Models for ionic compounds

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Some high volume pharmaceuticals

Ibuprofen
Diclofenac
Aspirin

Barbital
Furosemide
Penicilin

So what have these drugs in common?

This was actually a question to my dear students

These pharmaceuticals are acids

Ibuprofen
z = -1, pKa = 4.41

Diclofenac
z = -1, pKa = 4.18

Aspirin
z = -1, pKa = 3.48

Barbital
z = -1, pKa = 7.96

Furosemide
z = +1 and -1
pKa = 9.79 and 3.04

Penicilin
z = +1 pKa = 2.45

The result was obtained using the ACD/I-Lab service

These compounds are bases

Metformin
z=+2, pKa1 13.86

Hydrochlorothiazide
z=+2, pKa 9.57, 8.95

Amitriptyline
z=+1, pKa 9.18

Trimethoprim
z=+1, pKa 7.2

Morphin
z = -1, pKa = 9.50 (acid)
z = +1, pKa = 8.26 (base)

And what have these drugs in common?

More high volume pharmaceuticals

Metformin
antidiabetic

Hydrochlorothiazide
diuretics

Amitriptyline
antipsychotic

Trimethoprim
antibiotics

Morphin
narcoticum

And what have these drugs in common?
Impact of pH on speciation of ionics

\[ f_n = \frac{1}{1 + 10^{(pH - pK_a)}} \quad \text{and} \quad f_i = 1 - f_n \]

(Ibuprofen)

acid, pKa = 4.41

(Trimethoprim)

base, pKa = 7.2

(Weak) acids are ionic at high pH and bases at low pH

Systemic herbicides

- 2,4-D: systemic herbicide, pKa 2.98 (acid)
- Metsulfuron-methyl: systemic herbicide, pKa 4.11 (acid)
- Glyphosate: herbicide, multi-ionic, pKa 6.22 (of acid), + strong acids & weak base
- Glufosinate: herbicide, multi-ionic, pKa 3.22 (acids), pKa 9.7 (base)

Systemic fungicides

- Tridemorph: systemic fungicide, pKa 7.50 (base)
- Carbendazim: systemic fungicide, pKa 6.09 and 11.97 (base)
- Imazalil: systemic fungicide, pKa 6.75 (base)
- Cyprodinil: systemic fungicide, pKa 3.09 (base)

Systemic Pesticides

Herbicidal action is best when the chemical is distributed via phloem (to all growing parts of the plants, incl. roots). The phloem has a high pH (ca. pH 8), and weak acids accumulate in that. That’s why systemic herbicides are typically weak acids.

Fungi often attack via xylem (a dead pipe). Fungicides are good if accumulating and distributing in xylem. The xylem is acidic (ca. pH 5.5). That’s could be the reason why systemic fungicides are typically weak bases.

The REACH chemicals

149,000 chemicals pre-registered at the European Chemical Agency ECHA for REACH. Hereof:

- Ionic compounds
- and living cells

Source: Based on a random sample of 431 chemicals analyzed by Antonio Franco et al.
The Cell

Apoplast
dead
Symplast
living
Vacuole
waste

Biomembranes separate living from dead

The Electrical Field E

dead

living
e-
- 0.1 V

waste

pH 3-9
pH 7.5
pH 5-6

Separation of charges at the membranes

Comes a molecule
e.g., a base
K+
K+
K+
K+
K+

Positive charges accumulate in the symplast

Nernst Law 1889

\[
\frac{\text{C}_{\text{inside}}}{\text{C}_{\text{outside}}} = \exp\left(-\frac{z E F}{R T}\right)
\]

Z is valency, E is electrical field, R and F are constants

Example Potassium K+

\[
\frac{\text{Cl}}{\text{Co}} = \exp(- z E F / R T)
\]

Z = +1  E = - 0.1 V
F / (R T) = 39.6 (constant)
Cl / Co = exp(4) = 55

Chemical equilibrium = 1
Electrical equilibrium = 55
How comes an ion into the cell?

\[ \text{K}^+ \quad \text{e}^- \]

I want you

Nernst-Planck Equation describes the movement of ions in electrical fields

\[
J = \frac{P}{\exp \left( \frac{z \, E \, F}{RT} \right) - 1} \cdot \exp \left( \frac{z \, E \, F}{RT} \right) \cdot (C_{\text{outside}} - C_{\text{inside}})
\]

\( J \) is unit flux (kg m\(^{-2}\) s\(^{-1}\))

\( P \) is permeability (m s\(^{-1}\))

The electrical fields increases permeability!

Test: Did my audience understand me?

DDT is a neutral, lipophilic chemical

It will move into the

- A) Vacuole (waste)
- B) Apoplast (dead)
- C) Symplast (living)
- D) Lipids (fat)

Test: Did my audience understand me?

DDT is a neutral, lipophilic chemical

It will move into the

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Now comes the theory for the neutral molecules

Water apoplast

Water symplast

Water vacuole

"All is water and lipids"

Lipids

Lipids in membranes

Small oil droplets ("oleosomes")

\[ \text{C - C - C - C - C - C - C - C - C - C} \] "non-polar"
Fick’s 1st Law of Diffusion

\[ J = P \left( C_{\text{outside}} - C_{\text{inside}} \right) \]

Where:
- \( J \) is the flux of the substance
- \( P \) is the permeability
- \( C_{\text{outside}} \) and \( C_{\text{inside}} \) are the concentrations outside and inside the cell

\[ P = K_{\text{ow}} \frac{D}{\text{dx}} \]

\[ P = \text{Permeability} \ (\text{m/s}) \]

Uptake of lipophilics is by passive diffusion.

Summary

Uptake of neutral molecules:

\[ J = P \left( C_{\text{outside}} - C_{\text{inside}} \right) \cdot \text{Lipids} \cdot K_{\text{ow}} \]

Fick’s 1st Law of Diffusion

Uptake of ions:

\[ J = P \frac{N}{e^{N-1}} \left( C_{\text{outside}} - C_{\text{inside}} \right) \]

Nernst-Planck Equation

\[ N = z E F / ( RT) \] "Nernst number"

Chemical Equilibrium

\[ K_{\text{ow}} = \frac{C_{\text{lipids}} \text{ to } C_{\text{water}}}{\text{Partition coefficient n-octanol to water}} \]

\[ C_{\text{cell}} = \text{Water in cell} + \text{Lipids} \cdot K_{\text{ow}} \]

\[ C_{\text{water}} \]

Now comes the theory for the weak electrolytes:

- \( R-\text{COOH}^- \)
- \( R^+ \cdot \text{OH}^- \)

pKa 3 - 9

Common names:
- Dissociating chemicals
- Ionic compounds
- Weak acids
- Weak bases
- Amphoteric
- Zwitter charged compounds

Neutral, positive or negative
Fractions neutral and ionic

\[ fn = \frac{1}{1 + 10^{(pH - pKa)}} \]

Henderson-Hasselbalch

Summary of Processes

Ions are attracted by electrical fields
Lipophilic compounds sorb to lipids
Weak electrolytes are trapped
“Complexes” behave like neutrals

Transport inside vascular plants

Cuticle
Cuticle waxy layer
Xylem
Phloem symplast
Phloem symplast

2,4-dichlorophenoxy-acetic acid

\[ \log K_{ow} = 2.9 \text{ (neutral form)} \]
\[ \log K_{ow} = -0.24 \text{ (ionic form)} \]
pKa = 2.87 \text{ (weak acid)}
Kleier's model considers the flow in xylem (apoplast, pH 5.5) and phloem (symplast pH 8).

Phloem transport is due to the “ion trap”

Phloem transport is due to the “ion trap”

Kleier's model explains phloem mobility


A Nonlinear Dynamic Simulation Model for Xenobiotic Transport and Whole Plant Allocation Following Foliar Application
I. Conceptual Foundation for Model Development

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1988 to 1996 - Kleier didn’t consider electricity

Satchivi’s model (2000) calculates uptake and movement of weak electrolytes (pesticides) after spray application

The Basics of Satchivi's Model

The exchange terms consider the ion trap, but no electrics

\[
A = P_n \left( C_{sym} + \frac{1}{(1 + 10^{\frac{\langle 1 + 1 \rangle}{\langle 10^{\frac{1}{\langle 10^{\frac{P_d}{P_n} + P_d + P_n} \rangle} \rangle}})} \right) - \left( C_{sym} + \frac{1}{(1 + 10^{\frac{\langle 1 + 1 \rangle}{\langle 10^{\frac{1}{\langle 10^{\frac{P_n}{P_n} + P_d + P_n} \rangle} \rangle}})} \right) + P_m \left( C_{sym} + \frac{1}{(1 + 10^{\frac{1}{\langle 10^{\frac{P_d}{P_n} + P_d + P_n} \rangle} \rangle}} \right) - \left( C_{sym} + \frac{1}{(1 + 10^{\frac{1}{\langle 10^{\frac{P_n}{P_n} + P_d + P_n} \rangle} \rangle}} \right) \right)
\]

\[
J = P_n (C_{o} - C_i \times f_n) + P_d (C_{o} - C_i \times f_d)
\]

f = fraction, n = neutral, d = dissociated

Satchivi’s model is the model for the complete plant.

It is therefore quite complex and needs a lot of parameters.

That makes it hard to apply.
Summary

The modern models used in pesticide design (Kleier, Satchivi) do not use the Nernst-Planck equation.

The dominant effect considered is the ion trap for weak acids.

The Cell Model

The typical structure of a cell

(see from the perspective of a neutral compound)

Water
Lipids

The neutral compound "sees" aqueous phase and lipid phases.

BCF regressions for neutral compounds

Process:
The neutral chemical partitions into the aqueous and lipid phase (described by Kow).

Basic equation:
BCF = W + L \times Kow

Example:
\log(RCF - 0.82) = 0.77 \times \log K_{ow} - 1.52
Equivalent to RCF = 0.82 + 0.03 K_{ow}^{0.77}
The typical structure of an animal cell
(seen from the perspective of an ionic compound)

Processes for ionic compounds

Ionic compounds undergo extra effects:
- Ionizable compounds occur in (at least) two species, namely the neutral and the ionic molecule.
- Concentration ratios of the species change with pH.
- Ions are attracted or repelled by electrical fields.
- Ions are much more polar than the neutral molecules.
- Membrane permeabilities of ions are small.

BCF regressions for ionic compounds

Application of existing regressions (for neutrals) with apparent log Kow (= log D) as predictor

\[ D = f_n \times K_{OW,n} + f_i \times K_{OW,i} \]

\( f_n \): fraction neutral at given pH
\( f_i \): fraction ionic at given pH

For ionics: log D instead of log Kow in BCF regressions

\[ \log(\text{BCF}) = -1.52 + 0.77 \times \log D \]

Measured BCF in roots and water plants at variable pH

At pH ≠ 7 accumulation also for low log D → due to ion trap

The ion trap

Example: Accumulation of 2,4-D (pKa ~ 3) in water plants

The ion trap

The chemical diffuses into the cell as neutral compound, dissociates and … gets trapped!

For weak acids: at low external pH
For weak bases: at high external pH

The ion trap

Example: Accumulation of 2,4-D (pKa ~ 3) in water plants

measured data from Briggs, Pignato, De Carvalho et al.
Cell model calibrated with E → 0
**Equations for ionisable compounds**

neutral molecules \( J = P_i (a_i - a_d) \) 1st Fick’s Law

Ions \( J = P_e \frac{N}{e^N - 1} (a_d - a_i e^N) \) Nernst-Planck-equation

\( J = \text{flux}, P = \text{Permeability}, a = \text{activity}, N = z \frac{E}{F} / \text{RT} \)

Equilibrium: Flux in = flux out

\[
\frac{C_i}{C_o} = \frac{J_{in}}{J_{out}} = \frac{f_{in} P_i + f_{out} P_o - N (e^N - 1)}{f_{in} P_i + f_{out} P_o + e^N - N (e^N - 1)} = BCF
\]

\( f = a / C_i = \text{dissolved fraction} \)

\( n = \text{neutral}, d = \text{dissociated (ionic)} \)

**Activity as state variable**

Driving force for exchange is the activity gradient.

The ratio between activity and total (measurable) concentration is

\[
f_n = \frac{a_n}{C_i} = \frac{1}{W/\gamma_n + K_n/\gamma_n + W \times 10^{(\rho H - \rho K_n)/\gamma_d} + K_d/\gamma_d}
\]

where \( W \) is water content, \( \gamma \) is activity coefficient (n neutral, d ionic), \( K \) is partition coefficient (L x Kow)

**Fugacity**

Finding Feasible Activity

Mackay 1979 MAMI 2009

\[
C = \Theta \cdot Z \quad C = a \cdot F
\]

\( Z = \text{fugacity capacity} \)

\( F = \text{activity capacity} \)

**Dynamic solution**

Change of conc. in cytosol is flux in – flux out – flux to organelle + flux from organelle

\[
\frac{dC_c}{dt} = A_c \times J_{cyt} / V_c - A_c \times J_{cyt} / V_c - A_m \times J_{cm} / V_c + A_m \times J_{mc} / V_c
\]

Change of conc. in organelle is flux from cyt – flux to cyt

\[
\frac{dC_m}{dt} = A_m \times J_{mc} / V_m - A_m \times J_{mc} / V_m
\]

Analytical solution (2 x 2 matrix)

**Data Cell Model**

Table. Parameters of typical animal and plant cells.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Fish cytosol (100%)</th>
<th>Plant cytosol (10%)</th>
<th>Plant vacuole (90%)</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH cell sap</td>
<td>pH</td>
<td>7</td>
<td>7</td>
<td>5.5</td>
<td>-</td>
</tr>
<tr>
<td>Water content</td>
<td>W</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
<td>L L^{-1}</td>
</tr>
<tr>
<td>Lipid content</td>
<td>L</td>
<td>0.06</td>
<td>0.03</td>
<td>0.03</td>
<td>L L^{-1}</td>
</tr>
<tr>
<td>Membrane potential</td>
<td>E</td>
<td>-0.07</td>
<td>-0.10</td>
<td>+0.01</td>
<td>V</td>
</tr>
<tr>
<td>Ionic strength</td>
<td>I</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>mol L^{-1}</td>
</tr>
</tbody>
</table>
Summary of Findings

- Many pesticides and most pharmaceuticals are ionizable compounds
- Acids ionize at high pH, bases at low pH
- Ions are more polar and have a lower BCF than neutrals
- Lipophilic sorption is a dominant process for ionic compounds (as for neutral compounds) and is well predicted with log D
- Weak acids have the highest BCF at low pH (< 7)
- Weak bases have the highest BCF at high pH (> 7)
- The ion trap (for acids: at low pH, for bases: at high pH) may lead to unexpected accumulation

Test predicted BCF versus measured

The cell model can – to some extend – predict the ion trap

Results of the cell model - Acids

Chemical Equilibrium to water – log BCF plants

- Acids external pH 5
- Acids external pH 7

Results of the cell model - Bases

Chemical Equilibrium to water – log BCF plants

- Bases external pH 5
- Bases external pH 7

Results of the cell model - Bases

Chemical Equilibrium to water – log BCF plants

- Bases external pH 9
- Bases external pH 7

Adsorption in soil
Koc of ionic compounds
Solid-water sorption of ionics

- lipophilic + electrical interactions
- cations attracted, anions repulsed from colloids
- pH, $pK_a$, $K_{OW,n}$

$$K_{OC} = \phi_b \cdot K_{OC,\text{ion}} + \phi_{\text{ion}} \cdot K_{OC,\text{ion}}$$

$$\log K_{OC} = \log(\phi_b \cdot 10^{-pK_a + b} + \phi_{\text{ion}} \cdot 10^{-pK_a + d})$$

Regression equations for the Koc of ionics

- for acids, neutral molecules: $\log K'_{OC} = 0.54 \times \log K_{OC,\text{ion}} + 1.11$
- for acids, anion: $\log K'_{OC} = 0.11 \times \log K_{OC,\text{ion}} + 1.54$
- for bases, neutral molecules: $\log K'_{OC} = 0.37 \times \log K_{OC,\text{ion}} + 1.70$
- for bases, cation (1): $\log K'_{OC} = 0.42 \times \log K_{OC,\text{ion}} + 2.19$
- for bases, cation (2): $\log K'_{OC} = pK_{a,\text{ion}} \times f_{\text{ionic}}$

Franco & Trapp 2008, Env Tox Chem

“Standard Model” for ionic compounds

Modifications for Ionics

- from Cell Model into Standard Model

Fluxes and Processes as before – partition coefficients from cell model
Some Results

Predicted uptake of acids from soil into plants

<table>
<thead>
<tr>
<th>Category of the BCF of acids of varying strength at varying soil pH</th>
<th>Soil pH 5</th>
<th>Neutral soil pH</th>
<th>Soil pH 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong acids (pKa ≤ 1)</td>
<td>- roots + shoots o fruits</td>
<td>- roots + shoots o fruits</td>
<td>- roots + shoots o fruits</td>
</tr>
<tr>
<td>Moderate to weak acids (2 ≤ pKa ≤ 5)</td>
<td>o roots + shoots + fruits</td>
<td>o roots + shoots + fruits</td>
<td>o roots + shoots + fruits</td>
</tr>
<tr>
<td>Very weak acids (pKa ≥ 8)</td>
<td>o roots o shoots + fruits</td>
<td>o roots o shoots + fruits</td>
<td>o roots o shoots + fruits</td>
</tr>
</tbody>
</table>

where – BCF < 0.01, - BCF 0.01 to 0.1, o BCF 0.1 to 1, + BCF 1 to 10, ++ BCF > 10

Uptake of acids from soil into plants depends on soil pH. Strong acids are expected to move into leaves (via xylem), weak acids more into fruits (via phloem, at low soil pH).

Questions?

Research for a sustainable world

Environment & Resources DTU

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