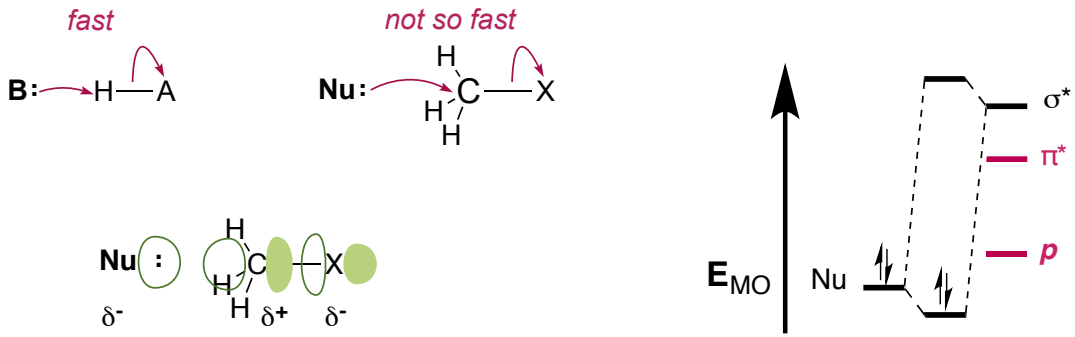
Topic 5: Addition to σ*
Proton Transfers and Acid-Base Equilibrium



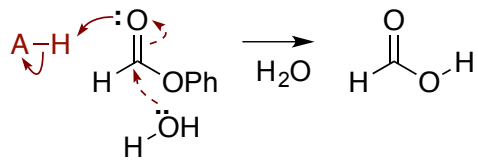
Addition to σ* orbital leads to bond cleavage

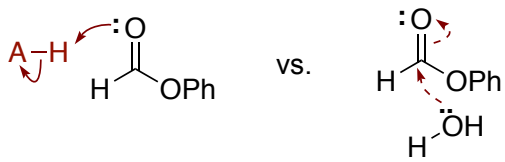
Hydrogen atoms are always attached to something.

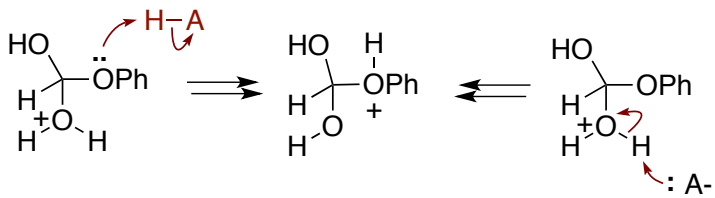
Read: **Fleming 4.1-4.2**
C&S 4.1.2, 4.2.1, 4.2.2

Questions about Proton Transfer Steps are Common

■ **What is the mechanism for this reaction?**

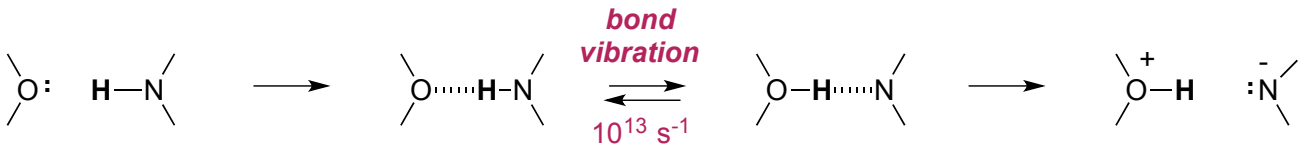






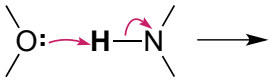
Proton Transfer - Geometry

■ **3-Step Eigen mechanism:** Step 1 = hydrogen bond

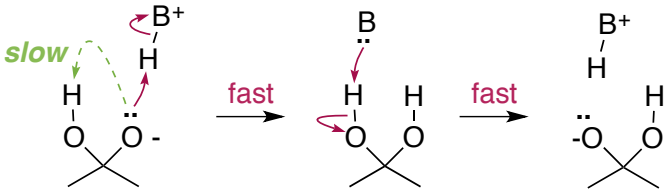


Eigen, M. in "Fast Reactions and Primary Processes in Chemical Kinetics" *Nobel Symposium* **1967**, 5, 245.

■ **Arrow-pushers: draw proton transfers as one step.**
(You can't push arrows with H-bonds.)



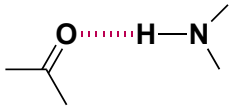
■ **Linear proton transfers are favored.** Transfer protons in 2 steps in tetrahedral intermediates.



Evidence for linear T.S. *(versus bent T.S.)*

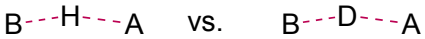
1. H-bonds are close to linear in most crystal structures
2. Largest kinetic isotope effect when proton transfer is linear

Crystal Structs:



H-bonds ≈ linear

Isotope FX:



slows most when T.S. = linear

Taylor, R.; Kennard, O. "Hydrogen-bond geometry in organic crystals." *Acc. Chem. Res.* **1984**, *17*, 320.

Proton Transfer - Kinetics

■ Look at this data

$$H_2O + H{-}A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^{+}H_2O{-}H + A^-$$

pK_a -1.7

Crooks, J. E. "Proton Transfer to and From Atoms Other Than Carbon." *Comprehensive Chemical Kinetics* **1977,** 8, 197.

H-A	pK_a	k_1 ($M^{-1}s^{-1}$)	k_{-1} ($M^{-1}s^{-1}$)
HF	3.2	10^8	10^{11}
CH_3CO_2H	4.7	10^6	10^{11}
H_2S	7.2	10^4	10^{11}
$MeCOCH_2CO_2Et$	9.0	10^{-3}	6×10^7
NH_4^+	9.3	25	$\sim 10^{11}$
H_3CNO_2	10.2	10^{-8}	6×10^2

■ **Proton transfers to and from heteroatoms are usually fast**

An exception in DMSO: Ritchie, C. D.; Lu, S. *J. Am. Chem. Soc.* **1989**, *111*, 8542.

■ **For N, O, S:**
Acids protonate bases at diffusion-controlled rate if $\Delta pK_a > 3$

pK_a' = 5 pK_a = -1.7

diffusion controlled

10^{11} M^{-1} s^{-1}

pK_a' = 9.3 pK_a = 9.8

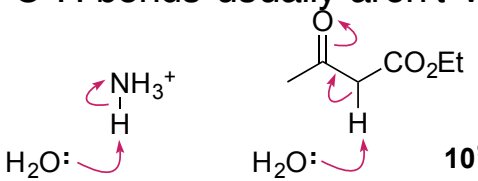
...not

10^7 M^{-1} s^{-1}

This is one of the few cases that where you can predict rate constants.

■ **Proton transfers to and from carbon are usually slow;** recall Eigen mechanism involves hydrogen bonding and C-H bonds usually aren't very good at hydrogen bonding.

pK_a ~ 9



10^9 slower!

Proton Transfer - Equilibrium

■ You can estimate K_{eq} from pK_as. pK_as are readily available because it is easy to perform titrations.

From chemical equations...

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \qquad K_a' = \frac{[A^-][H_3O^+]}{[HA][H_2O]}$$

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O \qquad K_a = \frac{[B][H_3O^+]}{[BH^+][H_2O]}$$

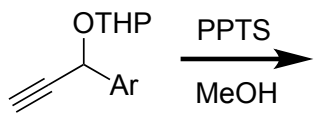
$$HA + B \rightleftharpoons A^- + BH^+ \qquad K_{eq} = \frac{[HA][B]}{[A^-][BH^+]}$$

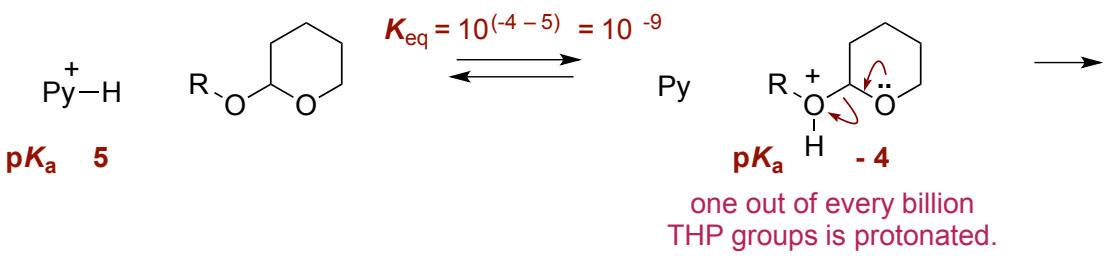
From math...

$$K_{eq} = \frac{K_a'}{K_a}$$

(Equilibria and kinetics of proton transfers)
Fersht, A. *Enzyme Structure and Mechanism.* 2nd Ed. W. H. Freeman, 1985. Pp. 148-149.

■ Acid-base equilibria usually precede important rate determining steps.
<u>Always</u> try to estimate ratios of relative concentrations of rxn intermediates





■ In organic solvents, the equation is approximate since we rarely know pK_as, but don't be afraid to approximate.

Use pK_as to Estimate Ratios: Stoichiometric Equilibria vs. Buffered Conditions

■ **Un-buffered organic reactions:**

Recall: $HA + B \rightleftharpoons A^- + BH^+$

$$K_{eq} = 10^{(pK_a(BH+) - pK_a(HA))}$$

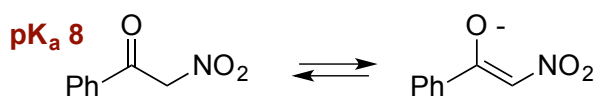
Example:

$$K_{eq} = 10^{(29.4-24.7)} \approx 10^5$$

Caveat: You rarely know pK_as in typical organic solvents.

The equation gives **useful** estimates, even when you apply *aqueous* pK_as to *organic* solvents. Don't be afraid to estimate.

■ **Buffered aqueous solution**. The most common buffered condition is the physiological pH range of 7.2-7.4 (approximately pH 7). You need to be able to estimate ratios of protonated to deprotonated species at pH 7.



pH			
10	**1**	**:**	**100**
9	**1**	**:**	**10**
8	**1**	**:**	**1**
7	**10**	**:**	**1**
6	**100**	**:**	**1**

When pH = pK_a ...
the ratio of **[HA] / [A-] = 1:1**

Structural Effects on Acidity

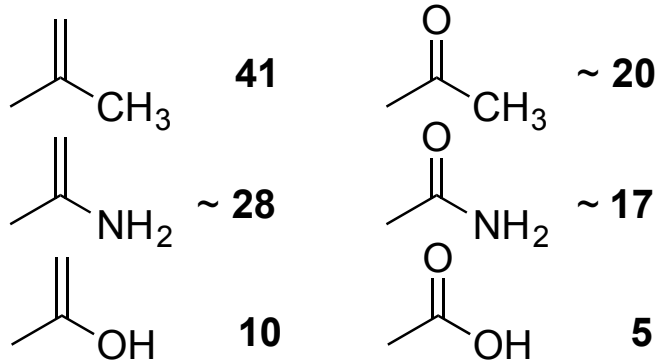
■ pK_as of acids are easy to measure (by titration), there are millions of tables. Unfortunately, organic chemists are usually interested in the conjugate base (the nucleophilic form).

■ Aqueous pK_as you should know...

1. Electronegativity

CH_3-CH_3	**50**
CH_3-NH_2	**~ 36**
CH_3-OH	**16**

2. Resonance



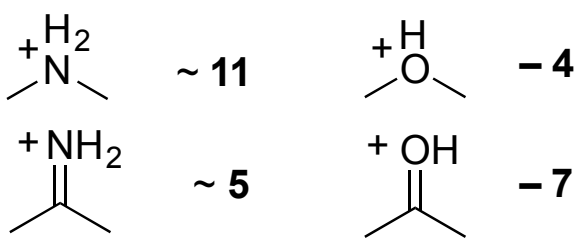
3. Hybridization

CH_3-CH_3	**50**
$CH_2=CH_2$	**41**
$CH\equiv CH$	**24**

5. Row

H-F	**3**
H—Cl	**– 8**
H—Br	**– 9**
H——I	**– 10**
Et—SH	**11**

4. Charge



H_2O	**15.7**	H_3O+	**– 1.7**

6. Polar

$HOCH_2OH$	**13.4**
H_3CCO_2H	**4.8**
FH_2CCO_2H	**2.7**
F_3CCO_2H	**– 0.3**

pK_a of $H_2C{=}CHOH$ = 10.5 *JACS* **1987**, 109, 4000.
pK_a of *i*-PrCH=NHMe+ = 6.9 *JACS* **1970**, 92, 5194.

Solvent Effects on Acid-Base Equilibria

Solution: $H_3C\text{-}Li$ < $H_3CH_2C\text{-}Li$ < $(H_3C)_2HC\text{-}Li$ < $(H_3C)_3C\text{-}Li$

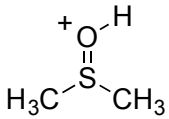
Gas phase?: $H_3C:^-$ $H_3CH_2C:^-$ $(H_3C)_2HC:^-$ $(H_3C)_3C:^-$

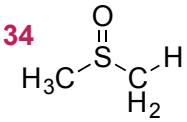
C&S A 3.4.2

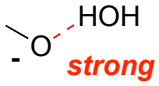
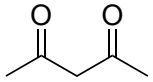
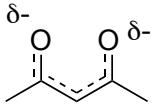
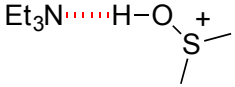
■ **Gas Phase Acidity**: *t*-BuOH > *i*-PrOH > EtOH > MeOH
In gas phase, larger anions are more stable than smaller anions

■ **DMSO vs. water:** DMSO tolerates more basic anions than water

$$HA + Me_2SO \rightleftharpoons A^- + Me_2SOH^+$$

pK_a **- 1.8** 

pK_a **34** 

	pK_as DMSO	H_2O	ΔpK_a	
HOH	27.5	15.7	**12**	 ***strong***
CH_3OH	27.9	15.3	**13**	
CH_3COOH	11.9	4.8	**7**	
CH_3COCH_3	26.5	~20	**7**	
PhOH	18.0	10.0	**8**	
	13.4	9.0	**4**	
Et_3NH^+	9.0	10.8	**– 2**	

■ **Water is better** than DMSO at stabilizing anions with localized negative charges (A-)
■ **DMSO is better** than water at stabilizing protonated ammonium ions (BH+)

Frederick G. Bordwell *Acc. Chem. Res.* **1988**, *21*(12); 456-463.