

Lecture 7 - Topic 2: Force Fields (Molecular Mechanics)

O P L S Force Fields

Optimal Potentials for Liquid Simulations Model

Presented By

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OUTLINE

- Introduction & Background
- Results
- Applications
- Summary

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COVERAGE

- Development of the OPLS FF.
- OPLS Concepts
- Force Field Equations

Time: 4 minutes

OUTLINE

- Introduction & Background
- **Results**
- Applications
- Summary

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COVERAGE

- Relative Energies
- Optimized Structures
- Energetic Results
- Molecular Volumes and Densities
- Heat Capacities and Compressibilities
- Radial Distribution Functions

Time: 15 minutes

OUTLINE

- Introduction & Background
- Results and Comparisons
- **Applications**
- Summary

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COVERAGE

- Crambin Properties
- Potential Functions for Nucleotide Bases

Time: 10 minutes

OUTLINE

- Introduction & Background
- Results and Comparisons
- Applications
- **Summary**

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COVERAGE

- Strengths
- Weaknesses

Time: 1 minute

Introduction and Background

- Development of the OPLS FF.
- OPLS – What is it?
- Force Field Equations
- Computational Methods



Development of OPLS

- Background work for OPLS comes from AMBER and the classical frameworks of Molecular Dynamics (MD) and Monte Carlo (MC) statistical mechanics.
- Laid out by Jorgensen from Yale.
- Has been applied to varied molecules:
 - simple molecules like C₂H₆ to
 - Complex molecules like proteins, DNA, etc.

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OPLS – what is it?

- Stands for Optimized Potentials for Liquid Simulation.
- Optimized – various parameters are chosen to calculate...
- Potentials – We are interested in calculating the potential energy for each structure.
- Liquid Simulation – Framework of Liquids being simulated using the computer to determine various properties of organic chemicals.

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OPLS - Types

- OPLS-UA (United Atom)

- Sites for non-bonded interactions are placed on all non-hydrogen atoms, and on hydrogen attached to the hetero-atoms or carbons in aromatic rings.
- The computation time is proportional to the total number of interaction sites squared.

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OPLS - Types

- OPLS – AA (All Atom)

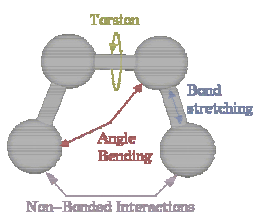
- More flexibility for charge distributions and torsion energetics.
- Computationally expensive
- Results are in more accord with the experimental results for
 - Free energies of compounds
 - Torsion Potentials

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Force Field Equations



| Energy | Component |
|--------------------------------------|-------------------|
| $E_{\text{bond}}(\varnothing)$ | Stretching Energy |
| $E_{\text{angle}}(\varnothing)$ | Bending Energy |
| $E_{\text{torsion}}(\varnothing)$ | Torsion Energy |
| $E_{\text{non-bonded}}(\varnothing)$ | Non-bonded Energy |

$$E(\varnothing) = E_{\text{bond}}(\varnothing) + E_{\text{angle}}(\varnothing) + E_{\text{torsion}}(\varnothing) + E_{\text{non-bonded}}(\varnothing)$$

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Specific Parameters for the OPLS Force Field



$$E_{\text{bond}}(\vartheta) = \sum K_r (r - r_{\text{eq}})^2$$

$$E_{\text{angle}}(\vartheta) = \sum K_{\vartheta} (\vartheta - \vartheta_{\text{eq}})^2$$

$$E_{\text{non-bonded}} = \sum_i \sum_j \left[q_i q_j e^2 / r_{ij} + 4 \epsilon_{ij} (\sigma_{ij}^{12} / r_{ij}^{12} - \sigma_{ij}^6 / r_{ij}^6) \right] f_{ij}$$

$$E_{\text{torsion}} = \sum_i V_1^i / 2 [1 + \cos(\vartheta_i + f_1)] + V_2^i / 2 [1 - \cos(2\vartheta_i + f_2)] + V_3^i / 2 [1 + \cos(3\vartheta_i + f_3)]$$

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$$E_{\text{bond}}(\vartheta) = \sum K_r (r - r_{\text{eq}})^2$$

Parameters:

- Req and Kr refer to values taken from AMBER force field.
- Kr refers to the spring constant between the two atoms.

$$E_{\text{angle}}(\vartheta) = \sum K_{\vartheta} (\vartheta - \vartheta_{\text{eq}})^2$$

Parameters:

Ktheta is a constant similar to Kr.

Parameters:

- The equation is in the form of a standard Coulomb + Lennard-Jones form.
- f_{ij} is a value between 1.0 and 0.5 - based on the intra-molecular interactions.

$$E_{\text{non-bonded}} = \sum_i \sum_j \left[\frac{q_i q_j e^2}{r_{ij}} + 4 \epsilon_{ij} \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^6}{r_{ij}^6} \right) \right] f_{ij}$$

Parameters:

- ϕ_i is the dihedral angle.
- V_1, V_2, V_3 are coefficients in the Fourier series.
- f_1, f_2, f_3 are phase angles.

$$E_{\text{torsion}} = \sum_i V_1^i / 2 \left[1 + \cos(\phi_i + f_1) \right] + V_2^i / 2 \left[1 - \cos(2\phi_i + f_2) \right] + V_3^i / 2 \left[1 + \cos(3\phi_i + f_3) \right]$$

Results

- Conformations
- Optimized Structures
- Energetic Results
- Molecular Volumes and Densities
- Heat Capacities, Compressibility

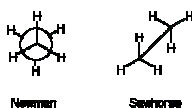


Relative Energies (kcal/mol) – Conformations of Hydrocarbons and Alcohols

Eclipsed Conformation



Staggered Conformation



| Molecule | Dihedral | Conformation | OPLS-AA | 6-31G |
|----------|----------|--------------|---------|-------|
| Ethane | H-C-C-H | 0 | 3.01 | 2.99 |
| | | 60 | 0.00 | 0.00 |

Notes:

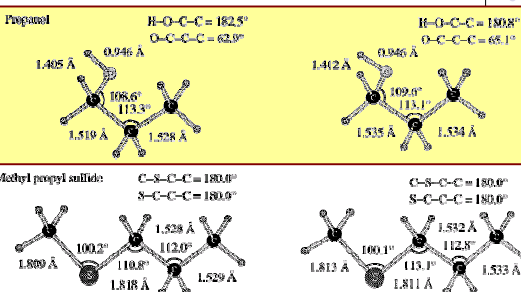
- 6-31G is a quantum mechanics technique used to estimate most of the chemical properties.
- OPLS-AA values were calculated using the OPLS-
- The various conformations have been illustrated in the diagram on the left.

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Optimized Structures – Comparisons between RHF/6-31G and OPLS-AA Calculations

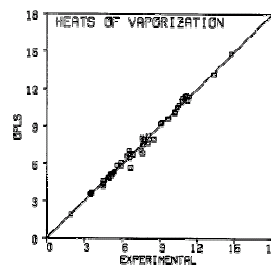


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Heat of Vaporization: OPLS versus Experimental Observations



$$\Delta E_{\text{vap}} = E_{\text{intra}}(\text{g}) - E_{\text{intra}}(\text{l}) - E_{\text{intra}}(\text{l})$$

$$\Delta H_{\text{vap}} = \Delta E_{\text{vap}} + RT - (H^0 - H)$$

$E_{\text{intra}}(\text{g})$ and $E_{\text{intra}}(\text{l})$ are intra-molecular energies for the gas and liquid phases.

$H^0 - H$ is the enthalpy departure – difference between the real and ideal gas.

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Energetic Results for Some Liquid Hydrocarbons

| liquid | T | $-E_{\text{vap}}(D)$ | $E_{\text{bind}}(D)$ | $E_{\text{bind}}(D)$ | ΔE_{vap} | exptl |
|--|--------|----------------------|----------------------|----------------------|-------------------------|-----------|
| CH ₃ OH | 25.00 | 5.49 ± 0.02 | 0.15 ± 0.01 | 0.47 ± 0.01 | 0.09 ± 0.02 | 5.57^b |
| CH ₃ CHO | 25.00 | 6.27 ± 0.02 | 0.78 ± 0.03 | 0.92 ± 0.03 | 0.79 ± 0.04 | 6.29^b |
| CH ₃ CH ₂ OH | 25.00 | 7.23 ± 0.05 | 0.24 ± 0.04 | 0.20 ± 0.02 | 7.00 ± 0.05 | 7.02^b |
| CH ₃ CH ₂ CH ₃ | 25.00 | 6.46 ± 0.04 | 0.09 ± 0.02 | 0.09 ± 0.01 | 6.09 ± 0.03 | 6.04^b |
| CH ₃ CH ₂ CHO | 25.00 | 7.20 ± 0.04 | 0.77 ± 0.04 | 0.90 ± 0.02 | 7.03 ± 0.05 | 7.04^b |
| CH ₃ CH ₂ CH ₂ OH | 25.00 | 8.70 ± 0.05 | 0.12 ± 0.03 | 0.42 ± 0.02 | 8.60 ± 0.07 | 8.19^b |
| acetone | 221.12 | 12.47 ± 0.03 | -20.74 ± 0.07 | -21.02 ± 0.05 | 15.71 ± 0.07 | 15.4^b |
| acetonitrile | 192.00 | 14.96 ± 0.04 | -22.76 ± 0.07 | -25.08 ± 0.02 | 15.90 ± 0.07 | |
| MeCN | 198.00 | 12.89 ± 0.03 | -9.05 ± 0.05 | -9.55 ± 0.02 | 15.57 ± 0.05 | 15.35 |
| MeOH | 25.00 | 15.35 ± 0.05 | -3.77 ± 0.04 | -3.07 ± 0.03 | 15.88 ± 0.05 | 15.2^b |
| EtOH | 25.00 | 11.46 ± 0.03 | 8.72 ± 0.06 | 8.79 ± 0.02 | 11.99 ± 0.07 | 11.75^b |
| EtOEt | -24.60 | 4.64 ± 0.02 | 8.14 ± 0.01 | 8.40 ± 0.01 | 5.12 ± 0.02 | 5.14^b |
| EtAc | 7.22 | 5.33 ± 0.03 | 8.91 ± 0.01 | 8.99 ± 0.05 | 5.97 ± 0.04 | 5.91^b |
| EtEt | 25.00 | 6.89 ± 0.02 | 8.16 ± 0.01 | 8.20 ± 0.02 | 6.89 ± 0.05 | 6.25^b |
| EtAc | 25.00 | 6.23 ± 0.02 | 2.702 ± 0.01 | 2.758 ± 0.02 | 7.40 ± 0.04 | 7.04^b |
| EtOH | 25.00 | 6.57 ± 0.05 | 9.34 ± 0.01 | 9.38 ± 0.03 | 7.45 ± 0.05 | 6.00^b |
| 1,3-dioxolane | 25.00 | 6.47 ± 0.03 | 2.112 ± 0.01 | 26.01 ± 0.05 | 6.74 ± 0.04 | 8.2^b |
| acetic acid | 25.00 | 12.69 ± 0.01 | -14.99 ± 0.01 | -15.12 ± 0.01 | 12.91 ± 0.02 | 12.48^b |
| acetic acid | 100.00 | 10.70 ± 0.01 | -13.78 ± 0.01 | -15.09 ± 0.02 | 11.44 ± 0.02 | 11.59^b |
| ethanol | 25.00 | 5.67 ± 0.02 | -9.37 ± 0.02 | -9.22 ± 0.02 | 6.22 ± 0.03 | 6.24^b |
| propanol | 25.00 | 7.09 ± 0.03 | 0.19 ± 0.04 | 0.22 ± 0.03 | 7.04 ± 0.05 | 7.00^b |
| propanone | 25.00 | 6.71 ± 0.03 | -3.22 ± 0.03 | -3.40 ± 0.03 | 7.24 ± 0.05 | 7.40^b |
| butanone | 25.00 | 8.01 ± 0.03 | 2.15 ± 0.03 | 2.17 ± 0.02 | 8.59 ± 0.04 | 8.25^b |

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OPLS Molecular Volumes and Densities for Liquid Hydrocarbons and Alcohols

| liquid | T | V_L | V_L | V_L | V_L |
|--------------|--------|-------|-------|-------|-------|
| ethanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| propanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| butanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| pentanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| hexanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| heptanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| octanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| nonanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| decanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| undecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| dodecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| tridecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| tetradecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| pentadecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| hexadecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| heptadecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| octadecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| nonadecanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| icosanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| docosanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| triacontanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |
| triacontanol | -12.00 | 14.0 | 15.0 | 16.0 | 17.0 |

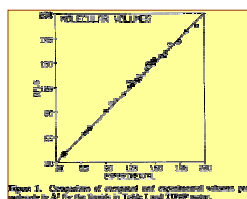


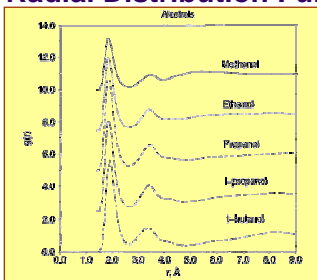
Figure 1. Comparison of computed and experimental volumes per molecule in Å³ for the liquids in Table 1 and 2.

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Radial Distribution Functions



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Applications of OPLS

- Protein Properties
- Nucleotides Properties



Crambin Protein

- 46 Residues - 326 Non-hydrogen atoms.
- 15 different residues - with Cys(6), Thr(6), Ala(5), Ile(5), Gly(4), Pro(4), Asn(3), Ser(3), Arg(2), Val(2), Tyr(2), Asp(1), Glu(1), Leu(1), Phe(1).
- Secondary structure 2 regions of α -helix and a small anti-parallel β -sheet



[Crambin Protein Structure](#)

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Crambin Structure

Table XIV. Results of Energy Minimizations for the Crambin Crystal

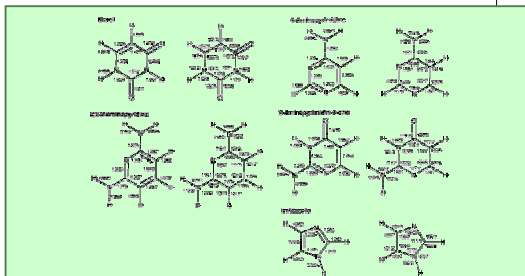
| property | force field | |
|------------------------|-------------|------------|
| | AMBER | AMBER/OPLS |
| final energy, kcal/mol | -6516.1 | -9015.1 |
| rms—protein, Å | 0.22 | 0.17 |
| rms—backbone, Å | 0.19 | 0.14 |
| rms—side chains, Å | 0.25 | 0.20 |
| rms— Φ , deg | 7.2 | 6.1 |
| rms— Ψ , deg | 7.9 | 5.6 |
| rms— ω , deg | 4.1 | 4.6 |
| rms— χ , deg | 10.9 | 11.5 |

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Nucleotide Bases



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OPLS Lennard-Jones Parameters for Nucleotide Bases and DAP

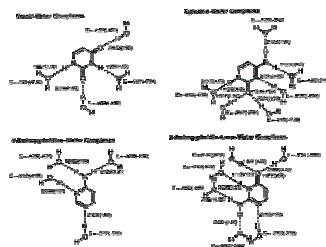
| atom | σ , Å | ϵ , kcal/mol |
|----------|--------------|-----------------------|
| O | 2.96 | 0.210 |
| N | 3.25 | 0.170 |
| C in C=O | 3.75 | 0.105 |
| other C | 3.50 | 0.080 |
| H on N | 0.00 | 0.000 |
| H on C | 2.50 | 0.050 |

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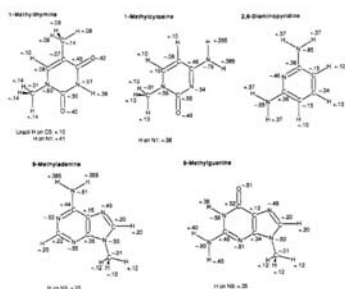
Base Water Complexes used to derive OPLS Parameters



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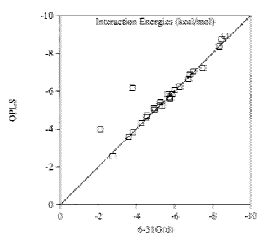
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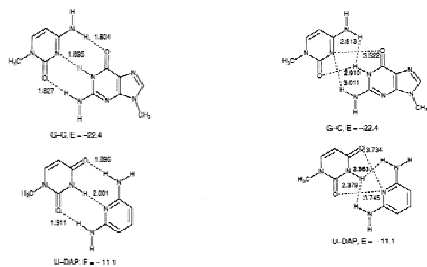
| base | OPLS | exp ^a | Singh and Kollman ^b | |
|----------|------|------------------|--------------------------------|----------|
| | | | STO-3G | Clementi |
| uracil | 3.71 | 3.86, 3.9 | 3.37 | 3.72 |
| thymine | 4.14 | 3.58 | 3.20 | 3.54 |
| cytosine | 7.20 | 7.10 | 5.67 | 6.14 |
| adenine | 2.54 | 3.16, 3.0 | 2.17 | 2.31 |
| guanine | 6.44 | 6.76 | 6.14 | 6.21 |

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Optimized Gas Phase Structures

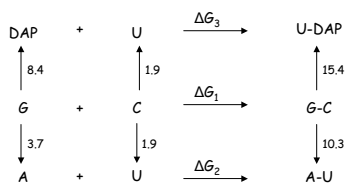


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Base Pair Interaction Energies



$$\Delta G_1 - \Delta G_2 = -4.7 \pm 0.3 \text{ kcal/mol}$$

$$K1/K2 = 2.8 \times 10^4$$

$$\Delta G_1 - \Delta G_3 = -5.1 \pm 0.7 \text{ kcal/mol}$$

$$K1/K3 = 5.5 \times 10^4$$

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Summary

- OPLS Strengths
- OPLS Weaknesses

Strengths

- Applied to different molecules with varied sizes.
- Can simulate molecular interactions with certain accuracy.

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Weaknesses

- Parameter tweaking is a specialized “art as well as science” which have been done to “fit” molecular modeling.
- Each molecule requires a different parameter setting, and hence finding and adjusting parameters is a manual process.

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THANK YOU!