Ion aggregates in biomolecular simulations: A force field problem

C9926: Problems and Issues of Molecular Modeling

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- Empirical force fields are developed and validated by experimental and ab initio computational data

- Fine-tuning of Lennard-Jones (LJ) parameters for monovalent ions (Na+, K+, and Cl-)

- Some of these parameters, in conjunction with different water models, have been evaluated

- Large dispersion of calculated properties, which is mainly due to incomplete experimental knowledge of ionic aqueous solutions at finite molarity

Example:

Spontaneous formation of NaCl aggregates in a simulation of "A-to-B" DNA transitions in >1 M salt solution using the AMBER adopted ion parameters and TIP3P water model.
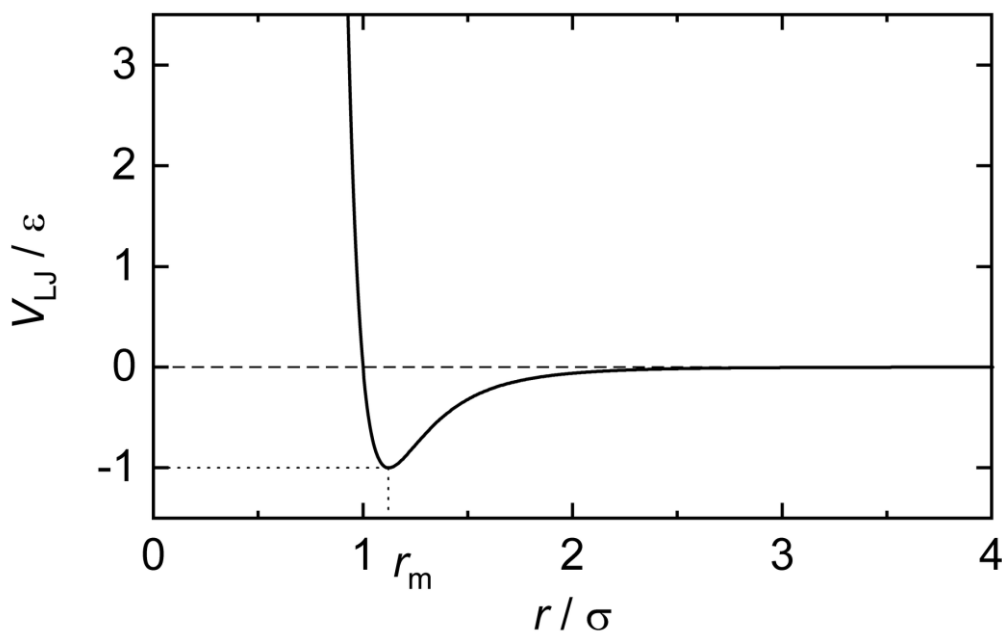
JCTC
Journal of Chemical Theory and Computation
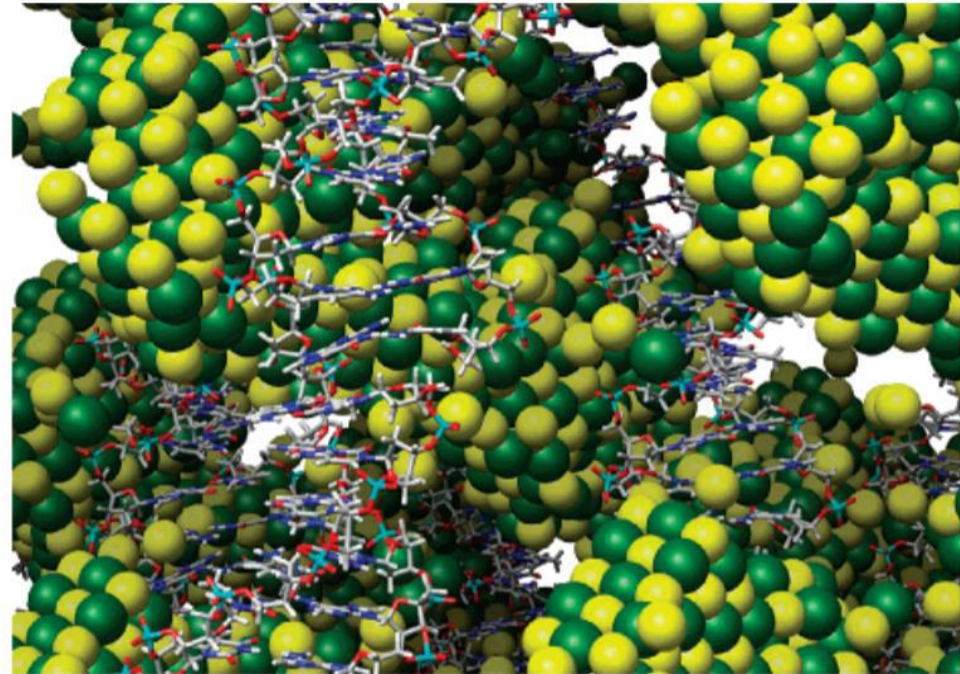
Spontaneous Formation of KCl Aggregates in Biomolecular Simulations: A Force Field Issue?

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MD simulations of aqueous KCl solutions
- three salt concentrations (1.0, 0.25, and 0.10 M)
- two water models (TIP3P and SPC/E)
- two LJ parameter sets for K+ (AMBER and Dang-Kollman)

Lennard-Jones (LJ) potential

Table 2. Lennard-Jones Parameters (r^* and ϵ) and Partial Charges (q) for the Water and Ion Models[a]

|	model	q^b	r^* (Å)[c]	ϵ (kcal/mol)[c]
water[d]	TIP3P	−0.8340	1.7683	0.1520
	SPC/E	−0.8476	1.7766	0.1553
K+	Amber	+1	2.6580	0.000328
	Dang	+1	1.8687	0.100000
Cl−	Amber	−1	2.4700	0.10
	Dang	−1	2.4700	0.10

[a] Note That the AMBER and Dang Parameters for the Cl− Ion Are Identical. [b] Partial charge for the oxygen atom of the water model and the monovalent ions. [c] r^* corresponds to the position of the Lennard-Jones minimum, and ϵ corresponds to the depth of this minimum. [d] For the TIP3P and SPC/E models, the OW−HW and HW−HW distances are constrained to 0.9572 and 1.5136 Å and to 1.0000 and 1.6330 Å, respectively.

Ion-ion radial distribution functions
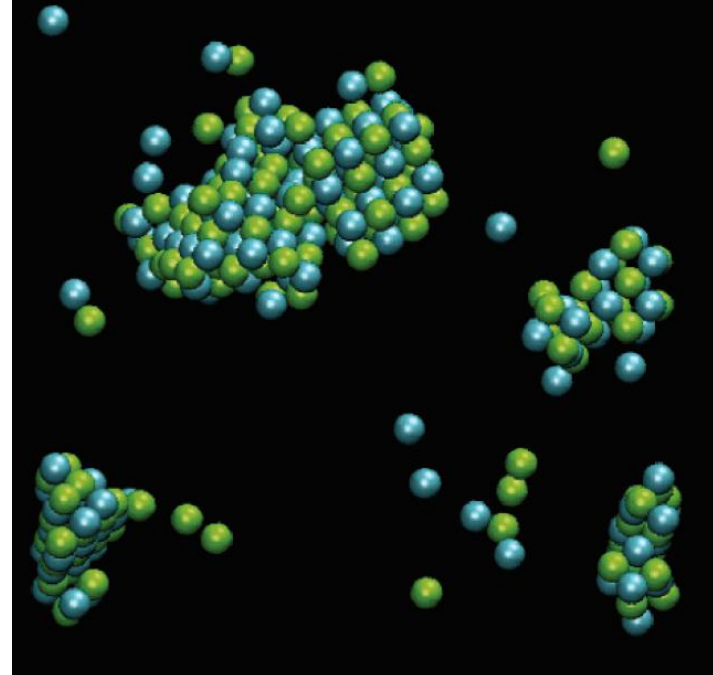## High salt concentration 0.1M
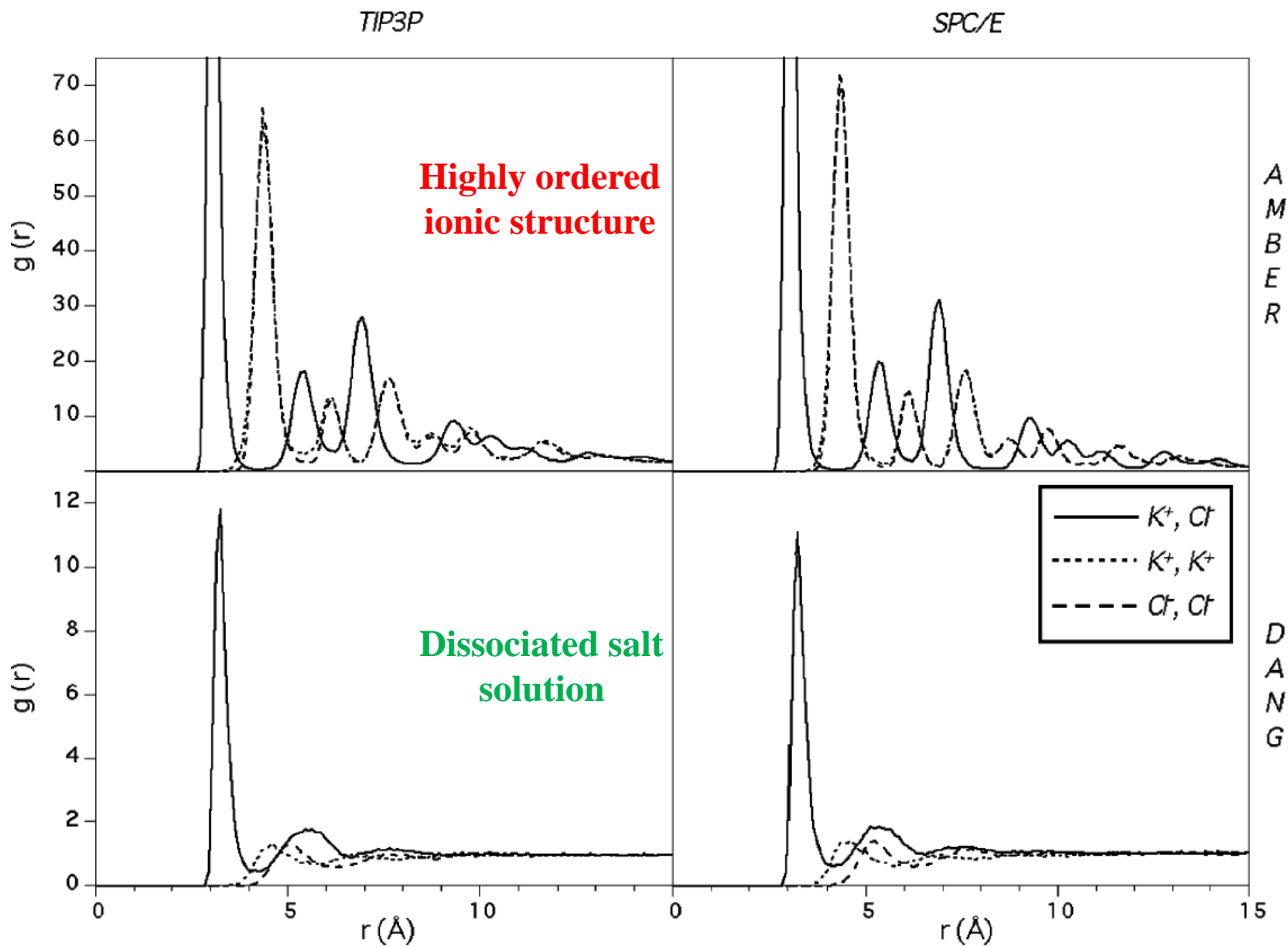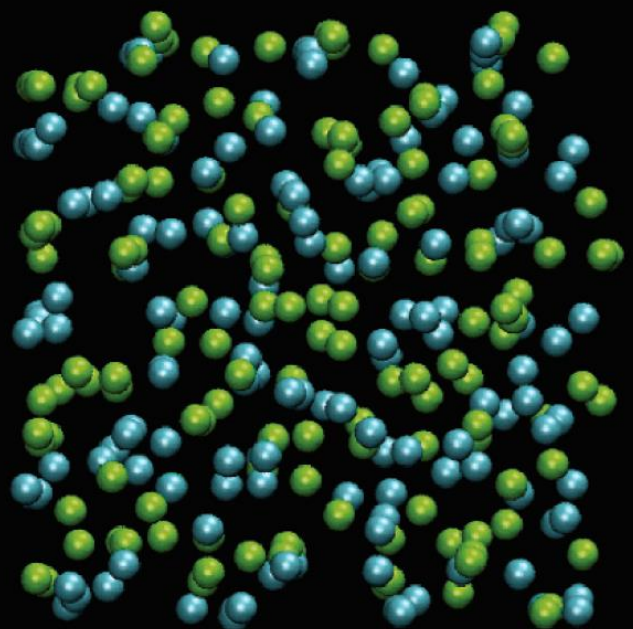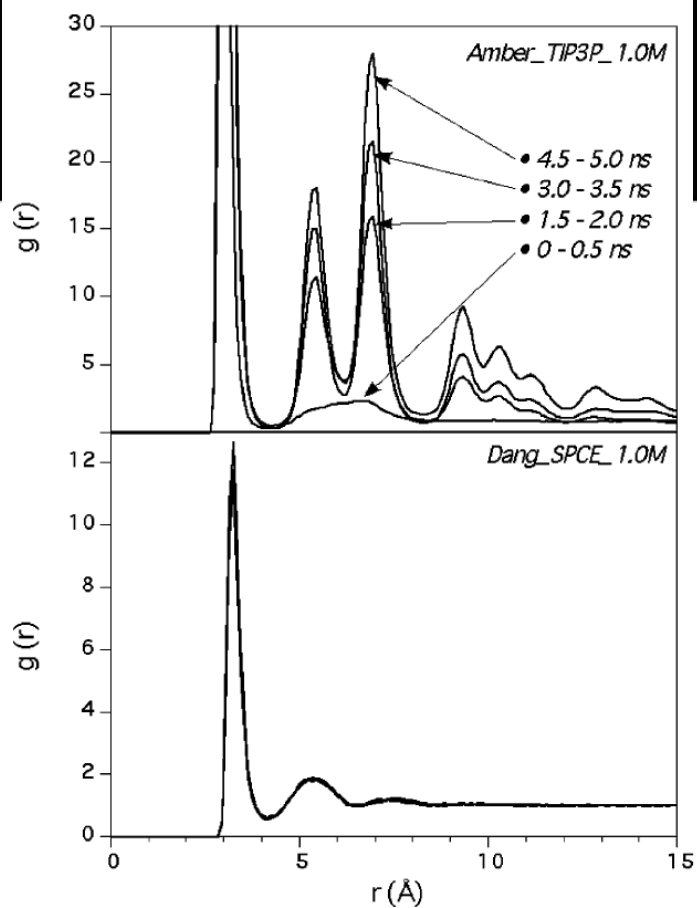
Rapid formation of KCL clusters in AMBER

K-Cl radial distribution functions

High salt concentration **0.1M**

Low salt concentration **0.01M**

K-Cl radial distribution functions

Amber_TIP3P_0.10M

No aggregation

Dang_SPC/E_0.10M

- 9 - 10 ns
- 6 - 7 ns
- 3 - 4 ns
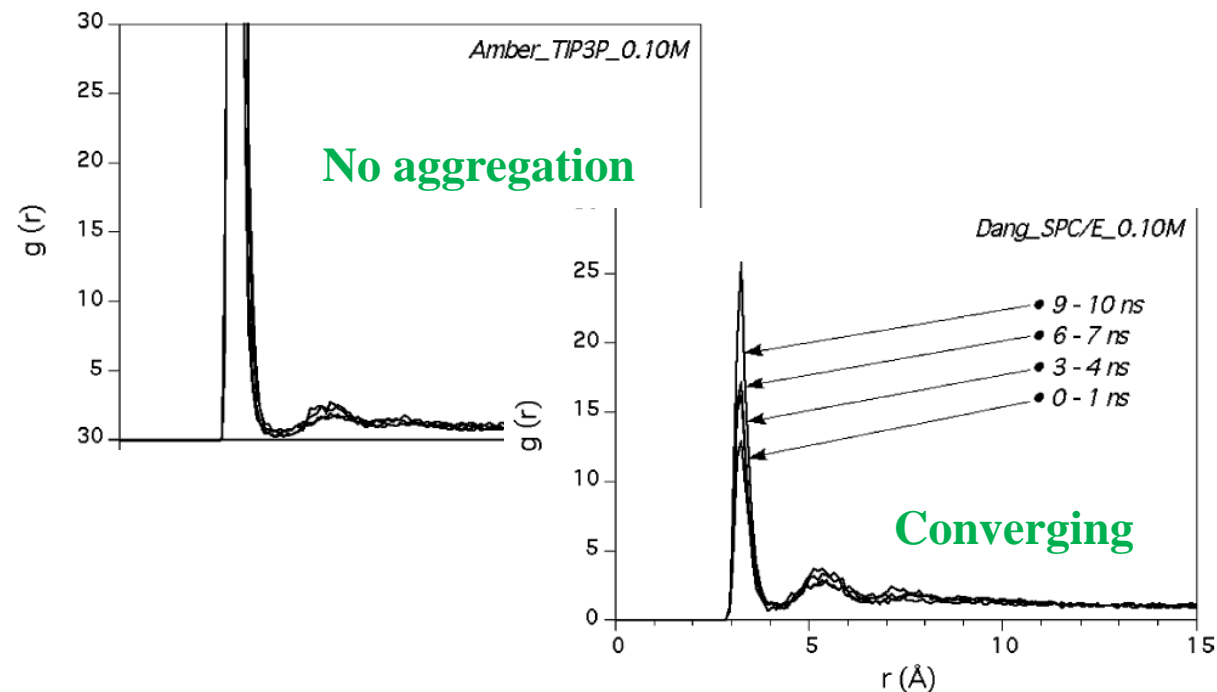- 0 - 1 ns

Converging

Table 3. First Maxima (r_{max}) of the Ion−Ion Radial Distribution Functions (See Figure 2) and Average Number of Ions (n) Present in Their First Coordination Shell

		K−K		K−Cl		Cl−Cl	
		r_{max} (Å)	n	r_{max} (Å)	n	r_{max} (Å)	n
1.0 M[a]	Amber_TIP3P	4.3	5.8	3.0	3.8	4.3	5.6
	Amber_SPC/E	4.3	5.9	3.0	3.9	4.3	5.7
	Dang_TIP3P	4.5	0.3	3.2	0.4	5.0	0.4
	Dang_SPC/E	4.6	0.3	3.2	0.4	5.2	0.4
0.25 M[a]	Amber_TIP3P	4.3	1.7	3.0	1.6	4.3	1.6
	Amber_SPC/E	4.2	1.1	3.0	1.3	4.3	1.1
	Dang_TIP3P	4.5	<0.1	3.2	0.1	5.3	<0.1
	Dang_SPC/E	4.5	<0.1	3.2	0.1	5.2	<0.1
0.10 M[b]	Amber_TIP3P	4.2	0.3	3.0	0.6	4.3	0.2
	Amber_SPC/E	4.3	0.1	3.0	0.5	4.8	0.1
	Dang_TIP3P	4.2	<0.1	3.2	0.1	5.1	<0.1
	Dang_SPC/E	4.5	<0.1	3.2	0.1	5.2	<0.1

[a] These values (1.0 and 0.25 M) have been calculated by using the last 500 ps of the 5 ns trajectories. [b] These values (0.10 M) have been calculated by using the last ns of the 10 ns trajectories.

Ion-water coordination numbers

Table 4. First Maxima (r_{max}) of the Ion−Water Radial Distribution Functions and First Coordination Shell Ion Hydration Number (n) Calculated for the Four 0.10 M Simulations[a]

	K−O$_w$		Cl−O$_w$	
	r_{max} (Å)	n	r_{max} (Å)	n
Amber_TIP3P_ (0.10M/1.0M)	2.73/2.74	6.2/2.2	3.23/3.24	7.0/2.4
Amber_SPC/E_ (0.10M/1.0M)	2.75/2.75	5.6/2.1	3.23/3.23	6.1/2.2
Dang_TIP3P_ (0.10M/1.0M)	2.82/282	7.2/6.9	3.24/3.24	7.6/7.1
Dang_SPC/E_ (0.10M/1.0M)	2.83/2.82	7.1/6.8	3.24/3.22	7.1/6.8
experimental	2.8	6.0−8.0	3.2	6.0−8.0

numbers of ions of opposite charge surrounding a given ion revealing the occurrence of KCl contact pairs

number of water molecules located in the first shell is larger for Dang, reflecting that AMBER favors the formation of ion pairs and aggregates

Issues of electronic polarizability using non-polarizable force fields

AMBER, CHARMM, GROMOS and OPLS have been successful in modeling many complex molecular systems. The hydration free energies can be computed accurately.

Serious problems:

- in low-polar solvents, e.g., ethers, and non-polar solvents, e.g., alkanes

- low-dielectric protein environment and lipid membranes

- For example, the dielectric constant of the inner part of Cytochrome c was found to be only about 1.5, which is lower than *pure electronic dielectric constant 2.0*

Electrostatic interactions of ions (point charges) are described as if they are in vacuum, completely disregarding the effect of electronic dielectric screening inherent to the condensed phase medium, where all charges are immersed in the electronic continuum, which weakens their interactions by a factor of about 2. Therefore, all the interactions are overestimated by a factor of about 2.

- Coulomb interaction of ions
- Interactions of ions with water molecules, or with partial atomic charges of a protein
- Interaction of charged residues in proteins Arg+/Lys+ with Glu-/Asp-

PERSPECTIVE

# Accounting for electronic polarization in non-polarizable force fields

Igor Leontyev and Alexei Stuchebrukhov*

MDEC model

- Model combines a non-polarizable (fixed-charge) force field for molecular dynamics (MD) with a phenomenological electronic continuum (EC)

- Uniform charge scaling based on the idea of uniform electronic continuum with an effective dielectric constant ε_{el} of 2, and point charges moving in it

- The interactions between charges are scaled by a factor $1/\varepsilon_{el}$ (i.e., individual charges are scaled by a factor of $1/\sqrt{\varepsilon_{el}}$)

Interaction energies of charged species

ab initio calculations
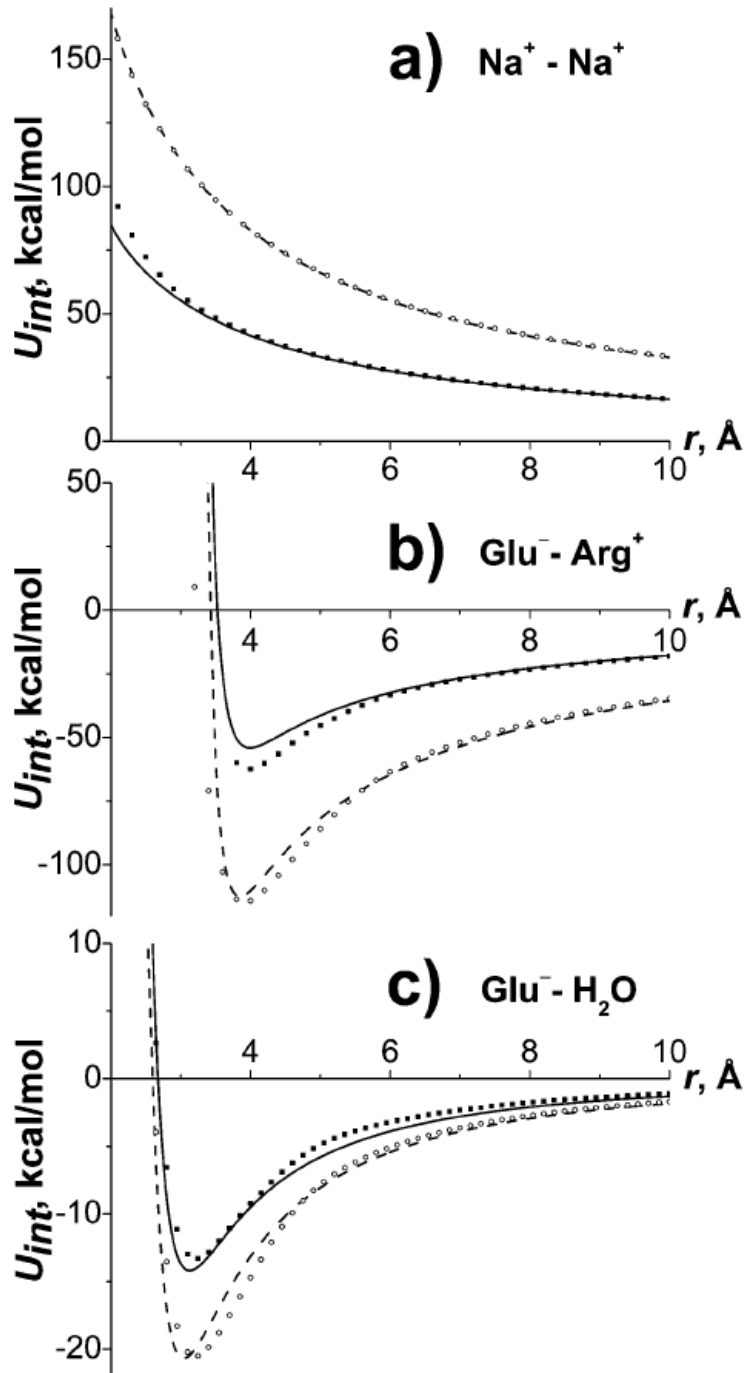
○   in gas-phase HF/6-31(d) calculation

□   in dielectric of 2.0

- - -   standard CHARMM and TIP3P

——   CHARMM with scaled charges ($\varepsilon_{el} = 2.0$), and TIP3P

Electronic screening effect of the dielectric environment on the interaction energies can be accurately reproduced by a simple **scaling** of charges

Water models

Dipole moment of water in vacuum ~ 1.85D and in liquid state ~ 2.9D to 3.2D.

This significant increase in dipole is also supported by the Kirkwood-Onsager model, which estimates the enhanced polarization of a molecule due to the reaction field of the polarized environment.

Yet, the dipole moment of TIP3P water model is 2.35D.

This was understood as a scaled dipole, so that the dipole–dipole interactions are screened by the electronic continuum by a factor $1/\varepsilon el$ (i.e., each dipole is scaled by a factor $1/\sqrt{\varepsilon el}$).

Considering the interaction of effective dipoles, $\mu eff = \mu/\sqrt{\varepsilon el}$ ~ 2:35D (where εel 1.78 is the electronic high-frequency dielectric constant of water).
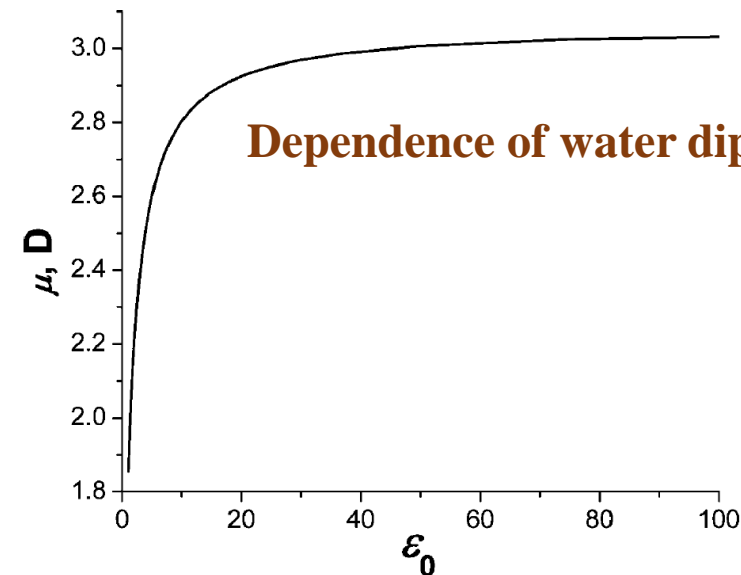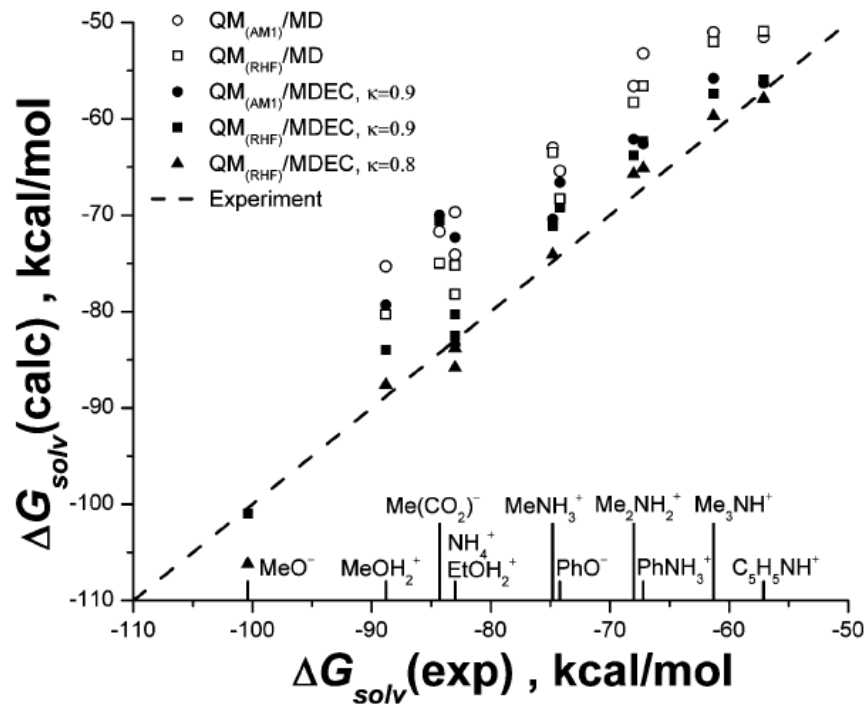

Dependence of water dipole on the polarity of the environment

In the **high-dielectric** region, $\varepsilon 0 > 20$, the water polarization is almost constant and like the water molecule in the bulk $\varepsilon 0 = 80$.

At **low-dielectric** region (proteins or membranes), $\varepsilon 0 < 20$, there is a significant dependence.

Solvation free energy

Solvation free energy consists of two parts:

the **nuclear** part evaluated by MD, and

the pure **electronic polarization** part evaluated by using the polarizable continuum model (i.e., by solving the Poisson equation with corresponding boundary conditions, with dielectric constant $\varepsilon = 1$ inside the solute region, and $\varepsilon = \varepsilon_{el}$ outside.

MDEC and the conventional non-polarizable MD reproduce experimental data within the experimental error in a **high-dielectric** media such as water.

However, the traditional non-polarizable MD significantly underestimate the solvation free energy in the **low-dielectric** media such as liquid cyclohexane or protein interior of protein Cytochrome c oxidase.

Microscopic interactions

PMF for an ion pair A+ and A- in benzene

■ Polarizable Drude oscillator model

○ Traditional non-polarizable CHARMM MD

△ Traditional non-polarizable CHARMM MD with scaled charges
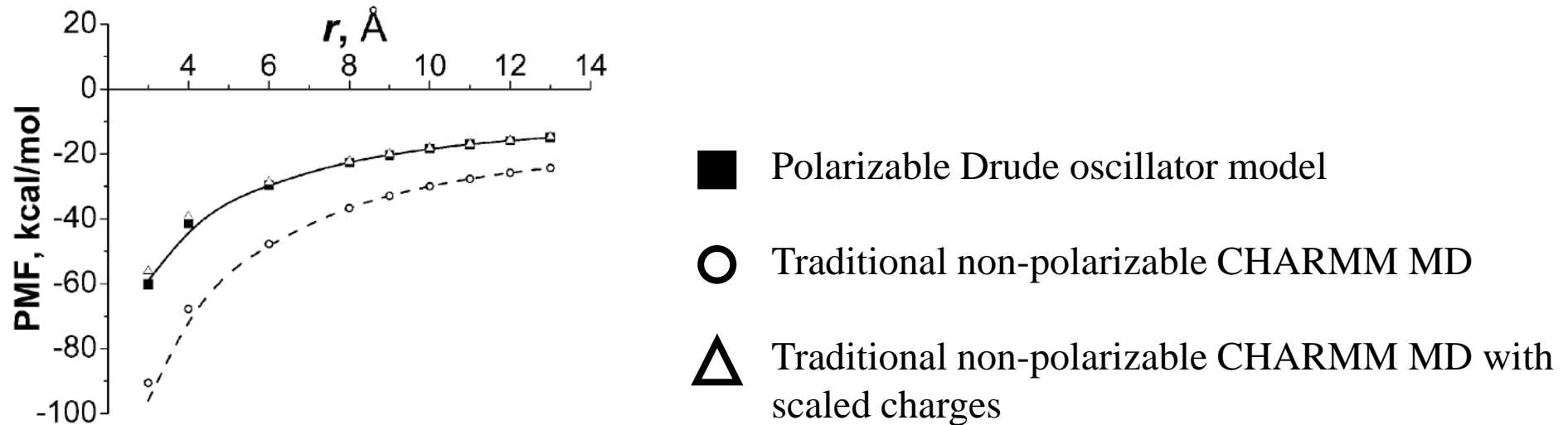
When the space between ionic spheres is larger than a size of solvent molecules, the effects of solvent microscopic structure becomes unimportant, and the average interaction, both in polarizable and non-polarizable models of benzene, can be approximated by a simple Coulomb law with an effective dielectric constant.

Dynamics of salt bridges in proteins

Distribution functions of the distance *d* between the atoms forming saltbridge

Salt bridge formed = no water in the cavity

a) no water in the catalytic cavity

b) 4 water molecules in the cavity
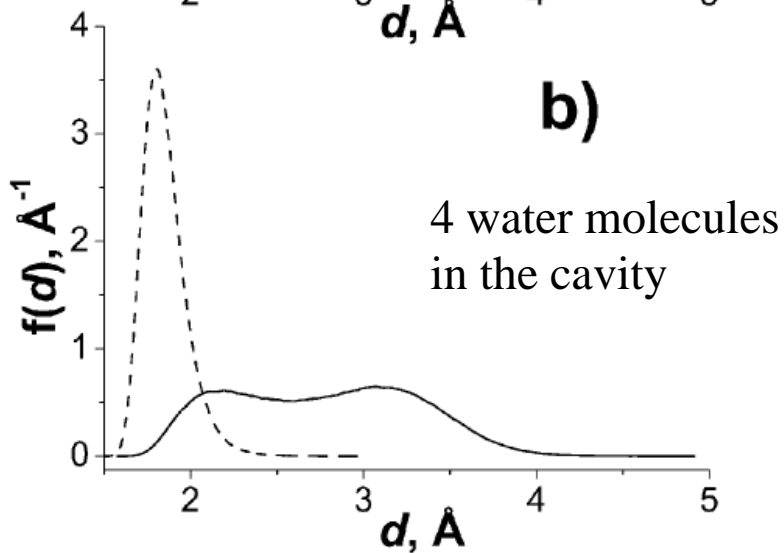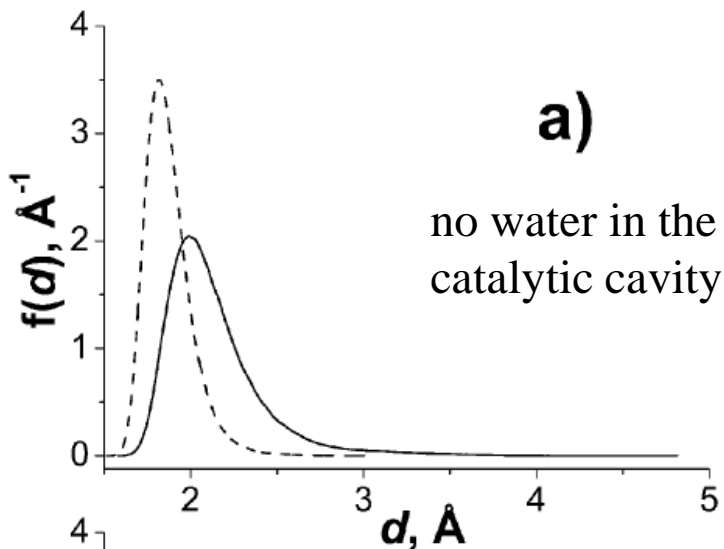
- - - Standard non-polarizable MD

——— MD with scaled charges of the ionized groups

Standard non-polarizable MD with and without water in the cavity lead to the conclusion that the salt bridge is formed 100% of the time .

Salt bridge is observed 98% or even 63% of the time in MD with scaled charges without and with water molecules in the cavity, respectively.