

# Simulação Computacional de Líquidos

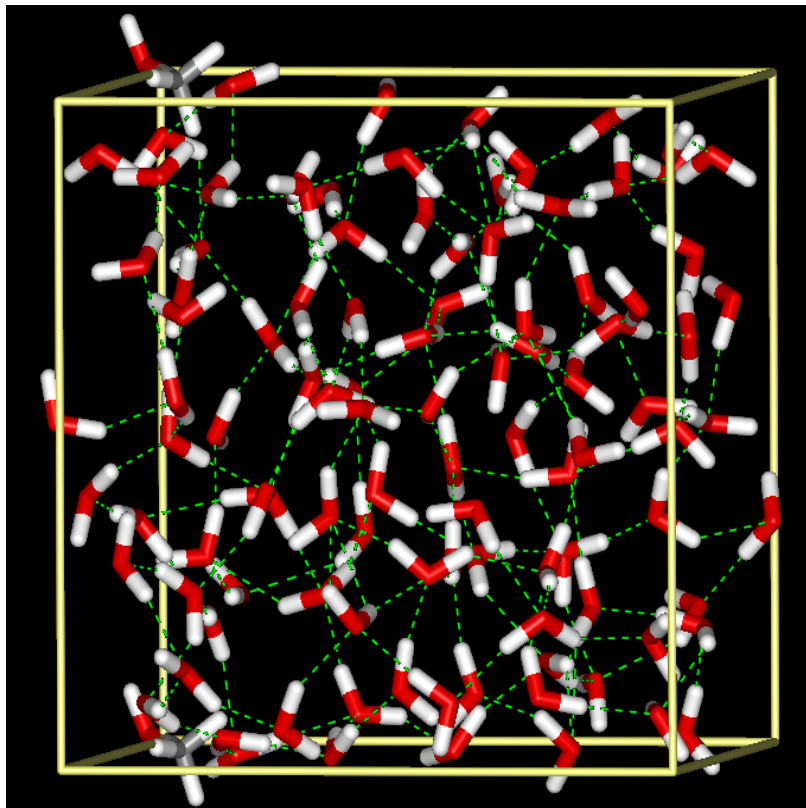
**Profa. Kaline Coutinho**

kaline@if.usp.br

Instituto de Física da USP

**Aula 6:** Como escolher o campo de força e os parâmetros:

- Artigos;
- Servidores: LigParGen;
- Programas: Antechamber do Ambertools.



# Campos de força: Função de energia típica

$$U = \sum_{bonds} \frac{1}{2} k_r (r - r_o)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_o)^2 + \sum_{torsions} \frac{V_n}{2} [1 + \cos(n\phi - \delta)] + \sum_{improper} \frac{V}{2} [1 + \cos(2\phi - 180)]$$

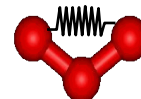
$$+ \sum_{elec} \frac{q_i q_j}{r_{ij}} + \sum_{LJ} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]$$

## ÁTOMOS LIGADOS

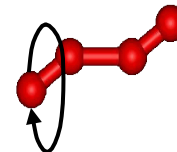
Estiramento da ligação



Abertura de ângulo



Rotação torcional



Torção imprópria (planares e tetraedrico)

## ÁTOMOS NÃO-LIGADOS

Interação eletrostática

Interação Lennard-Jones

# Potencial de átomos não ligados implementado no programas

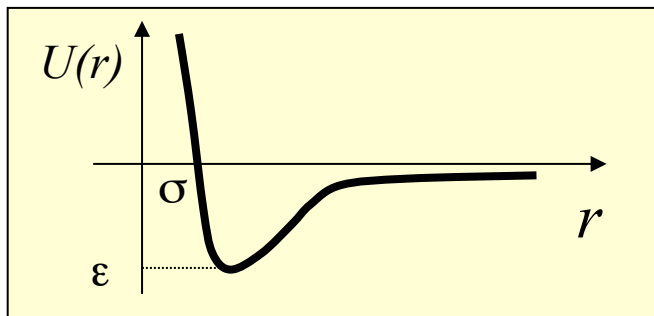
$$u_{\text{nb}} = \sum_i \sum_j f_{ij}^{\text{Q}} \frac{q_i q_j e^2}{r_{ij}} + f_{ij}^{\text{LJ}} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]$$

$f_{ij}^{\text{Q}} = f_{ij}^{\text{LJ}} = 0$  para as interações: 1-2 e 1-3

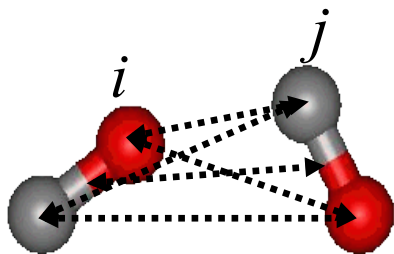
para as interações: 1-4

$f_{ij}^{\text{LJ}} = 0.5$  and  $f_{ij}^{\text{Q}} = 1/1.2$  for the AMBER

$f_{ij}^{\text{Q}} = f_{ij}^{\text{LJ}} = 0.5$  for the OPLS



para as interações: além 1-4  $f_{ij}^{\text{Q}} = f_{ij}^{\text{LJ}} = 1$



Regras de combinação

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$$

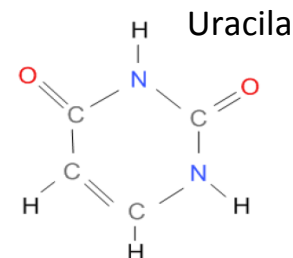
$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad \text{ou} \quad \sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}$$

# Levantamento bibliográfico

## OPLS Potential Functions for Nucleotide Bases. Relative Association Constants of Hydrogen-Bonded Base Pairs in Chloroform

*J. Am. Chem. Soc.* **1991**, *113*, 2810-2819

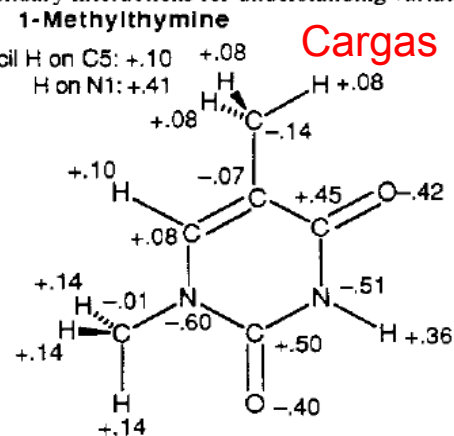
Julianto Pranata, Scott G. Wierschke, and William L. Jorgensen\*



**Abstract:** Potential functions in the OPLS format have been developed for the nucleotide bases and 2,6-diaminopyridine by fitting to the results of ab initio 6-31G(d) calculations for numerous base-water complexes. These potential functions yield dipole moments and base pair interaction energies in good agreement with available experimental data. The potential functions were tested further in Monte Carlo simulations with statistical perturbation theory to calculate the relative free energies of binding in chloroform for 9-methylguanine with 1-methylcytosine (G-C) versus 9-methyladenine with 1-methyluracil (A-U), and for G-C versus 1-methyluracil with 2,6-diaminopyridine (U-DAP). The calculations predict the G-C complex to be more stable than both the A-U and U-DAP complexes by about 5 kcal/mol. The similar stabilities for complexes like A-U and U-DAP are observed experimentally, though the quantitative enhancement in going to G-C appears to be exaggerated in the simulations. The large difference in association constants between G-C and the similarly triply hydrogen-bonded U-DAP is traced to the gas-phase interaction energies, which favors G-C by about 10 kcal/mol. This in turn is caused by the different arrangement of hydrogen bond donor and acceptor sites in the two complexes, which leads to secondary electrostatic interactions that disfavor U-DAP relative to G-C. The general importance of such secondary interactions for understanding variations in association is discussed.

**Table I.** OPLS Lennard-Jones Parameters for Nucleotide Bases and DAP

atom	$\sigma$ , Å	$\epsilon$ , 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



# Principais resultados do artigo publicado

HF/6-31G(d)

## Uracil–Water Complexes

OPLS values in parentheses

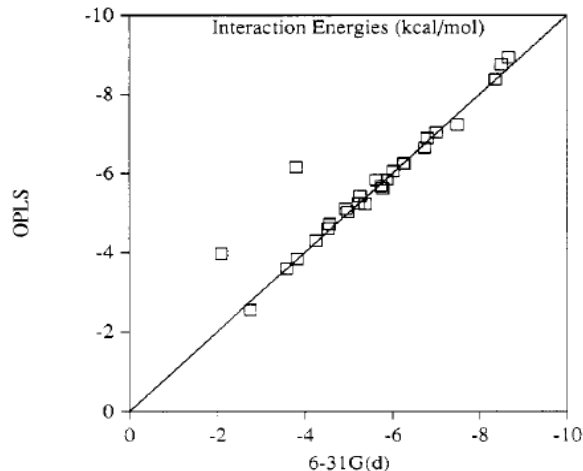
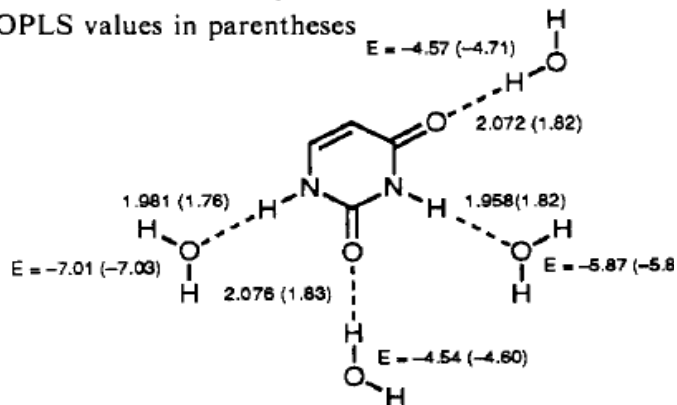


Figure 4. Comparison between ab initio 6-31G(d) and OPLS interaction energies.

Table II. Dipole Moments (D) for Nucleotide Bases

base	OPLS	exp <sup>a</sup>	Singh and Kollman <sup>b</sup>	
			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

<sup>a</sup> Reference 29. <sup>b</sup> Reference 30.

# Comparação: OPLS x QM

Geometria otimizada obtida com nível de cálculo B3LYP/6-31G\*, cargas fitadas no nível B3LYP/6-311+G\* usando o esquema CHELPG, parâmetros LJ extraídos de J. Am. Chem. Soc. **1991**, 113, 2810-2819.

QM

Z	x(Å)	y(Å)	z(Å)	q (e-)	ε(kcal/mol)	σ (Å)		q(e-)(PCM)
7	0.042462	-0.983289	0.000205	-0.666997	0.170	3.25	(N em Nucleotídeo)	-0.692748
6	-1.212503	-0.397468	-0.000316	0.843344	0.105	3.75	(C em C=O em Nucleotídeo)	0.907864
7	-1.186964	0.982065	0.000036	-0.519467	0.170	3.25	(N em Nucleotídeo)	-0.546892
6	-0.022526	1.715839	0.000353	0.167021	0.080	3.50	(C em Nucleotídeo)	0.228041
6	1.204718	1.114048	0.000093	-0.482111	0.080	3.50	(C em Nucleotídeo)	-0.536146
6	1.284574	-0.336891	-0.000018	0.860565	0.105	3.75	(C em C=O em Nucleotídeo)	0.916752
1	0.053387	-2.019947	0.000777	0.365781	0.000	0.00	(H ligado a N em Nucleotídeo)	0.384420
8	2.333260	-1.007489	-0.000391	-0.609804	0.210	2.96	(O em Nucleotídeo)	-0.699299
1	2.125366	1.703892	0.000077	0.179905	0.050	2.50	(H ligado a C em Nucleotídeo)	0.194816
1	-0.152801	2.804437	0.000647	0.127071	0.050	2.50	(H ligado a C em Nucleotídeo)	0.149355
1	-2.103434	1.460922	-0.000340	0.348640	0.000	0.00	(H ligado a N em Nucleotídeo)	0.383165
8	-2.262834	-1.056749	-0.000049	-0.613948	0.210	2.96	(O em Nucleotídeo)	-0.689329

Dipolo Quântico: 4.6251 D

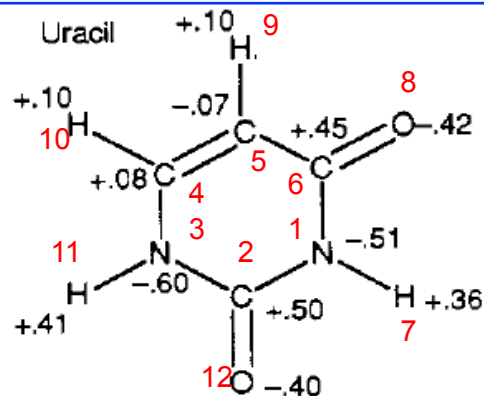
Dipolo Fitado: 4.6440 D

Dipolo Quântico: 6.0322 D

Dipolo Fitado: 6.0264 D

**Table I.** 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



# Campo de Força

A escolha dos parâmetros é crucial.

- Usualmente os parâmetros de solventes, aminoácidos e ácidos nucleicos, açúcares e carboidratos são muito bons devido a grande quantidade de resultados experimentais. É recomendado pegar a parametrização completa destes sistemas.

- Mas e os solutos (inibidores, sensores, anestésicos, etc.) ?

Em geral, quando os resultados experimentais não estão disponíveis: para o potencial intramolecular e intermolecular (parâmetros Lennard-Jones) são considerados transferíveis, entretanto as cargas atômicas são calculadas usando mecânica quântica (QM  $\Rightarrow$  HF/6-31G\* Pop=MK ou ChelpG).

Nós recomendamos para pesquisa científica:

QM  $\Rightarrow$  Método: MP2 ou B3LYP; Base: aug-cc-pVDZ ou cc-pVDZ; com Density=Current Pop= ChelpG SCRF=PCM

# Cuidado com os solventes

## Solvation and Conformation of Methanol in Water<sup>1</sup>

William L. Jorgensen\* and Jeffrey D. Madura

```
C:\Users\Kaline\Documents\Pesquisa\Simulacoes\Solvente\MethanolinWater.txt *
*
1
6   metanol in water OPLS (JACS 105, 1407 (1983))
1 8   -1.15888      0.78077      -0.00000     -0.620      0.161  3.126
2 1   -2.06398      1.10076      -0.00000      0.430      0.000  0.000
3 6   -1.15888     -0.64923     -0.00000     -0.110      0.039  3.879
4 1   -0.13122     -1.01256     -0.00000      0.100      0.039  2.442
4 1   -1.67271     -1.01256      0.88999      0.100      0.039  2.442
4 1   -1.67271     -1.01256     -0.88999      0.100      0.039  2.442
$end

C:\Users\Kaline\Documents\Pesquisa\Simulacoes\Solvente\methanol.txt
*
1   density= 0.77g/cm3
6   methanol liquid from OPLS( JPC 90,1276 (1986) )
1 8   1.837572     -0.054784     -0.590399     -0.700  0.170  3.070
2 1   1.233853      0.719007     -0.539438      0.435  0.000  0.000
3 6   2.743241      0.010645      0.509310      0.265  0.207  3.775
4 1   3.413692      0.875275      0.421168      0.000  0.000  0.000
4 1   2.220572      0.064728      1.474688      0.000  0.000  0.000
4 1   3.346387     -0.900276      0.486349      0.000  0.000  0.000
$end
```

## Optimized Intermolecular Potential Functions for Liquid Alcohols

William L. Jorgensen

**Atenção:** Podem existir vários modelos para o mesmo solvente. Escolha o que reproduzir as propriedades experimentais mais importantes para seu trabalho.

**Exemplo:** Metanol tem parâmetros diferentes quando for soluto e quando for solvente.

Uma propriedade muito importante que todo solvente simulado deve descrever é a densidade com menos que 2-4% de erro.



# Gerando topologias OPLS no servidor LigParGen:

<http://zarbi.chem.yale.edu/ligpargen/>

No site do servidor LigPanGen, fazer o upload do arquivo com a geometria da molécula em PDF selecionar passos de otimização (0 se já estiver otimizada), métodos de cargas (ver sugestão na figura), submeter e fazer o download dos arquivos TOP e GRO do GROMACS.

## Step 1: Input structure

### SMILES

Enter SMILES Code

**OR** upload MOL / PDB file (Structures **MUST** include all hydrogens)

Escolher Arquivo alanina.pdb

## Step 2: Options

Molecule Optimization Iterations 0

Select charge model:

1.14\*CM1A-LBCC (Neutral molecules)

1.14\*CM1A<sup>1</sup> (Neutral or Charged molecules)

Molecule charge 0

Submit Molecule

Sample Benzene

<sup>1</sup> For charged molecules, CM1A charges are NOT scaled by a factor 1.14

# Como gerar o arquivo PDB

Se já tiver uma geometria otimizada com cálculo quântico (mol-opt.xyz) pode usar o programa openbabel (download livre). Na VM usar o comando:

```
$ sudo apt-get install openbabel
```

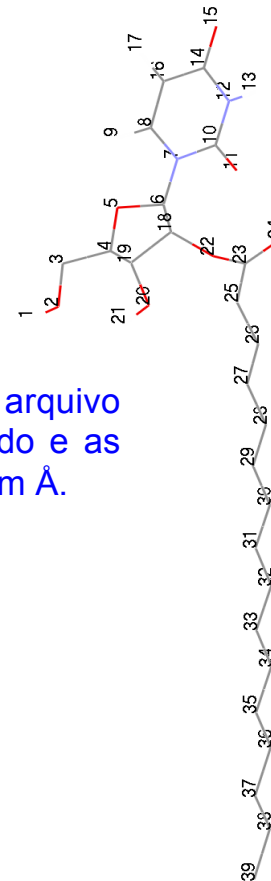
Depois de instalado gerar um arquivo no formato PDB a partir do arquivo xyz ou outros formatos.

```
$ obabel -ixyz mol-opt.xyz -opdb mol-opt.pdb
```

Se não, vários programas gráficos podem gerar a molécula já no formato PDB

# Exemplo de arquivo PDB: molécula Uradinapalmitoil (UP2)

```
TITLE      Protein
REMARK    THIS IS A SIMULATION BOX
CRYST1   40.000   40.000   40.000   90.00   90.00   90.00 P 1
MODEL     1
ATOM      1  H5* UP2      1      8.937   1.721  19.728   1.00   0.00
ATOM      2  O5* UP2      1      8.057   1.314  19.995   1.00   0.00
ATOM      3  C5* UP2      1      7.699   1.255  21.392   1.00   0.00
ATOM      4  C4* UP2      1      6.619   0.207  21.669   1.00   0.00
ATOM      5  O4* UP2      1      6.239   0.093  23.047   1.00   0.00
ATOM      6  C1* UP2      1      5.096  -0.763  22.947   1.00   0.00
ATOM      7  N1  UP2      1      4.342  -0.799  24.230   1.00   0.00
ATOM      8  C6  UP2      1      4.054   0.378  24.934   1.00   0.00
ATOM      9  H6  UP2      1      4.417   1.333  24.561   1.00   0.00
ATOM     10  C2  UP2      1      3.940  -2.032  24.772   1.00   0.00
ATOM     11  O2  UP2      1      4.172  -3.076  24.161   1.00   0.00
ATOM     12  N3  UP2      1      3.255  -2.072  25.994   1.00   0.00
ATOM     13  H3  UP2      1      2.987  -2.951  26.381   1.00   0.00
ATOM     14  C4  UP2      1      2.968  -0.876  26.687   1.00   0.00
ATOM     15  O4  UP2      1      2.349  -0.903  27.746   1.00   0.00
ATOM     16  C5  UP2      1      3.371   0.343  26.148   1.00   0.00
ATOM     17  H5  UP2      1      3.156   1.266  26.690   1.00   0.00
ATOM     18  C2* UP2      1      4.277  -0.229  21.774   1.00   0.00
ATOM     19  C3* UP2      1      5.312   0.518  20.948   1.00   0.00
ATOM     20  O3* UP2      1      5.280   0.012  19.596   1.00   0.00
ATOM     21  H3* UP2      1      6.083   0.366  19.099   1.00   0.00
ATOM     22  O2* UP2      1      3.713  -1.293  20.962   1.00   0.00
ATOM     23  C21 UP2      1      2.476  -1.316  20.445   1.00   0.00
ATOM     24  O22 UP2      1      1.584  -1.901  21.055   1.00   0.00
ATOM     25  C22 UP2      1      2.256  -0.626  19.148   1.00   0.00
ATOM     26  C23 UP2      1      2.463  -1.530  17.929   1.00   0.00
ATOM     27  C24 UP2      1      2.249  -0.721  16.643   1.00   0.00
ATOM     28  C25 UP2      1      2.489  -1.571  15.394   1.00   0.00
ATOM     29  C26 UP2      1      2.308  -0.714  14.140   1.00   0.00
ATOM     30  C27 UP2      1      2.576  -1.521  12.874   1.00   0.00
ATOM     31  C28 UP2      1      2.415  -0.627  11.639   1.00   0.00
ATOM     32  C29 UP2      1      2.691  -1.398  10.348   1.00   0.00
ATOM     33  C210 UP2     1      2.530  -0.479   9.139   1.00   0.00
ATOM     34  C211 UP2     1      2.818  -1.233   7.836   1.00   0.00
ATOM     35  C212 UP2     1      2.665  -0.309   6.640   1.00   0.00
ATOM     36  C213 UP2     1      2.955  -1.051   5.332   1.00   0.00
ATOM     37  C214 UP2     1      2.803  -0.113   4.131   1.00   0.00
ATOM     38  C215 UP2     1      3.087  -0.849   2.817   1.00   0.00
ATOM     39  C216 UP2     1      2.941   0.083   1.622   1.00   0.00
TER
ENDMDL
```



**ATENÇÃO:** o arquivo  
\*.pdb é formatado e as  
distâncias são em Å.

# Formato do arquivo PDB dentro do bloco MODEL ... ENDMDL:

## Record Format

COLUMNS	DATA TYPE	FIELD	DEFINITION
1 - 6	Record name	"ATOM "	
7 - 11	Integer	serial	Atom serial number.
13 - 16	Atom	name	Atom name.
17	Character	altLoc	Alternate location indicator.
18 - 20	Residue name	resName	Residue name.
22	Character	chainID	Chain identifier.
23 - 26	Integer	resSeq	Residue sequence number.
27	AChar	iCode	Code for insertion of residues.
31 - 38	Real(8.3)	x	Orthogonal coordinates for X in Angstroms.
39 - 46	Real(8.3)	y	Orthogonal coordinates for Y in Angstroms.
47 - 54	Real(8.3)	z	Orthogonal coordinates for Z in Angstroms.
55 - 60	Real(6.2)	occupancy	Occupancy.
61 - 66	Real(6.2)	tempFactor	Temperature factor.
77 - 78	LString(2)	element	Element symbol, right-justified.
79 - 80	LString(2)	charge	Charge on the atom.

```

1 2 3 4 5 6 7 8
123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890
MODEL
ATOM 1 N ALA A 1 11.104 6.134 -6.504 1.00 0.00 N
ATOM 2 CA ALA A 1 11.639 6.071 -5.147 1.00 0.00 C
...
...
ATOM 293 1HG GLU A 18 -14.861 -4.847 0.361 1.00 0.00 H
ATOM 294 2HG GLU A 18 -13.518 -3.769 0.084 1.00 0.00 H
TER 295 GLU A 18
ENDMDL
```

# Gerando topologias AMBER no servidor Antechamber:

- Ambertools é um conjunto de programas que auxiliam o programa AMBER (<https://ambermd.org/GetAmber.php#ambertools>). É preciso se cadastrar para baixar. Nele pode ser encontrado o programa Antechamber que gera topological de moléculas através de comandos de linha.
- Para mais informações do Antechamber ver o tutorial: <http://ambermd.org/tutorials/basic/tutorial4b/>



The Amber Project  
Chemistry through a Computational Lens

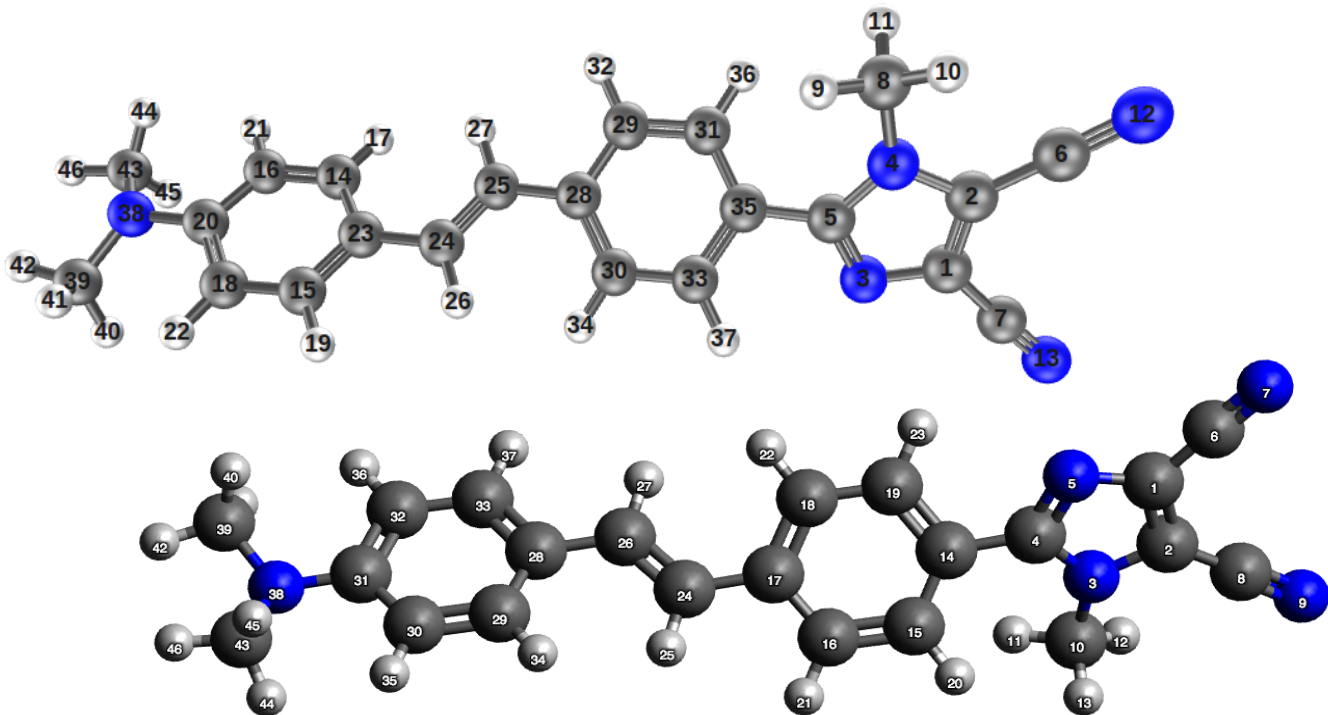
AmberTools20   Amber20   Manuals   Tutorials   Force Fields   Contacts   History

**How to obtain AmberTools20**

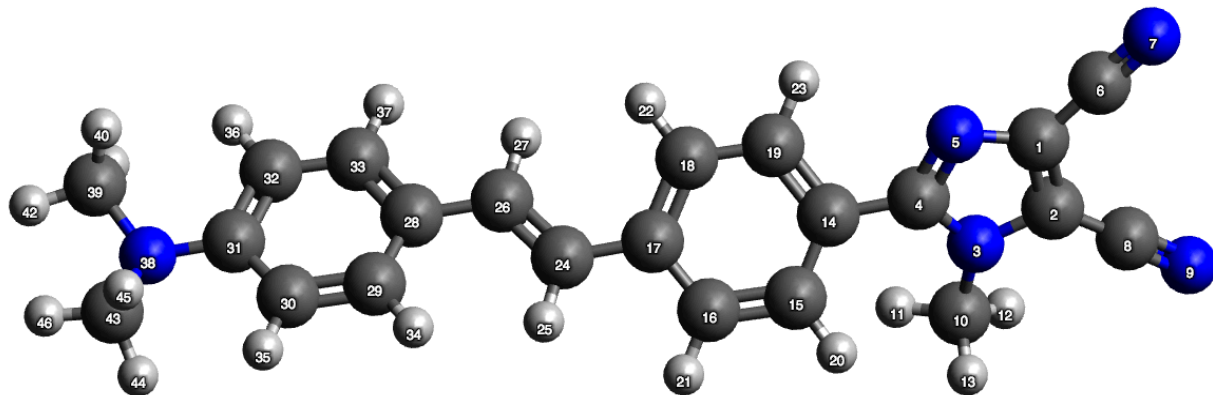
AmberTools is a free, useful standalone package and a prerequisite for installing Amber itself. The AmberTools suite is free of charge, and its components are mostly released under the GNU General Public License (GPL). A few components are included that are in the public domain or which have other, open-source, licenses. The *libpander* and *libpbsa* libraries use the LGPL license.

Useful links:  
Amber Home  
Download Amber

# Cuidado com a numeração das átomos antes de usar os servidores:



O ideal é ir numerando os grupo que se conectam seguindo uma ordem que o átomo com numeração maior deve estar conectado a um de numeração menor. A numeração do átomo corresponde a posição na linha.



46

dci05c OPT(MP2/CC-PVDZ) q(Density Pop=MK)

C	-6.110097	1.000568	-0.284350	C	-2.692531	-0.056802	-0.211635	C	3.967285	0.238223	0.154977
C	-6.296048	-0.297657	0.226960	C	-2.084661	-1.259750	-0.634174	C	4.638971	-0.555523	-0.804078
N	-5.032299	-0.841768	0.310437	C	-0.688063	-1.356785	-0.698395	C	6.031721	-0.674609	-0.810120
C	-4.149280	0.115995	-0.150528	C	0.145681	-0.267260	-0.352356	C	6.838043	-0.005227	0.151638
N	-4.782484	1.243730	-0.508876	C	-0.480754	0.948283	0.023118	C	6.166029	0.820852	1.091298
C	-7.140258	1.959110	-0.547595	C	-1.872424	1.052105	0.101300	C	4.771192	0.930786	1.088534
N	-8.012313	2.740161	-0.756966	H	-2.698179	-2.109137	-0.951911	H	4.068040	-1.070839	-1.584256
C	-7.467294	-1.001865	0.620789	H	-0.228234	-2.295269	-1.029731	H	6.492535	-1.290827	-1.584998
N	-8.434715	-1.606200	0.961451	H	0.132292	1.829021	0.240720	H	6.729140	1.385695	1.837068
C	-4.730247	-2.150975	0.887887	H	-2.348524	1.996309	0.383282	H	4.289837	1.574736	1.834611
H	-3.719578	-2.120236	1.316122	C	1.602932	-0.427992	-0.413022	N	8.224741	-0.165195	0.177873
H	-5.464648	-2.362249	1.678672	H	1.964182	-1.297872	-0.977466	C	8.996888	0.826873	0.912001
H	-4.786457	-2.938486	0.120598	C	2.509883	0.377008	0.211500	H	8.850648	1.860198	0.533032
				H	2.137619	1.191103	0.849171	H	8.732306	0.810085	1.981008
								H	10.063304	0.569857	0.833701
								C	8.861600	-0.685429	-1.023616
								H	8.508799	-1.706332	-1.238755
								H	8.679216	-0.057053	-1.920596
								H	9.945773	-0.743395	-0.848506