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LECTURE 13: ISOTOPE EFFECTS

Reading: A&D, Ch 8.

PS#6 due Tues, 10/20.

Recall: Rate & Kinetics → Energy of TS
→ composition of TS

LFER's → Substituent effects on TS energies

Isotope Effects → Bonds breaking/forming in TS

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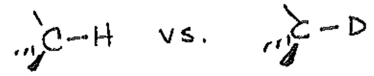
ORIGIN OF ISOTOPE EFFECTS



Change in mass, <u>not</u> electronic properties.

Mass affects vibrational frequency of the bond/spring...

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

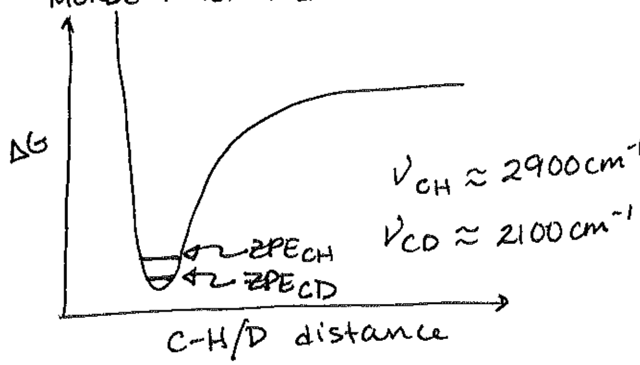
$$\mu = \frac{m_A m_B}{m_A + m_B}$$

ν = frequency
k = spring force constant
μ = reduced mass

Heavier mass = lower frequency

③ FREQUENCY (ν) ∝ entropy ∝ width of energy well...

MORSE POTENTIAL:



$\nu_{CH} \approx 2900\ cm^{-1}$

$\nu_{CD} \approx 2100\ cm^{-1}$

ZPE = zero-point energy (lowest quantized energy level)

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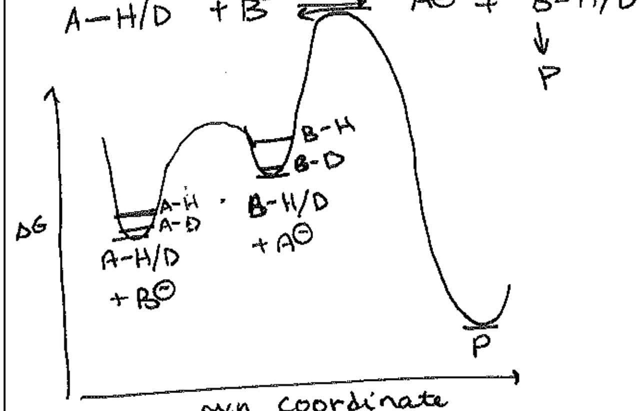
A–H/D + B⊖ ⇌ A⊖ + B–H/D
↓
P



EQUILIBRIUM ISOTOPE EFFECT
→ CAN BE <u>REALLY</u> BIG.

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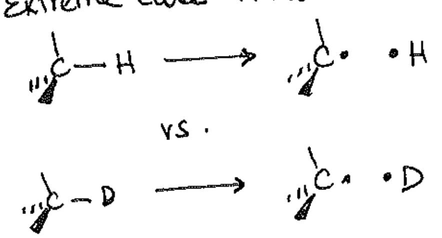
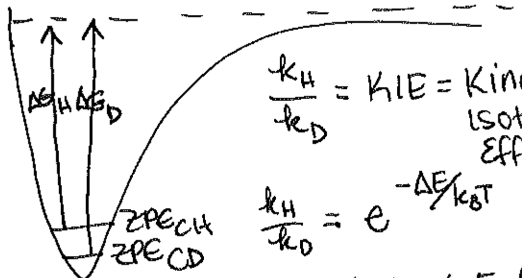
KINETIC ISOTOPE EFFECTS

Extreme case: HOMOLYTIC BOND CLEAVAGE





$\frac{k_H}{k_D}$ = KIE = Kinetic Isotope Effect

$$\frac{k_H}{k_D} = e^{-\Delta E/k_B T}$$

Max KIE ≈ 6.5 for a "normal" org rxn.

⑥ But, we usually are interested in cases where C–H/D bond is <u>not</u> fully cleaved...

Consider linear t.s.:

A–H + B → A + H–B
↳ [A····H····B]‡ ↗

Vibrational frequencies:

1) Asymmetric stretch ≡ rxn coordinate
A→← H ←→B (no frequency in t.s.)

2) Bending
A···H···B (↑ ↓ ↑)

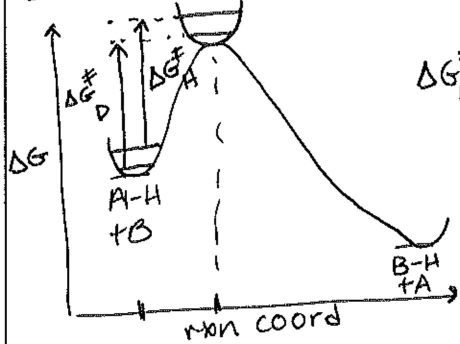
3) wag
A·····H···B (↑ ↓)

Not much difference between SM & TS. (2) and (3)

4) Symmetric stretch
A←·H·→B
NEW to ts.
Not in A–H or H–B.

(7) Symmetric Stretch can be affected by isotopes...

Case 1: EARLY T.S./EXOTHERMIC

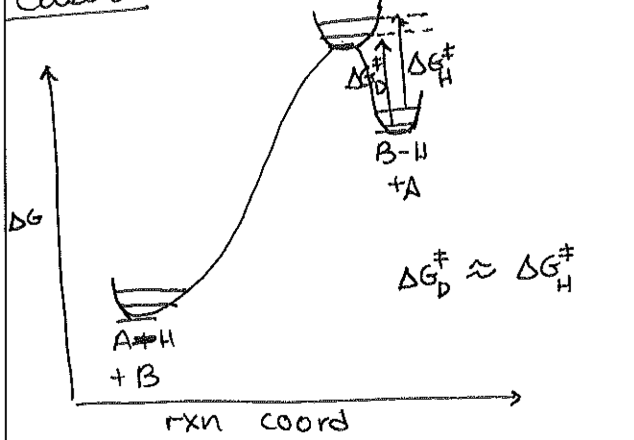


$\Delta G^{\ddagger}_D \approx \Delta G^{\ddagger}_H$

A<·H·>·····B ≈ A<H

small KIE

(8) Case 2: LATE T.S./ENDOTHERMIC

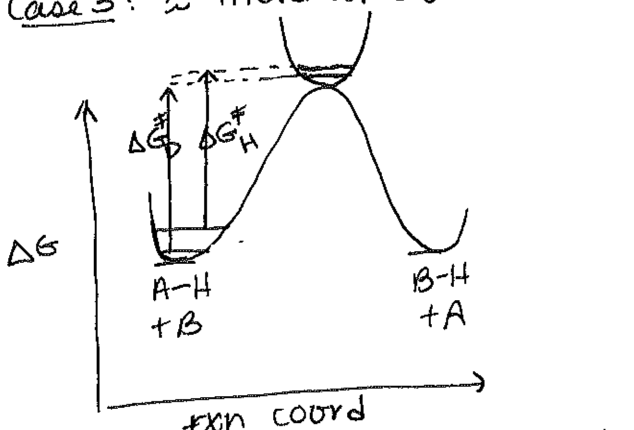


$\Delta G^{\ddagger}_D \approx \Delta G^{\ddagger}_H$

A··<·H·>B ≈ H>B ≈ H>A

small KIE ← if, then

(9) Case 3: ≈ THERMONEUTRAL



symmetric stretch holds H in place:

$\Delta G^{\ddagger}_D > \Delta G^{\ddagger}_H$

A·<· H ·>· B

(10)

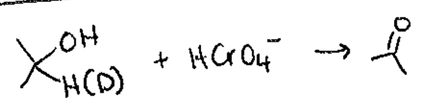
Kinetic Isotopes arise when $\Delta G^{\ddagger}_D \neq \Delta G^{\ddagger}_H$

(can get more complicated for nonlinear ts.'s)

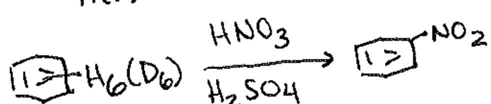
Primary KIE ⇒ Some degree of bond breaking of C–H/D in/before rds.

(11) Examples:

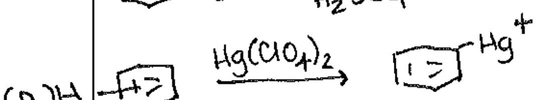
KIE



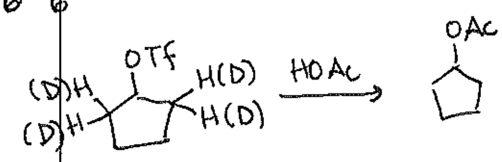
7.7



≈ 1



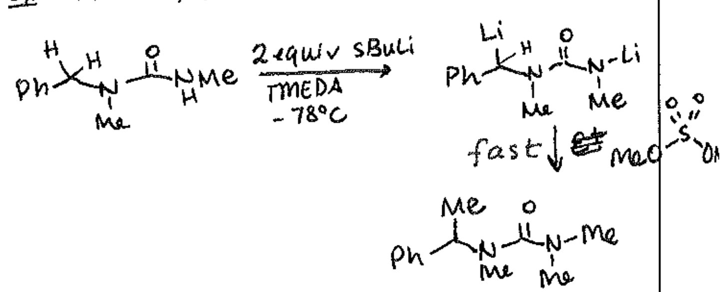
6.75



2.06

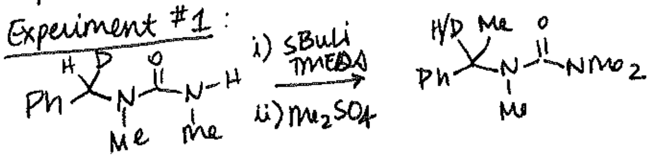
(12) DIRECTED LITHIATION

ex: Resek, Beak. JACS 1994, 116, 405.



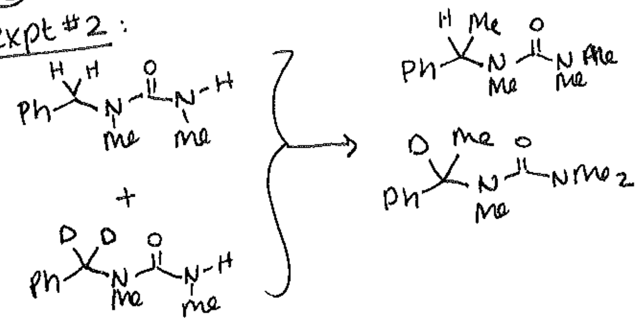
Expectation: 1° KIE ⇒ C–H breaking.

Experiment #1:



$(k_H/k_D)_{intra} = 13 \pm 3$

(13) expt #2:

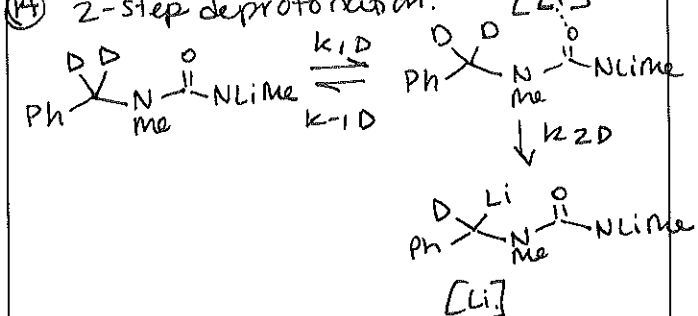


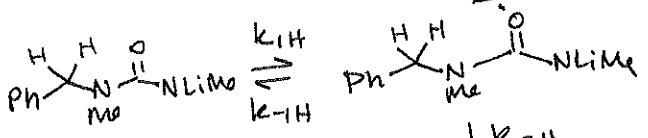
~1:1

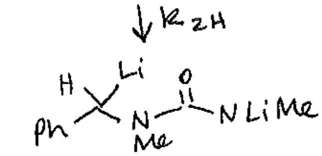
$$\left(\frac{k_H}{k_D}\right)_{inter} = 2.0 \pm 0.7$$

Why are they different?

(14) 2-step deprotonation:





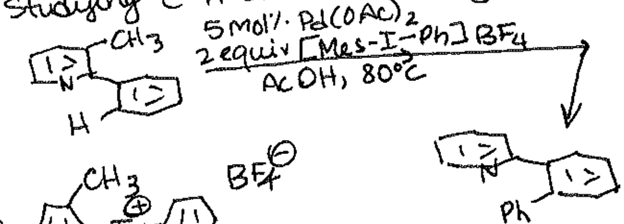


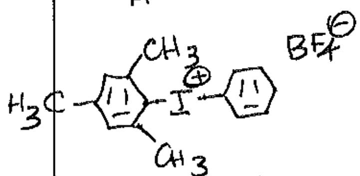
k_{-1H} vs. k_{2H}

k_{-1D} vs. k_{2D}

(15) Example: Sanford et al. JACS 2009, 131(31), 11234.

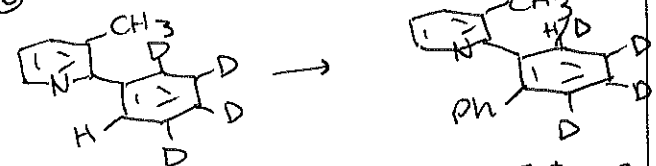
Studying C-H activation by Pd cat:



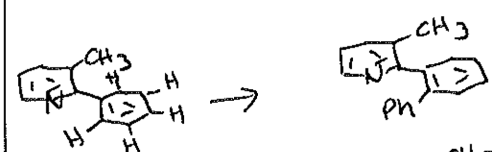


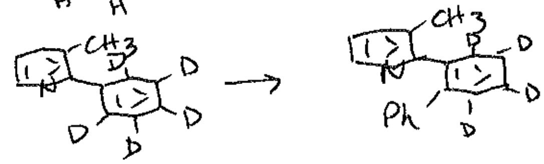
[Mes-I-Ph]BF_4

(16)



$$\left(k_H/k_D\right)_{intra} = 2.5 \pm 0.2$$





$$\left(k_H/k_D\right)_{inter} = 1.0$$

(17) Why the difference?

C-H/D activation occurs after the r.d.s.

(18) Secondary Isotope Effects

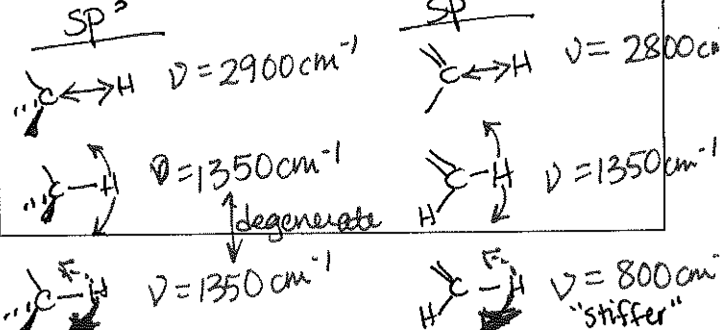
Due to rehybridization (not breaking of C-H/D bond).

(See A&D, 8.1.3 for more fundamental explanation.)

Change in hybridization ⇒ Change in relative ZPE's.

C-H stretch

Bending



(19)

$sp^3 \rightarrow sp^2 \quad 1.4 > \frac{k_H}{k_D} > 1.0$

$sp^2 \rightarrow sp^3 \quad 0.7 < \frac{k_H}{k_D} < 1.0$

↑ Inverse Isotope Effect

Note: These values are small, so experimental error may overwhelm the KIE.

Can also do isotope effects w/ heavier atoms, but effects are *really* small. & Hard to measure.

(20) Solution: Singleton Experiment

Singleton & Thomas JACS 1995, 117, 9357.

Insight: Use natural abundance...

As rxn proceeds, starting materials become enriched in isotopically slower-reacting components

$$\frac{R}{R_0} = (1-F)^{(1/KIE)-1}$$

R = isotopic enrichment in recovered SM

R_0 = isotopic enrichment at beginning

F = Fractional conversion of reactants

Measure enrichment by ^2H & ^{13}C NMR.

Toward completion, $F \rightarrow 1$.

$R/R_0 \rightarrow \infty \Rightarrow$ KIE's are magnified.

(21)

ex: KIE = 1.05

⇓

99% conversion → ~25% enrichment of slower-reacting component!

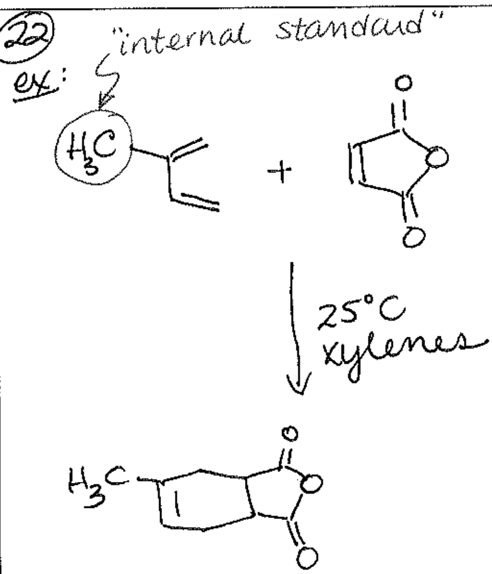
Need to measure conversion carefully!

Need to go almost to full conversion.

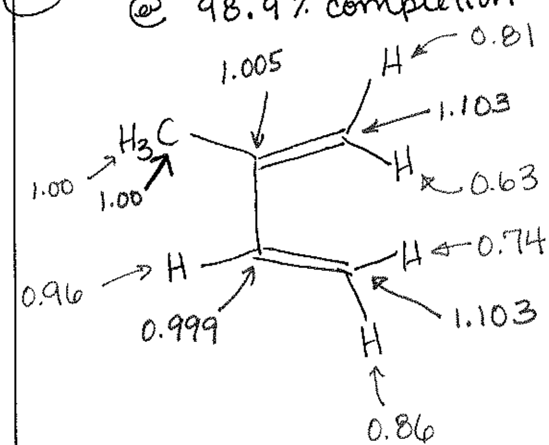
Need enough material to isolate RSM & determine enrichment.

(22)

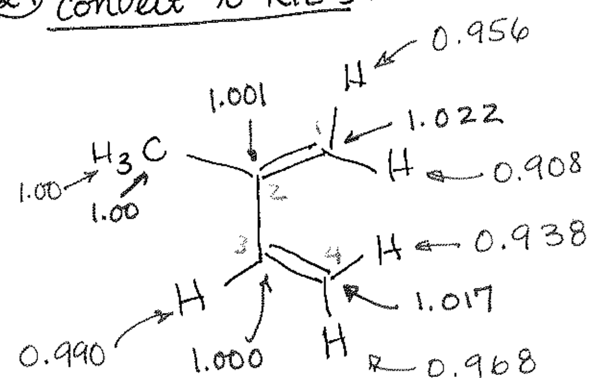
ex:



(23) Relative ^2H & ^{13}C enrichment @ 98.9% completion



(24) Convert to KIE's:



2° KIE's on H: $sp^2 \rightarrow sp^3$

Bigger on C1 than C4 ⇒ Asynchronous

KIE's on C1 & C4 ⇒ Bond forming.

This approach is particularly powerful when combined w/ computational predictions.