

Why the Sulfinyl Group is special in DMSO ?

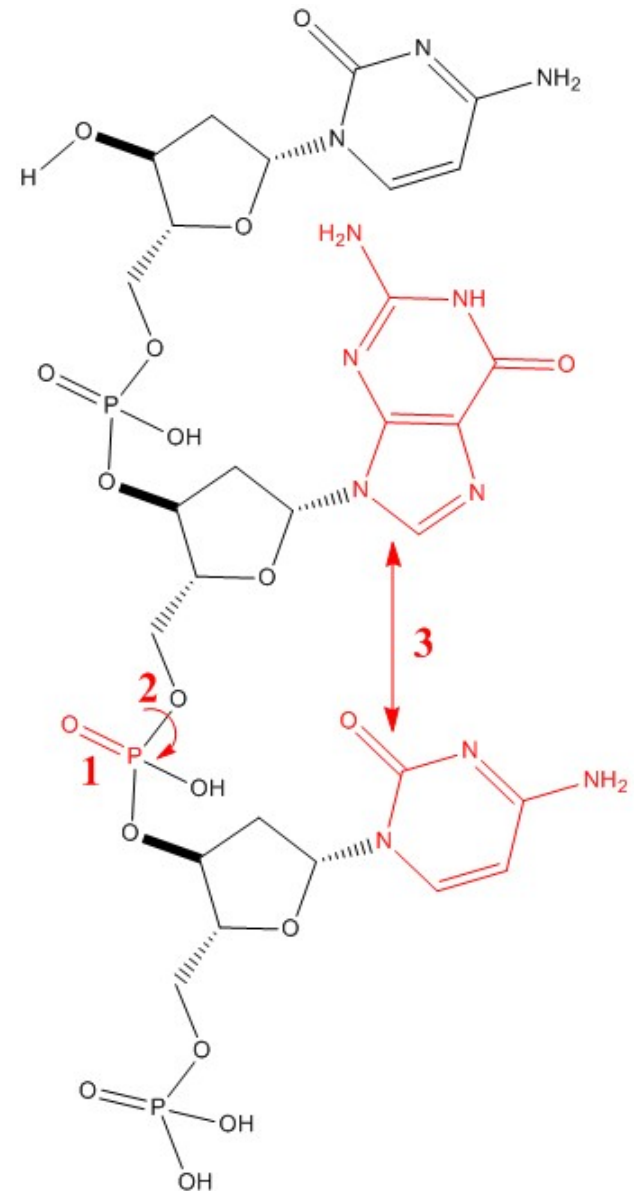
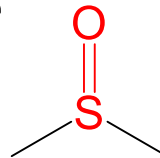
Chao Lv June 4, 2014

The Parameterization of Dimethyl Sulfoxide (DMSO)

Nucleic Acids are known to be difficult to be parameterized because:

1. The interaction between **P=O** and ions
2. The “Anomeric Effect” around the **P-O** dihedral
3. The Packing of Nitrogenous Bases (Penetration Effect)

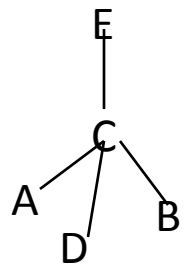
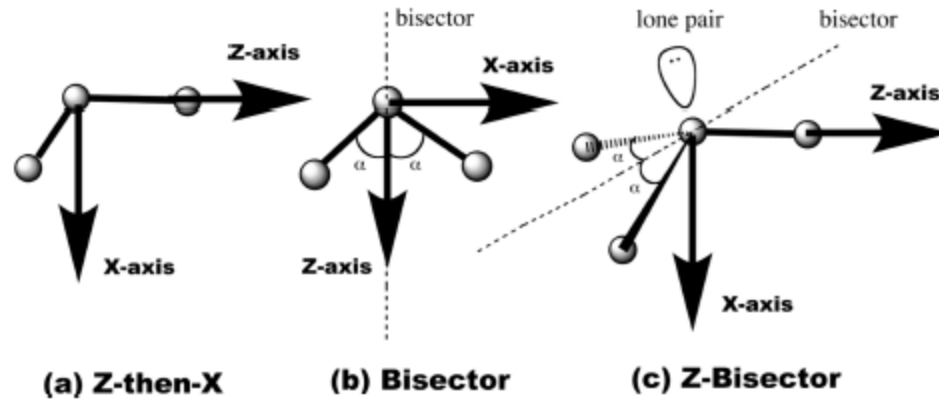
Since **S=O** and **P=O** have similar structure, let us start a **simple molecule DMSO**



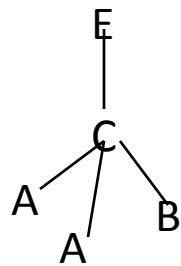
General Procedure of the Parameterization

- STEP 1: Use low level theory (MP2/6-311G(1d,1p)) to optimize the molecule and perform GDMA program to **initialize multipoles**
- STEP 2: Use POEDIT to **convert global coordinate frame multipoles** from GDMA **to local coordinate frame ones**
- STEP 3: Re-optimized the structure with MP2/aug-cc-pVTZ and use POTENTIAL to **fit multipoles to the high level QM potential**
- STEP 4: Fit **valence and torsion** parameters
- STEP 5: Fit **vDW** parameters to **dimer structures, interaction energy, pure liquid density and heat of vaporization**
- ❖ Atomic polarizability values are obtained from

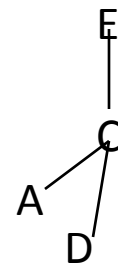
Local Coordinate Frame



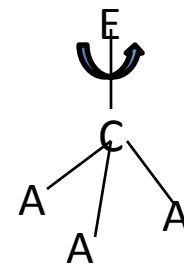
Z-then-X



Bisector
Z-Bisector



Z-then-X
Z-Bisector



Z-Only
Bisector ($D_x=0$)
Z-then-X ($D_x=0$)

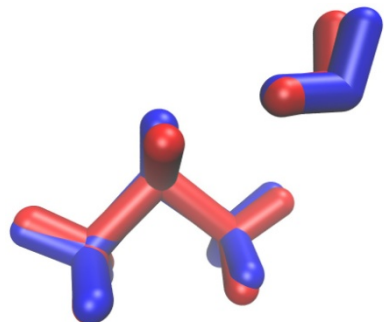
Parameter Test and Refinement

1. Thermodynamic properties of pure liquid, such as density, heat of vaporization, diffusion constant, viscosity, dielectric constant etc.
2. Interaction energy and thermo properties with other solvents, usually with water.
3. Interaction energy and thermo properties with ions, for example, Na^+ , K^+ , Cl^- , Mg^{2+} , Ca^{2+} etc.

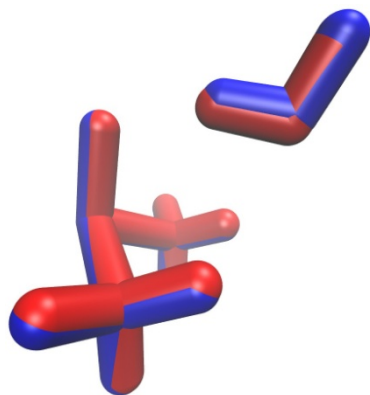
The Thermodynamic Properties of Pure Liquid

Properties	288.15K	298.15K	313.15K
Density(g/cm ³)	1.1068 (1.1047)	1.0963 (1.0955)	1.0803 (1.0803)
Heat of Vaporization (kcal/mol)		12.40 (12.64)	
Diffusion Constant (10 ⁻⁹ m ² /s)		0.57 (0.80)	

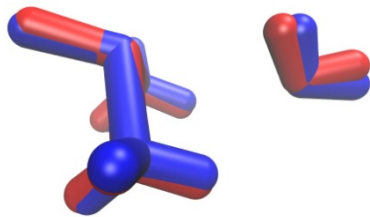
The Structures and Interaction Energies of DMSO-Water Dimers



AMOEBA: -8.5906 kcal/mol
BSSE: -8.2579 kcal/mol no BSSE: -8.7097 kcal/mol

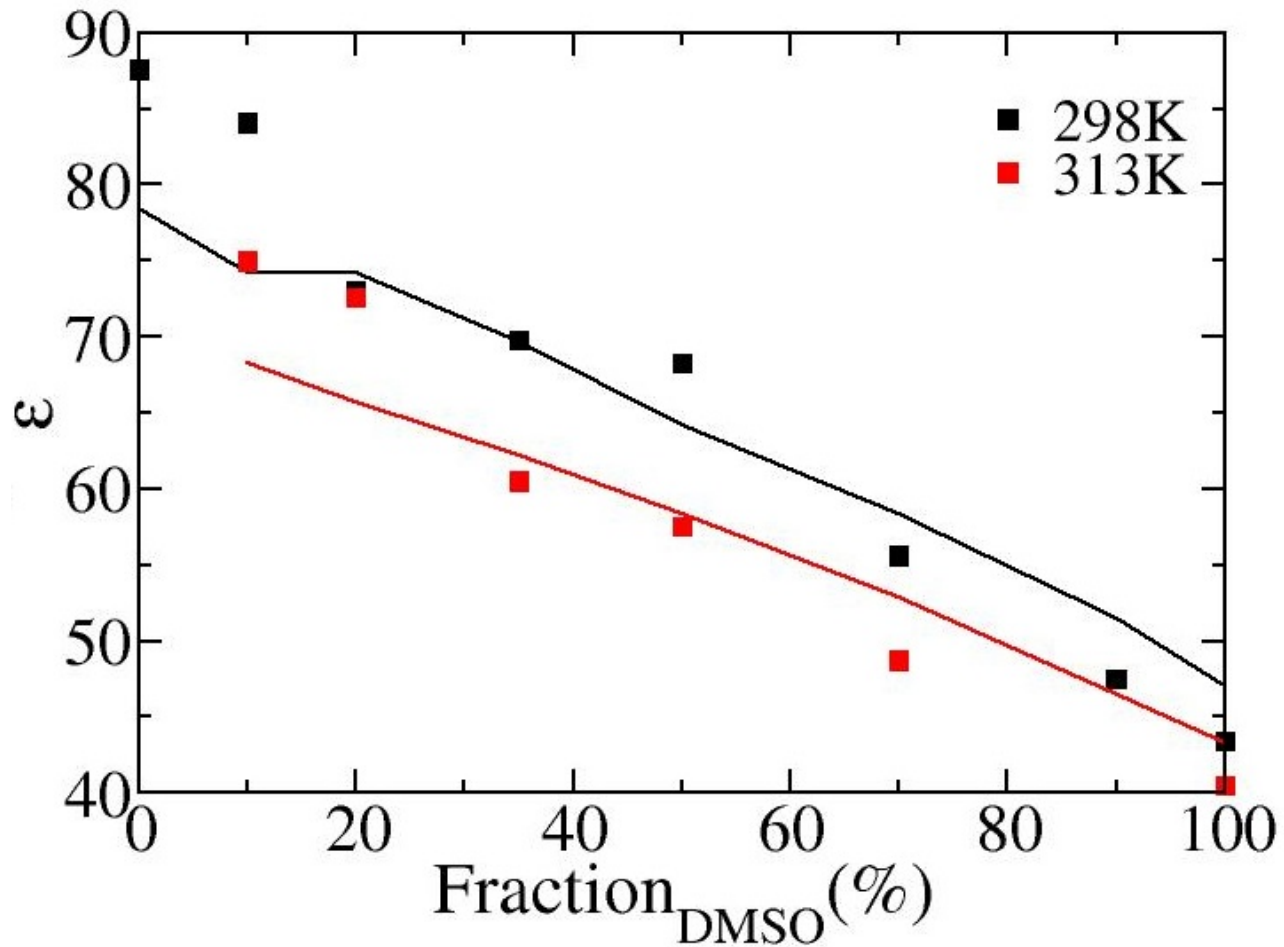


AMOEBA: -9.1277 kcal/mol
BSSE: -9.7674 kcal/mol no BSSE: -10.7813 kcal/mol

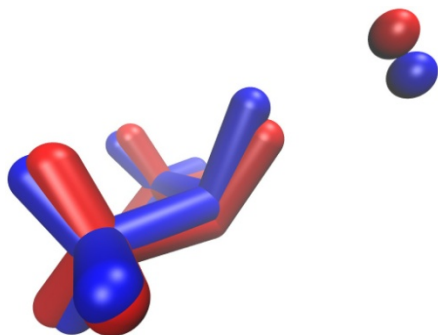


AMOEBA: -3.6805 kcal/mol
BSSE: -4.0599 kcal/mol no BSSE: -4.7000 kcal/mol

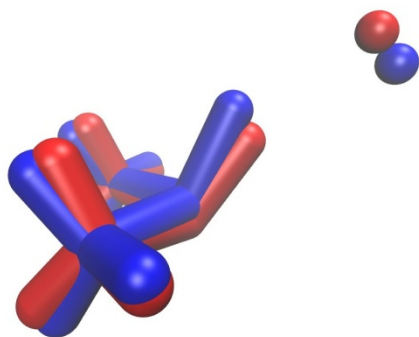
The Dielectric Constant of DMSO-Water Mixture at Different Temperatures



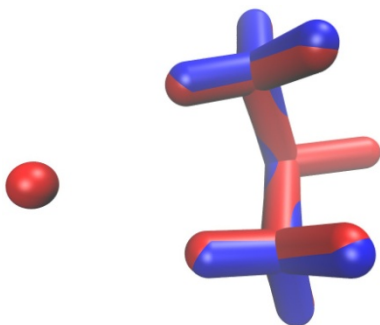
Can This Set of Parameters Reproduce the Interaction Energies of DMSO-Ion ?



DMSO- Na^+
AMOEBAs: -35.6033 kcal/mol
BSSE: -39.0621 kcal/mol no BSSE: -39.4135 kcal/mol



DMSO- K^+
AMOEBAs: -28.4076 kcal/mol
BSSE: -31.5446 kcal/mol no BSSE: -32.2223 kcal/mol



DMSO- Cl^-
AMOEBAs: -20.5006 kcal/mol
BSSE: -19.7601 kcal/mol no BSSE: -20.9021 kcal/mol

How do the Inaccurate Parameters affect the Ion Solvation Energies ?

Ion	Na ⁺	K ⁺	Cl ⁻	NaCl	KCl
Hydration Free Energy (kcal/mol)	-109.1 (-92.7 ^a)	-91.6 (-75.7 ^a)	-60.1 (-73.4 ^a)	-169.2 (-171.6 ^b)	-151.7 (-155.1 ^b)

❖ Estimated according to Extrathermodynamic Assumption

a Marcus, Y *Ion Properties*. CRC Press, **1997**

b Kelly, C.P., Crammer, C.J., Truhlar, D.G. *J. Phys. Chem. B*, **2007**, 111, 408-422

Problems of Extrathermodynamic Assumption

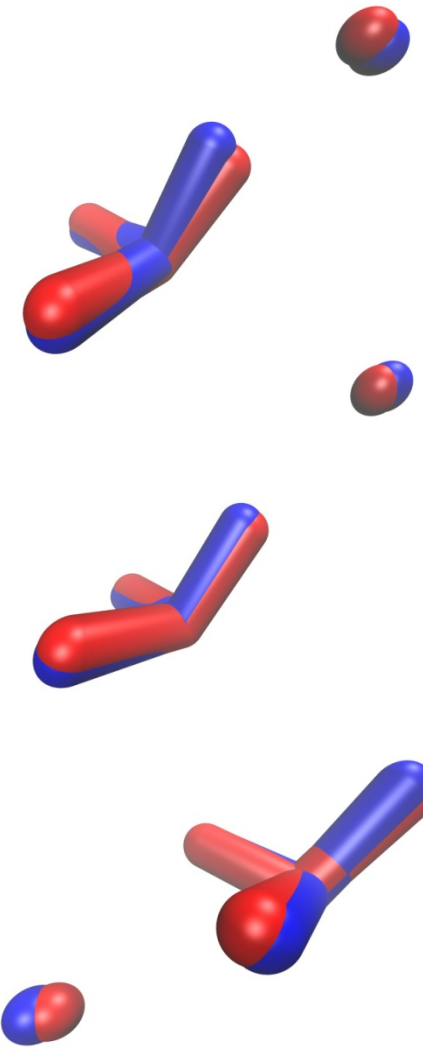
$$\Delta G(\text{Ph}_4\text{As}^+, \text{H}_2\text{O} > \text{S}) = \Delta G(\text{Ph}_4\text{B}^-, \text{H}_2\text{O} > \text{S})$$

Table I. Formal Solubility Products (Molar Concentrations) of Electrolytes Expressed as Solvent Activity Coefficients at 25° with Methanol as Reference Solvent^a

Solute	pK _s ^a MeOH	Log (^M γ ^{S_A+})(^M γ ^{S_B-}) = pK _s (solvent) - pK _s (MeOH)							
		MeOH	H ₂ O	HCONH ₂	DMF	DMAC	DMSO	CH ₃ CN	HMPT ^b
Ph ₄ AsBPh ₄	8.5 ^c	0.0	8.2	-0.2 ^c	-4.8 ^c	-5.1 ^c	-5.2 ^c	-3.3 ^c	-5.4 ^c
Ph ₄ C	3.7 ^a	0.0	-1.6 ^d	-1.4 ^d	...	-0.5 ^d	...
Ph ₄ Sn	3.6 ^d	0.0	-1.6 ^d
Ferrocene	1.2 ^e	0.0	3.6 ^f	-0.3 ^f	...
Ph ₄ AsI ^h	(1.4)	0.0	3.7	+0.3	-0.3	+0.6	...
Ph ₄ AsSCN ^h	(1.2)	0.0	4.4
Ph ₄ AsPic ^e	3.6	0.0	5.2	-1.5	...
Ph ₄ AsClO ₄ ^e	4.7	0.0	3.5
KBPh ₄	5.0 ⁱ	0.0	2.5 ⁱ	-2.3 ^{e,h}	...
KClO ₄ ⁱ	4.5	0.0	-2.8	...	(-4.4)	...	(-5.3)
KPic ⁱ	4.2	0.0	-0.8	...	(-4.4)	+0.3	...
KCl ⁱ	2.5	0.0	-3.4	...	+2.9	+4.7	...
KI ⁱ	(0.2)	0.0	(-0.7)	(+1.8)	...



Are the Inaccurate Interaction Energies Purely due to S=O ? A H₂SO Study



The image displays three 3D molecular models of sulfuric acid (H₂SO) in different orientations. Each model consists of a central sulfur atom (red) bonded to two oxygen atoms (blue) and two hydrogen atoms (red). The models are arranged vertically on the left side of the slide.

H₂SO-Na⁺

AMOEBA: -29.3799 kcal/mol

BSSE: -32.6804 kcal/mol no BSSE: -33.0443 kcal/mol

H₂SO-K⁺

AMOEBA: -23.7005 kcal/mol

BSSE: -26.4304 kcal/mol no BSSE: -27.1521 kcal/mol

H₂SO-Cl⁻

AMOEBA: -20.7510 kcal/mol

BSSE: -21.6238 kcal/mol no BSSE: -22.3140 kcal/mol

Adjustment of the Oxygen Polarizability Value

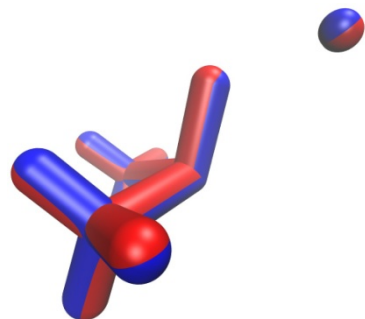
New set of parameters:

vdw	73	3.56 (3.52)	0.1120	O
			
polarize	189	3.0800 (3.3000)	0.45(0.39)	S
polarize	190	1.3670 (0.8370)	0.45(0.39)	O

Test of Molecule Polarizability (\AA^3) using new parameters:

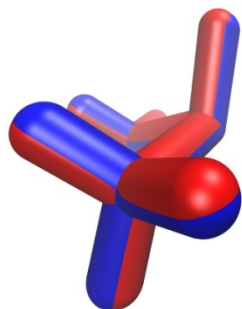
	α_{xx}	α_{yy}	α_{zz}
AMOEBA	6.730	8.228	8.505
Aug-cc-pVTZ	7.325	7.948	8.560

Changes in the Interaction Energies of DMSO-Ions



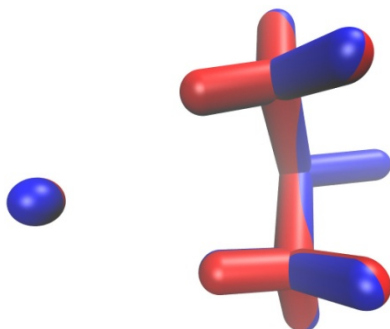
DMSO-Na⁺

AMOEBAs: -38.1582 kcal/mol (-35.6033 kcal/mol)
BSSE: -39.0621 kcal/mol no BSSE: -39.4135 kcal/mol



DMSO-K⁺

AMOEBAs: -30.0900 kcal/mol (-28.4076 kcal/mol)
BSSE: -31.5446 kcal/mol no BSSE: -32.2223 kcal/mol



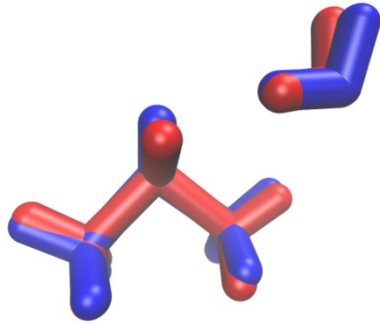
DMSO-Cl⁻

AMOEBAs: -20.4455 kcal/mol (-20.5006 kcal/mol)
BSSE: -19.7601 kcal/mol no BSSE: -20.9021 kcal/mol

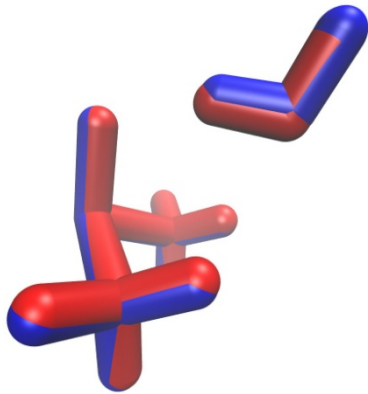
Changes in the Ion Solvation Free Energies and Diffusion Constant

Ion	NaCl	KCl
Hydration Free Energy (kcal/mol)	-171.1 (-169.2) -171.6	-154.9 (-151.7) -155.1
Diffusion Constant: 0.62 (0.57)	0.8 ???	

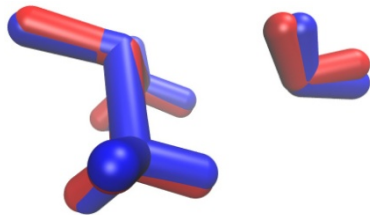
Does the New Set of Parameters affect the Interaction Energies of DMSO-Water ?



AMOEBAs: -8.2871 kcal/mol (-8.5806 kcal/mol)
BSSE: -8.2579 kcal/mol no BSSE: -8.7097 kcal/mol



AMOEBAs: -8.9573 kcal/mol (-9.1277 kcal/mol)
BSSE: -10.7813 kcal/mol no BSSE: -9.7647 kcal/mol

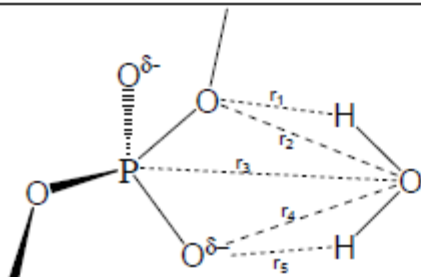


AMOEBAs: -3.6761 kcal/mol (-3.6805 kcal/mol)
BSSE: -4.0599 kcal/mol no BSSE: -4.7000 kcal/mol

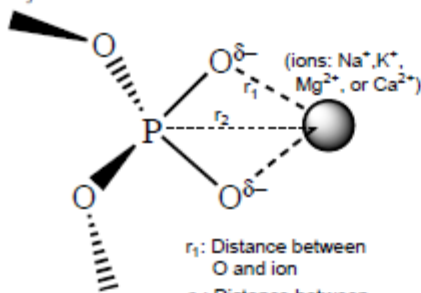
Does P=O has similar interaction features with ions and water ?

Table 7. The QM and MM calculated interactions between dimethyl phosphate(DMP) and some ligands. Units: D--- Å; E_{inter}--- Kcal/mol.

Ligands of DMP and dimer structures	<i>ab initio</i>		AMOEBA		AMBER <i>ff99</i>	
	D	E _{inter}	D	E _{inter}	D	E _{inter}
H ₂ O	r ₁ =2.347 r ₂ =3.040 r ₃ =3.567 r ₄ =2.781 r ₅ =1.817	15.981	r ₁ =2.459 r ₂ =3.070 r ₃ =3.551 r ₄ =2.796 r ₅ =1.848	16.524	r ₁ =2.114 r ₂ =2.898 r ₃ =3.374 r ₄ =2.653 r ₅ =1.749	18.802
Na ⁺	r ₁ =2.296 r ₂ =2.714	137.376	r ₁ =2.315 r ₂ =2.826	141.572	r ₁ =2.271 r ₂ =2.720	135.527
K ⁺	r ₁ =2.565 r ₂ =3.021	122.017	r ₁ =2.570 r ₂ =3.082	127.391	r ₁ =2.564 r ₂ =3.033	119.766
Mg ²⁺	r ₁ =1.944 r ₂ =2.478	391.711	r ₁ =1.980 r ₂ =2.637	379.345	r ₁ =1.822 r ₂ =2.376	357.146
Ca ²⁺	r ₁ =2.189 r ₂ =2.742	324.890	r ₁ =2.263 r ₂ =2.879	319.169	r ₁ =2.507 r ₂ =3.048	254.385



r₁: O(sp³)---HW distance
r₂: O(sp³)---OW distance
r₃: P---OW distance
r₄: O^{δ-}---OW distance
r₅: O^{δ-}---HW distance
W: Water



r₁: Distance between O and ion
r₂: Distance between P and ion
(ions: Na⁺, K⁺, Mg²⁺, or Ca²⁺)

Why is S=O (or P=O) special S⁺-O⁻ or S=O ?

Table 3 Natural bond orbital (NBO) analyses of (CH₃)₂S, (CH₃)₂SO and (CH₃)₂SO₂, at the B3PW91/6-311G(3df,2p) level. When the results are the same for two bonds or two lone pairs in a molecule, this is indicated in parentheses

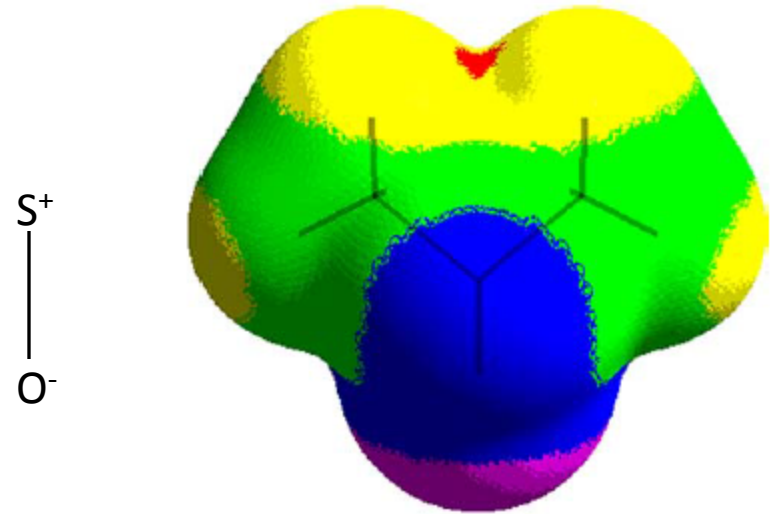
Molecule	Bond (BD) or lone pair (LP)	Atom, percent contribution	% s	% p	% d	% f
(CH ₃) ₂ S	BD: S-C (2)	S: 47.47	16.80	82.52	0.67	0.01
		C: 52.53	23.15	76.64	0.19	0.02
	LP: S	S: 100.00	67.31	32.67	0.02	0.00
	LP: S	S: 100.00	0.00	99.95	0.03	0.02
(CH ₃) ₂ SO	BD: S-C (2)	S: 46.88	15.79	82.66	1.54	0.01
		C: 53.12	21.54	78.39	0.07	0.00
	BD: S-O	S: 35.77	20.67	77.92	1.34	0.06
		O: 64.23	22.73	76.01	1.25	0.02
	LP: S	S: 100.00	49.23	50.63	0.13	0.00
	LP: O	O: 100.00	76.25	23.67	0.08	0.00
LP: O	O: 100.00	0.94	98.32	0.74	0.01	
(CH ₃) ₂ SO ₂	BD: S-C (2)	S: 47.32	23.13	75.04	1.83	0.00
		C: 52.68	21.95	77.76	0.29	0.00
	BD: S-O (2)	S: 33.97	26.94	71.13	1.89	0.04
		O: 66.03	27.65	71.32	1.02	0.01
	LP: O (2)	O: 100.00	72.25	27.65	0.09	0.00
	LP: O (2)	O: 100.00	0.00	99.32	0.67	0.01
	LP: O (2)	O: 100.00	0.02	99.31	0.65	0.01

❖ S⁺-O⁻ not S=O

Clark, T., Murray, J.S., Lane, P. *J. Mol. Model.* **2008**, 14, 689-697.

What does it imply if S^+-O^- ?

1. **O** is more negative than expected and **S** is positive around the σ -hole area.
2. Vdw radius of **O** should be larger than normal and that of **S** should be smaller. (Does this affect the calculation of diffusion constant?)
3. The reason that **O** has abnormal larger polarizability may be due to the co-existence of LP on **O** and empty 3d orbital on **S**.
(Example: C=O in acetone, LP but no 3d.
C-S-C in dimethyl sulfide, 3d but no LP)



Clark, T., Murray, J.S., Lane, P. J.
Mol. Model. **2008**, 14, 689-697.

What need to be done?

- I. Enlarge the vdw radius of **O** and decrease that of **S**, simultaneously to obtain better diffusion constant
- II. Re-calculate the thermodynamic properties of pure liquid and DMSO-Water mixture to test if the modification affect those properties
- III. Use similar idea to parameterize $(\text{CH}_3)_3\text{PO}_4$, H_3PO_4 and $(\text{CH}_3)_2\text{PO}_4^-$ and the calculate the properties of those molecules.