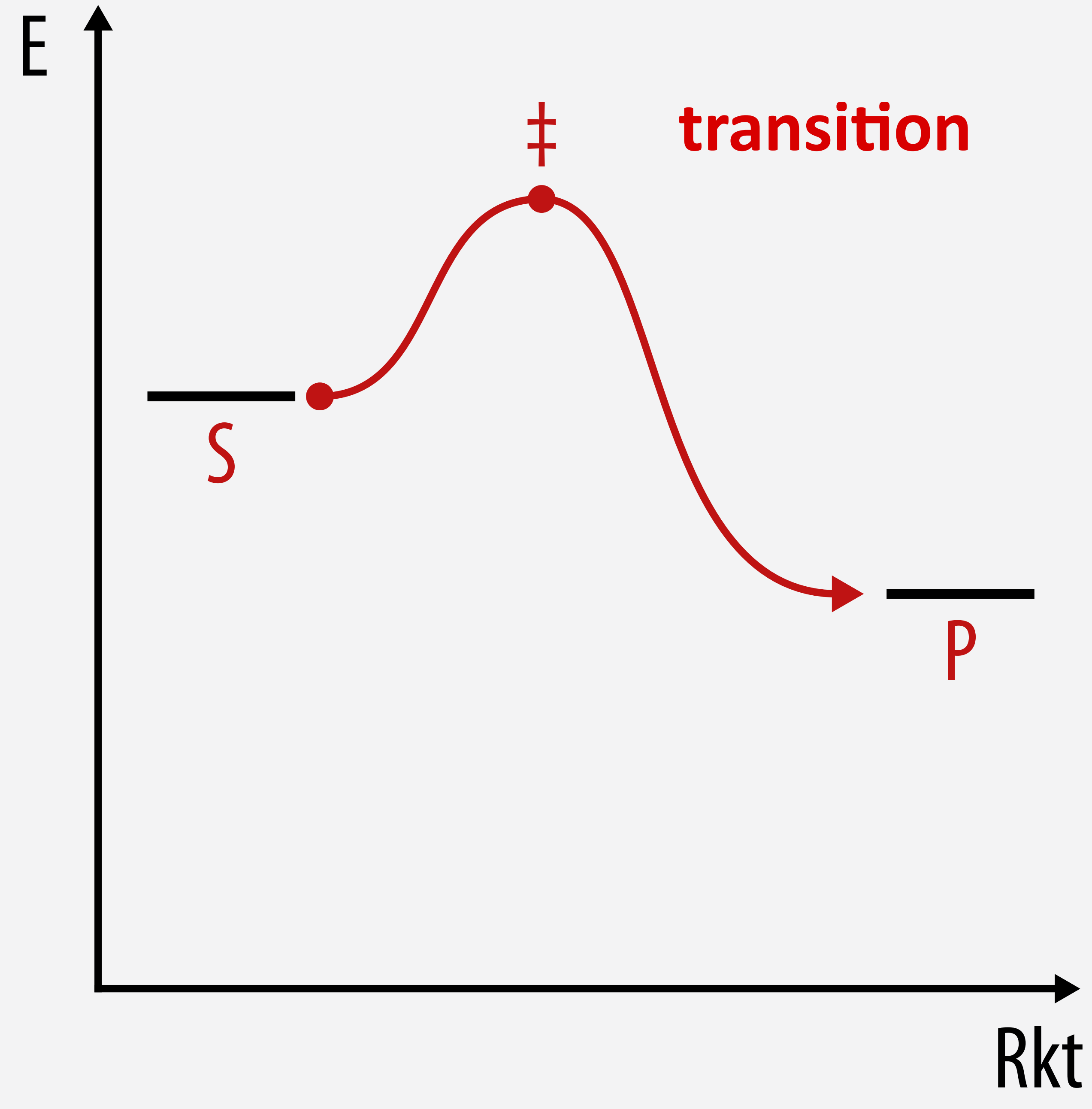
$$\frac{k_{2f}}{k_{2r}} = \frac{[C][D]}{[A][B]} = K$$

- **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





- **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)**

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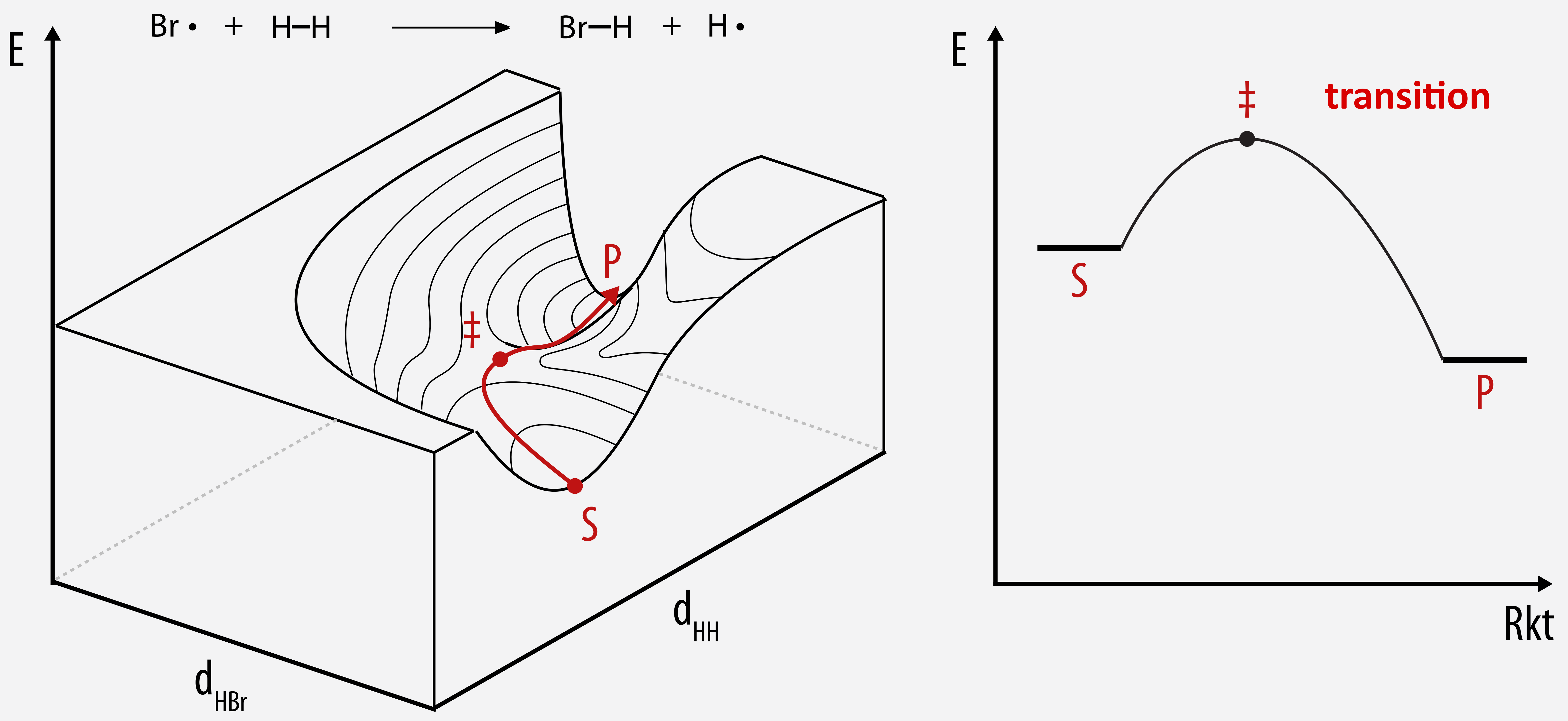

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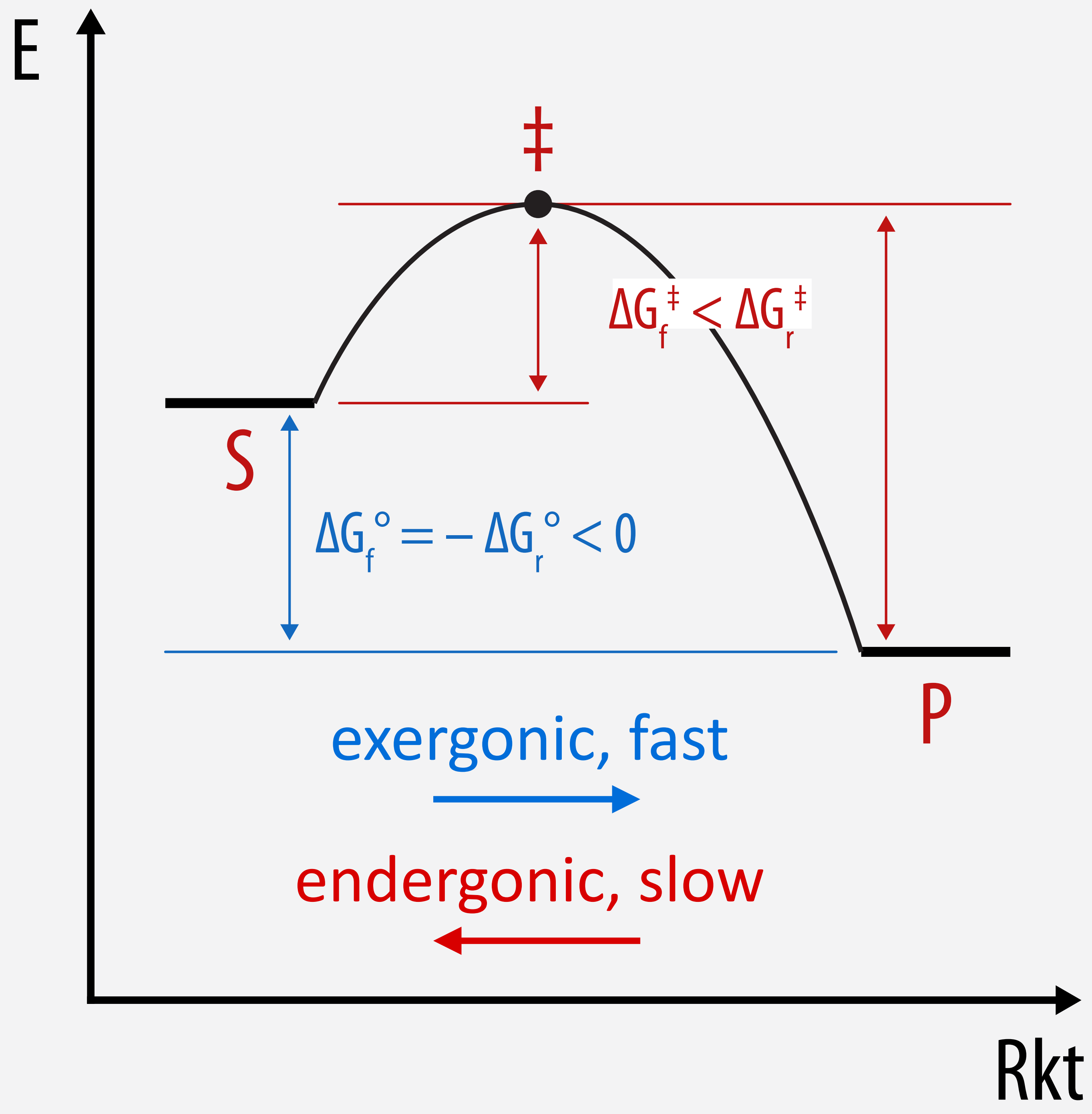
Relation of Reaction Profiles, Thermodynamics, and Kinetics

- reaction profiles illustrate both thermodynamics and kinetics of chemical reactions



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

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

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

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

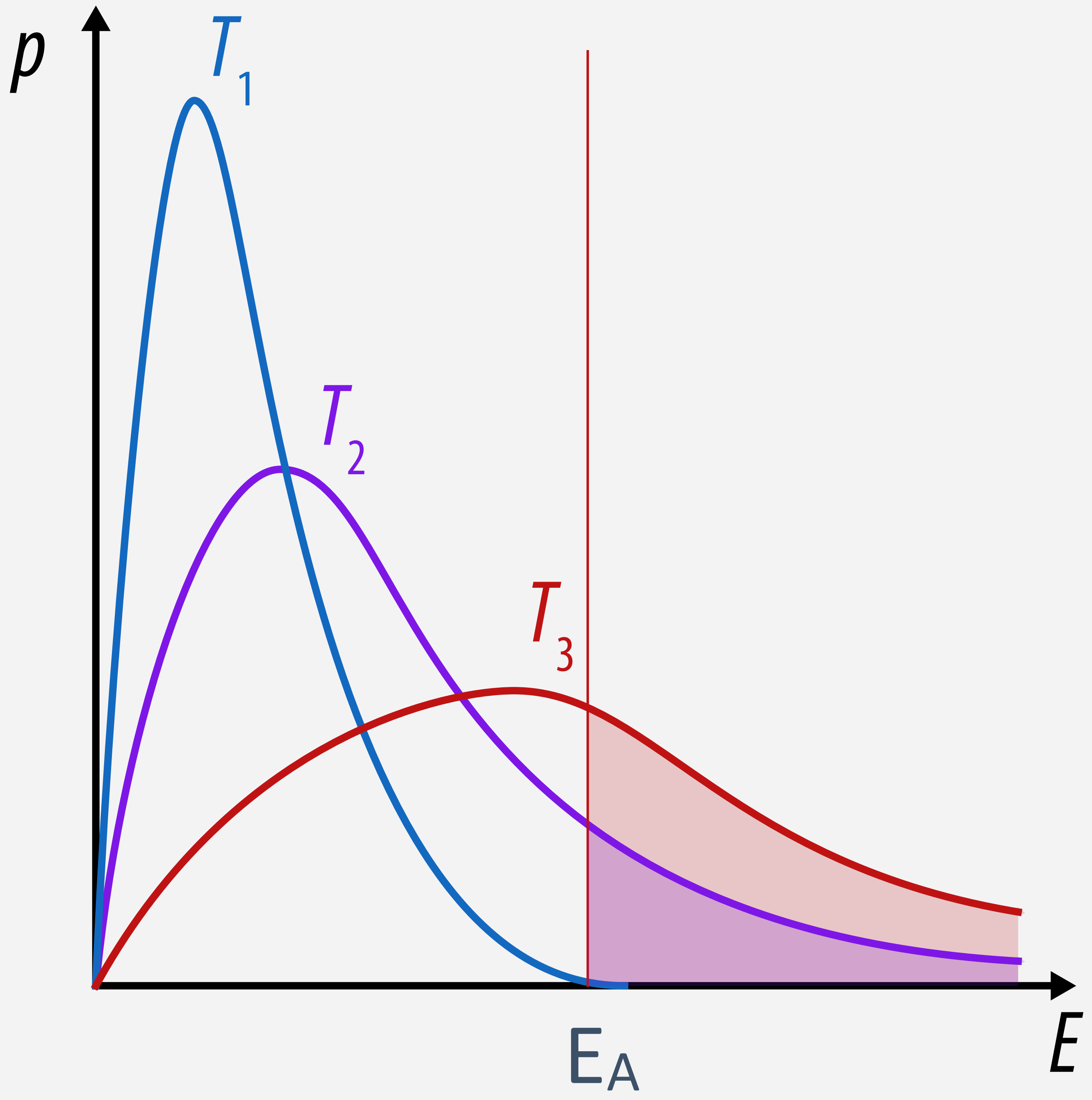
$$E_{A,f} \approx \Delta G_f^{\ddagger} = -RT \ln k_f$$

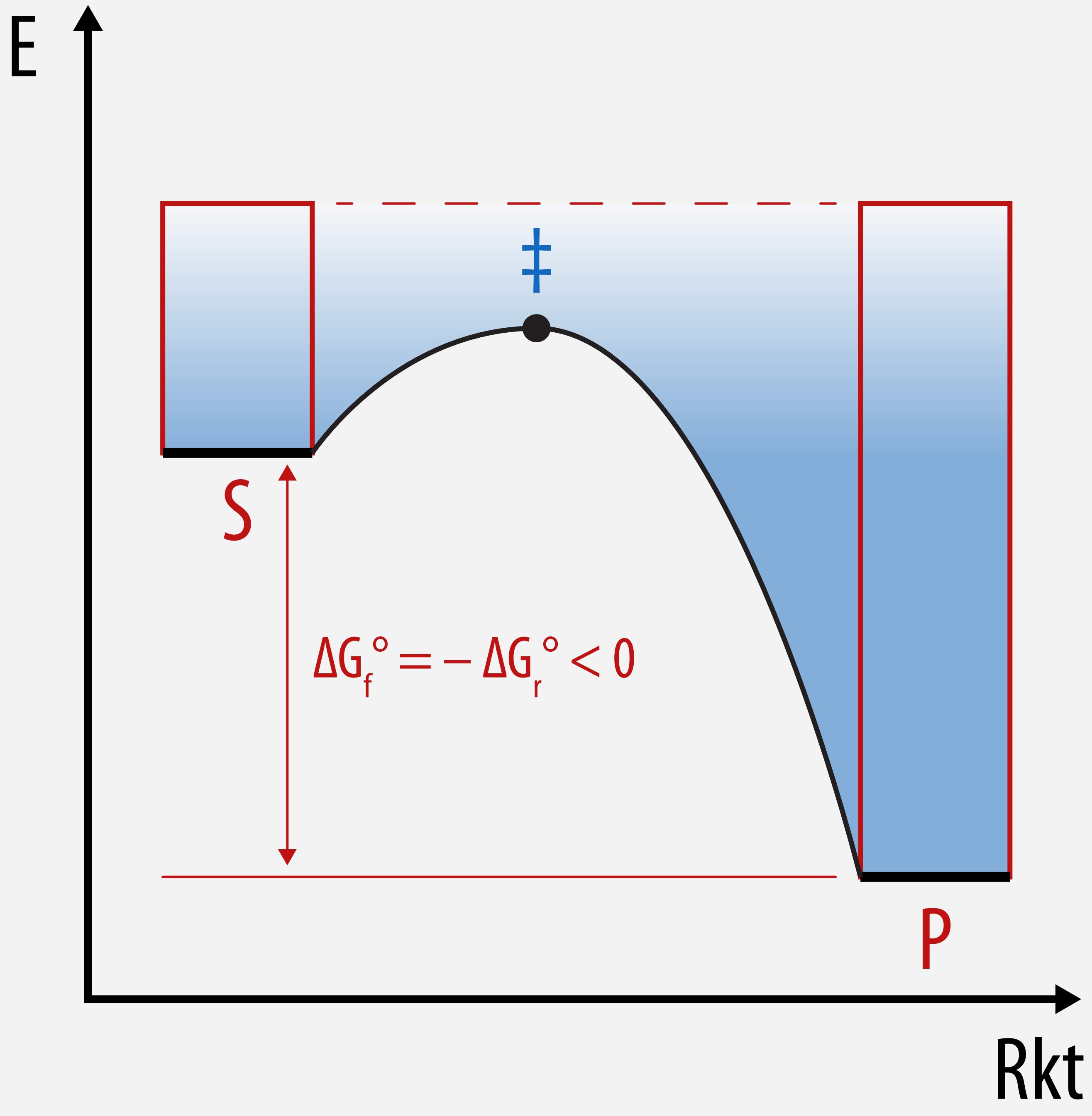
- **standard free reaction energy Δ*G*° is difference between (S) and (P) energies**
- **Δ*G*° is also the difference between free transition energies Δ*G*‡ of forward/reverse reactions**
- **reaction rates *k* depend on activation energies E_A ≈ Δ*G*‡ of chemical reactions**

Reaction Kinetics and Thermal Energy

- molecules have energies according to the Boltzmann probability distribution p

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



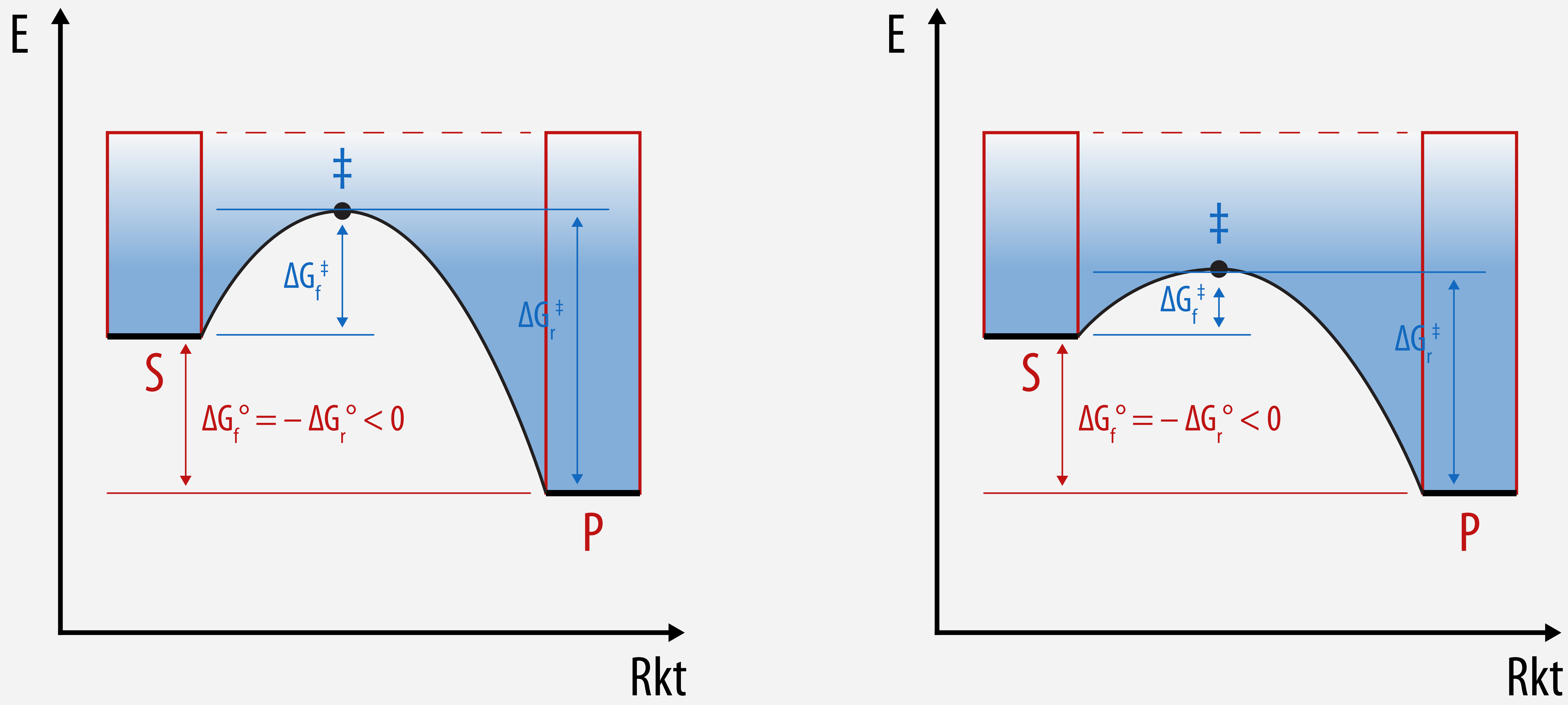


- **at higher temperatures, a larger fraction of molecules overcomes activation energy E_A**
- **both forward and reverse reaction are accelerated**

Reaction Profiles: Thermodynamics and Kinetics

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

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

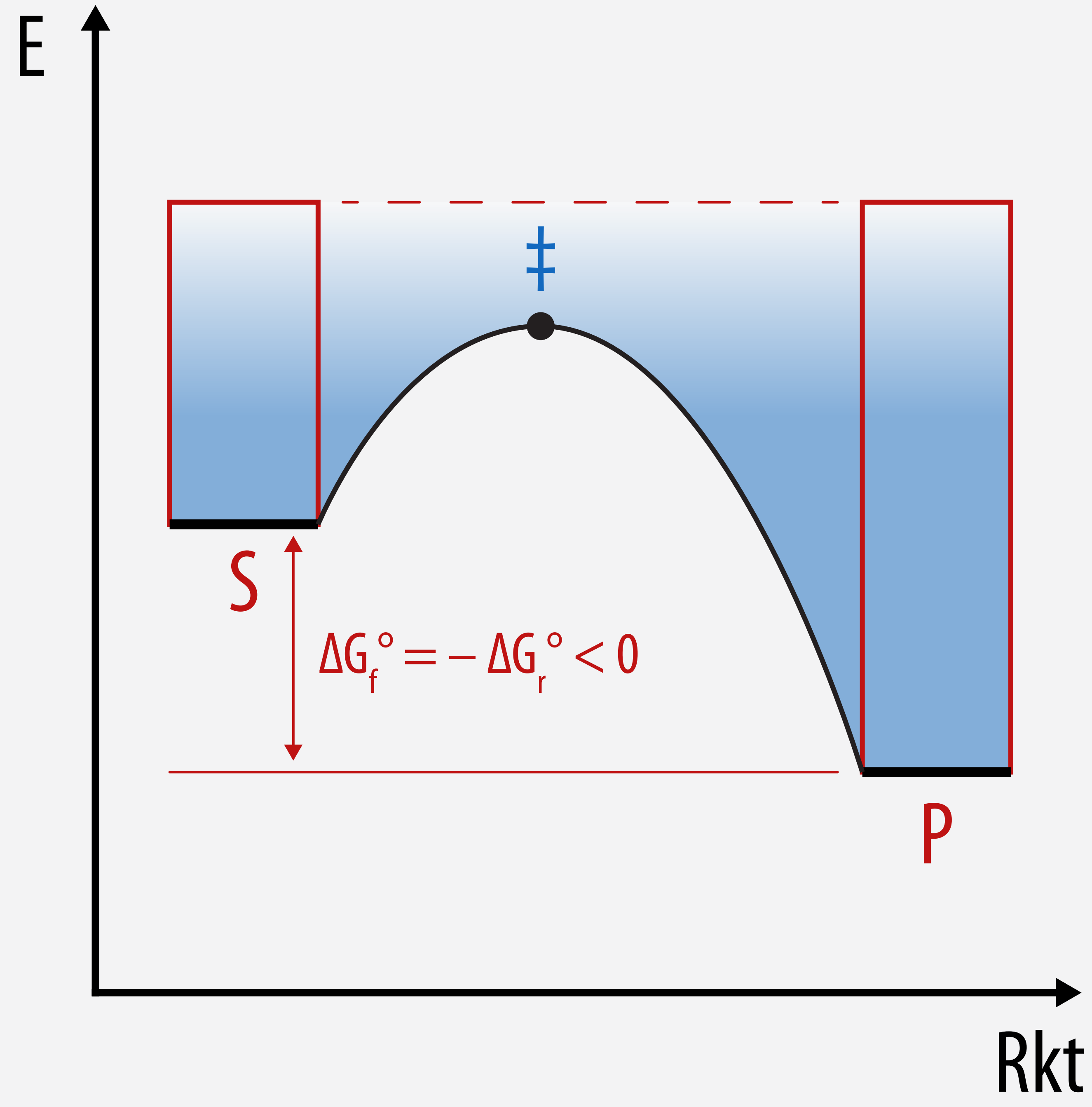


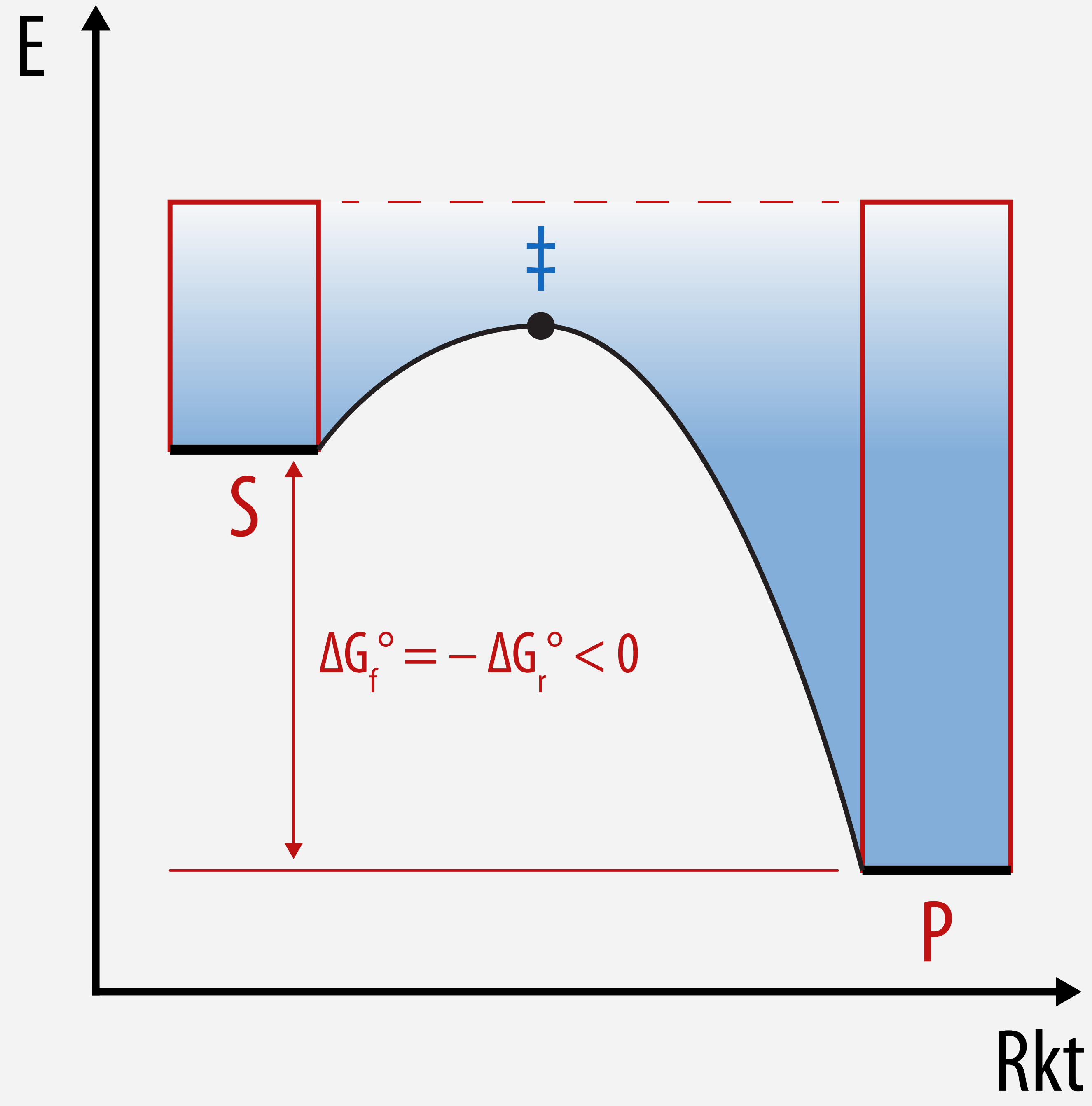
- **at a lower activation barrier, forward/reverse reaction both accelerated by same ratio**
- **catalyst provides new reaction pathway with lower activation barrier (same equilibrium)**

Kinetic Interpretation of the Equilibrium

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

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



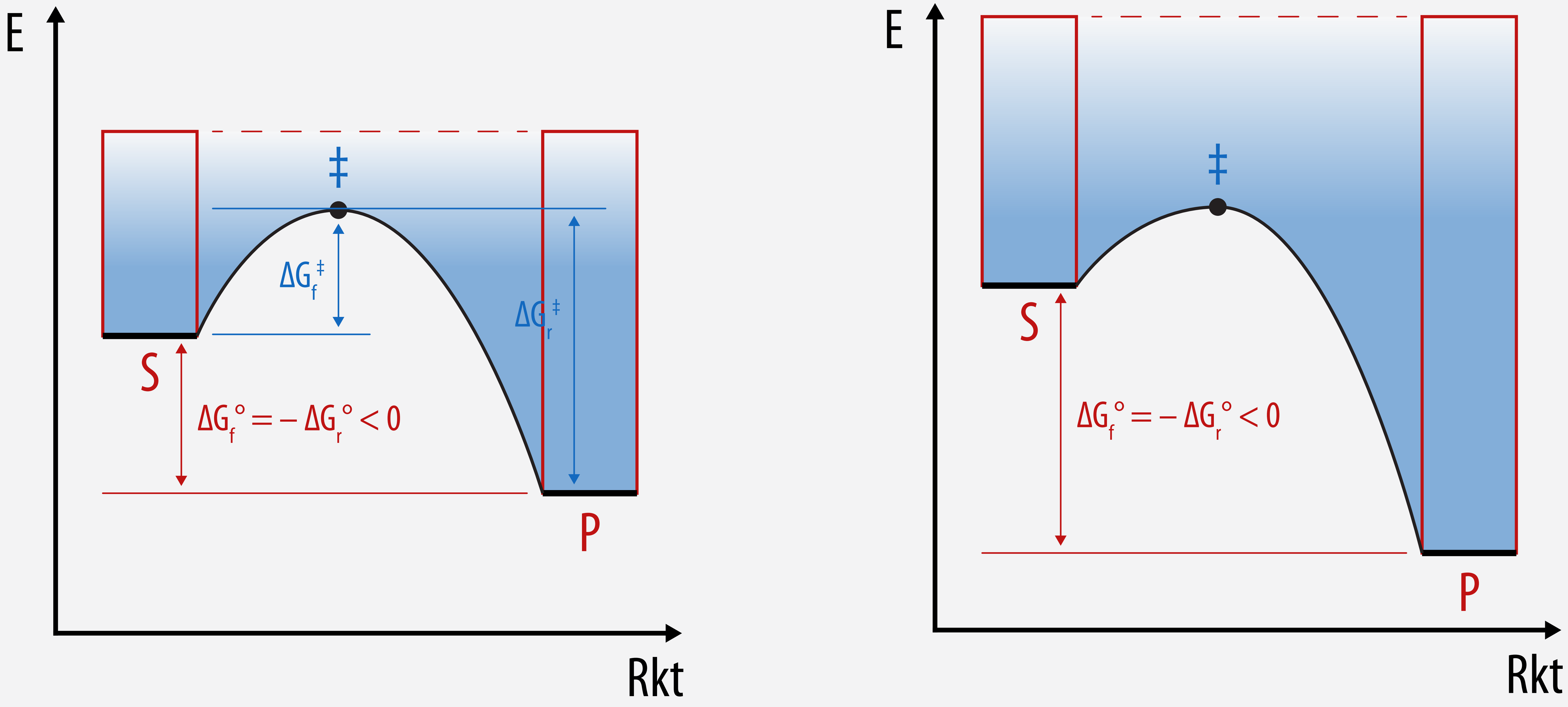


- **forward reaction accelerated, reverse reaction decelerated**
- **ratio of activation energies and hence equilibrium constant *K* changes,**

Reactions at Different Temperatures

- change in temperature will both change kinetics and thermodynamics

$$\Delta G_R^{\ominus} = \Delta H_R^{\ominus} - T\Delta S_R^{\ominus} \quad \text{and} \quad \Delta G_R^{\ominus} = -RT\ln K_R$$
$$\Delta G_f^{\ddagger} = -RT\ln k_f \quad \text{and} \quad \Delta G_r^{\ddagger} = -RT\ln k_r$$

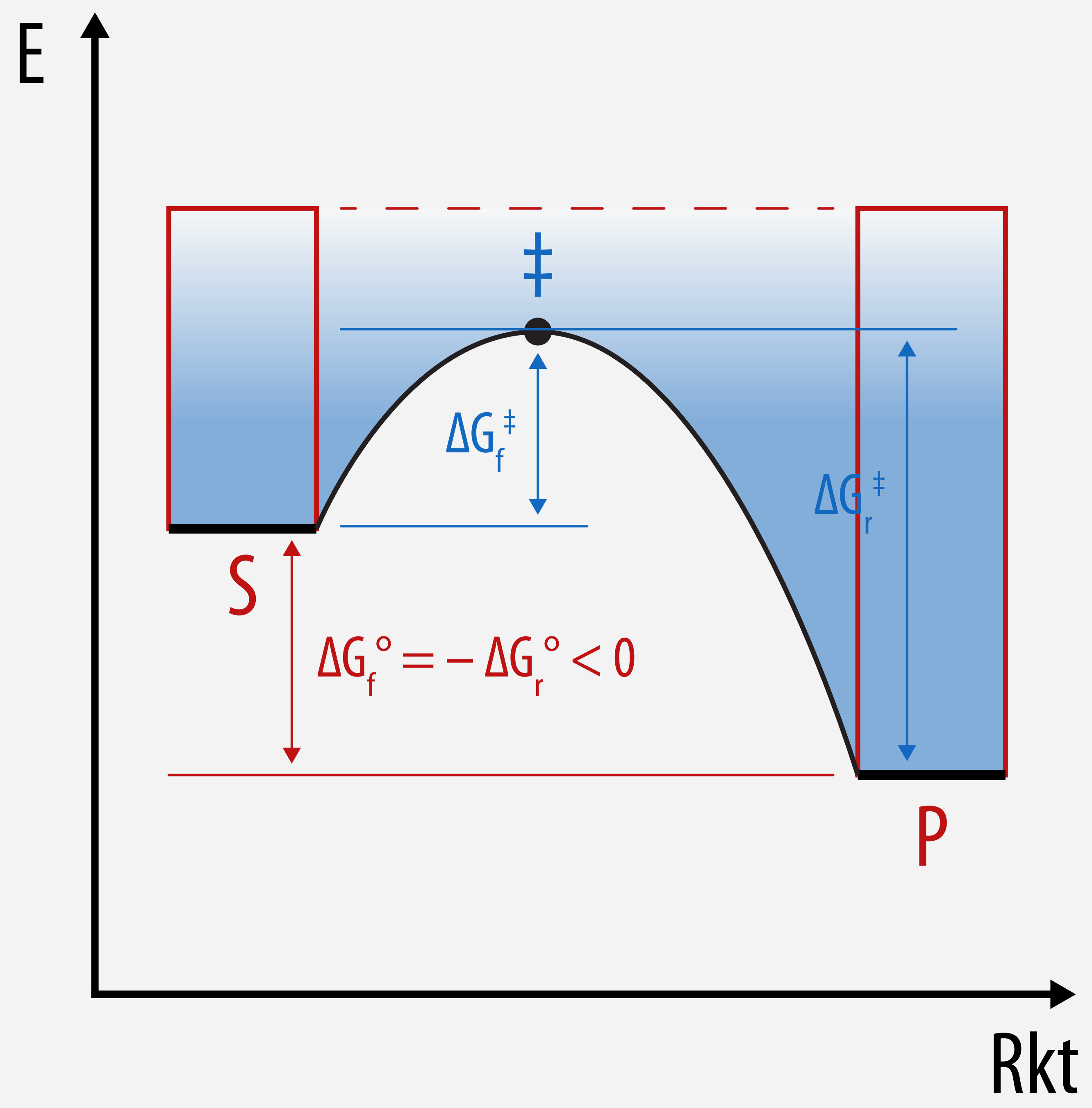


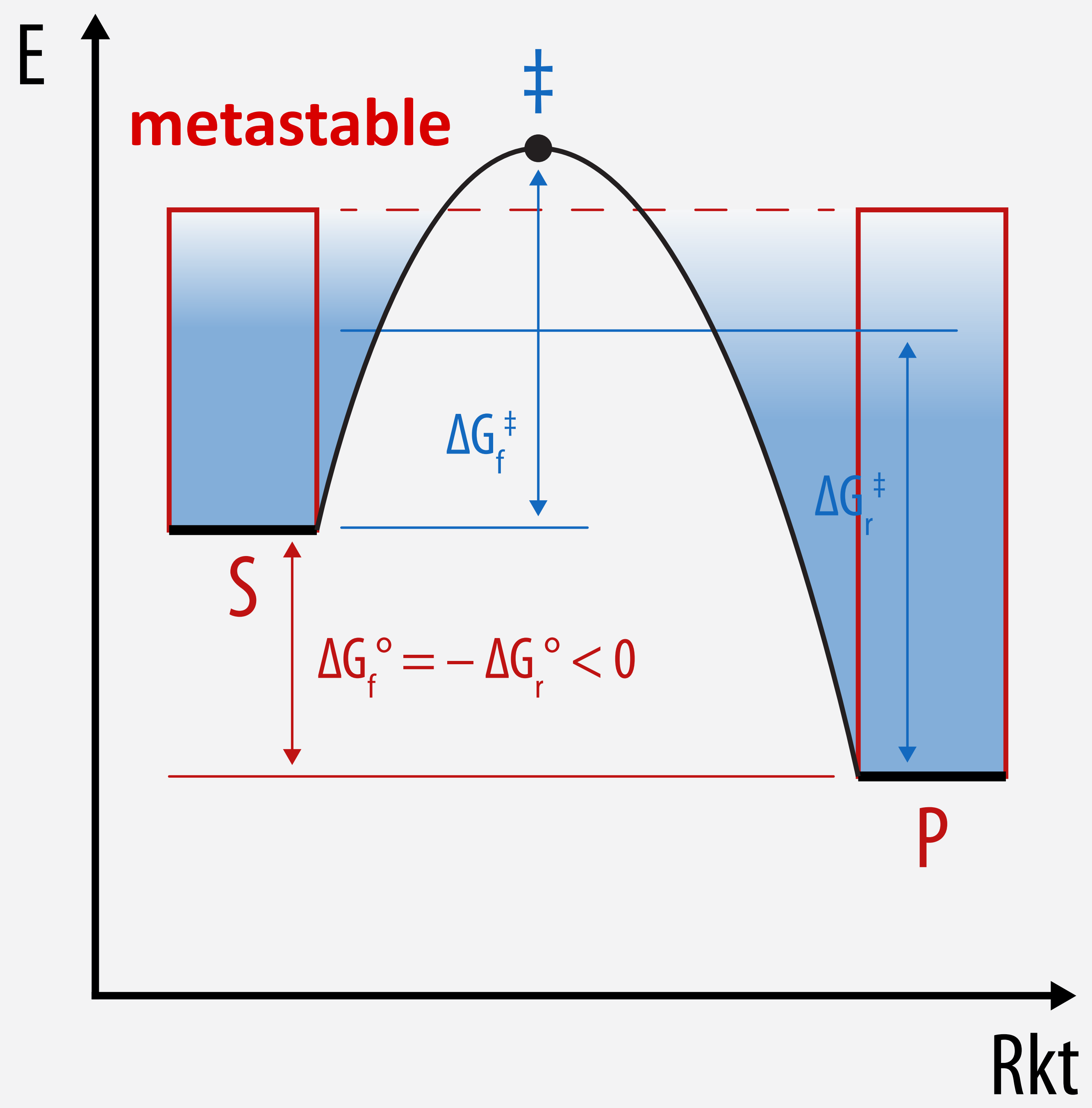
- **temperature change affects equilibrium itself (Gibbs / Gibbs-Helmholtz equations)**
- **change in temperature also changes relative reaction rates (Maxwell distribution)**

Metastable States

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

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

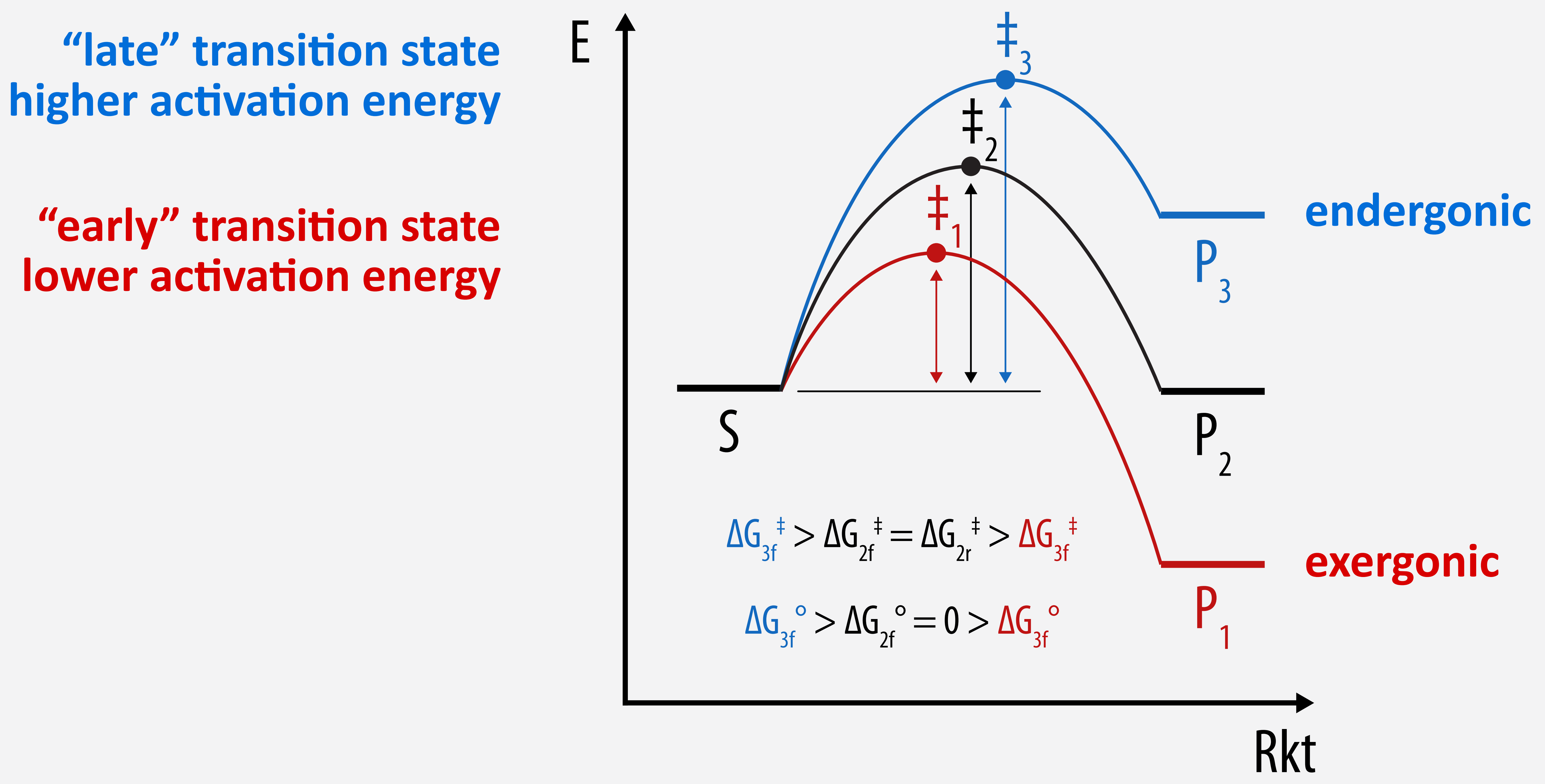




- **for "very high" activation barriers, forward and reverse reaction become "infinitely slow"**
- **even "high-energy reactants" are "kinetically stable", "kinetically trapped", "metastable"**

Hammond Postulate and Polanyi Principle

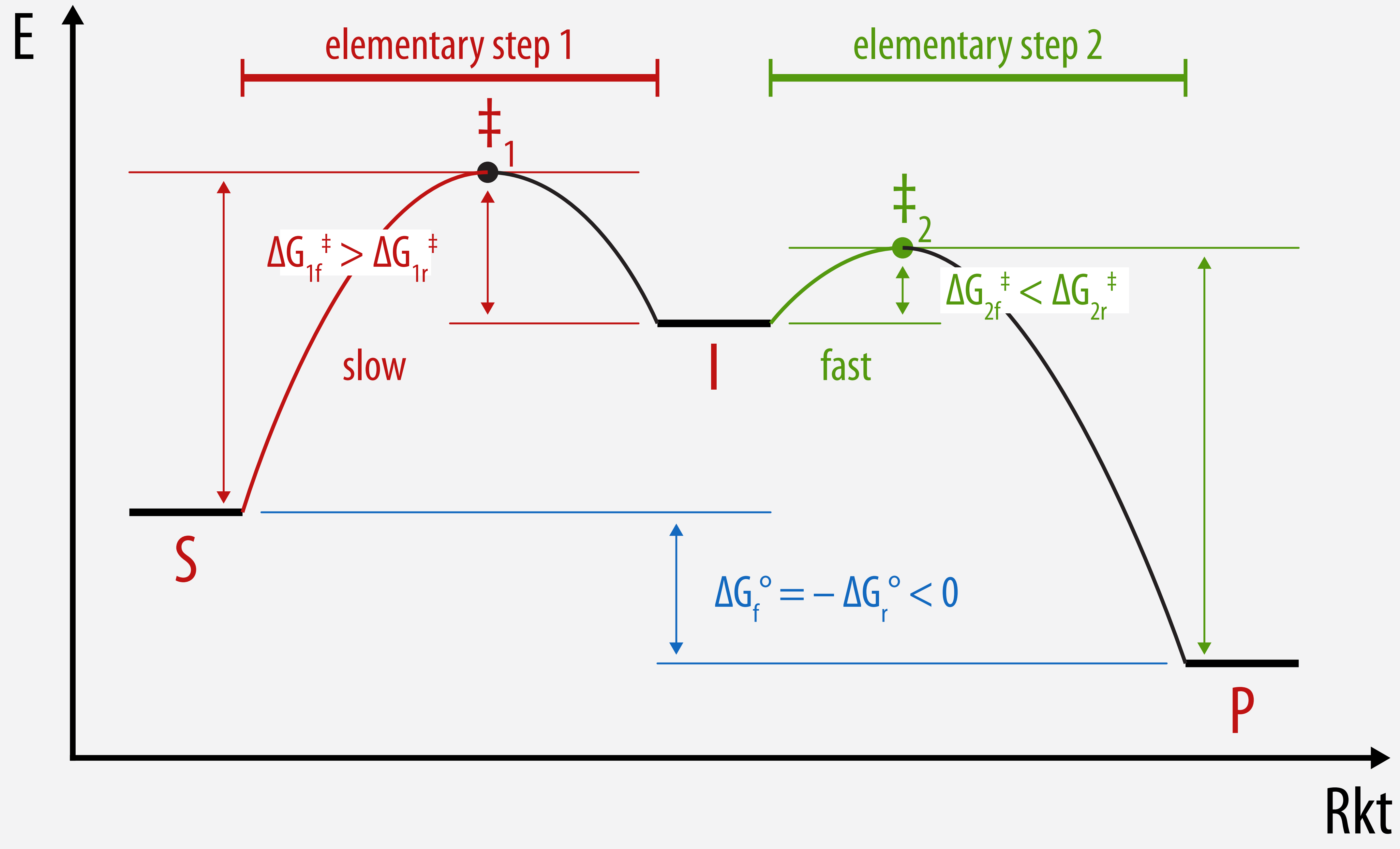
- Polanyi Principle and Hammond Postulate for mechanistically similar, single-step reactions



- **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



- **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)**

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**