INTRODUCTION TO SOLVATION MODELS FOR THEORETICAL CHEMISTRY

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**Solvation** is an interaction of a solute with the solvent, which leads to stabilization of the solute species in the solution.

IUPAC, Compendium of Chemical Terminology, 2\textsuperscript{nd} ed. (the “Gold Book”) (1997)
**Solvation** is an interaction of a solute with the solvent, which leads to stabilization of the solute species in the solution.

IUPAC, Compendium of Chemical Terminology, 2nd ed. (the “Gold Book”) (1997)

**Solvation** – the process of surrounding solute particles (ions) by solvent
Solvent is a substance that dissolves a solute, resulting in solution
**Solvent** is a substance that dissolves a solute, resulting in solution

usually a liquid, but can also be a solid (e.g. alloys) or a gas (e.g. air)
**Solvent** is a substance that dissolves a solute, resulting in solution

**SOLVENTS**

**POLAR**

\[ \varepsilon > 15 \]

**NON-POLAR**

\[ \varepsilon < 15 \]

\( \varepsilon \) – dielectric constant
Solvent is a substance that dissolves a solute, resulting in solution

**SOLVENTS**

**POLAR**
- Water
- Acetone
- Methanol
- ...

**NON-POLAR**
- Toluene
- Cyclohexane
- Chloroform
- ...

...
Solvent is a substance that dissolves a solute, resulting in solution.
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**Solvents**

- **Polar**: Protic solvent contains labile proton (usually has a hydroxyl, carboxyl or amine group).
- **Non-Polar**: Aprotic solvents cannot donate protons.
  - **Protic solvent**: is a solvent that contains labile proton (usually has a hydroxyl, carboxyl or amine group).
  - **Aprotic solvents**: cannot donate protons.
**Solvent** is a substance that dissolves a solute, resulting in solution.

**SOLVENTS**

**POLAR**
- Protic
  - Water
  - Formic acid
  - ...

**APROTIC**
- Acetone
- Tetrahydrofuran
- ...

**NON-POLAR**
SOLVATION MODELS

EXPLICIT MODELS

consider molecular details of each solvent molecule

IMPLICIT MODELS

treat solvent as a continuous medium

source: www.k-state.edu
SOLVATION MODELS

EXPLICIT MODELS
consider molecular details of each solvent molecule

IMPLICIT MODELS
treat solvent as a continuous medium

HYBRID MODELS
Treat first (and second) solvation sphere explicitly while the rest of the solvent is treated in implicit way
SOLVATION MODELS

EXPLICIT MODELS

IMPLICIT MODELS

Each model can be further subdivided based on the used level of theory:

QM (quantum mechanical) or MM (classical)

HYBRID MODELS
EXPLICIT MODELS
EXPLICIT MODELS

- Include individual solvent molecules
- Calculate free energy of solvation by simulating solute-solvent interactions
EXPLICIT MODELS

- Include individual solvent molecules
- Calculate free energy of solvation by simulating solute-solvent interactions

<table>
<thead>
<tr>
<th>Solute-solvent interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>QM</td>
</tr>
<tr>
<td>by solving the Schrödinger equation</td>
</tr>
<tr>
<td>HF</td>
</tr>
<tr>
<td>DFT</td>
</tr>
<tr>
<td>MP2</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>CC</td>
</tr>
<tr>
<td>...</td>
</tr>
</tbody>
</table>
EXPLICIT MODELS (MM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SPC</th>
<th>TIP3P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r(\text{OH})$, Å</td>
<td>1.0</td>
<td>0.9572</td>
</tr>
<tr>
<td>$\text{HOH}$, deg</td>
<td>109.47</td>
<td>104.52</td>
</tr>
<tr>
<td>$A \times 10^{-3}$, kcal Å$^{12}$/mol</td>
<td>629.4</td>
<td>582.0</td>
</tr>
<tr>
<td>$B$, kcal Å$^6$/mol</td>
<td>625.5</td>
<td>595.0</td>
</tr>
<tr>
<td>$	ext{q(O)}$</td>
<td>−0.82</td>
<td>−0.834</td>
</tr>
<tr>
<td>$	ext{q(H)}$</td>
<td>+0.41</td>
<td>+0.417</td>
</tr>
</tbody>
</table>

$$V_{LJ}(r) = \frac{A}{r^{12}} - \frac{B}{r^6},$$
$$V_{E} = \frac{1}{4\pi\varepsilon_{0}} \frac{Q}{r},$$

source: [http://www1.lsbu.ac.uk/water/water_models.html](http://www1.lsbu.ac.uk/water/water_models.html)
great webpage about water models!
### Explicit Models – MM

<table>
<thead>
<tr>
<th>Model</th>
<th>Type</th>
<th>( \sigma ) Å</th>
<th>( \epsilon ) kJ mol(^{-1} )</th>
<th>( l_1 ) Å</th>
<th>( l_2 ) Å</th>
<th>( q_1 ) (e)</th>
<th>( q_2 ) (e)</th>
<th>( \theta^* )</th>
<th>( \phi^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSD (^{\text{[113]}})</td>
<td>a</td>
<td>3.016</td>
<td>15.319</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>109.47</td>
<td>109.4</td>
</tr>
<tr>
<td>SPC (^{\text{[104]}})</td>
<td>a</td>
<td>3.166</td>
<td>0.650</td>
<td>1.0000</td>
<td>-</td>
<td>+0.410</td>
<td>-0.8200</td>
<td>109.47</td>
<td>-</td>
</tr>
<tr>
<td>SPC/E (^{\text{[111]}})</td>
<td>a</td>
<td>3.166</td>
<td>0.650</td>
<td>1.0000</td>
<td>-</td>
<td>+0.4238</td>
<td>-0.8476</td>
<td>109.47</td>
<td>-</td>
</tr>
<tr>
<td>SPC/( \text{( D_2)O} ) (^{\text{[200]}})</td>
<td>a</td>
<td>3.166</td>
<td>0.650</td>
<td>1.0000</td>
<td>-</td>
<td>+0.4350</td>
<td>-0.8700</td>
<td>109.47</td>
<td>-</td>
</tr>
<tr>
<td>SPC/Fw (^{\text{[994]}})</td>
<td>a</td>
<td>3.166</td>
<td>0.650</td>
<td>1.0120</td>
<td>-</td>
<td>+0.410</td>
<td>-0.8200</td>
<td>113.24</td>
<td>-</td>
</tr>
<tr>
<td>TIP3P (^{\text{[180]}})</td>
<td>a</td>
<td>3.15061</td>
<td>0.6364</td>
<td>0.9572</td>
<td>-</td>
<td>+0.4170</td>
<td>-0.8340</td>
<td>104.52</td>
<td>-</td>
</tr>
<tr>
<td>TIP3P/Fw (^{\text{[994]}})</td>
<td>a</td>
<td>3.1506</td>
<td>0.6368</td>
<td>0.9600</td>
<td>-</td>
<td>+0.4170</td>
<td>-0.8340</td>
<td>104.5</td>
<td>-</td>
</tr>
<tr>
<td>iAMOEBA (^{\text{[2031]}}</td>
<td>a</td>
<td>3.6453</td>
<td>0.8235</td>
<td>0.9584</td>
<td>-</td>
<td>+0.29701</td>
<td>-0.59402</td>
<td>106.48</td>
<td>-</td>
</tr>
<tr>
<td>QCT (^{\text{[1231]}}</td>
<td>a^{15}</td>
<td>3.140</td>
<td>0.753</td>
<td>0.9614</td>
<td>-</td>
<td>+0.6064</td>
<td>-1.2128</td>
<td>104.06</td>
<td>7</td>
</tr>
<tr>
<td>PPC (^{\text{[211]}}</td>
<td>b</td>
<td>3.23400</td>
<td>0.6000</td>
<td>0.9430</td>
<td>0.06</td>
<td>+0.5170</td>
<td>-1.0340</td>
<td>106.00</td>
<td>127.0</td>
</tr>
<tr>
<td>TIP4P (^{\text{[180]}}</td>
<td>c</td>
<td>3.15365</td>
<td>0.6480</td>
<td>0.9572</td>
<td>0.15</td>
<td>+0.5200</td>
<td>-1.0400</td>
<td>104.52</td>
<td>52.26</td>
</tr>
<tr>
<td>TIP4P-Ew (^{\text{[649]}}</td>
<td>c</td>
<td>3.16435</td>
<td>0.680946</td>
<td>0.9572</td>
<td>0.125</td>
<td>+0.52422</td>
<td>-1.04844</td>
<td>104.52</td>
<td>52.26</td>
</tr>
<tr>
<td>TIP4P-FQ (^{\text{[197]}}</td>
<td>c</td>
<td>3.15365</td>
<td>0.6480</td>
<td>0.9572</td>
<td>0.15</td>
<td>+0.631</td>
<td>-1.261</td>
<td>104.52</td>
<td>52.26</td>
</tr>
<tr>
<td>TIP4P/Ice (^{\text{[188]}}</td>
<td>c</td>
<td>3.1668</td>
<td>0.8822</td>
<td>0.9572</td>
<td>0.1577</td>
<td>+0.5897</td>
<td>-1.1794</td>
<td>104.52</td>
<td>52.26</td>
</tr>
<tr>
<td>TIP4P/2005 (^{\text{[944]}}</td>
<td>c</td>
<td>3.1589</td>
<td>0.7749</td>
<td>0.9572</td>
<td>0.1546</td>
<td>+0.5564</td>
<td>-1.1128</td>
<td>104.52</td>
<td>52.26</td>
</tr>
<tr>
<td>TIP4P/2005f (^{\text{[1765]}}</td>
<td>c</td>
<td>3.1644</td>
<td>0.7749</td>
<td>0.9419</td>
<td>0.1546</td>
<td>+0.5564</td>
<td>-1.1128</td>
<td>107.4</td>
<td>53.7</td>
</tr>
</tbody>
</table>

*source: [http://www1.lsbu.ac.uk/water/water_models.html](http://www1.lsbu.ac.uk/water/water_models.html)*

about 46! distinct water models

Water model **has to be compatible** with the model describing the rest of the system!

Always **read the original paper describing how given force field has been derived**
EXPLICIT MODELS – MD

“real life” example

Water density

EXPLICIT MODELS – MD

“real life” example


TIP3P

TIP4P

TIP5P

SPC/E

EK-peptide

\[ \text{turn} \quad \alpha\text{-helix} \quad 3_{10}\text{-helix} \]
IMPLICIT MODELS
Solvent is an uniform, polarizable medium with fixed dielectric constant while the solute is placed inside the cavity in the medium.

Free energy of solvation is given by

\[ \Delta G_{\text{solv}} = \Delta G_{\text{cav}} + \Delta G_{\text{disp}} + \Delta G_{\text{elec}} \left( + \Delta G_{\text{hb}} \right) \]
IMPLICIT MODELS

Free energy of solvation is given by

\[ \Delta G_{\text{solv}} = \Delta G_{\text{cav}} + \Delta G_{\text{disp}} + \Delta G_{\text{elec}} \ (\ + \ \Delta G_{\text{hb}}) \]

Free energy required to form the solute cavity

(due to the entropic penalty of reorganization of the solvent molecules around the solute and the work done in creating the cavity)
IMPLICIT MODELS

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Free energy required to form the solute cavity

(due to the entropic penalty of reorganization of the solvent molecules around the solute and the work done in creating the cavity)

Van der Waals interaction between solute and solvent.
Free energy of solvation is given by

$$\Delta G_{\text{solv}} = \Delta G_{\text{cav}} + \Delta G_{\text{disp}} + \Delta G_{\text{elec}} (\text{+}\Delta G_{\text{hb}}$$

- Free energy required to form the solute cavity
  (due to the entropic penalty of reorganization of the solvent molecules around the solute and the work done in creating the cavity)
- Van der Waals interaction between solute and solvent.
- Electrostatic component
  (polarization between solute and solvent induces charge redistribution)
Free energy of solvation is given by

$$\Delta G_{\text{solv}} = \Delta G_{\text{cav}} + \Delta G_{\text{disp}} + \Delta G_{\text{elec}} \, (\!+\! \Delta G_{\text{hb}})$$

- **Free energy required to form the solute cavity**
  - (due to the entropic penalty of reorganization of the solvent molecules around the solute and the work done in creating the cavity)

- **Van der Waals interaction between solute and solvent.**
- **Electrostatic component**
  - (polarization between solute and solvent induces charge redistribution)
- **Hydrogen bonding term**
IMPLICIT MODELS
Solute shape cavity of vacuum is introduced into the solvent.
Solute shape cavity of vacuum is introduced into the solvent

Solute charge density is placed in solute the cavity
Solute shape cavity of vacuum is introduced into the solvent.

Solute charge density is placed in solute the cavity.

Solvent molecules reorient and polarize in response to the solute charge density.
Solute shape cavity of vacuum is introduced into the solvent.

Solute charge density is placed in solute the cavity.

Solvent molecules reorient and polarize in response to the solute charge density.

Solute polarizes in response to solvent polarization.

IMPLICIT MODELS
IMPLICIT MODELS

Models differ in the following aspects:
1) Size and shape of the solute cavity
IMPLICIT MODELS

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1) Size and shape of the solute cavity
2) Level of solute description
IMPLICIT MODELS

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1) Size and shape of the solute cavity
2) Level of solute description
3) Dielectric medium description
IMPLICIT MODELS

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1) Size and shape of the solute cavity
2) Level of solute description
3) Dielectric medium description
4) The cavity calculation method
IMPLICIT MODELS

Models differ in the following aspects:
1) Size and shape of the solute cavity
2) Level of solute description
3) Dielectric medium description
4) The cavity calculation method
5) Representation of charge distribution
IMPLICIT MODELS

1) Size and shape of the solute cavity

spherical  ellipsoidal  van der Waals
IMPLICIT MODELS

1) Size and shape of the solute cavity

atoms

source: ieeexplore.ieee.org
IMPLICIT MODELS

1) Size and shape of the solute cavity

source: ieeexplore.ieee.org
IMPLICIT MODELS

1) Size and shape of the solute cavity

source: ieeexplore.ieee.org
IMPLICIT MODELS

1) Size and shape of the solute cavity

- van der Waals surface
- solvent excluded surface (SES) (Connolly surface, molecular surface)
- probe
- atoms

source: ieeexplore.ieee.org
IMPLICIT MODELS

1) Size and shape of the solute cavity

- van der Waals surface
- solvent accessible surface (SAS) (Lee-Richards molecular surface)
- probe
- atoms
- solvent excluded surface (SES) (Connolly surface, molecular surface)

source: ieeexplore.ieee.org
IMPLICIT MODELS

2) Level of solute description

Level of description
2) Level of solute description

Level of description

- classical molecular mechanics
- semi-empirical quantum mechanics
- DFT
- post-HF MP2, CI, CC, ...

ACCURACY
3) Dielectric medium description

- In most cases, homogenous static medium with fixed dielectric constant
3) Dielectric medium description

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- Rarely, distance (from the solute) dependence may be allowed
IMPLICIT MODELS

3) Dielectric medium description

- In most cases, homogenous static medium with fixed dielectric constant

- Rarely, distance (from the solute) dependence may be allowed

- Exceptionally, the rate of the process dependence may be introduced (the response of the solvent is different for “fast” processes)
4) The cavity calculation method
5) Representation of charge distribution
IMPLICIT MODELS

Polarizable Continuum Model (PCM)

- **Cavity**
  - Overlapping van der Waals spheres (PCM and CPCM)
  - Solvent accessible surface
  - Isodensity surface (IPCM, SCIPCM)

- **Electrostatic potential from solute and polarization of solvent must obey Poisson equation**

- **Electrostatic interactions calculated numerically**

- **Different formulations:** DPCM, IPCM, SCIPCM, IEFPCM, ...

Gaussian09: SCFR=PCM
IMPLICIT MODELS

Conductor-like Screening Model (COSMO)

- **Cavity**
  - Based on solvent accessible surface (SAS)
- **Electrostatic interactions are treated in more approximated manner**
  - Solvent treated as conductor not dielectric ($\varepsilon = \infty$)
- **Good approximation in very polar solvents**
IMPLICIT MODELS

Accuracy of Continuum Models

PCM > COSMO
Accuracy of Continuum Models

PCM > COSMO

not always!

experimental confirmation needed!
HYBRID MODELS
HYBRID MODELS

QM/MM approach

source: www.essexgroup.soton.ac.uk

source: http://www.nobelprize.org
HYBRID MODELS

\[ E = E_{QM} + E_{MM} + E_{QM/MM} \]

Energy of the QM subsystem

Energy of the MM subsystem

Interaction energy
HYBRID MODELS

\[ E = E_{QM} + E_{MM} + E_{QM/MM} \]

Energy of the QM subsystem

Energy of the MM subsystem

Interaction energy

Difficult part: how do QM and MM interact?
# HYBRID MODELS

## CURRENT APPROACHES:

- **Karplus & co-workers:**
  - **QM:** DFT, HF, AM1
  - **MM:** CHARMM
  - **QM/MM:** link atoms

- **Friesner & co-workers:**
  - **QM:** DFT, HF
  - **MM:** OPLS-AA
  - **QM/MM:** hybrid orbitals

- **Gao & co-workers:**
  - **QM:** AM1
  - **MM:** CHARMM
  - **QM/MM:** hybrid orbitals*

- **Yang & co-workers:**
  - **QM:** DFT
  - **MM:** CHARMM
  - **QM/MM:** link atoms*

* specific parametrization
HYBRID MODELS

USE CAREFULLY!
TEST THOROUGHLY!

source: journals.sfu.ca
SUMMARY
## EXPLICIT vs. IMPLICIT MODELS

### Method

<table>
<thead>
<tr>
<th>Explicit Solvent (all-atom description)</th>
<th>Implicit Solvent (continuum description)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>• Full details on the molecular structures</td>
<td>• Many atoms $\rightarrow$ expensive</td>
</tr>
<tr>
<td>• Realistic physical picture of the system</td>
<td>• Long equilibration</td>
</tr>
<tr>
<td></td>
<td>• Often solvent and solute are not polarizable.</td>
</tr>
<tr>
<td></td>
<td>• Small size of the system $\rightarrow$ large fluctuations</td>
</tr>
<tr>
<td></td>
<td>• Artificial boundary between the solute and solvent</td>
</tr>
<tr>
<td></td>
<td>• “Bad” model for treating short range effects (dispersion and cavity)</td>
</tr>
</tbody>
</table>

*source: www.k-state.edu, events.prace-ri.eu/event/210/material/22/0.pdf*
EXAMPLES
IMPLICIT vs. EXPLICIT MODELS

Generalized Born model

exp. NMR structure

TIP3P model

IMPLICIT vs. EXPLICIT MODELS

PS-PEG nanoparticles self-assembly

Spaeth et al. JCP 134 (2011) 164902
Thank you very much for your kind attention
N$^{15}$ nuclear shielding of diazines in solution

D. Mennucci, JACS 124 (2002) 1506

Part of a solvent effect is missing

Solvent effect is correct