COSMOlogic
Predicting Solutions

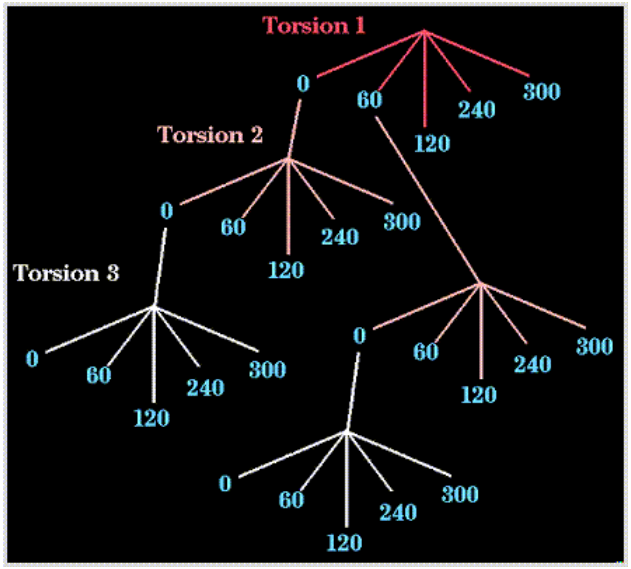
Conformations

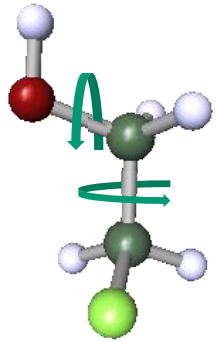
Relevance and Examples

Conformers

Definition

- Conformers are all geometries of a molecule with the same connectivity, which can be transformed into each other without bond breaking at room temperature.
- Population of the different conformations depend on the temperature and the environment (gas/solvent/mixture)
- „Conformational explosion“ as the number of rotatable bonds increases

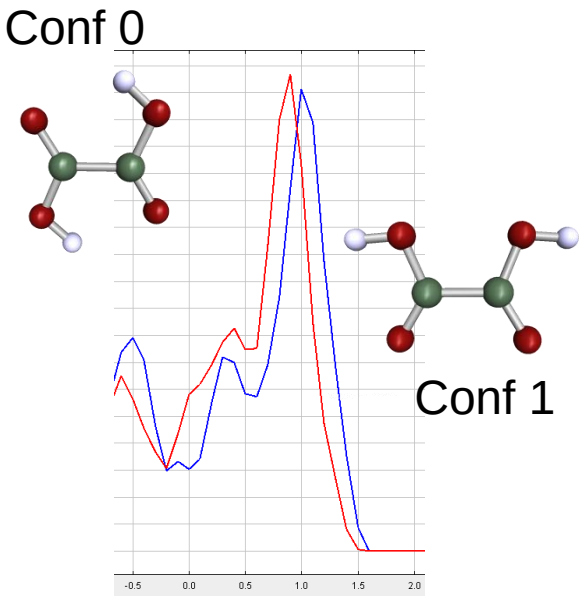




Why Conformations?

Conformers have

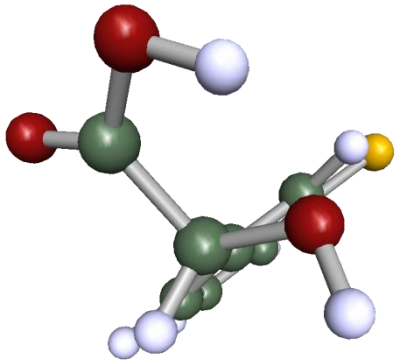
- Different σ-profiles
- Different σ-potentials
- Changing relevance in different solvents



	Predicted conformer weight in		
Conformer	H2O	Ethylbenzoate	Hexane
Conf 0	0.3%	46.20%	99.5%
Conf 1	99.7%	53.80%	0.5%

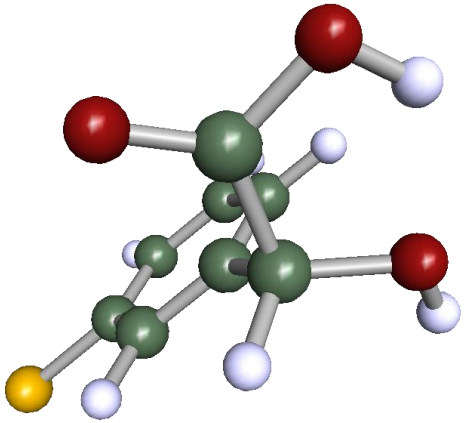
Example 1

Predictions for 3-Chloro-Mandelicacid



Lowest energy conformer vs. conformer set

	conformer 0	conformer set	difference
μ in H2O (kcal/mol)	-1.02	-2.00	-0.98
μ in Hexane (kcal/mol)	0.94	-0.54	-1.48
ln(γ) in H2O	4.43	4.51	0.09
ln(γ) in Hexane	7.73	6.98	-0.75
solubility in log(x) H2O	-1.92	-1.96	-0.04
solubility in log(x) Hexane	-3.36	-3.03	0.33



Other conformer (+0.45 kcal/mol) vs. conformer set

	conformer 2	conformer set	difference
μ in H2O (kcal/mol)	-0.78	-2.00	-1.22
μ in Hexane (kcal/mol)	-0.17	-0.54	-0.37
ln(γ) in H2O	5.33	4.51	-0.81
ln(γ) in Hexane	6.36	6.98	0.62
solubility in log(x) H2O	-2.31	-1.96	0.35
solubility in log(x) Hexane	-2.76	-3.03	-0.27

Example 2

LogP

logP (octanol / water partitioning)

Compound	# conf	all conf.	lowest E_COSMO	Exp.
Mandelicacid	6	1.23	0.57	0.74
oxalicacid	4	0.05	1.25	-0.81
1,2-diaminoethane	3	-1.11	-1.42	-1.31
2-aminoethanol	8	-1.10	-0.75	-1.31
ethyleneglycol	5	-1.31	-1.15	-1.36
2-fluorophenol	2	1.80	1.99	1.71
Total Error RMSE in log-units		**0.42**	**0.89**	

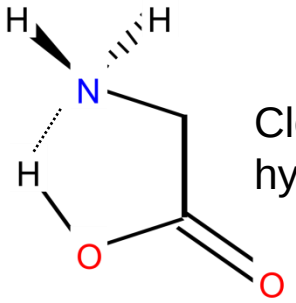
Exp.: http://www.cdc.gov/niosh/ipcsneng/neng0529.html
Hansch,C et al. (1995), Thor database

Conformer Relevance

Which conformers are required in COSMO*therm*

Importance criteria

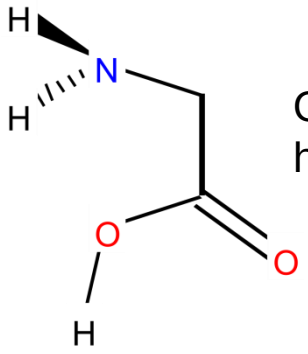
- Low energy in COSMO
- Open / closed intramolecular H-bonds
- High / low surface polarity forms



Closed intramolecular hydrogen bond

Negligible conformations

- High energy (> 5kcal/mol above lowest)
- Alkane tail changes
- Same μ as lower energy conformers



Open intramolecular hydrogen bond

Conformers and COSMO-RS

Summary

- COSMO-RS has been extended to use conformations (only in COSMO*therm*)
- Most relevant for $G_{solv}(H_2O)$ and partitioning
- High relevance for multifunctional molecules
- Errors are often small, but might easily reach > 1 kcal/mol for some systems