Overview

- Brønsted acidity and basicity in solution
  - $pK_a$ values
- Influence of solvent
  - Polarity, acidity, basicity
- What non-aqueous $pK_a$ data are available
- How to estimate $pK_a$ of X on solvent S?
Why do we need non-aqueous $pK_a$ data?

- Most reactions and processes run **heterolytically**
  - Very often involving acid-base interactions
  - Very often in non-aqueous solutions
  - For understanding them $pK_a$ values are necessary

- Design of **novel acids and bases**

- Development of **theoretical calculation methods**

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Acidity of molecules

- Brønsted acidity of a **molecule** refers to its ability to donate proton to other molecules
  - Usually defined in terms of equilibrium constants ($K_a$, $pK_a$) or deprotonation energies ($GA$ or $\Delta G_{\text{acid}}$)

**This is the main topic of this talk**
Acidity of media

- Brønsted acidity of a medium refers to its ability to donate proton to molecules in the medium
  - In aqueous solution: pH
  - Strongly acidic solutions: $H_0$
  - “Unified pH Scale” ($pH_{abs}$)

Acidity of molecules in solution

- Acidity of molecules in solution is defined in the framework of the Brønsted theory via the $pK_a$ values

$$\text{HA} + S \xleftrightarrow{K_a} A^- + SH^+$$

$$pK_a = -\log K_a = -\log \frac{a(A^-) \cdot a(SH^+)}{a(\text{HA})}$$

- $pK_a$: the lower the value, the more acidic
- Acidity of an acid is very different in different solvents!
Basicity of molecules in solution

- Basicity of a molecule B in solution is defined as the **acidity** of its **conjugate acid** (its $pK_a$ value)

\[
\text{BH}^+ + \text{S} \rightleftharpoons \text{B} + \text{SH}^+ \\
pK_a = -\log K_a = -\log \frac{a(B) \cdot a(\text{SH}^+)}{a(\text{BH}^+)}
\]

$pK_a$: the higher the value, the more basic

Basicity of a base is very different in different solvents!

Acidity and basicity of molecules in the gas phase

- Acidity/basicity of molecules in the gas phase is expressed via deprotonation **Gibbs' free energy**

\[
\text{HA} \rightleftharpoons \text{A}^- + \text{H}^+ \\
\Delta G_{\text{acid}}^o = -RT \ln K_a
\]

\[
\text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+ \\
\Delta G_{\text{base}}^o = -RT \ln K_a
\]
Gas phase

Dissociation in the gas phase
\[ \Delta G^\circ_{a}(HA) >> 0 \]

- Desolvation
\[ \Delta G^\circ_{ds}(HA) > 0 \]

\[ -\Delta G^\circ_{a}(SH^+) << 0 \]

\[ \Delta G^\circ_{s}(A^-) << 0 \]

Solution

Dissociation in solution
\[ \Delta G^\circ_{a}(HA,s) \]

\[ -\Delta G^\circ_{a}(SH^+) = -265.9 \text{ kcal/mol} \]

\[ \Delta G^\circ_{s}(A^-) = -77.6 \text{ kcal/mol} \]

Gas phase: Acetic acid

Dissociation in the gas phase
\[ \Delta G^\circ_{a}(HA) = +341.1 \text{ kcal/mol} \]

- Desolvation
\[ \Delta G^\circ_{ds}(HA) = +6.7 \text{ kcal/mol} \]

\[ -\Delta G^\circ_{a}(SH^+) = -265.9 \text{ kcal/mol} \]

\[ \Delta G^\circ_{s}(A^-) = -77.6 \text{ kcal/mol} \]

H\textsubscript{2}O

Dissociation in solution
\[ \Delta G^\circ_{a}(HA,s) = +6.5 \text{ kcal/mol} \]
### Acidity in solution and in the gas phase

<table>
<thead>
<tr>
<th>Acid</th>
<th>(pK_a) (water)</th>
<th>(pK_a) (MeOH)</th>
<th>(pK_a) (DMSO)</th>
<th>(pK_a) (MeCN)</th>
<th>(\Delta G_a) (GP) kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBr</td>
<td>(-9)</td>
<td>(-7)</td>
<td>5.5</td>
<td>318.3</td>
<td></td>
</tr>
<tr>
<td>2,4-Dinitrophenol</td>
<td>4.09</td>
<td>7.9</td>
<td>5.1</td>
<td>16.7</td>
<td>308.6</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>4.76</td>
<td>9.6</td>
<td>12.3</td>
<td>23.51</td>
<td>341.1</td>
</tr>
</tbody>
</table>

- Solvation energies are very different
- In water HBr is \(10^{13}\) times **stronger** than 2,4-DNP
- In the gas phase HBr is \(10^7\) times **weaker** than 2,4-DNP

1 \(pK_a\) unit \(\equiv 1.36\) kcal/mol

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### Acids in different media


http://tera.chem.ut.ee/~ivo/HA_UT/
Acids in different media

http://tera.chem.ut.ee/~ivo/HA_UT/

Bases in different media

http://tera.chem.ut.ee/~ivo/HA_UT/
Generalised acid-base reaction in a non-aqueous solvent

\[ (AH)_S + (:B)_S \rightleftharpoons (AH\cdots B)_S \rightleftharpoons (A^-\cdots HB^+)_S \text{ or } (A^-:HB^+)_S \]

- \( K_1 \) \hspace{1cm} \( K_2 \) \hspace{1cm} \( K_3 \)
- \( K_3 \) \hspace{1cm} \( K_4 \)

- HB complex \hspace{1cm} HB complex \hspace{1cm} contact ion pair
- solvent-separated ion pair \hspace{1cm} free ions

How far the process goes depends on
--1-- Acid and base strengths of the compounds
--2-- Solvent
How does solvent influence $pK_a$?

- By solvating the species
  - Ions are much solvated much stronger
    - First approximation: neglect neutrals
  - Especially small ions and/or with localized charge

- HB acceptor properties / basicity
  - Solvation of $H^+$, $HA$, $BH^+$

- HB donor properties / acidity
  - Solvation of $A^-$, $B$:

- Dielectric constant
  - Promotes dissociation

Solvent acidity and basicity: $pK_{auto}$

$$K_{auto} \quad (SH)_S + (SH)_S \rightleftharpoons (SH^+_2)_S + (S^-)_S$$

$$K_{auto} = a(AH^+_2) \cdot a(S^-) \quad pK_{auto} = -\log K_{auto}$$

- $pK_{auto}$ defines the span of $pK_a$ scale
  - Differentiating ability
- High $pK_{auto}$ is preferable
Solvent acidity, basicity and $pK_{\text{auto}}$

Some solvents

<table>
<thead>
<tr>
<th>Solvent/medium</th>
<th>$\varepsilon$</th>
<th>HBA: DN, B’</th>
<th>HBD $\alpha$</th>
<th>$pK_{\text{auto}}$</th>
<th>Useful for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas phase</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Any acid or base</td>
</tr>
<tr>
<td>Heptane</td>
<td>1.94</td>
<td>0.0</td>
<td>0</td>
<td>–</td>
<td>(Any acid or base)*</td>
</tr>
<tr>
<td>THF</td>
<td>7.47</td>
<td>20, 287</td>
<td>0</td>
<td>Very high</td>
<td>Weak acids, strong bases**</td>
</tr>
<tr>
<td>1,2-Dichloro-Ethane</td>
<td>10.7</td>
<td>0.1, 40</td>
<td>Very high</td>
<td>Strong acids, weak bases**</td>
<td></td>
</tr>
<tr>
<td>MeCN</td>
<td>35.9</td>
<td>14.1, 160</td>
<td>0.19</td>
<td>ca 39</td>
<td>Strong acids, weak bases</td>
</tr>
<tr>
<td>DMSO</td>
<td>46.7</td>
<td>29.8, 362</td>
<td>0</td>
<td>ca 33</td>
<td>Weak acids, strong bases</td>
</tr>
<tr>
<td>Methanol</td>
<td>33</td>
<td>High</td>
<td>0.98</td>
<td>18.9</td>
<td>Medium acids and bases</td>
</tr>
<tr>
<td>Vesi</td>
<td>81</td>
<td>High</td>
<td>1.17</td>
<td>14.0</td>
<td>Medium acids and bases</td>
</tr>
</tbody>
</table>

* Solubility issues
** Ion-pair acidities and basicities
Self-consistent acidity scale (pK$_a$ scale) in MeCN

http://tera.chem.ut.ee/~ivo/HA_UUT/
1,2-DCE acidity scale

- The most acidic equilibrium acidity scale in a constant-composition medium

Relative acidities
- Not easy to anchor
- Some values available in literature, but are very doubtful

http://tera.chem.ut.ee/~ivo/HA_UT/

1,2-DCE acidity scale

- Ion pair acidities
- Counter-ion:
  - t-BuP,(pyrr)H+

Aqueous pK_a (H_0) values down to -10 .. -15

In pipeline:
- Weaker acids
- Weak bases

**Self-consistent basicity scale in MeCN (1)**

- Anchor: Pyridine
- Free ions
- Titrants:
  - TfOH
  - t-BuP$_1$(pyrr)


A. Kütt, PhD thesis

... and other works

http://tera.chem.ut.ee/~ivo/HA_UT/

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**Self-consistent basicity scale in MeCN (2)**


A. Kütt, PhD thesis

... and other works

http://tera.chem.ut.ee/~ivo/HA_UT/
Self-consistent basicity scale in MeCN (3)

A. Kütt, PhD thesis ... and other works
http://tera.chem.ut.ee/~ivo/HA_UT/

Pyridine 12.5
Aniline 10.6
Triphenylphosphine 7.6
Diphenylamine 6.0
2-NO₂-Aniline 4.8

Self-consistent basicity scale in THF
- Anchor: Triethylamine
- Ion pairs
  - Counterion MeSO₃⁻
- Titrants:
  - MeSO₃H
  - t-BuP₄(pyrr)
  - Liberation of bases: KH

Typical issue: no pKa data for X in solvent S

- Possible solutions:
  - Measure
  - Compute
    - Usually correlations are needed for corrections
  - Correlate between solvents
    - Reliable data of similar compounds are needed in both solvents
      - Best if large span
      - Works best within a homogeneous compound series
    - Not between any solvents
  - Cross-use between solvents
    - Only suitable for "stronger-weaker" statements

Sometimes correlations are good …

MeCN vs THF, cationic acids

\[ p_{K_a}^{\text{THF}} = 0.86 \cdot p_{K_a}^{\text{MeCN}} - 3.4 \]

\[ R^2 = 0.967 \]

… Sometimes tricky

MeCN vs Pyridine, neutral acids

\[ p_{K_a}^{\text{Pyridine}} = 1.12 \cdot p_{K_a}^{\text{MeCN}} - 15.0 \]

\[ R^2 = 0.968 \]
$pK_a$ Correlation possibilities

Legend:

- **Reliable**
- **Lower reliability**
- **Not reliable**

"+": real data available


Absolute values vs differences

Thanks to all these people!

Slides: https://analytical.chem.ut.ee
Overview: http://tera.chem.ut.ee/~ivo/HA_UT/
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Thank you for your attention!