# Website for Class Notes

**http://www.ch.ic.ac.uk/local/organic/tutorial/**

- Look under:
  3rd Year Organic Chemistry
  Donna Blackmond: Physical Organic

- Handouts Available:
  Course Summary
  Handouts 1, 2, etc (each week’s lecture notes in turn)

# Reactivity of Organic Compounds

- Bonds may be broken and formed in the following ways:

$R{:}X \rightarrow R\cdot \quad \cdot X$ *homolytic fission (radical formation)*

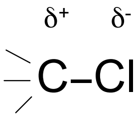
$R{:}X \rightarrow R{:}^{\ominus} \quad X^{\oplus}$ *heterolytic fission*

$R{:}X \rightarrow R^{\oplus} \quad {:}X^{\ominus}$ *heterolytic fission*

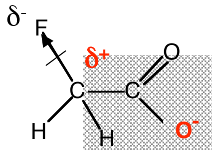
- Reactivity toward a particular reagent is influenced by any factors that influence the relative availability of electrons in particular bonds or atoms.
  - Inductive or field effects
  - Mesomeric effects
  - Hyperconjugation

# Reactivity of Organic Compounds

- Inductive effects
  - Permanent polarisation in molecule’s ground state, manifested in physical properties such as dipole moment.



*electron density is greater near Cl than C*



*electron-withdrawing polar (or inductive) effect between C-F bond dipole and $O^-$.*

$pK_a$ acetic acid = 4.76
$pK_a$ fluoroacetic acie = 2.66

  - *<u>Field effects</u>* refer to an analogous unequal distribution of electrons operating through space (or through solvent).

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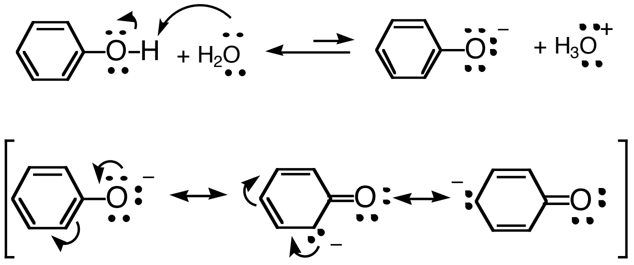
# Reactivity of Organic Compounds

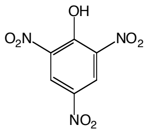
- Mesomeric effects

Electron re-distribution occurring in conjugated systems via π orbitals.

<u>Example: Phenol</u>. Delocalisation of negative charge via π orbitals helps stabilise the phenoxide ion, making **phenol more acidic** than would otherwise be predicted.

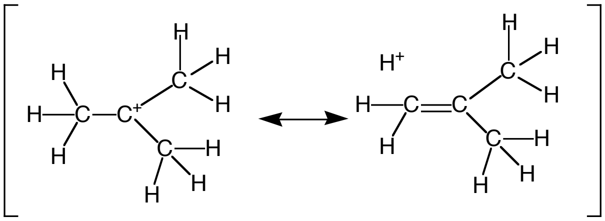


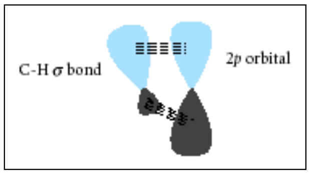
| $pK_a$ values | |
|---|---|
| phenol | 9.95 |
| cyclohexanol | 17 |
| picric acid | 0.96 |



# Reactivity of Organic Compounds

- Hyperconjugation
  - Alkyl groups can allow electron release through a mechanism different from induction.
  - Delocalisation occurs through overlap between bonding electrons in σ bonds with unoccupied 2p orbital of the carbocation.





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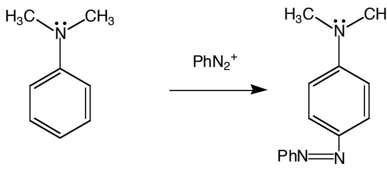
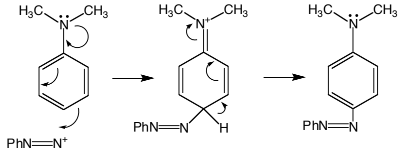
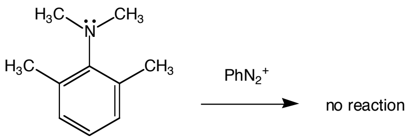
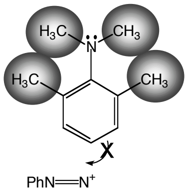
# Reactivity of Organic Compounds

- Steric Effects
  - The electronic factors we have been discussing may be attenuated by steric factors.
    - Delocalisation of electrons via π orbitals can only occur if those orbitals can be aligned in space.







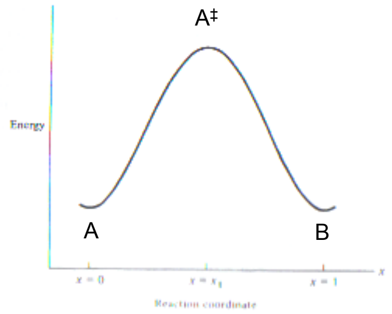


# Models for Characterizing Reaction Progress

- Review: Transition State Theory
  - In a unimolecular elementary reaction, the reacting molecules pass through a configuration of maximum potential energy called the ***transition state***.

$$A \xrightarrow{k_1} B$$

$$A \underset{}{\overset{K^{\mp}}{\rightleftharpoons}} A^{\mp} \xrightarrow{k^{\mp}} B \qquad \left[A^{\mp}\right] = K^{\mp}\left[A\right]$$



$$rate \;=\; k_1\left[A\right] \;=\; k^{\mp}\left[A^{\mp}\right] \;=\; k^{\mp}K^{\mp}\left[A\right]$$

$$k_1 = k^{\mp}K^{\mp}$$

Reaction rate constant $k_1$ is related to the activation parameters k‡ and K ‡

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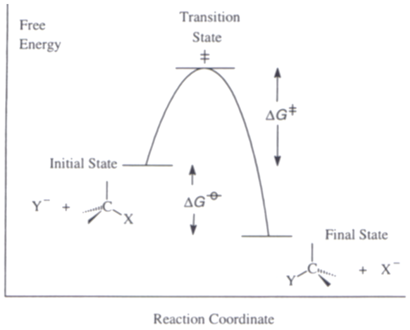
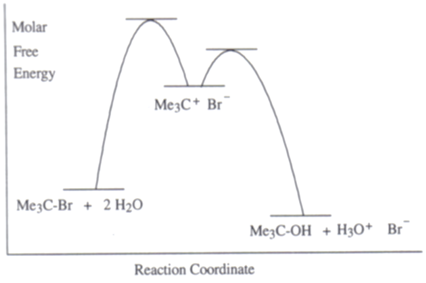
# Reaction Coordinate

- The reaction coordinate (the x-axis in an energy diagram) is a parameter we use to describe the progress of the reaction.
  - This axis is not necessarily time, it could be a structural parameter or group of parameters, e.g., fraction of bond dissociation.
  - Energy maxima are transition states, energy minima (other than reactants or products) are reactive intermediates.



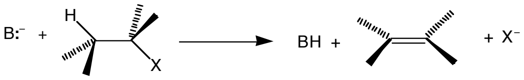
Reaction with no intermediate

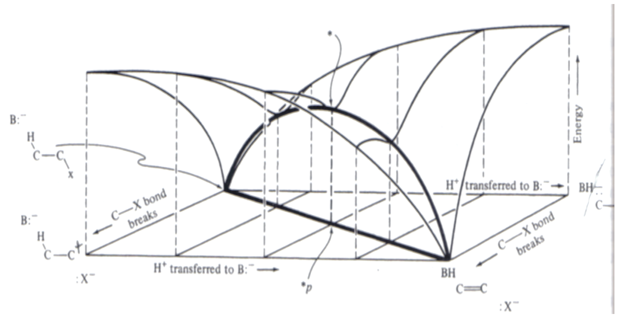


Reaction with an intermediate

# Reaction Coordinate

- Things get more complicated: An energy diagram is really an energy surface.
- Consider a reaction where two processes must take place (either separately or concerted), such as a 1,2 elimination reaction:





- Base removes a proton (if this occurs first, the process is an E1cB mechanism).
- Leaving group departs (if this occurs simultaneously with proton removal, the process is an E2 mechanism (shown in bold in figure).

*Lowry and Richardson, section 2.7.*

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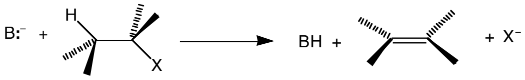
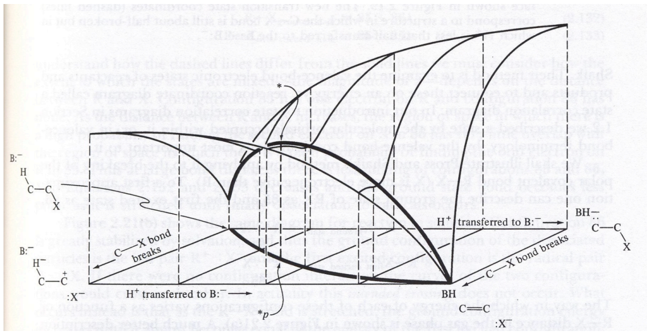
# Reaction Coordinate

- In this case, C-X bond breaking proceeds further than $H^+$ transfer has proceeded at the transition state.



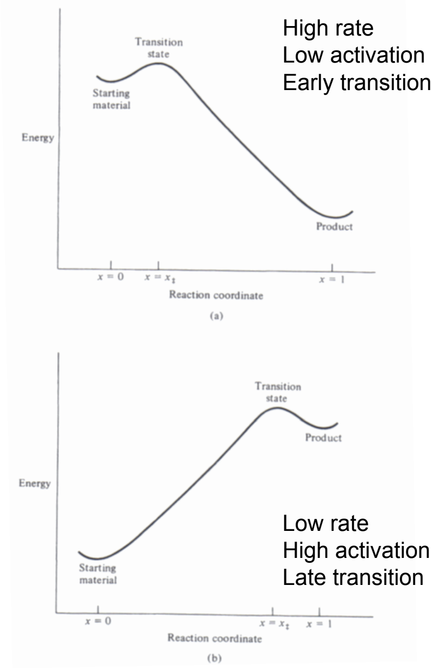


- Exothermic reaction, with starting materials at higher energy than products.

*Lowry and Richardson, section 2.7.*

# Models for Characterizing Reaction Progress

- The **Hammond Postulate** (or Hammond-Leffler Postulate)
  - A reaction involving reactants of high energy will require relatively little change in geometry to reach the transition state compared to a reaction involving reactants of low energy.
  - In highly ***exothermic reactions***, the transition state should resemble the ***reactants*** (early transition state).
  - In highly ***endothermic reactions***, the transition state should resemble the ***products*** (late transition state).



High rate
Low activation energy
Early transition state

Low rate
High activation energy
Late transition state

Lowry and Richardson, section 2.7.

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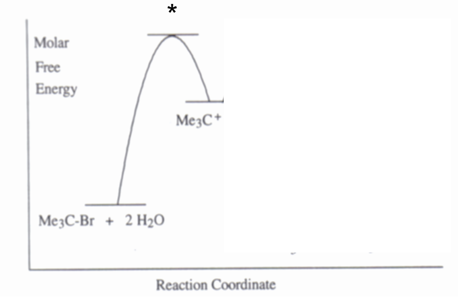
# Models for Characterizing Reaction Progress

- The **Hammond Postulate** (or Hammond-Leffler Postulate)
  - A classic example where we use the Hammond postulate is in rationalizing the $S_N1$ mechanism for nucleophilic substitution of alkyl halides.
  - The highly reactive carbocation intermediate $Me_3C^+$ is suggested to resemble the first, rate-limiting transition state *.

$$Me_3C - Br \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Me_3C^+ \quad Br^-$$

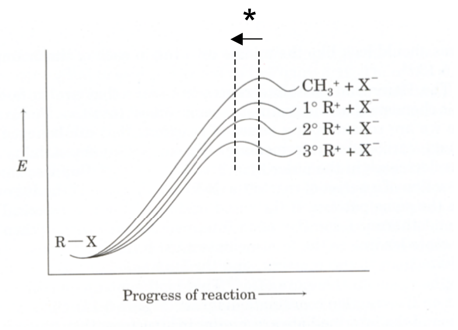
$$Me_3C^+ + OH^- \xrightarrow{k_2} Me_3C - OH$$



Maskill, Mechanisms of Organic Reactions Oxford Chemistry Primers No. 45.

# Models for Characterizing Reaction Progress

- The **Hammond Postulate** (or Hammond-Leffler Postulate)
  - Any change that helps to stabilize the products relative to the reactants should shift the transition state toward the reactants.
  - The transition state for the carbocation intermediate is predicted to move towards the reactants as the intermediate species becomes more stabilized.



*Carroll, section 5.1.*

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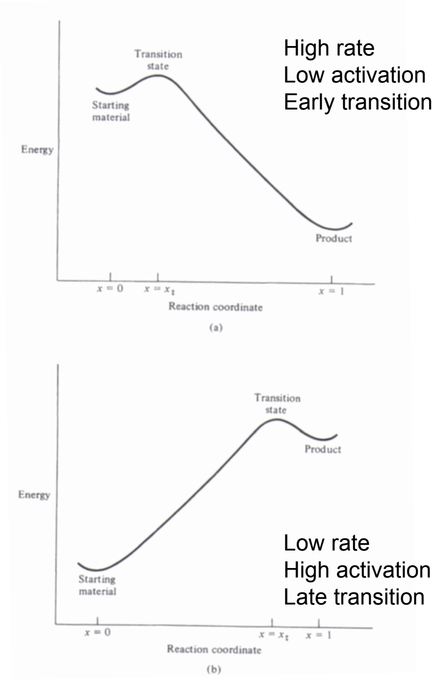
# Models for Characterizing Reaction Progress

- **Fundamental Problems with the Hammond Postulate:**
  - The Hammond postulate makes a connection between rate (kinetics) and and equilibrium (thermodynamics ) that has no theoretical basis.

    Transition states involve kinetics, intermediate species involve thermodynamics.
  - Use of the Hammond postulate is based primarily on enthalpy considerations and neglects the effects that activation entropies can have on reaction rates.



High rate
Low activation energy
Early transition state

Low rate
High activation energy
Late transition state

# Models for Characterizing Reaction Progress

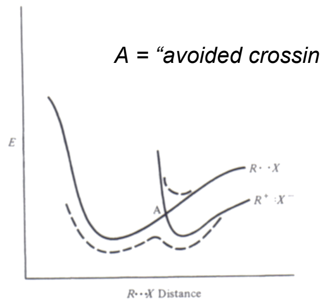
- **Valence bond model**: predicts how the structure of the transition state will change with changes in the reactants and reaction conditions, via examination of the valence-bond electronic states over the course of the reaction.
  - For the case of a polar covalent bond dissociation:

    $\text{R-X}_{\text{ground state}} = \text{R}\cdot\cdot\text{X}$

    $\text{R–X}_{\text{first excited state}} = \text{R}^{+}\ \text{:X}^{-}$

  - Reaction barriers are formed because reactants have to open their octet valence shells, stretching or even breaking bonds, which results in climbing an energy hill to find an energy state onto which they can cross.

*A = “avoided crossing”*



*lower dashed line = path of reaction progress*

*Lowry and Richardson, section 2.7.*

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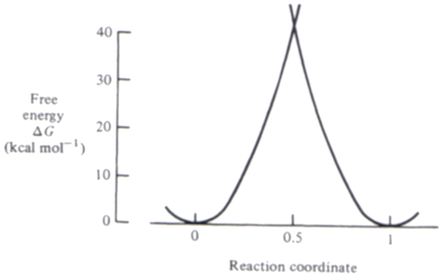
# Models for Characterizing Reaction Progress

- **Marcus Theory.** Activation barriers are made up of a thermodynamic portion (arising from the overall free energy change) and an intrinsic kinetic portion that would exist if reactants and products had the same free energy.
  - The reaction coordinate is made up of two potential energy surfaces, one for stretching the reactant bonds and one for stretching the product bonds.
  - These potential energies (in two dimensions) are approximated by parabolas.
  - The difference in free energies of the reactants and products are then superimposed on the energy diagram for this “symmetric transformation”.



*Lowry and Richardson, section 2.7.*

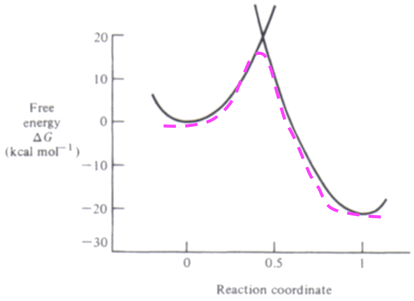
# Models for Characterizing Reaction Progress

- **Marcus Theory.** Activation barriers are made up of a thermodynamic portion (arising from the overall free energy change) and an intrinsic kinetic portion that would exist if reactants and products had the same free energy.

  - The reaction's ΔG° value dictates how we move the product free energy minimum relative to the reactants.
  - The displacement of the parabolic curves determines the position of the transition state.

    ***exothermic reaction:*** early transition state

    ***endothermic reaction:*** late transition state



*Products are more stable than reactants in this case.*

*Lowry and Richardson, section 2.7.*

# Models for Characterizing Reaction Progress

- All these models suggest a relationship between kinetics and thermodynamics: *the position of the transition state (kinetics) should vary with the overall thermodynamics of the reaction*.

- It is important to emphasize that *there is no theoretical connection between equilibrium thermodyamics and rate*.

- Therefore, relationships between rate and thermodynamic properties must be considered as qualitative and empirical: they must be checked out for each new case.

- One such proposed relationship is the **Bronsted Catalysis Law**. This is an example of a *linear free energy relationship*.

# The Bronsted Catalysis Law

- The rate at which a particular base B- removes a proton from various acids HA may be related to the strength of the acid (faster rates for stronger acids).
- This relationship between rate and equilibrium is called the Bronsted Catalysis Law:

$$k = C \cdot K_a^{\alpha} \qquad \log k = \alpha \log K_a + \log C$$

rate constant

equilibrium constant

α relates rate and equilibrium constants

- This relationship is derived from consideration of the free energy relationships involved.

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# The Bronsted Catalysis Law

- Consider the free energy diagram for proton transfer reactions between a series of acids $HA_1$ to $HA_n$ with a single base $B^-$:

$$\Delta G_1^{\mp} - \Delta G_n^{\mp} = \alpha\left(\Delta G_1^{\circ} - \Delta G_n^{\circ}\right)$$

*definitions*:

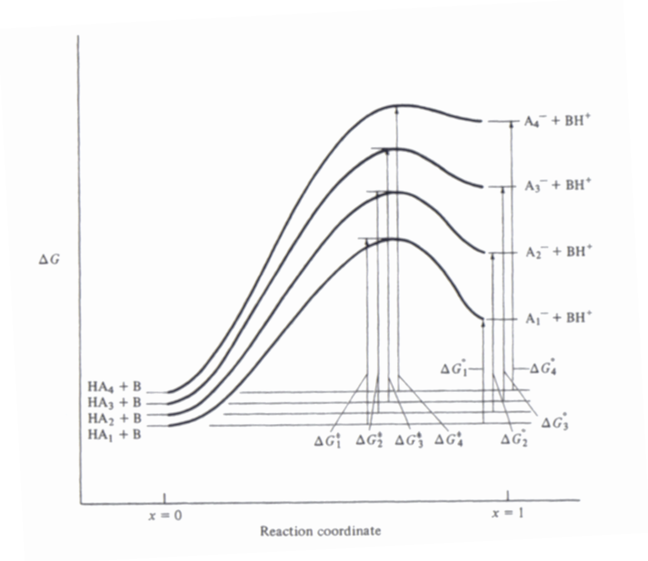
$$-\Delta G^{\circ} = 2.303RT\log K$$

$$\Delta G^{\mp} = 2.303RT\left(\log k - \log\frac{\boldsymbol{k}T}{h}\right)$$

*substituting*:

$$\log k_1 - \log k_n = \alpha\left(\log K_n - \log K_1\right)$$

$$\boxed{\log k = \alpha \log K_n + \log C}$$



$\boldsymbol{k}$ = Boltzmann constant   h = Planck's constant

*Lowry and Richardson, section 3.3.*

# Bronsted Catalysis Law and the Hammond Postulate

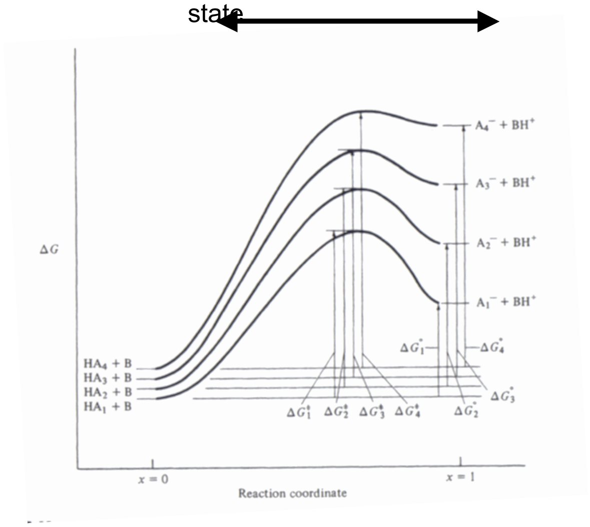
- For exothermic reactions where the transition state is close to the reactants, the activation free energy $\Delta G^{‡}$ should not be affected very much by small changes in the thermodynamic $\Delta G^{o}$.

  ⇨ $\alpha$ should be close to zero.

- For endothermic reactions where the transition state is close to the products, the activation free energy $\Delta G^{‡}$ should account for most of the change in the thermodynamic $\Delta G^{o}$.

  ⇨ $\alpha$ should be close to one.

The value of $\alpha$ is affected by the position of the transition state

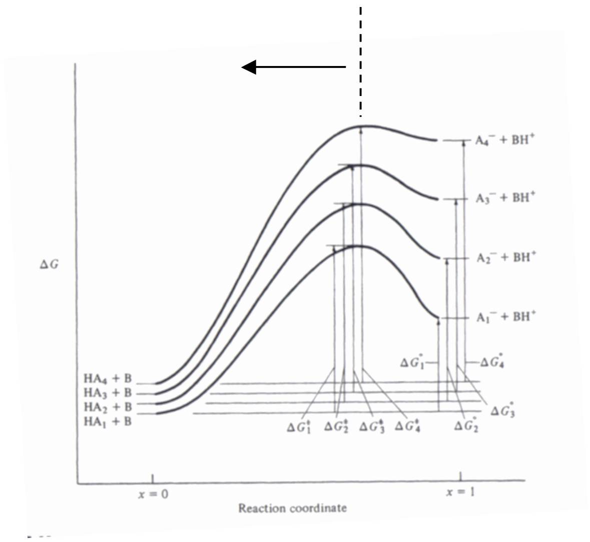


# Bronsted Catalysis Law and the Hammond Postulate

- However, the Hammond postulate also tells us that the position of the transition state should be a function of the relative stability of the conjugate acid-base pair.

- The position of the transition state should shift to the left as the conjugate acid $A^-$ becomes more stable relative to the reactants.

- But if $\alpha$ changes within this sequence of acids $HA_1$ to $HA_n$, then we don't have a free energy relationship.



# Paradox (or failure?) of the Hammond Postulate

- We need α to be a constant in order to have this free energy relationship:

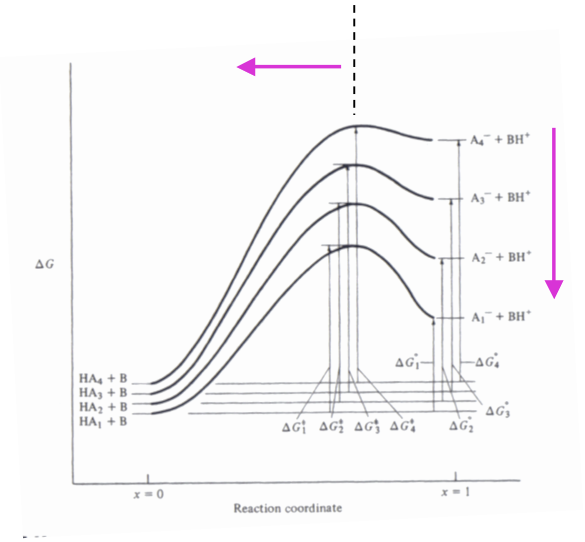
$$\boxed{\log k = \alpha \log K_n + \log C}$$

- But α should be *changing* as the position of the transition state changes.

- In fact, careful studies show that α does not change if a similar series of acids are compared with the same base.

- (Bordwell and Hughes, *J. Am. Chem. Soc.*, **1985**, *107*, 4737.)

α close to zero α close to one



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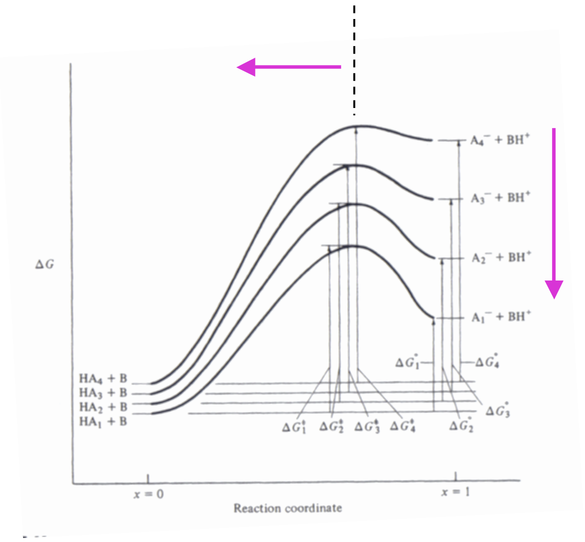
# Paradox (or failure?) of the Hammond Postulate

- In fact, careful studies show that α does not change if a similar series of acids are compared with the same base.

$$\boxed{\log k = \alpha \log K_n + \log C}$$

- The Bronsted Catalysis Law (an empirical linear free energy relationship) ***is valid*** within carefully chosen groups of acids or bases.

- The Hammond postulate (an empirical statement of the “Reactivity-Selectivity Principle”) ***is not valid*** for these groups of reactions.



# The Reactivity-Selectivity Principle

- The **Reactivity-Selectivity Principle** states that *the more reactive a species is, the less selective it is about what it reacts with.*
- When is this ***not*** true?
  - *When the reaction mechanism changes over the series of reactions under study.*
  - *When the product-determining step has particular orbital symmetry requirements.*