Linear Free Energy Relationships

- Linear free energy relationships are attempts to develop quantitative relationships between **structure** and **activity**.

Consider a particular reaction between two substrates. We might carry out a series of reactions by varying one of the reactants slightly, for example by examining substituents with a range of electronegativities.

We might expect that the reaction rate, or the position of the equilibrium between reactants and products, will change as we change the reactant in this way.

If the same series of of changes in conditions affects a second reaction in exactly the same way as it affected the first reaction, we say that there exists a ***linear free energy relationship*** between the two sets of effects.

Such relationships can be useful in helping to elucidate reaction mechanisms and in predicting rates or equilibria.

The Hammett Equation

One of the earliest examples of a LFER between:

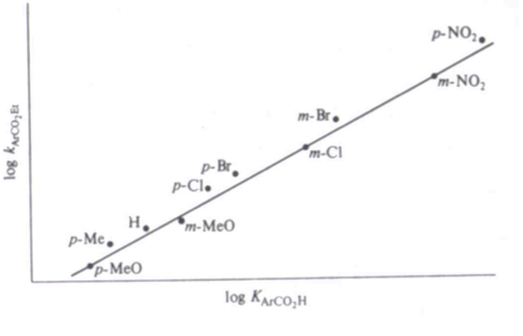
- the ***rate*** of base catalysed hydrolysis of a group of ethyl esters to form a series of carboxylic acids.
- the ***equilibrium*** position of the ionisation in water of the corresponding group of acids.

$$RCOOEt + OH^- \xrightarrow{k} RCOO^- + EtOH$$

$$RCOOH + OH^- \underset{}{\overset{K}{\rightleftarrows}} RCOO^- + H_2O$$

- A direct relationship was found between these processes for a specific set of compounds, the *p*- and *m*-substituted benzoic acids (R=Ar).

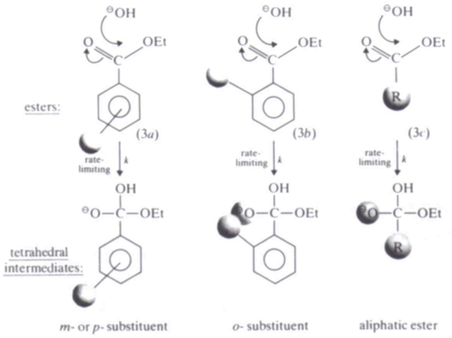
$$\log k = \rho \log K + C$$



- Caveats:
  - Ortho isomers do not fall on the line.
  - Aliphatic acids do not fall on the line.

The Hammett Equation

- Why do ortho isomers and aliphatic compounds not exhibit the straight line relationship?
- Steric considerations:
  - Crowding is increased in the tetrahedral transition state for *o*-isomers.
  - Flexibility of aliphatic compounds means that correlation between transition state structure and equilibrium position may not be strong.



Derivation of the Hammett Equation

- The relationship between the two reactions is given by:

$$\log k = \rho \log K + C$$

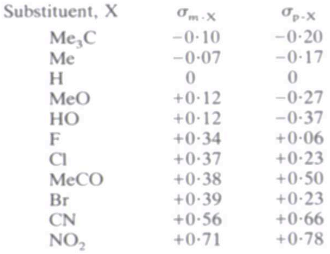
- Considering the unsubstituted carboxylic acid as the "base case" reaction, we can subtract its value from both sides of the equation.

$$\log k - \log k_H = \rho\left(\log K - \log K_H\right)$$

These are simply the pK_a values of the substituted and unsubstituted benzoic acids.

$$\log\left(\frac{k}{k_H}\right) = \rho \cdot \left(pK_{a(H)} - pK_a\right) = \rho \cdot \sigma$$

The term ($pK_{a(H)}$ - pK_a) is given the symbol σ_m or σ_p for meta and para-substituted benzoic acids and is known as the ***substitution constant***. This can be calculated for any substituted benzoic acid for which we can find (or measure) pK_a.

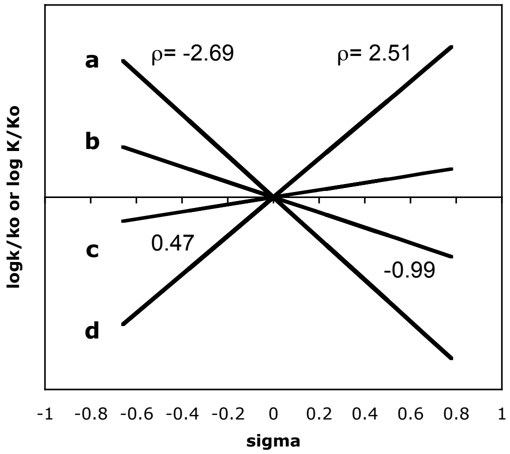


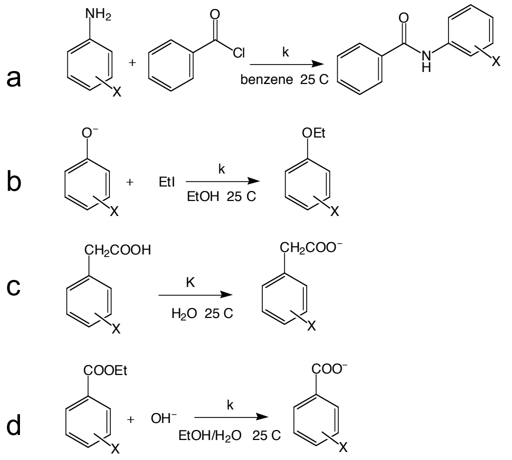
Substituent, X	$\sigma_{m\cdot X}$	$\sigma_{p\cdot X}$
Me_3C	−0·10	−0·20
Me	−0·07	−0·17
H	0	0
MeO	+0·12	−0·27
HO	+0·12	−0·37
F	+0·34	+0·06
Cl	+0·37	+0·23
MeCO	+0·38	+0·50
Br	+0·39	+0·23
CN	+0·56	+0·66
NO_2	+0·71	+0·78

Derivation of the Hammett Equation

- Hammett found that many other reactions also showed straight-line correlations of their rate or equilibrium behavior for a series of substituents with the equilibrium behavior of benzoic acid (manifested as σ).

$$\log\left(\frac{k}{k_H}\right) = \rho\cdot\sigma \quad or \quad \log\left(\frac{K}{K_H}\right) = \rho\cdot\sigma$$





The Hammett Equation

- The equation describing the straight line correlation between a series of reactions with substituted aromatics and the hydrolysis of benzoic acids with the same substituents is known as the Hammett Equation.

$$\log\left(\frac{k}{k_H}\right) = \rho\cdot\sigma \quad or \quad \log\left(\frac{K}{K_H}\right) = \rho\cdot\sigma$$

Log of the ratio of either the reaction rate constant or the equilibrium constant

ρ = reaction constant

Proportionality constant between log of k (or K) values and σ

σ = substituent constant

A measure of the total polar effect exerted by substituent X (relative to no substituent) on the reaction centre.

recall:

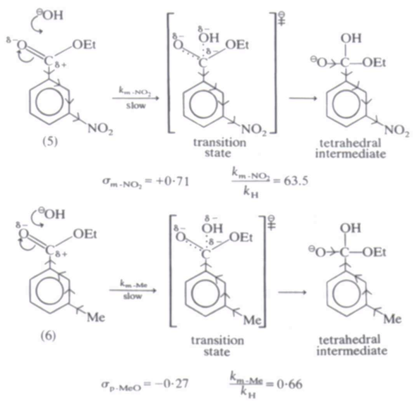
$\sigma = -(pK_a - pK_a(H))$

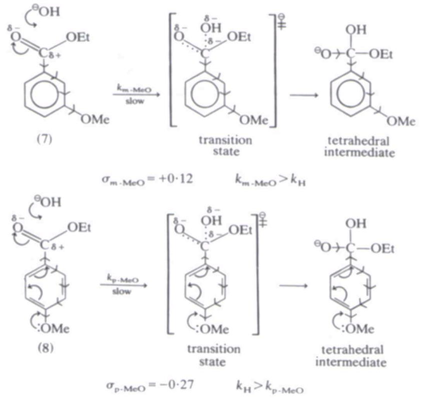
−ve = electron-donating

+ve = electron-withdrawing

Physical Meaning of σ and ρ

- The substituent constant σ is a measure of the total polar effect exerted by substituent X (relative to no substituent) on the reaction centre.





Electron-withdrawing *m*-NO_2 (σ = +0.71) increases stability of tetrahedral intermediate compared to electron-donating *m*-CH_3 (σ = -0.07).

Methoxy substituent can be electron-withdrawing due to inductive effects (*meta*, σ = +0.12) , or electron-donating (*para,* σ = -0.27) due to mesomeric effects.

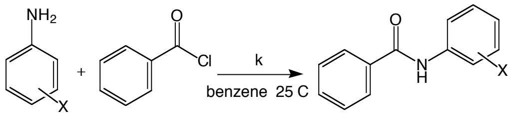
Physical Meaning of σ and ρ

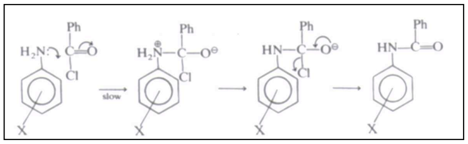
- The reaction constant ρ is the slope of the line correlating log k or log K with the sigma values of the substituents.
- The **sign** of the slope tells whether a reaction rate is accelerated or suppressed by electron-donating vs. electron withdrawing substituents.
  - **Negative** ρ is diagnostic of the development of **positive charge at the reaction centre** in the transition state of the rate-limiting step.
    - rate will be ***suppressed*** **by electron-withdrawing substituents**.
  - **Positive** ρ is diagnostic of the development of **negative charge at the reaction centre** in the transition state of the rate-limiting step.
    - rate will be ***accelerated*** **by electron-withdrawing substituents**.
- The **magnitude** of ρ is a measure of how susceptible a reaction is to the electronic characteristics of the substituent.

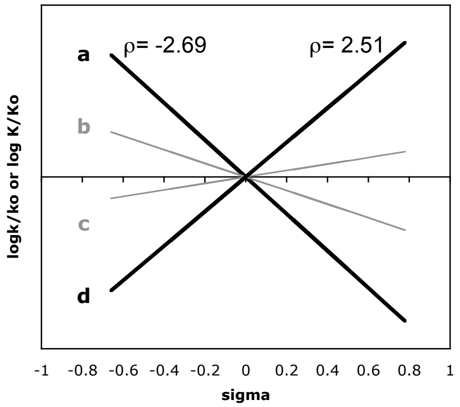
Significance of ρ

- Let's consider again two of the reaction examples we looked at previously:

a



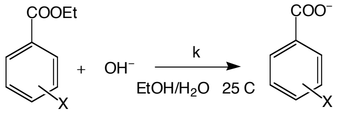


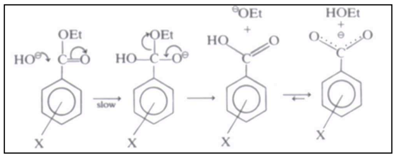


electron-donating ←

electron-withdrawing →

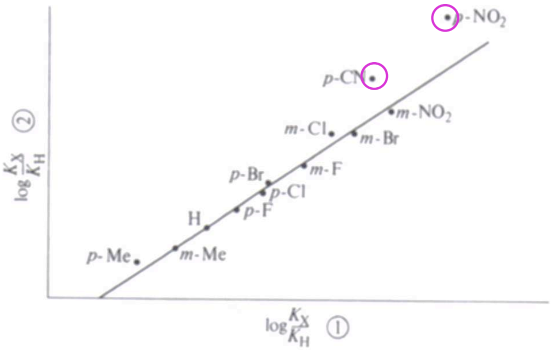
d

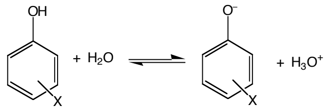




A Closer Look at Substituent Constants

- In many cases, we find that strongly electron-withdrawing or strongly electron-donating substituents don't fall on the line predicted by the Hammett correlation.
- Example: *p*-CN and *p*-NO_2 are above the line; this suggests that compounds with these substituents act as **stronger** acids than we would have predicted from their σ values.

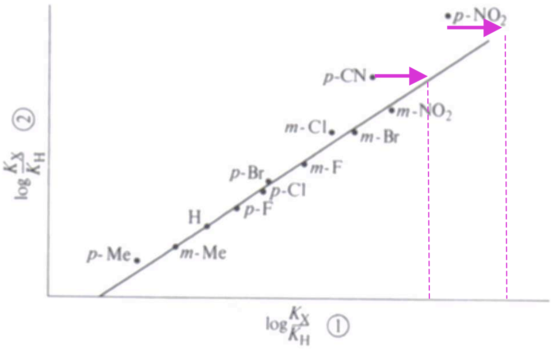


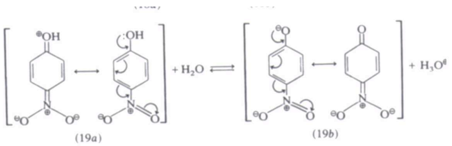


When electron-withdrawing due to to mesomeric effects can be extended to the reaction centre via "***through conjugation",*** the result is an even more stabilized species.

Modified Substituent Constants σ^- Scale

- We can develop new σ values for these substrates by separating out these through-conjugation effects from inductive effects.
- Develop line with ρ value based on *m*-substituents only, which cannot exhibit mesomeric effects. The amount by which certain substituents deviate from the line can be added to their σ values to produce a new scale of σ^- value.





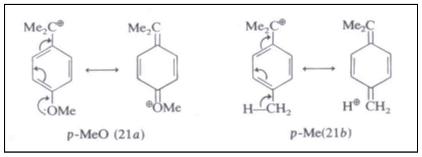
(19a) (19b)

substituent	σ_p	σ_p^-
CO_2Et	0.45	0.68
COMe	0.50	0.84
CN	0.66	0.88
CHO	0.43	1.03
NO_2	0.78	1.27

Modified Substituent Constants σ^+ Scale

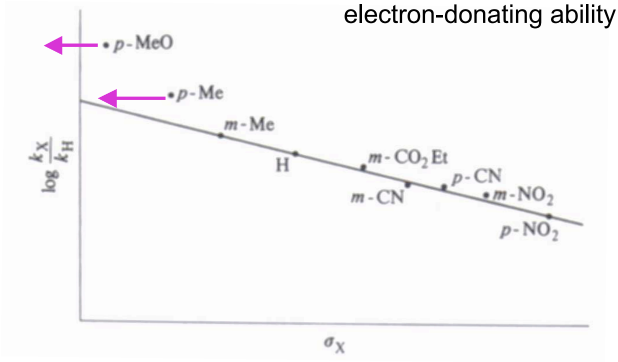
- Similarly, in some cases,we find that strongly ***electron-donating*** substituents don't fall on the line predicted by the Hammett correlation.

<u>Example:</u> S_N1 solvolysis of *p*-substituted tertiary halides



p-MeO (21a) p-Me(21b)

p-OCH_3 and *p*-CH_3 are above the line; through-conjugation enhances their electron-donating ability.



σ^+ scale:

substituent	σ_p	σ_p^+
C_6H_5	-0.01	-0.18
Me	-0.17	-0.31
MeO	-0.27	-0.78
NH_2	-0.66	-1.30
NMe_2	-0.83	-1.70

Uses of Hammett Plots

- How do we make use of Hammett plots?
  - Calculation of k or K for a specific reaction of a specific compound:

$$\log \frac{k_x}{k_H} = \rho \cdot \sigma_x$$

If we know ρ for a particular reaction, then we can calculate the rate (or equilibrium) constant for any substituent relative to that for the unsubstituted compound (because we also know σ for the substituent).

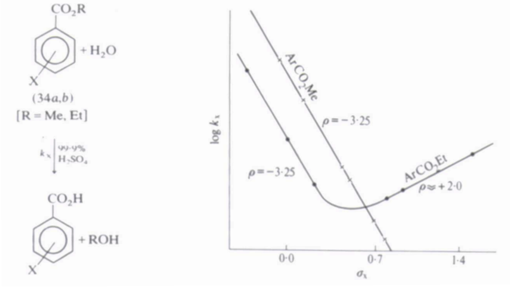
  - To provide information about reaction pathways:
    - Magnitude and sign of ρ tell about development of charge at reaction centre.
    - If σ^+ or σ^- gives a better correlation than σ, then we know we have a reaction where through conjugation is important.
    - **Deviations from linearity:** arguably, the most mechanistically informative Hammett plots are ones that *don't* give straight lines!

Deviations from Linearity in Hammett Plots

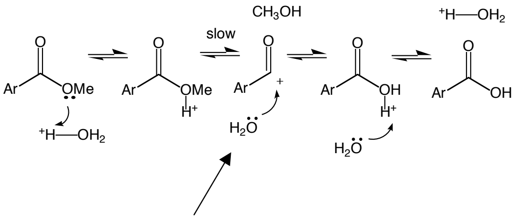
- **Concave Upwards** deviation:

Compare the Hammett plots for the hydrolysis of $ArCO_2R$ (R= Me and Et) **carried out in 99.9% H_2SO_4**.

  - Me esters show well-behaved plot with ρ = -3.25
  - Et esters show well-behaved plot with ρ = -3.25 switching to ρ = + 2.0



Mechanism for Me esters:



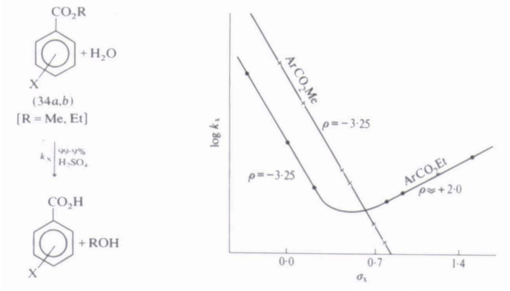
Positive charge develops at reaction centre during rate-limiting step

Deviations from Linearity in Hammett Plots

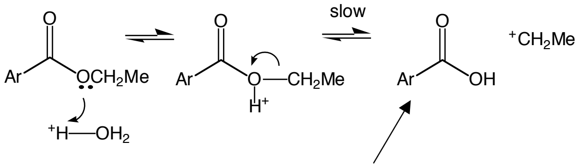
- **Concave Upwards** deviation: What happens for Et esters?

Change in mechanism: positive charge near reaction centre is ***decreased*** in rate-limiting step, leading to a positive ρ value.

Mechanism changes for Et esters but not Me esters because a stable carbocation $^+CH_2Me$ can be formed in Et ester case.



Mechanism for Et esters:



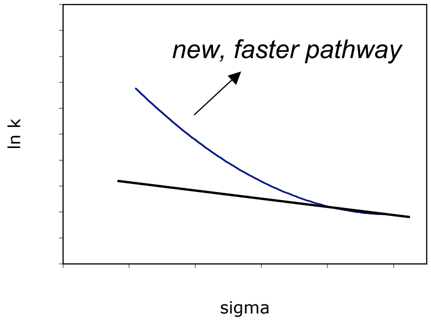
For electron-withdrawing substituents: Positive charge at reaction centre is ***decreased*** during rate-limiting step.

Deviations from Linearity in Hammett Plots

- **Concave Upwards** deviation:

Concave upwards deviation can usually be taken as evidence of a change in reaction mechanism.

  - Any new pathway coming into play must be faster than the original pathway, or the original pathway would continue to dominate.
  - A faster pathway gives an upward curving deviation.



Deviations from Linearity in Hammett Plots

- **Concave Downwards** deviation:

  Concave downwards deviation can also be observed, as in this example of the cyclodehydration of substituted 2-phenyltriarylmethanol compounds:

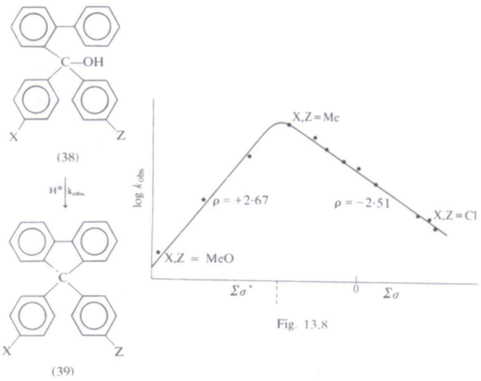


Fig. 13.8

Positive ρ for electron-donating X,Z substituents

Negative ρ for electron-withdrawing X,Z substituents

Deviations from Linearity in Hammett Plots

- **Concave Downwards** deviation:

  Reaction mechanism: E1 elimination of H_2O to form a carbocation followed by an internal electrophilic substitution.

  Which step is rate-limiting, **a)** or **b)** ?

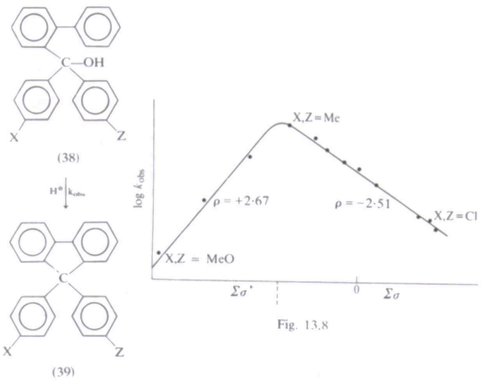
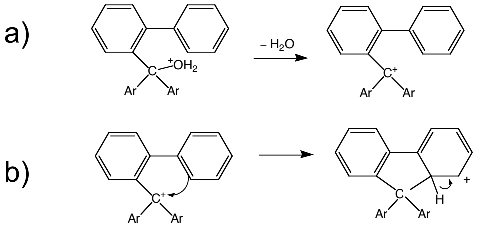
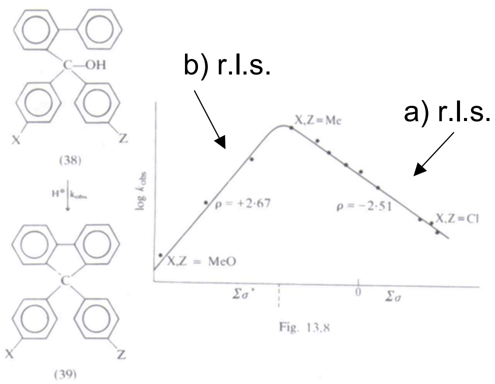


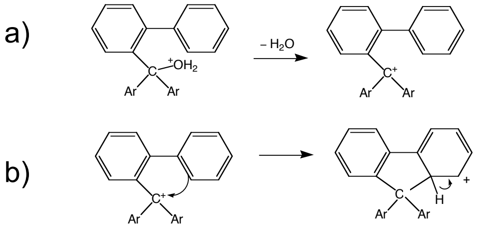
Fig. 13.8



Deviations from Linearity in Hammett Plots

- **Concave Downwards** deviation: Which step is rate-limiting?
  - In **a),** positive charge at the reaction centre is increasing (ρ = negative). This suggests that **a)** is rate-limiting for the ***right*** of the Hammett pot.
  - In **b),** positive charge at the reaction centre is decreasing (ρ = positive). This suggests that **b)** is rate-limiting for the ***left*** of the Hammett plot.





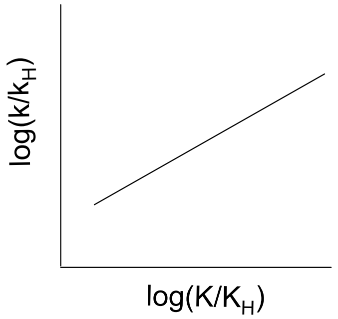
Deviations from Linearity in Hammett Plots

- **Concave Upwards** deviation:
  - indicates ***change*** in reaction mechanism.
- **Concave Downards** deviation:
  - indicates ***same*** mechanism, ***change*** in rate-limiting step.

Thermodynamic Implications of Hammett Plots

- We have mentioned several times that linear free energy relationships make a correlation between thermodynamic (ΔG°) and transition state (ΔG‡) properties of the reaction, which is grounded on an empirical and not a theoretical basis.

$$RCOOEt + OH^- \xrightarrow{k} RCOO^- + EtOH$$



$$RCOOH + OH^- \underset{}{\overset{K}{\rightleftarrows}} RCOO^- + H_2O$$

Rate constant:

$$-2.303RT \cdot \log\left(\frac{k}{k_H}\right) = \left(\Delta H^{\ddagger} - \Delta H_x^{\ddagger}\right) - T\left(\Delta S^{\ddagger} - \Delta S_x^{\ddagger}\right)$$

Equilibrium constant:

$$-2.303RT \cdot \log\left(\frac{K}{K_H}\right) = \left(\Delta H^o - \Delta H_x^o\right) - T\left(\Delta S^o - \Delta S_x^o\right)$$

Thermodynamic Implications of Hammett Plots

- Why do these relationships work?
- The implicit meaning of a linear Hammett plot is that one or more of the following three conditions is satisfied in each series of reactions:
  - ΔH is linearly related to ΔS for the series
  - ΔH is constant for the series
  - ΔS is constant for the series

Rate constant: $-2.303RT \cdot \log\left(\frac{k}{k_H}\right) = \left(\Delta H^{\ddagger} - \Delta H_H^{\ddagger}\right) - T\left(\Delta S^{\ddagger} - \Delta S_H^{\ddagger}\right)$

Equilibrium constant: $-2.303RT \cdot \log\left(\frac{K}{K_H}\right) = \left(\Delta H^o - \Delta H_H^o\right) - T\left(\Delta S^o - \Delta S_H^o\right)$