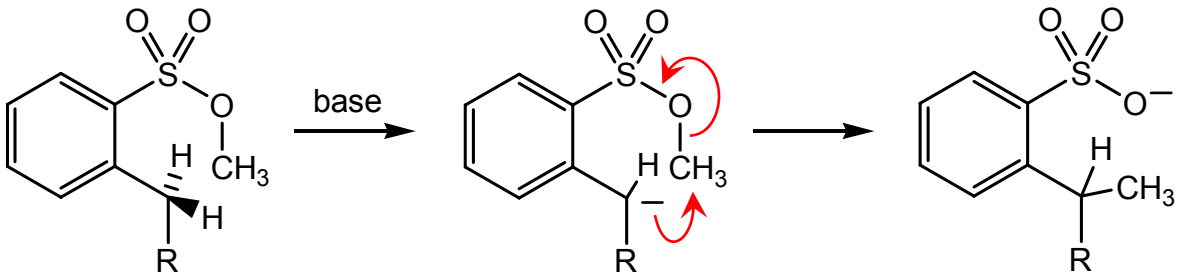
Isotope Tracking

Easier way to use isotopes in mechanistic analysis is to simply track location of isotope in products.

Classic Example: Eschenmoser's experiment.



Expected that reaction was ***intra***molecular.

Tenud, L.; Farouq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2054.

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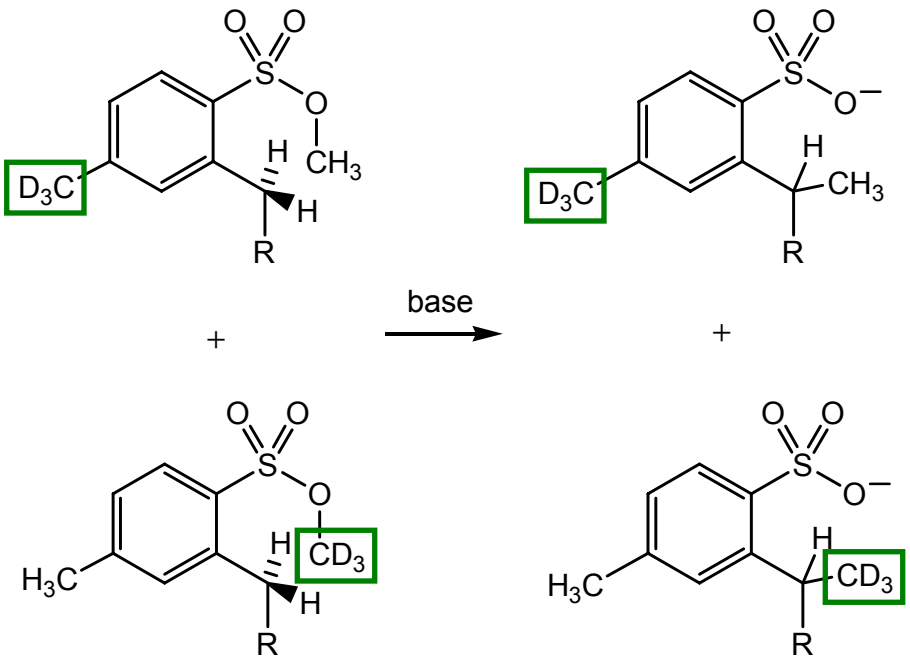

(expected)

Tenud, L.; Farouq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2054.

Isotope Tracking

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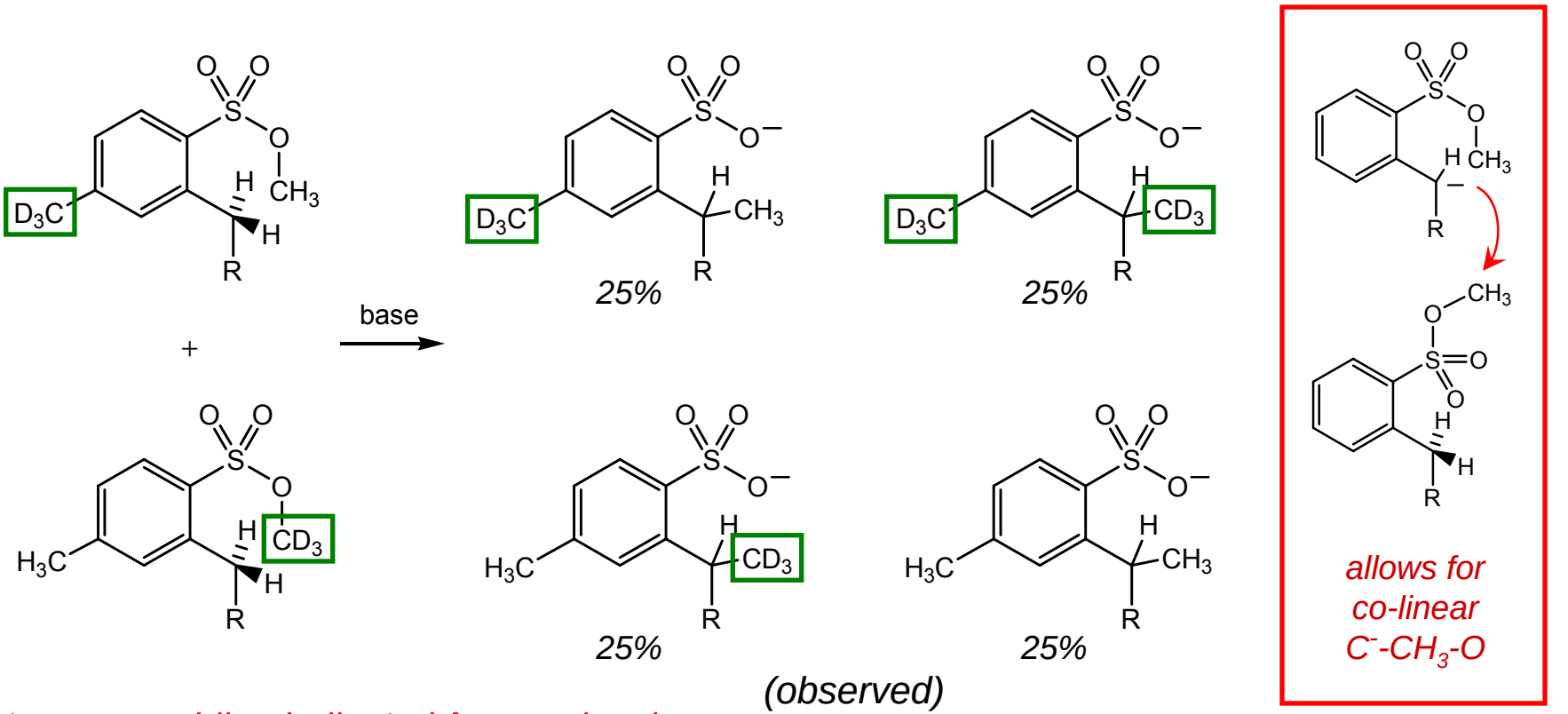

Isotope scrambling indicated ***inter***molecular mechanism.

Tenud, L.; Farouq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2054.

Diverting Intermediates and Mechanistic Clocks

- Sometimes is possible to test hypotheses about mechanisms, intermediates by intentionally diverting them.
- For more info, read *MPOC* Chapter 8.8.

Understanding Rate-Determining Transition States

Why?

- **Optimize reaction conditions.** Knowing about rate-determining step may lead to improvements.
- **Design catalysts.** Catalysts only work if they lower the energy of the rate-determining transition state.
- **Design therapeutic inhibitors.** Pharmaceuticals that bind enzyme active site better than the natural transition state can stop catalytic activity.

Principles of Catalysis

Review:

$$\mathbf{E} + \mathbf{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{ES}$$

$$\mathbf{ES} \xrightarrow{k_{cat}} \mathbf{E} + \mathbf{P}$$

$$\mathbf{S} \longrightarrow \mathbf{P}$$

Set of reactions regenerates **E**.

Used $[\mathbf{E}]_{tot} = [\mathbf{E}] + [\mathbf{ES}]$ to derive

$$\frac{\partial[\mathrm{P}]}{\partial t} = \frac{k_{cat}[\mathrm{E}]_{tot}[\mathrm{S}]}{K_M + [\mathrm{S}]},$$

$$K_M = \frac{k_{cat} + k_{-1}}{k_1}$$

(Michealis-Menton equation)

Principles of Catalysis

Review:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES$$

$$ES \xrightarrow{k_{cat}} EP$$

$$EP \overset{fast}{\rightleftharpoons} E + P$$

$$S \longrightarrow P$$

We'll assume catalyst actually binds product complex as well.

Principles of Catalysis

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES$$

$$ES \xrightarrow{k_{cat}} EP$$

$$EP \overset{fast}{\rightleftharpoons} E + P$$

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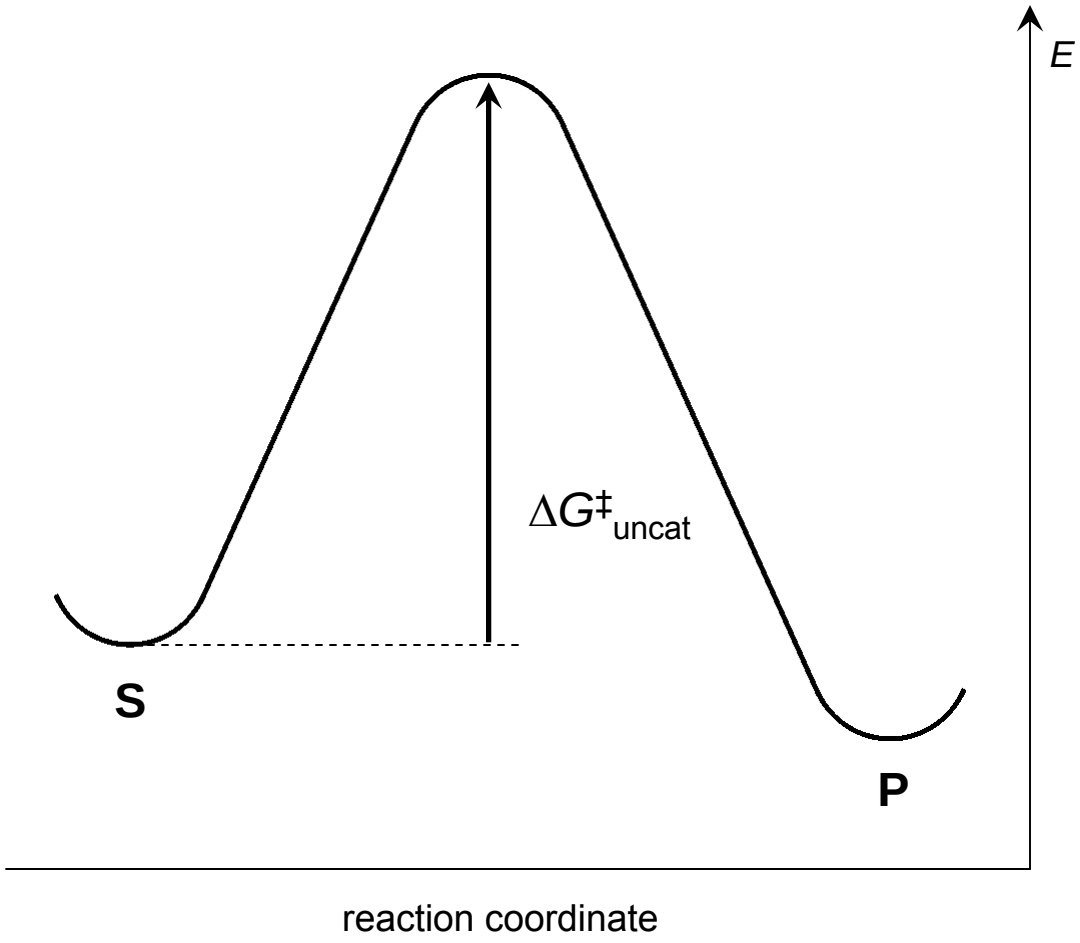
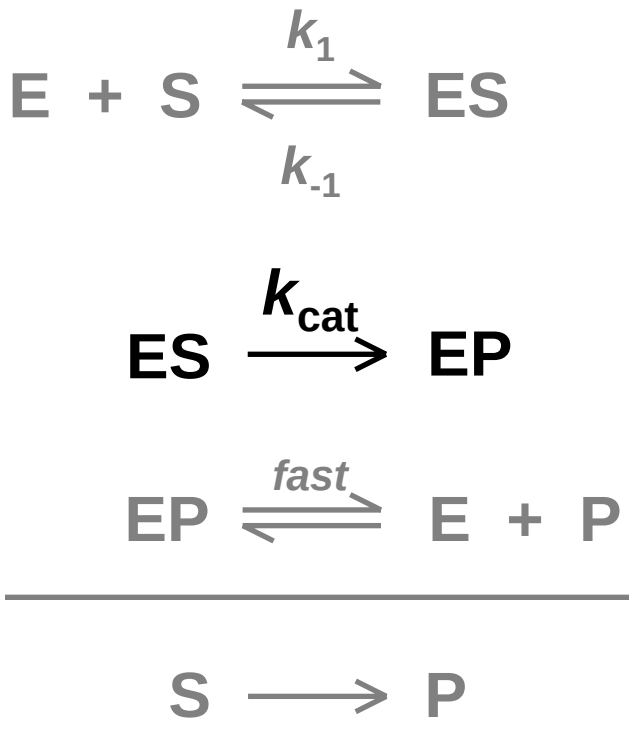
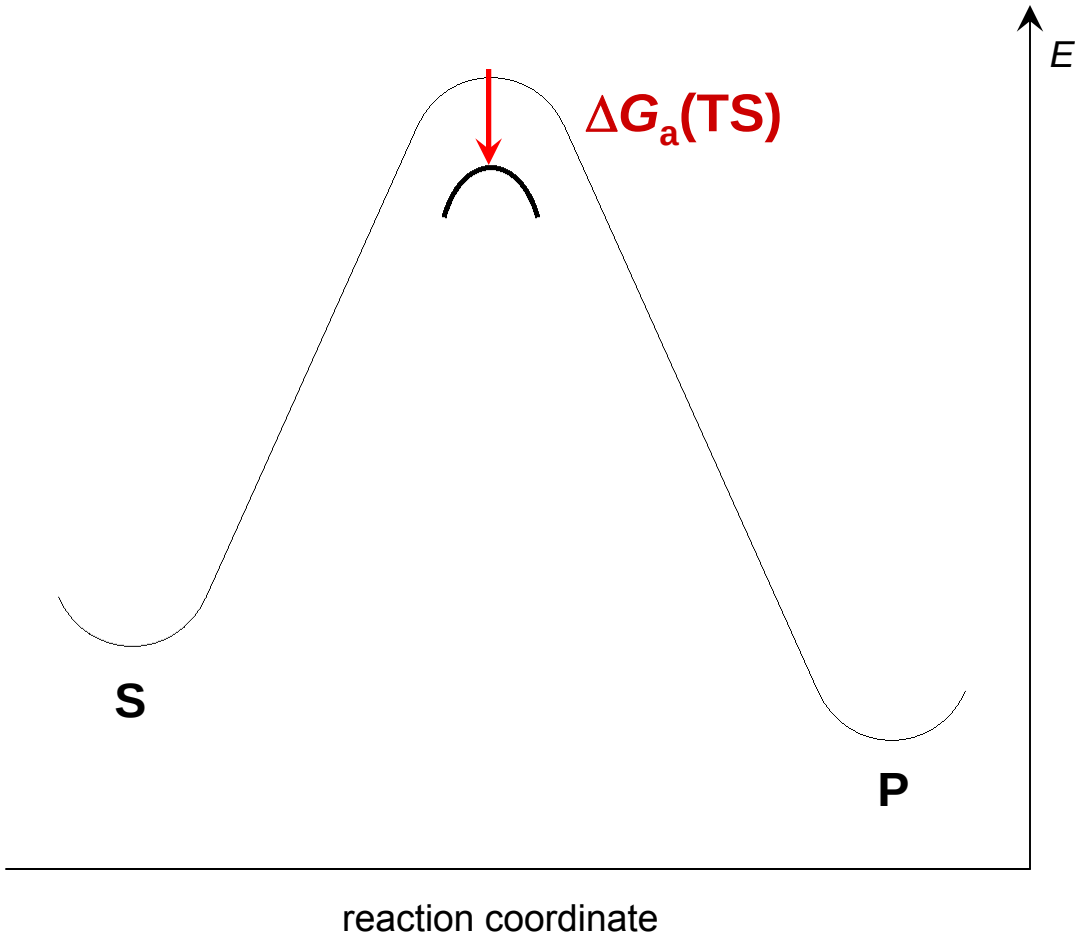


Principles of Catalysis

Catalysts stabilize (bind) the transition state.





Principles of Catalysis

Pauling's Hypothesis: By definition, catalysts must bind the transition state more strongly than starting materials.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES$$

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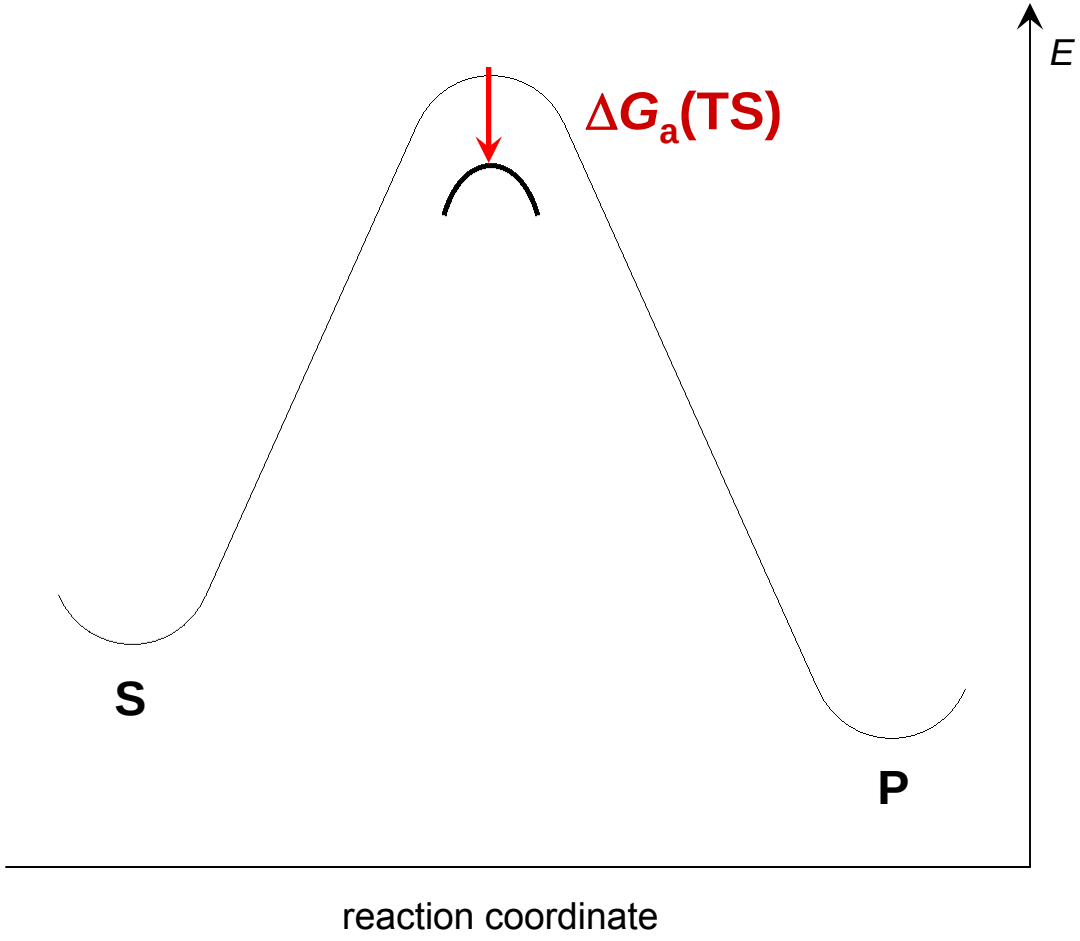

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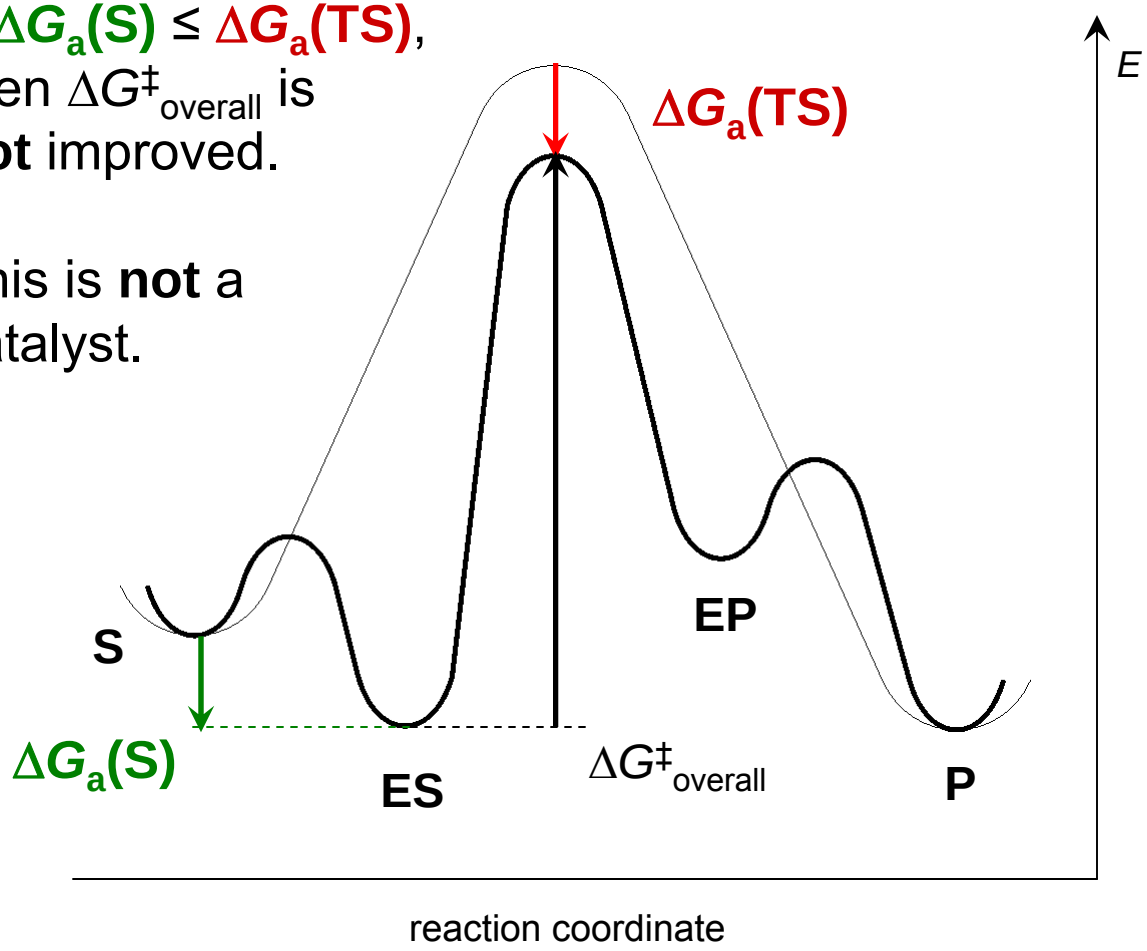
If $\Delta G_a(S) \leq \Delta G_a(TS)$, then $\Delta G^{\ddagger}_{overall}$ is **not** improved.

This is **not** a catalyst.



Principles of Catalysis

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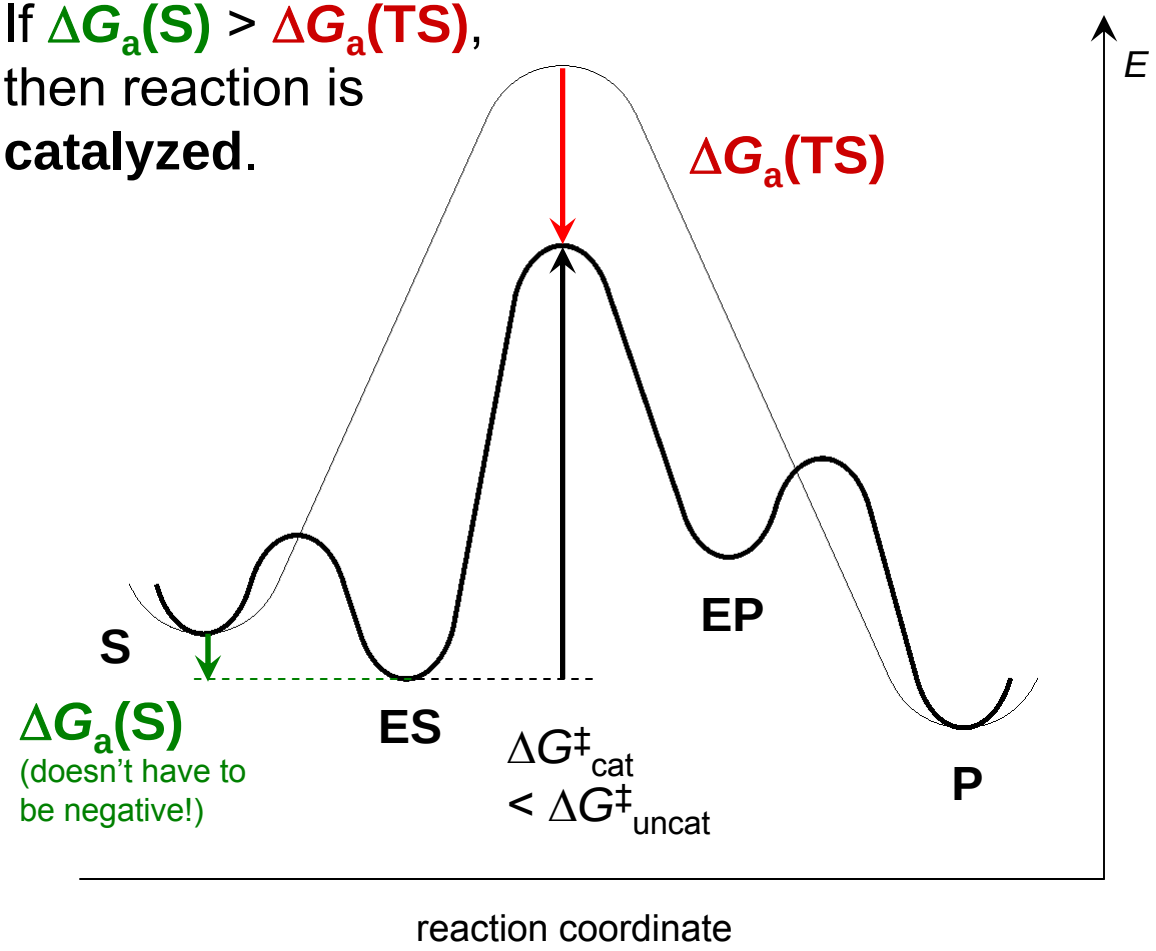
$$ES \xrightarrow{k_{cat}} EP$$

$$EP \overset{fast}{\rightleftharpoons} E + P$$

$$S \longrightarrow P$$

If $\Delta G_a(S) > \Delta G_a(TS)$, then reaction is **catalyzed**.



Principles of Catalysis

Pauling's Hypothesis: By definition, catalysts must bind the transition state more strongly than starting materials.

Another way of looking at it:

$$E + S \underset{}{\overset{K_a(S)}{\rightleftharpoons}} E{\cdot}S$$

k_{uncat} ↓ ↓ k_{cat}

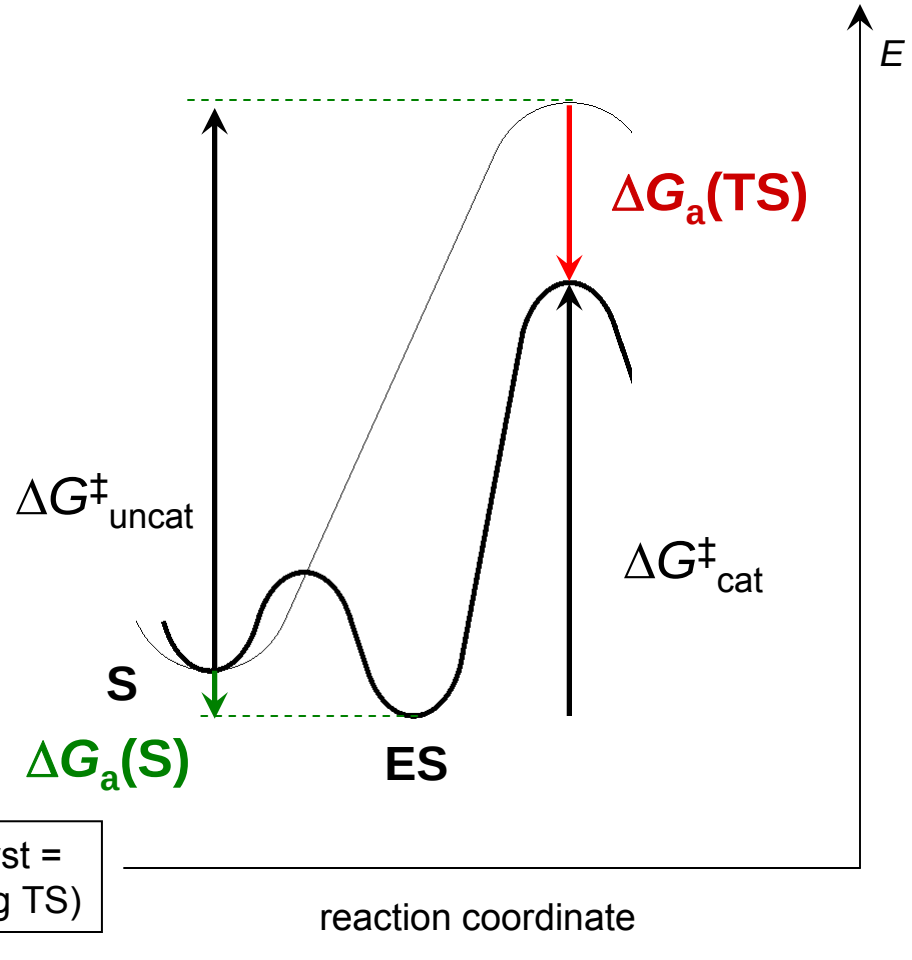
$$E + [TS]^{\ddagger} \overset{K_a(TS)}{\rightleftharpoons} [E{\cdot}TS]^{\ddagger}$$

$$\Delta G^{\ddagger}_{uncat} - \Delta G^{\ddagger}_{cat} = \Delta G_a(S) - \Delta G_a(TS)$$

or

$$\frac{k_{cat}}{k_{uncat}} = \frac{K_a(TS)}{K_a(S)}$$

(rel. effectiveness of catalyst = rel. effectiveness of binding TS)



Principles of Catalysis

Anslyn & Dougherty draw:

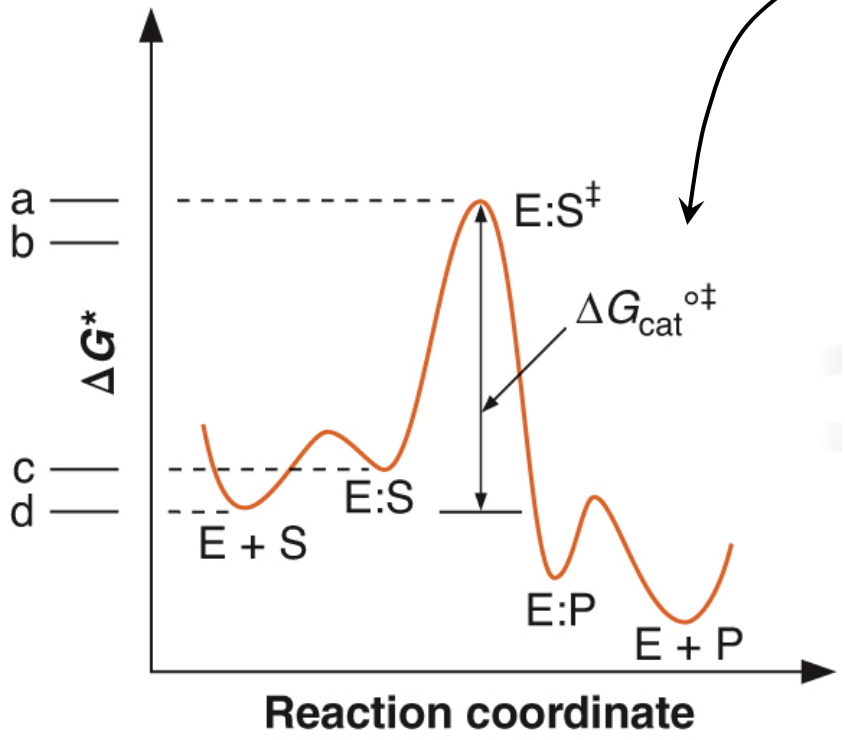


Figure 9.17, p.528

Warning:
This notation conflicts with mine.

For me,

$$E + S \underset{}{\overset{K_a(S)}{\rightleftharpoons}} E{\cdot}S$$

k_{uncat} ↓ ; ↓ k_{cat}

$$E + [TS]^{\ddagger} \overset{K_a(TS)}{\rightleftharpoons} [E{\cdot}TS]^{\ddagger}$$

$\Delta G^{\ddagger}_{cat}$ comes from this step.