Acidity and basicity

The two faces for the molecule
Acidity and basicity - Introduction

• In the early 20th century two definitions were available for acids and bases

1. **Brønsted and Lowry** defined an acid as being a proton donor and a base as a proton acceptor (in aqueous medium).

2. **Lewis** defined an acid as being electron pair acceptors and base as electron pair donor (in nonaqueous medium).

• The definition of Brønsted and Lowry is the most useful for discussions of ionic equilibria in aqueous media.

• Drugs can be classified as acids, bases, neutral, or zwitterionic (i.e. weak acids or bases)

• Many drugs have the potential to exist as ionic species when dissolved in a variety of biological matrices (most drugs are ionized in the range of 60–90% at physiological pH).

• Most human tissues are quite close to neutral pH with the exception of gastric and duodenal pH.
• So we can describe molecular acidity and basicity as dynamical ionization process.

• The degree of ionization affects several key molecular properties including solubility which affects lipophilicity (partition or distribution coefficient) which affects permeability or diffusion.

• All molecules are able to ionize

• If the molecular ionization depends on H\(^+\) concentration it can behave as acid or base

• For both acids or bases the molecule is dissociated to into its ion components which includes the conjugated ion (\( \text{A}^- \)) and H\(^+\) ion.
So we can describe molecular acidity and basicity as dynamical ionization process.

For both acids or bases:
1. The ionized form (Hydrophilic > Lipophilic)
2. The un-ionized form (Hydrophilic < Lipophilic)

It is the un-ionized form of substances that preferentially traverses the cell membranes by passive diffusion.

Only small amount of ionized species can permeate membranes by passive diffusion,
As we studied in the intermolecular interactions the conductivity of the medium (dielectric constant or $\varepsilon$) will affects the interaction between opposite charges.

If we assume the interaction between conjugated $^-\text{ion}$ ( ) and $^+\text{ion}$ is a weak covalent or almost ionic interactions, then we can expect that the interaction will be stronger in lipid (low conductivity) and weaker in water (high conductivity).

Therefore:
- The ions will attract each other strongly in hydrophobic layer thus the molecule exist mainly as unionized
- The ions will attract each other weakly in hydrophilic layer thus the molecule exist as mainly unionized

**Diagram:***

\[ K_{on\ lipo} > K_{off\ lipo} \]
\[ K_{off\ lipo} > K_{on\ lipo} \]
Henderson–Hasselbach equation is dynamics

- The derivatization of Henderson–Hasselbach formula by considering acid as AH and base as B

\[
\begin{align*}
K_a &= \frac{K_{\text{off}}}{K_{\text{on}}} = \frac{[A^-][H^+]}{[AH]} \\
\log K_a &= \log \left( \frac{[A^-]}{[AH]} \right) + \log [H^+] \\
pH &= pK_a - \log \left( \frac{[AH]}{[A^-]} \right)
\end{align*}
\]
Henderson–Hasselbach equation is dynamics

- A second way of derivatization of Henderson–Hasselbach equation if we treat acid as AH and base as BOH

\[ \text{K}_a = \frac{K_{off}}{K_{on}} = \frac{[A^-][H^+]}{[AH]} \]

\[ \log K_a = \log \frac{[A^-]}{[AH]} + \log [H^+] \]

\[ pH = pK_a - \log \frac{[acid]}{[base]} \]

Only use this form if you can identify which species are acids and bases

\[ K_b = \frac{K_{off}}{K_{on}} = \frac{[B^+][OH^-]}{[BOH]} \]

\[ \log K_b = \log \frac{[B^+]}{[BOH]} + \log [OH^-] \]

\[ pOH = 17 - pH \]

\[ pK_b = 17 - pK_a \]

\[ pOH = pK_b - \log \frac{[BOH]}{[B^+]} \]

\[ -1 \times 17 - pH = 17 - pK_a - \log \frac{[BOH]}{[B^+]} \]

\[ pH = pK_a - \log \frac{[B^+]}{[BOH]} \]
However you view the complex .... acid is acid and base is base

- Therefore, we can view any molecule as a dissociable complex with the equilibrium measured as $K_d$.
- If you want to view the complex as XH, then the dissociation constant is named $K_a$.
- If you want to view the complex as XOH, then the dissociation constant is named $K_b$.

<table>
<thead>
<tr>
<th>XH View</th>
<th>A$^-$ + H$^+$ $\rightleftharpoons$ $\frac{K_{on}}{K_{off}}$ AH</th>
<th>B + H$^+$ $\rightleftharpoons$ $\frac{K_{on}}{K_{off}}$ BH$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid</td>
<td>$K_a = \frac{K_{off}}{K_{on}}$</td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>$K_b = \frac{K_{off}}{K_{on}}$</td>
<td></td>
</tr>
</tbody>
</table>

It is preferred to view them as XH since most of the books use $K_a$. 
"• $K_a = \frac{K_{off}}{K_{on}}$  
  $p_S = -\log K_a$  
  $pK_a = -\log K_a$

• pKa is the pH at which 50% of the compound is in ionized form $K_{off} = K_{on}$

When pH=pKa  
[HA]=[A⁻]  
Acid

When pH=pKa  
[B]=[BH⁺]  
Base

A⁻ + H⁺  $\xrightarrow{K_{on}}$  AH  $\xrightarrow{K_{off}}$  BH⁺
However you view the complex .... acid is acid and base is base

- Example of strong acid

\[ \text{H}_2\text{SO}_4 = \text{HSO}_4^- + \text{H}^+ \]

\[ pK_a = -\log K_a \]

\[ K_a = \frac{K_{off}}{K_{on}} = \frac{[\text{HSO}_4^-][\text{H}^+]}{[\text{H}_2\text{SO}_4]} = \frac{10^5}{1} = 10,000 \text{ molecules dissociated for } 1 \text{ molecule undissociated} \]

\[ pK_a = -\log 10^5 = -5 \]

The speed of \( K_{off} \) is 10,000 times more than \( K_{on} \)

\( \text{pH} = 5 \) لغرض نزع الهاييدروجن من نصف الجزيئات
However you view the complex .... acid is acid and base is base

• Example of weak acid

\[
\begin{align*}
\text{H}_3\text{C} & \text{O}^- + \text{H}^+ \quad \text{K}_{\text{on}} \quad \text{K}_{\text{off}} \quad \text{H}_3\text{C} \text{O}^- \\
\end{align*}
\]

\[
K_a = \frac{K_{\text{off}}}{K_{\text{on}}} = \frac{[\text{CH}_3\text{COO}^-][\text{H}^+]}{[\text{CH}_3\text{COOH}]} = \frac{1}{10^{4.8}} = \text{one molecule dissociated for} \quad \frac{63,096 \text{ molecule undissociated}}{63,096 \text{ molecule undissociated}}
\]

\[
pK_a = -\log 10^{-4.8} = 4.8
\]

The speed of \( K_{\text{off}} \) is 63,000 times less than \( K_{\text{on}} \)

Means

= At no change in pH: 1 mol is ionized and 63,096 mol unionized.

= At pH 5: half of the acetic acid will be ionized and the other half is unionized
However you view the complex ....acid is acid and base is base

• Example of weak base

Electrons are involved in pi resonance
And not available to accept proton

\[
K_a = \frac{K_{off}}{K_{on}} = \frac{[\text{Pyridine}][H^+]}{[\text{PyrdineH}^+]} = \frac{1}{10^5} = \frac{1 \text{ molecule dissociated for}}{100,000 \text{ molecules undissociated}}
\]

\[pK_a = -\log 10^{-5.3} = 5\]

A weak conjugate acid does not easily donate its proton
(1 molecule in 100,000 donates a proton)

Therefore a weak base willingly accepts a proton
(100,000 molecules accept a proton for every one not accept)
However you view the complex ....acid is acid and base is base

- Example of strong base

\begin{align*}
\text{NaOH} + \text{H}^+ & \rightleftharpoons \text{Na}^+\text{OH}_2 \\
K_a = \frac{K_{off}}{K_{on}} &= \frac{[\text{NaOH}][\text{H}^+]}{[\text{NaOH}\text{H}^+]} = \frac{1}{10^{16}} = \frac{1 \text{ molecule dissociated for}}{100,000,000,000,000 \text{ molecules undissociated}} \\
pK_a &= -\log 10^{-16} = 16
\end{align*}

The speed of \( K_{off} \) is \( 10^{16} \) times less than \( K_{on} \)

\[ pK_a = -\log K_a \]

A weak conjugate acid does not easily donate its proton (1 molecule in 100,000,000,000,000 donates a proton)

Therefore a strong base willingly accepts a proton (100,000,000,000,000 molecules accept a proton for every one not accept)
However you view the complex .... acid is acid and base is base

$\text{H}_2\text{N} + \text{H}^+ \xrightarrow{K_{on}} \text{PhCH}_2\text{NH}_2^+$

$\text{PhCH}_2\text{NH}_2^+ \xrightarrow{K_{off}} \text{PhCH}_2\text{NH}_2$

$pK_a = -\log K_a$

A weak conjugate acid does not easily donate its proton

(1 molecule in 1,000,000,000 donates a proton)

Therefore a strong base willingly accepts a proton

(1,000,000,000 molecules accept a proton for every one)

Q) Why benzyllamine is stronger base than pyridine?
A) The availability of electron pair is more in benzyllamine due to absence of nearby pi system
How molecular structure can affect pKa?

- The acidity of a molecule is affected by the ease of dissociation of AH. Any structural effect which stabilize the dissociated ions A- and H+ will going to increase acidity:

1. Stabilization of A- ion by resonance which will lead to increase in $K_{off}$

Phenoxide anion is stable by resonance this means that phenol can give stable anion upon donating its proton "act as an acid" and remain stable.

\[
\begin{align*}
\text{phenol} & \xrightarrow{K_{off}} \text{phenoxide} \\
\text{phenol} & \xrightarrow{K_{on}} \text{phenoxide}
\end{align*}
\]

\[
\begin{align*}
\text{phenol} & \xrightarrow{K_{off}} \text{phenoxide} \\
\text{phenol} & \xrightarrow{K_{on}} \text{phenoxide}
\end{align*}
\]

pKa=10  pKa=14.6  pKa=14
How molecular structure can affect pKa?

2. The electrophilicity for the atom bearing the hydrogen (H)

The more the atom is electrophilic → the higher will be the loss of H⁺ → the stronger will be the acid

<table>
<thead>
<tr>
<th></th>
<th>CH₄</th>
<th>NH₃</th>
<th>H₂O</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>~50</td>
<td>38</td>
<td>15.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Electronegativity</td>
<td>2.5</td>
<td>3.0</td>
<td>3.4</td>
<td>4.0</td>
</tr>
</tbody>
</table>

• similarly, if electron-withdrawing group (EWG) is connected to the atom bearing the H, the atom will be more electrophilic, thus more acidic.
How you can differentiate the compound whether is it AH or B?

In order to draw the equilibrium formula you need to know what are the unionized (AH or B) and ionized (A⁻ or BH⁺) forms of your compound.

Important notes:
1. If your compound has H atom which can be easily lost it is (AH acid)
2. If your compound has –ve charge which can accept H it is (A⁻ base)
3. If your compound has neutral with free electron pairs it is (B base)
4. If your compound has +ve charge which can donate H it is (BH⁺ acid)

Usually, compounds which have COOH or OH close to pi system, it can easily give protons, thus are closer to acidic

Usually compounds which have N atom which carries unshared pair of electrons are closer to basic

Since we are treating compounds as dissociation equilibrium, we can not absolutely say that particular compound is acid or base, however, we can say whether it is more acidic or more basic compared to other compound
Acidic face

- Common acidic groups available in drug molecules with its pKa.
- You can notice that the hydrogen bearing atom is close to pi system.
- The pi system will stabilize the molecule after losing the $H^+$
• Examples of acidic drugs

- Tolbutamide: hypoglycemic agent
- 4-hexylresorcinol: topical anesthetic
- Aspirin: NSAID
- Cephalexin: Antibacterial agent
• Common basic groups available in drug molecules with its pKa.

\[
\begin{align*}
\text{R} & \text{NH}_2 & 10.0 \\
\text{R} & \text{NH} & 10.6-11.0 \\
\text{R} & \text{N} & 9.8-10.8 \\
\text{C}_6\text{H}_5 & \text{NH}_2 & 4.6 \\
\text{HN} & \text{N} & 6.5 \\
\text{N} & & 5.2
\end{align*}
\]

• You can notice that the hydrogen bearing atom is not close to pi system for strong bases (i.e. free electrons on nitrogen atom are not delocalized by pi system) thus can accept H⁺
• Examples of basic drugs

- Atropine: Anticholinergic agent
- Morphine: Opioid analgesic
- Ketoconazole: Antifungal agent
- Diphenhydramine: Antihistaminic agent
Diphenylamine ($pK_a = 0.8$)

The N atom have lone pair of electrons which are responsible for its basicity. The N can bind H\(^+\) to form NH\(^+\)

However, those electrons are close to aromatic rings thus may involve in resonance and become less available to bind H\(^+\)

Therefore, $K_{off}$ is larger than $K_{on}$ $\Rightarrow$ $\downarrow pK_a$
Where the compound is best absorbed?

• Measuring the degree of ionization of a compound at particular pH is important to estimate its absorption.

• The unionized form of the compound (AH) is more lipophilic and can better penetrate the lipophilic cell membranes of the cells lining the GIT.

• Therefore, if drug س has lower pKa than drug ص then:
  
  Drug س is absorbed in stomach better than drug ص
  
  Drug ص is absorbed in intestine better than drug س
**Where the compound is best absorbed?**

- Drugs which have carboxylic acids \((\text{RCOOH})\)
- The absorption of these drugs is mainly in stomach
- Examples of such drugs are

\[
\begin{align*}
\text{Blood} & \xrightarrow{\text{RCOOH}} \text{Blood} \\
\text{Stomach pH=1} & \quad \text{Intestine pH=8} \\
K_{\text{on}} & > K_{\text{off}} \\
K_{\text{on}} & < K_{\text{off}}
\end{align*}
\]
Where the compound is best absorbed?

- Drugs which have basic nitrogen ($\text{RNH}_2$)
- The absorption of these drugs is mainly in intestine
- Examples of such drugs are

![Diagram showing the absorption process](image_url)

- $K_{on} > K_{off}$ in Intestine pH=8
- $K_{on} < K_{off}$ in Stomach pH=1
How much compound is really absorbed?

Therefore, to best measure the absorption we should consider both dissociation constants ($K_a$ and $P$).

Either of them is not enough to measure the absorption:
- Not all compounds have suitable $K_a$ will be absorbed
- Not all compounds have suitable $P$ will be absorbed
How much compound is really absorbed?

- For the compound to be absorbed it should have suitable lipophilic/hydrophilic balance.
- Lipophilic/hydrophilic balance is measured by partition coefficient.
- Partition coefficient is the ratio of partitioning of compound between lipophilic layer (octanol) and hydrophilic layer (water).
- Diffusion coefficient for a compound is affected by its ionization potential (pKa) and structure

\[
\text{Diffusion coefficient} = \text{Ionizability (Ka)} + \text{Partition coefficient (P)}
\]

LogD at pH 8 is 0.16 = pKa is 7 + LogP is -0.2

Therefore, gentamicin has bad absorption (Low logD) even it is mainly unionized in intestine (pH=8) due to its structural properties (low Log P)
In order to know how much compound is absorbed, we need to understand the dissociation constant between ionized and unionized forms (Ka) of the compound as well as the dissociation constant between lipid and water phases (P).

The terms lipohilicity and hydrophobicity are often used interchangeably.

**Hydrophobicity** is the association of non-polar groups or molecules in an aqueous environment, which arises from the tendency of water to exclude non-polar molecules.

**Lipophilicity** represents the affinity of a molecule for a lipophilic environment.

For many years the standard system in which to measure lipophilicity has been the n-octanol/water partition system. The equilibrium of a neutral (unionized) compound between n-octanol and water is measured (at 20 °C).

\[
K_{on \ lipo} > K_{off \ lipo} \\
K_{off \ hydro} > K_{on \ hydro}
\]
Hydrophilic/Lipophilic behavior ± ionization behavior

- **Log P**: Log of the partition coefficient of the compound between an organic phase (e.g., octanol) and an aqueous phase (e.g., buffer) at a pH where all of the compound molecules are in the neutral form (unionized).

\[
P = \frac{\text{unionized form in octanol}}{\text{unionized form in water}} = \frac{[AH]_o}{[AH]_w}
\]

Is used if we **ignore** the ionization equilibrium (i.e. assume the molecules are all unionized). It is not dependent on pKa.

- **Log D**: Log of the distribution coefficient of the compound between an organic phase (e.g., octanol) and an aqueous phase (e.g., buffer) at a specified pH (x). A portion of the compound molecules may be in the ionic form (ionized) and a portion may be in the neutral form (unionized)

\[
D = \frac{\text{all forms in octanol}}{\text{all forms in water}} = \frac{[AH]_o+[A^-]_o}{[AH]_w+[A^-]_w}
\]

Is used if we **consider** the ionization equilibrium (i.e. assume the molecules are ionized and unionized). It is dependent on pKa.

\[
K_{\text{on lipo}} > K_{\text{off lipo}}
\]

\[
K_{\text{off hydro}} > K_{\text{on hydro}}
\]
Hydrophilic/Lipophilic behavior ± ionization behavior

\[
\text{dissociation of compound in water} = \frac{K_{\text{off hydro}}}{K_{\text{on hydro}}} \quad \text{(depend on structure)}
\]

\[
\text{dissociation of compound in lipid} = \frac{K_{\text{off lipo}}}{K_{\text{on lipo}}} \quad \text{(almost zero)}
\]

\[
\text{dis. of ionized comp. bet lipid and water} = \frac{K_{\text{off ion}}}{K_{\text{on ion}}} \quad \text{(almost zero)}
\]

\[
\text{dis. of unionized comp. bet lipid and water} = \frac{K_{\text{off union}}}{K_{\text{on union}}} \quad \text{(depend on structure)}
\]
How D is calculated?

\[
D = \frac{\text{all forms in octanol}}{\text{all forms in water}} = \frac{[AH]_o + [A^-]_o}{[AH]_w + [A^-]_w}
\]

\[
D = \frac{[AH]_o}{[AH]_w + [A^-]_w} + \frac{[A^-]_o}{[AH]_w + [A^-]_w}
\]

\[
\frac{1}{D} = \frac{[AH]_w + [A^-]_w}{[AH]_o}
\]

\[
P = \frac{[AH]_o}{[AH]_w}
\]

\[
[D] = 10^{pK_a - pH}
\]

\[
\frac{1}{D} = \frac{1}{P} + \frac{[A^-]_w}{P[AH]_w}
\]

\[
\frac{1}{D} = \frac{1}{P} + 10^{PH - pK_a}
\]

\[
D = \frac{P}{1 + 10^{pK_a - PH}}
\]

For bases

For acids
Think ....

Lipinski’s rule of 5 represent a set of conditions that if met in a molecule, it will have high probability for absorption through GIT.

1. A molecular mass ≤ 500;
2. A calculated value of log P ≤ 5 (P is octanol/water partition coefficient)
3. No. of hydrogen bond acceptor groups ≤ 10 (e.g. -O- and -N-, etc.);
4. No. of hydrogen bond donor groups ≤ 5 (e.g. NH and OH, etc.).

Why Lipinski's rule contains no condition for pKa?