

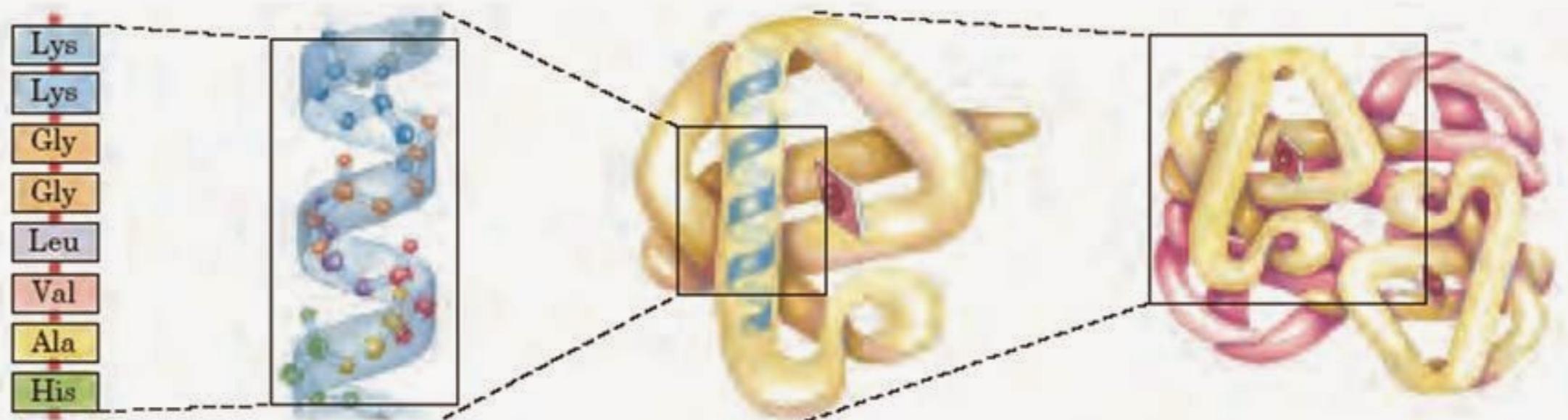
# Trabajando con Moléculas, ligandos y proteínas.

## Representación, visualización y modelamiento molecular (3D).

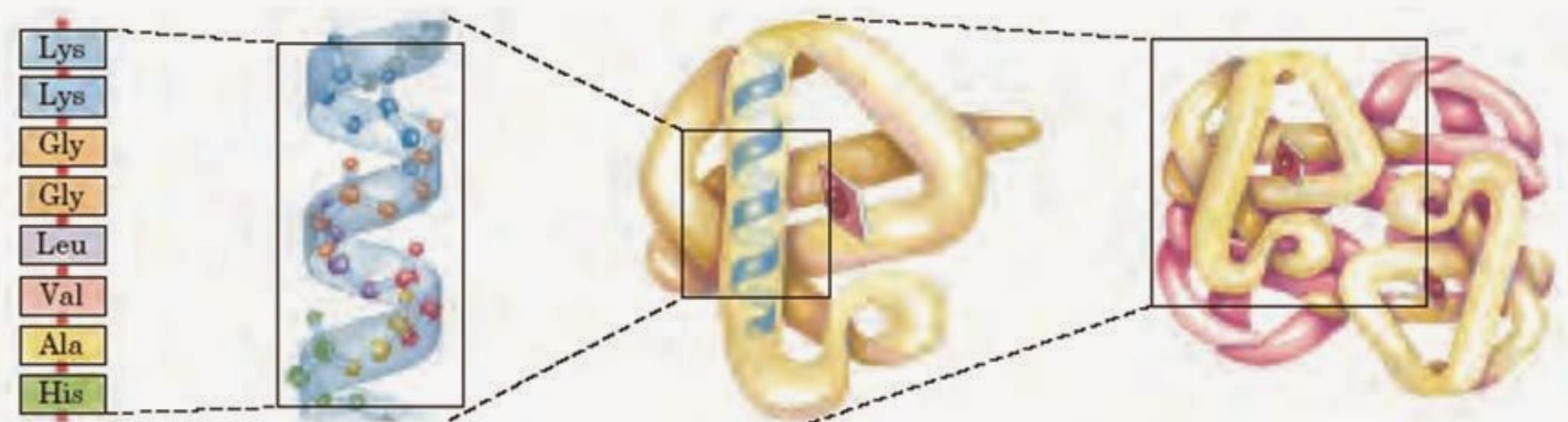
### Representación, visualización y modelamiento molecular (3D)



# En resumen, la estructura de una proteína.



# En resumen, la estructura de una proteína.



## Primaria

Combinación ilimitada de aminoácidos.

Unión Peptídica

Secuencia

## Secundaria

Hélice

Hoja Plegada

Puente de Hidrógeno

Conformación

## Terciaria

Globular

Fibrosa

Puente de Hidrógeno,  
Interacciones hidrofóbicas,  
salinas, electrostáticas.

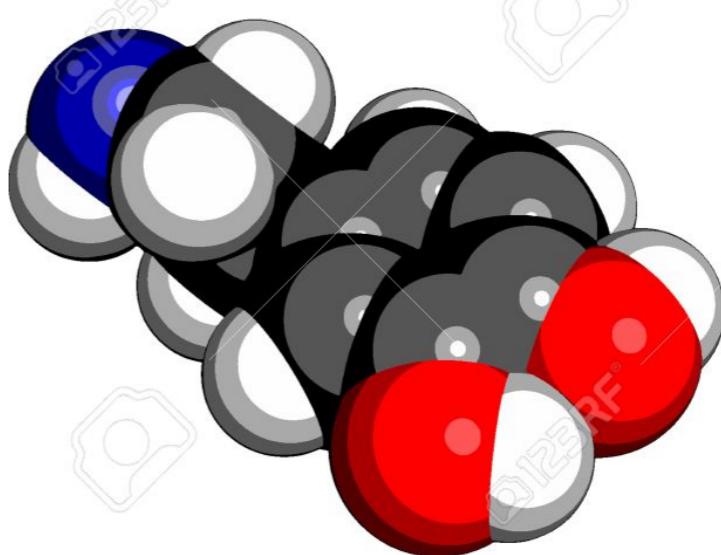
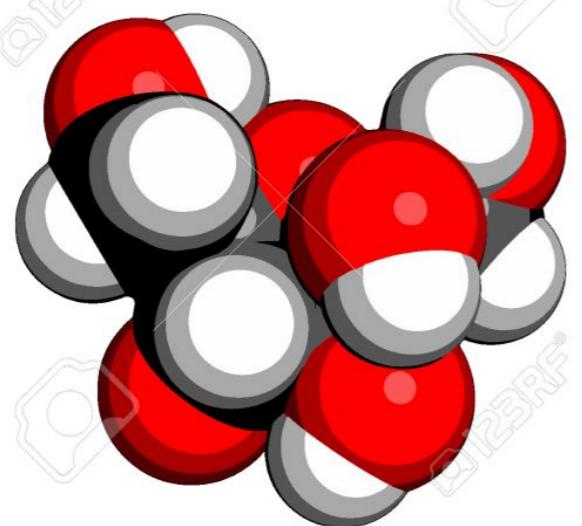
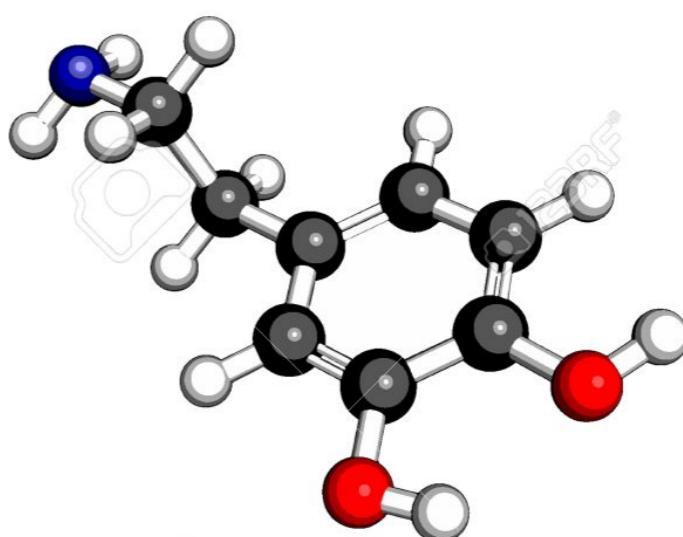
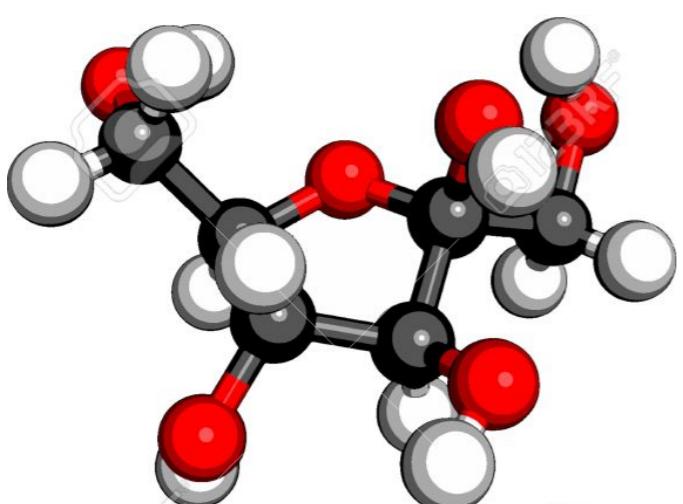
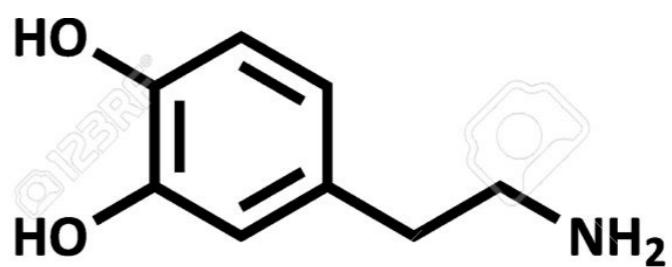
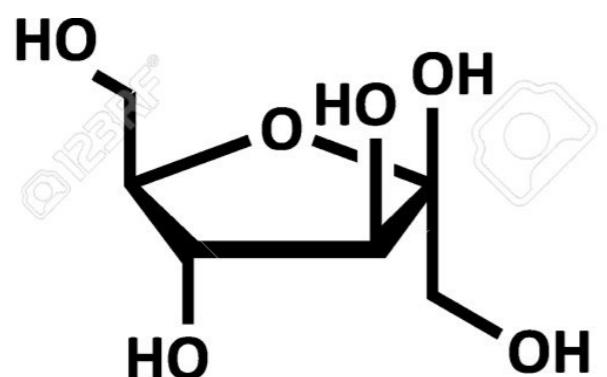
## Cuaternaria

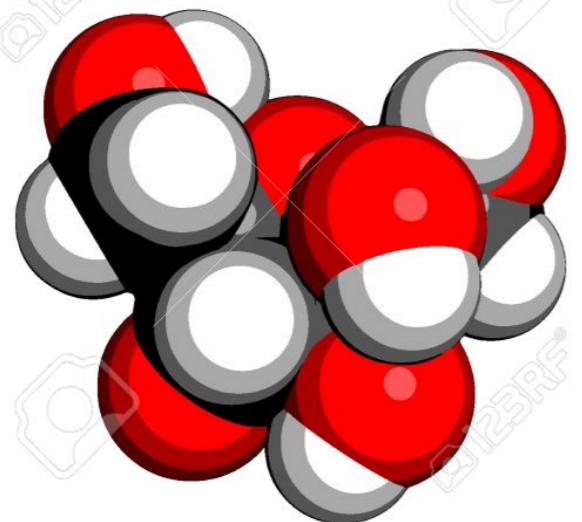
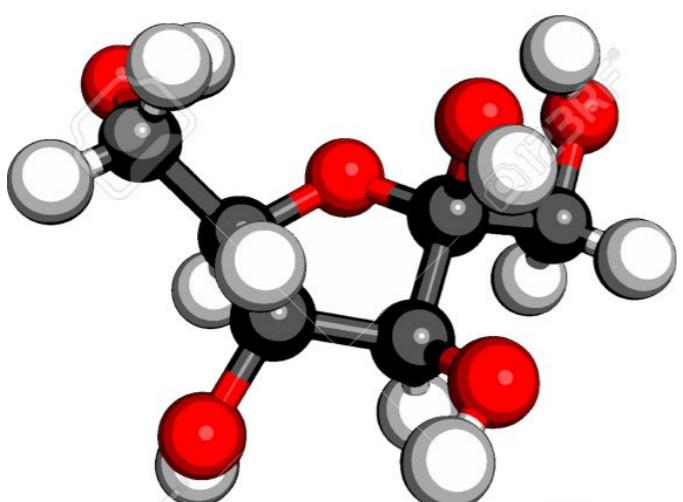
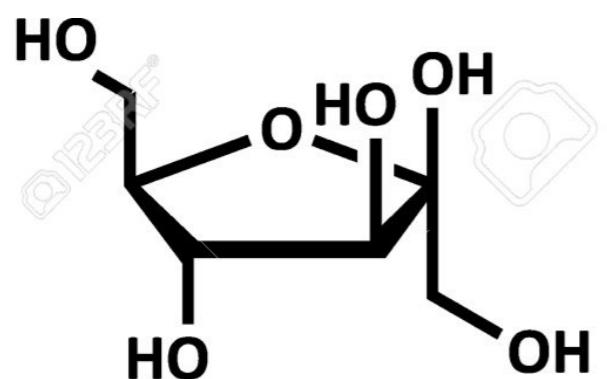
Subunidades iguales

Subunidades distintas

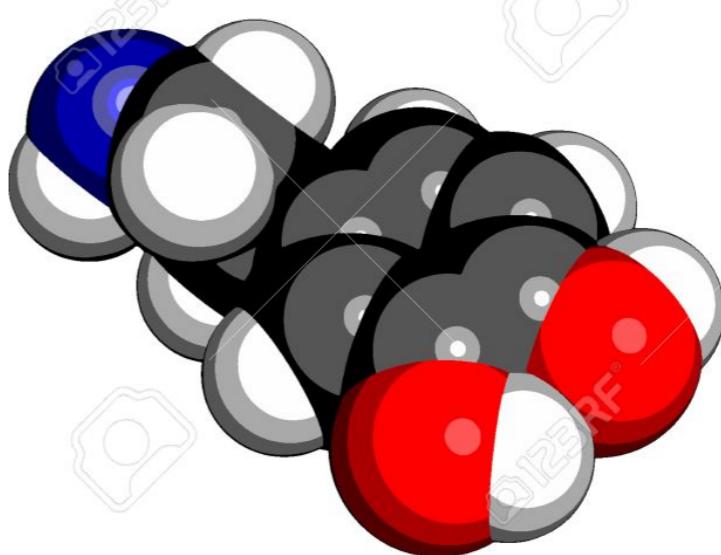
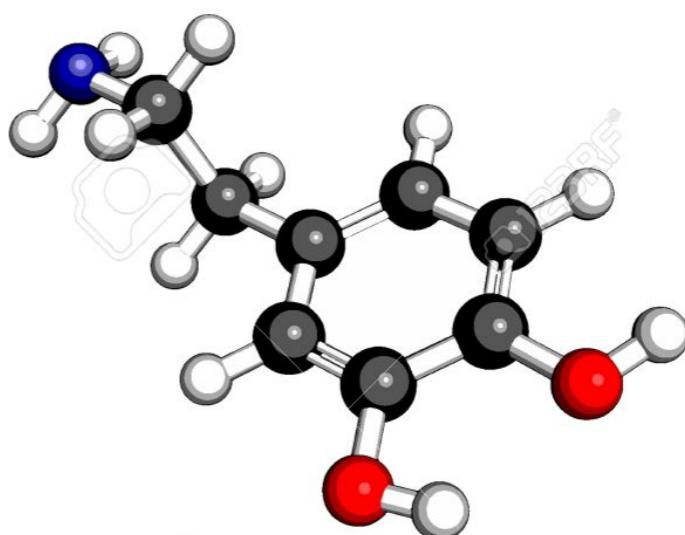
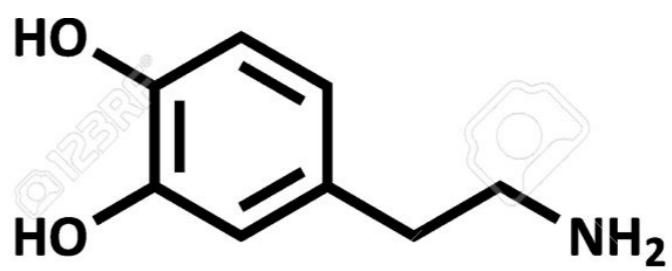
Fuerzas diversas no covalentes.

Asociación 62





Fructosa

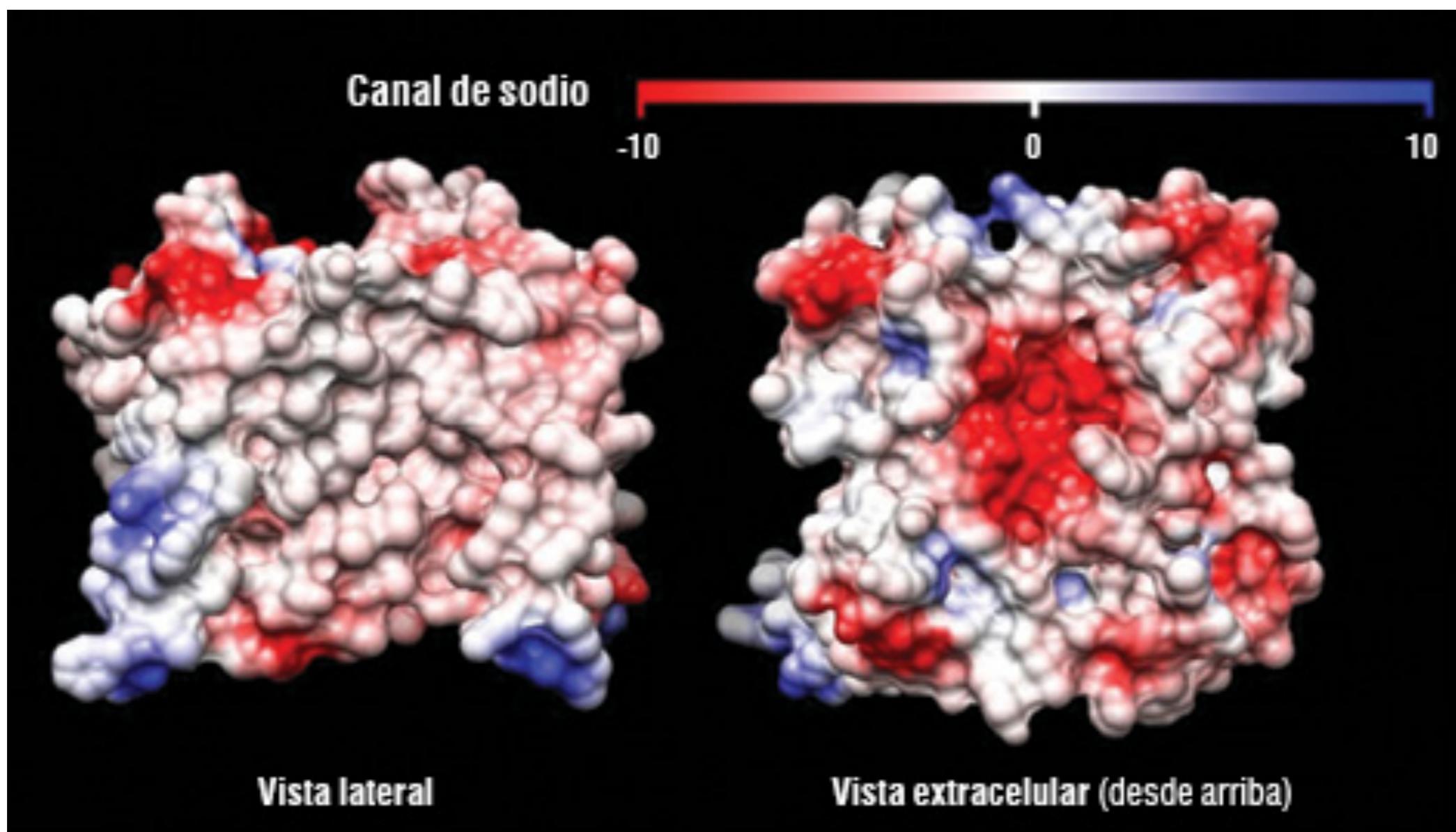


Dopamina

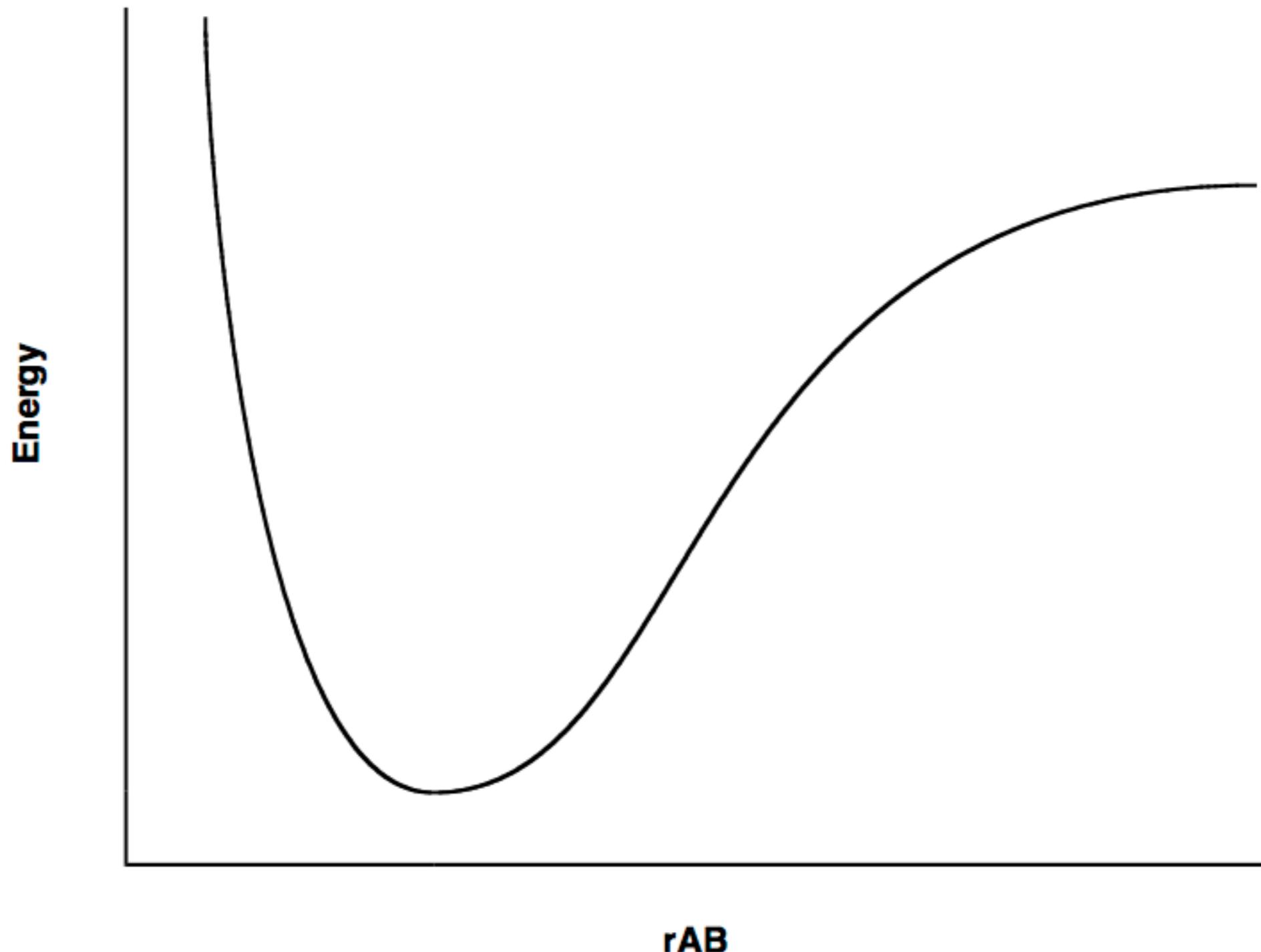
# Superficie de Energía Potencial (SEP)

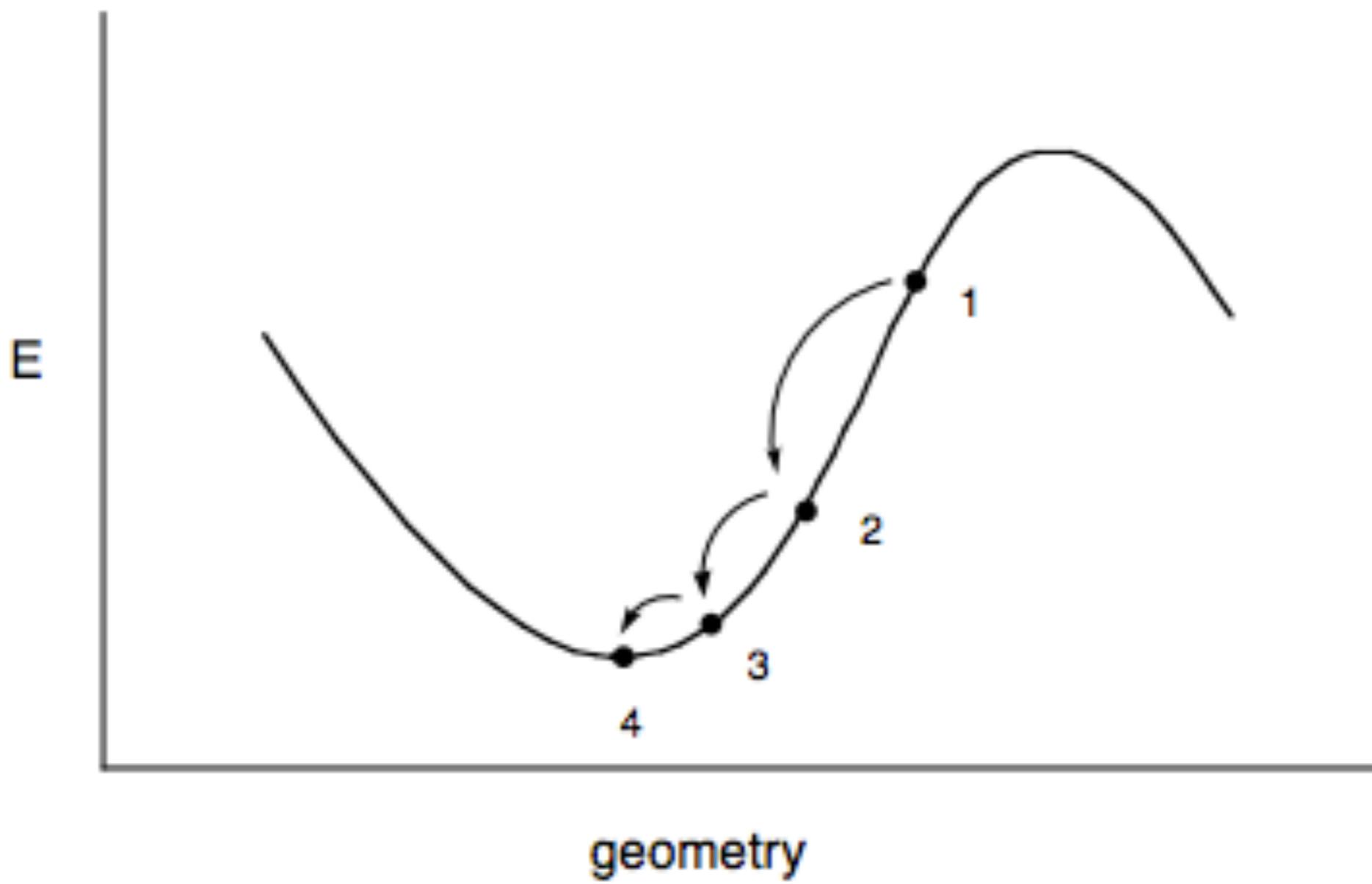
Describe:

- Una molécula o conjunto de moléculas con una composición atómica constante o también un sistema donde tiene lugar una reacción química.
- Las energías relativas para distintos conformómeros.



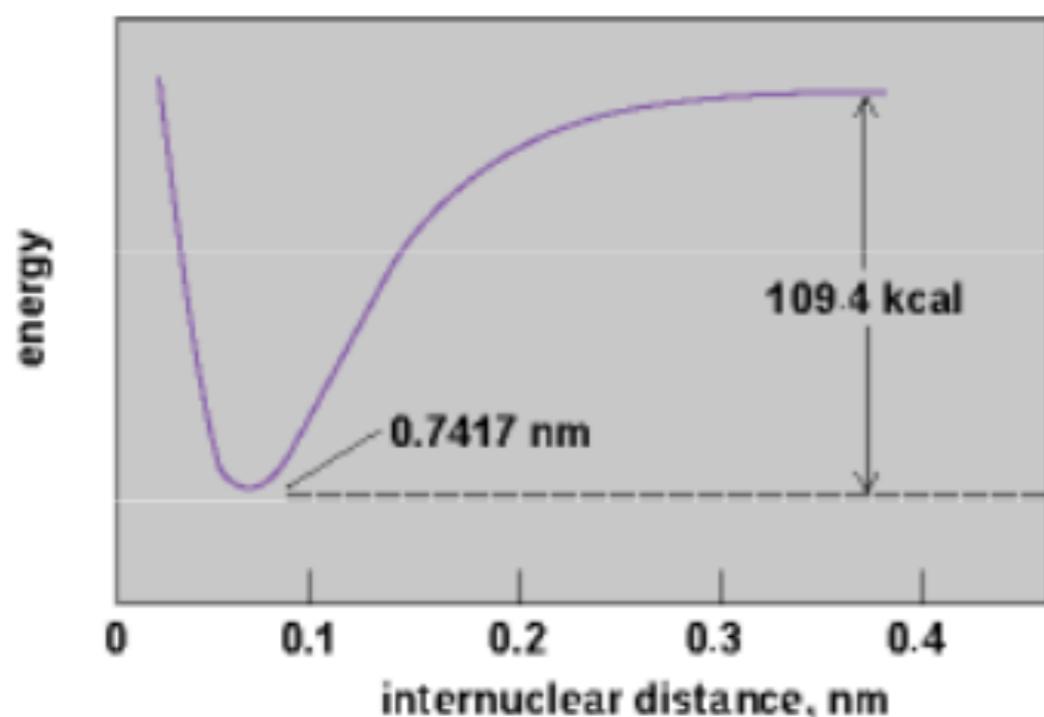
## Standard Diatomic Bond Stretch



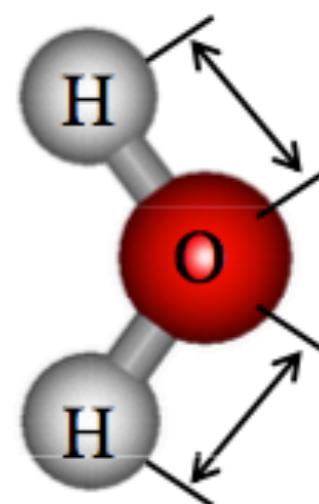
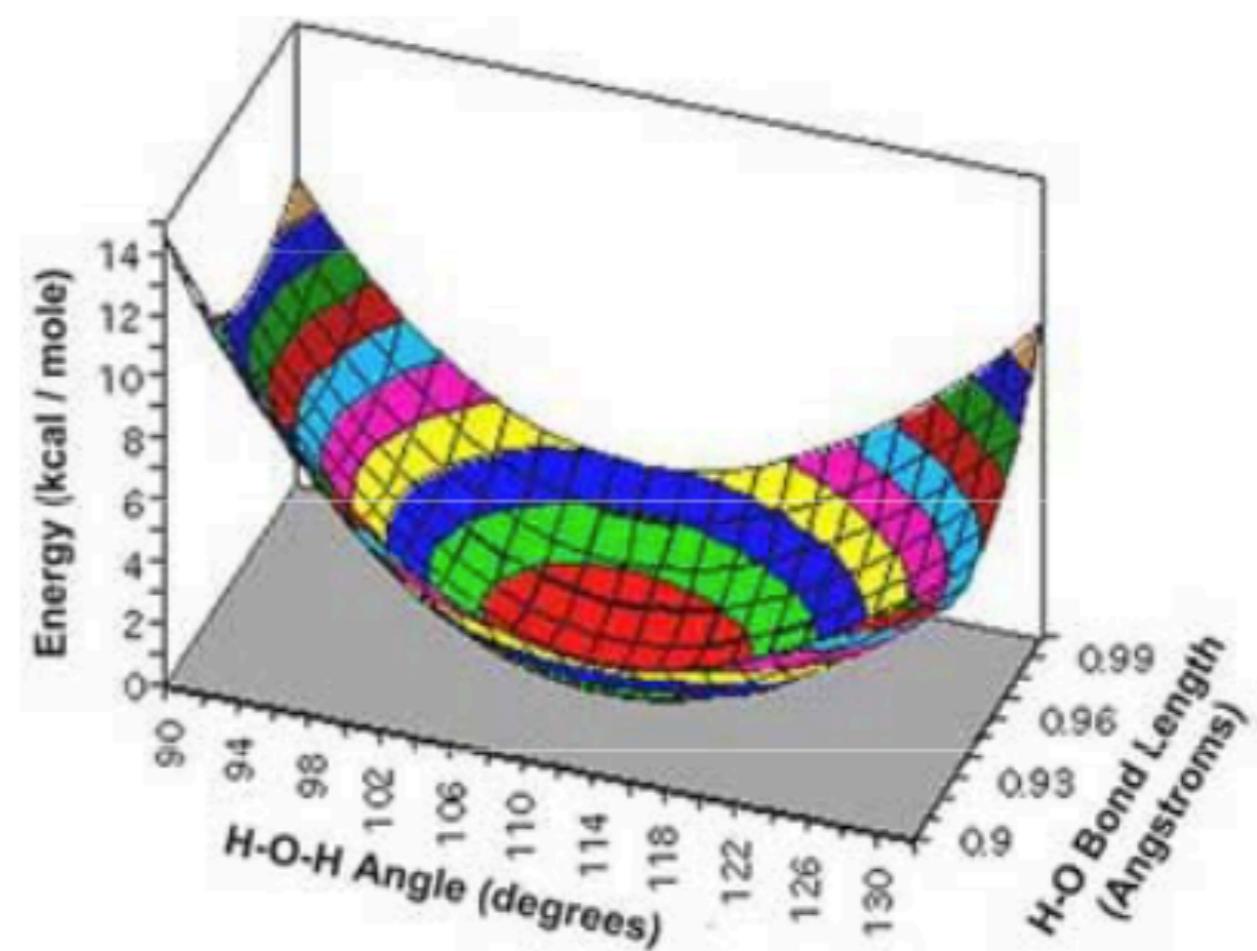


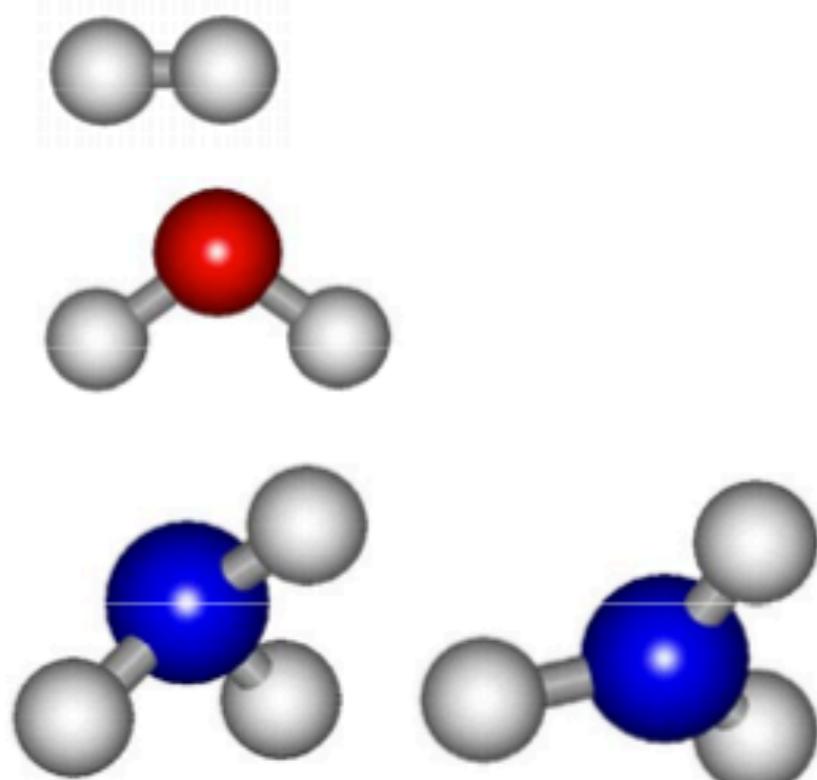
**Figure 1.** The process of energy minimization changes the geometry of the molecule in a step-wise fashion until a minimum is reached.

$\text{H}_2$



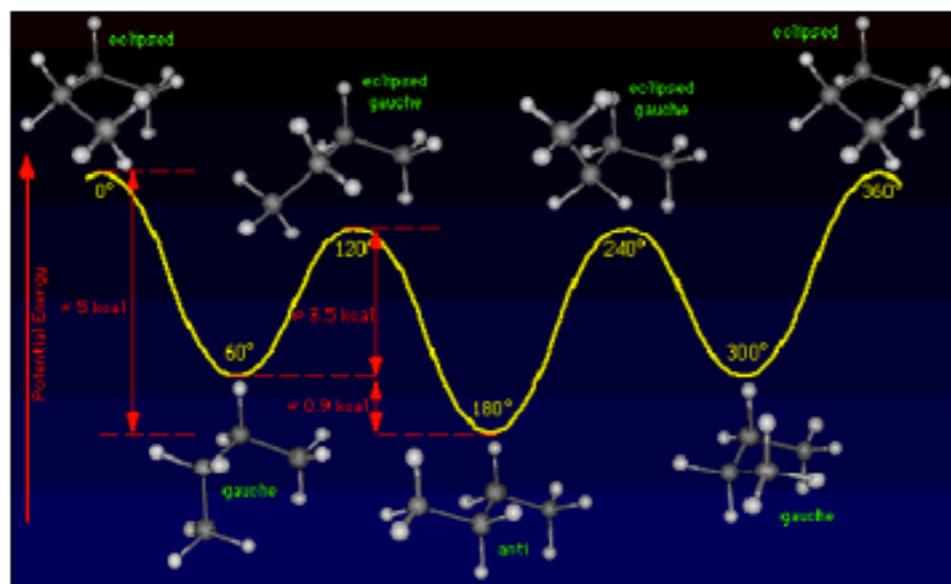
$\text{H}_2\text{O} - 3\text{N}-6=3$





- One configuration is known for  $H_2$
- One configuration is known for  $H_2O$
- The planar and pyramidal configurations are known for  $NH_3$

Possible Conformations ( $3^n$ ) for linear alkanes  $CH_3(CH_2)_{n+1}CH_3$

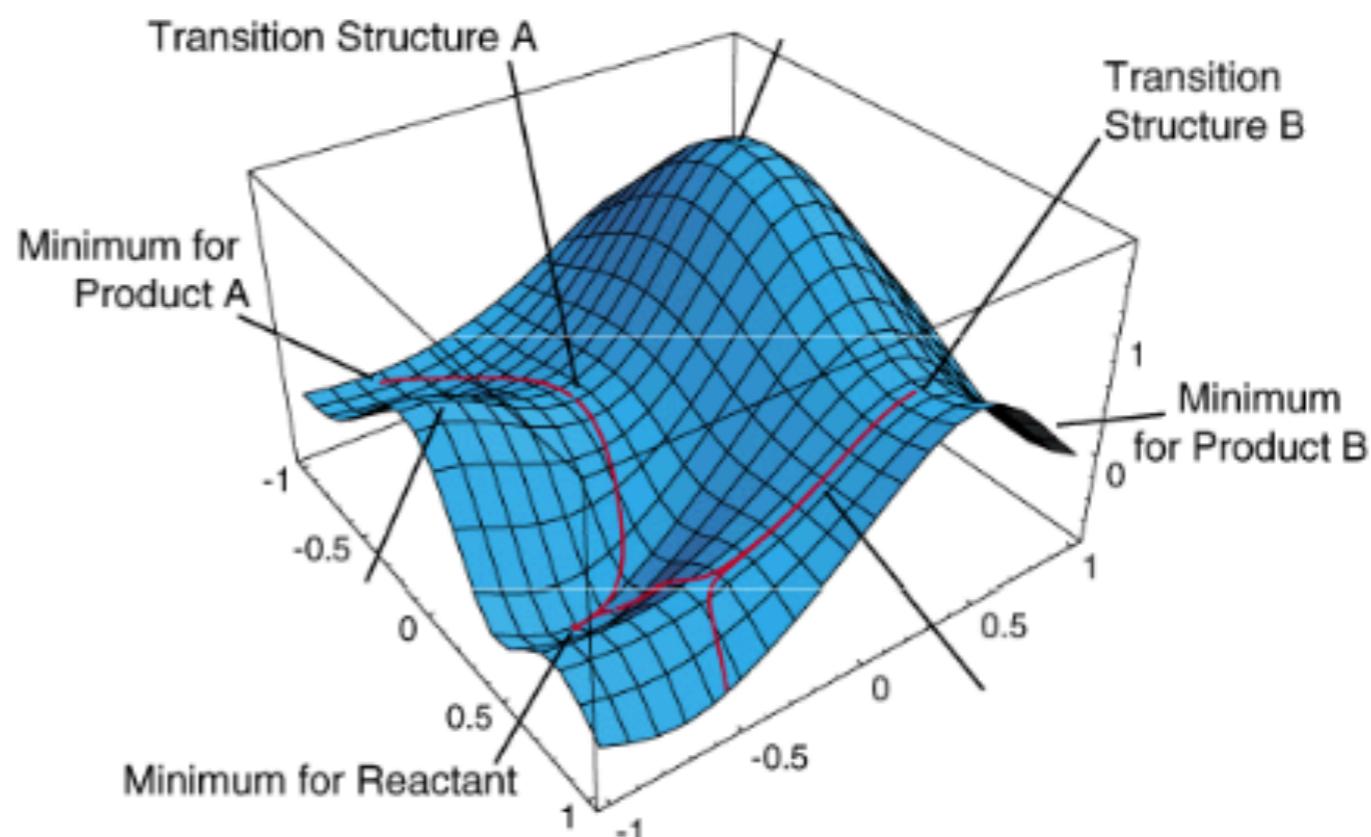


$n = 1$	3
$n = 2$	9
$n = 5$	243
$n = 10$	59,049
$n = 15$	14,348,907

# Optimization/Goals

- Find the **Local Minimum** Structure
- Find the **Global Minimum** Structure
- Find the **Transition State** Structure

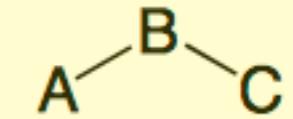
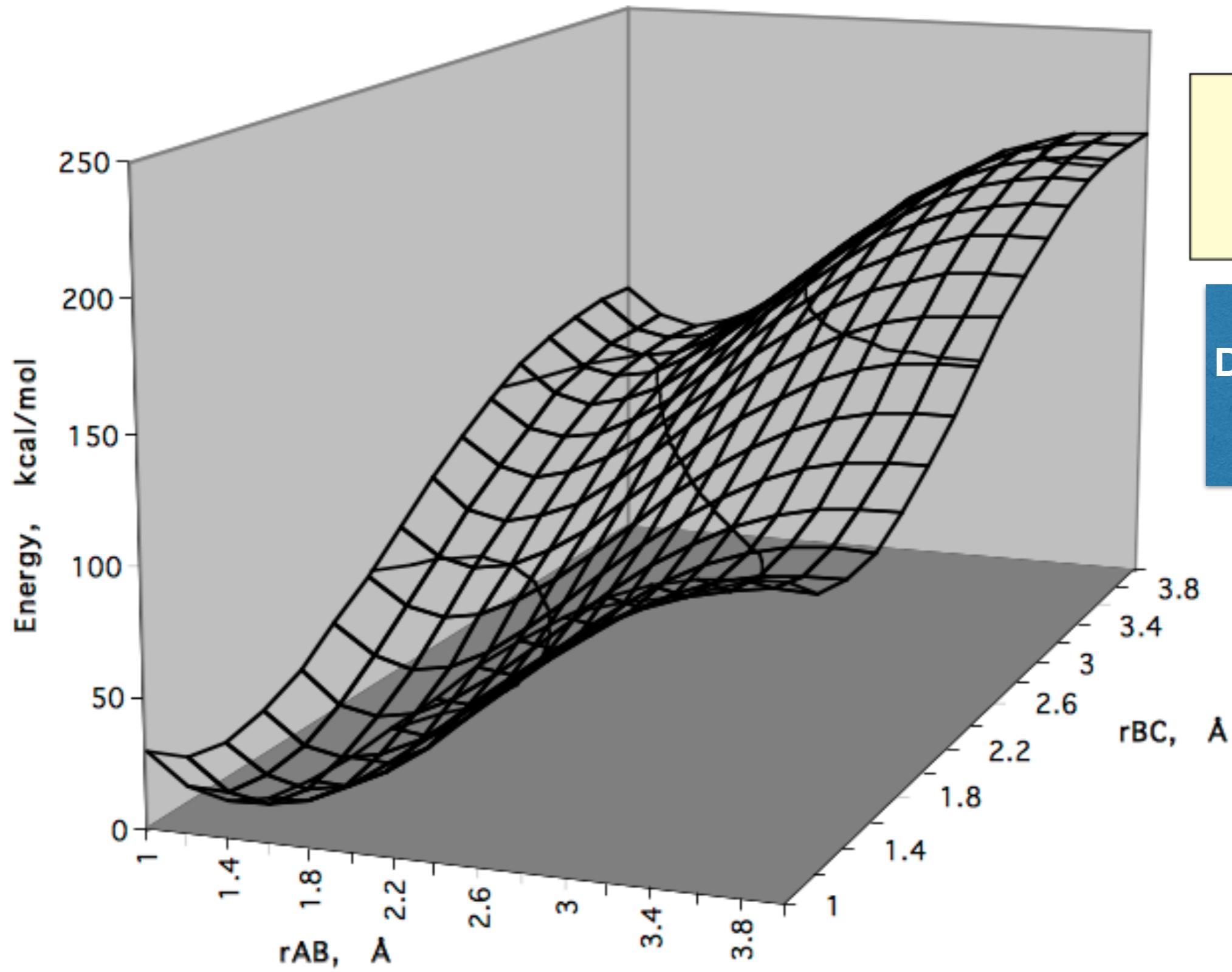
We would like to Find the **Reaction Pathway** Connecting Two Minima and Passing through the Transition State Structure



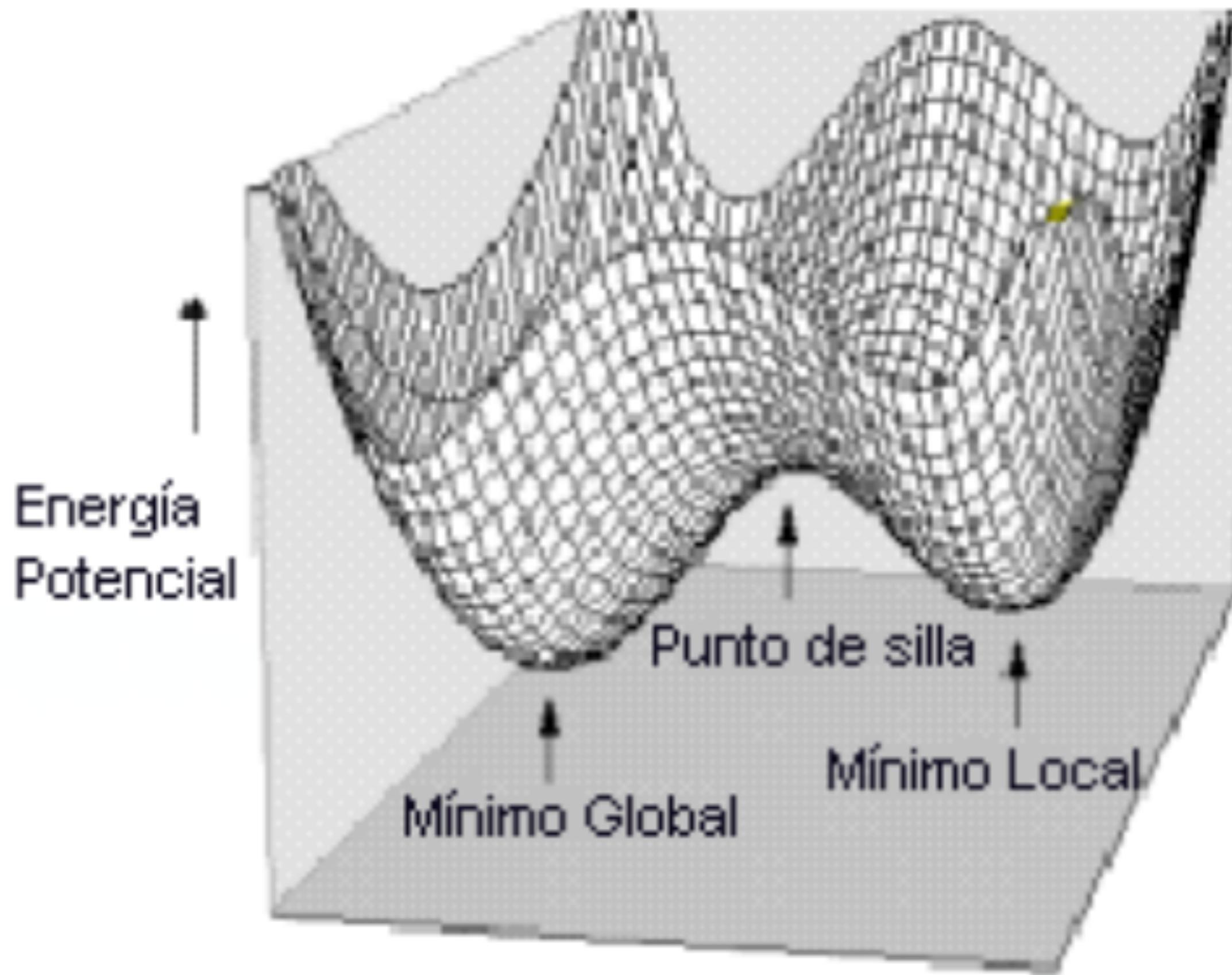
Geometry optimization is the name for the procedure that attempts to find the configuration of minimum energy of the molecule.

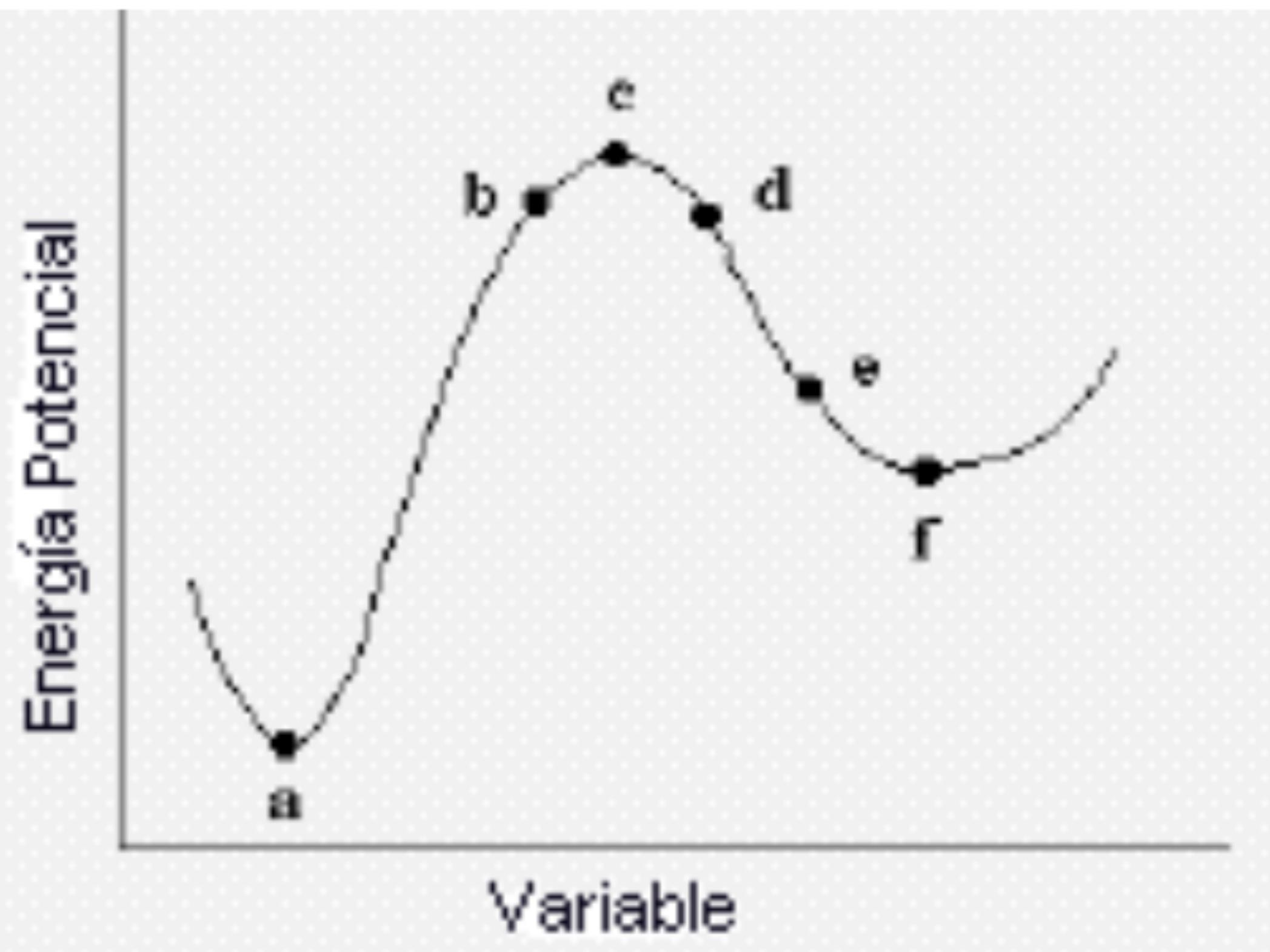
Los puntos críticos de una SEP son:

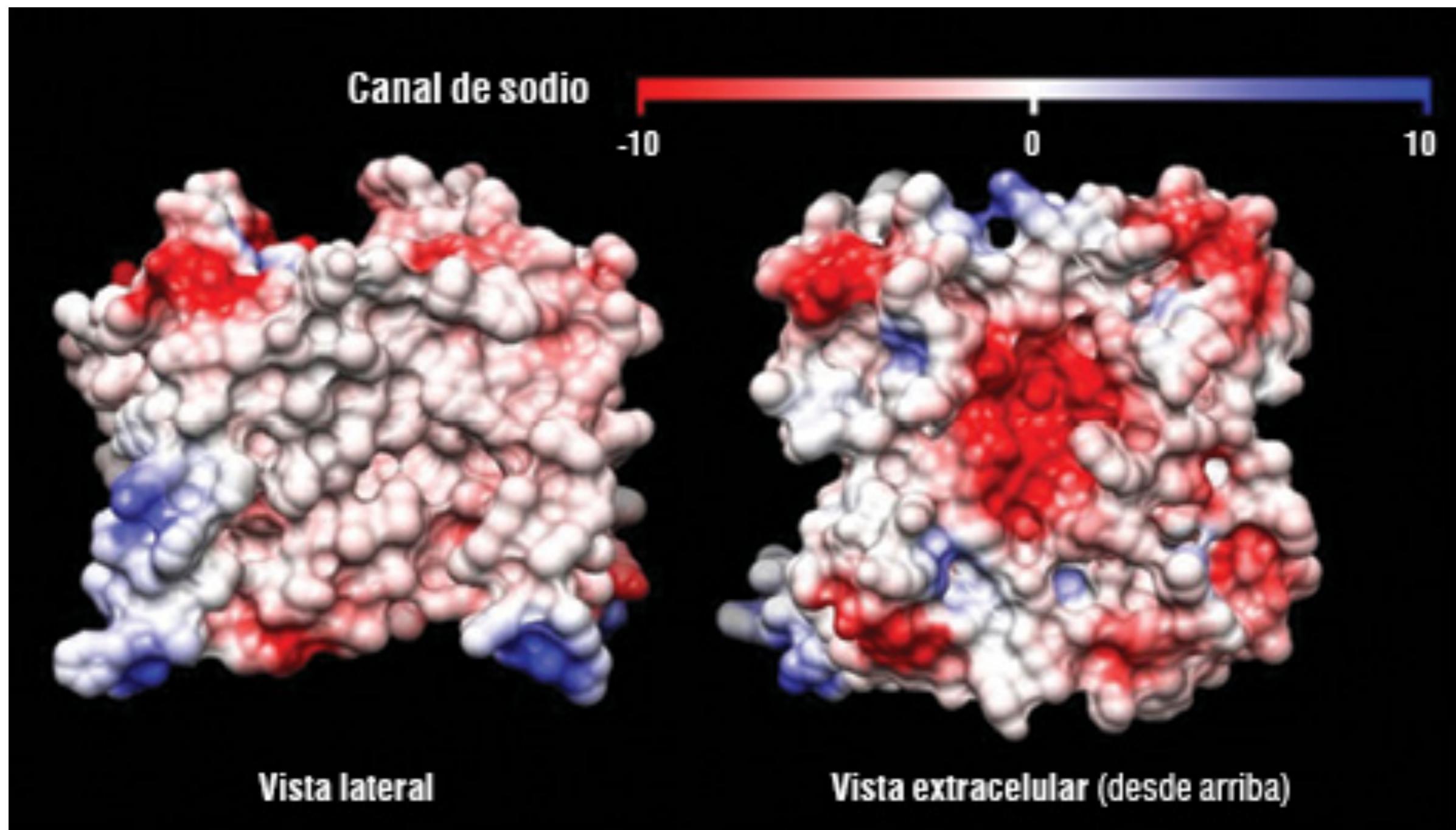
- **Mínimo global:** Es la energía mas baja y nos indica la conformación más estable. Solo existe un mínimo global para cada molécula.
- **Mínimo local:** Mínimo distintos del anterior, que constituyen regiones donde un cambio en la geometría en cualquier dirección nos da una geometría de mayor energía.
- **Punto de silla:** Es el punto entre dos energías extremas. El punto silla se define como un punto en la SEP en el cual hay un incremento de energía en todas las direcciones excepto una, y para el cual la pendiente (primera derivada) de la superficie es cero.



**GRADOS  
DE LIBERTAD:**  
**3N-6**





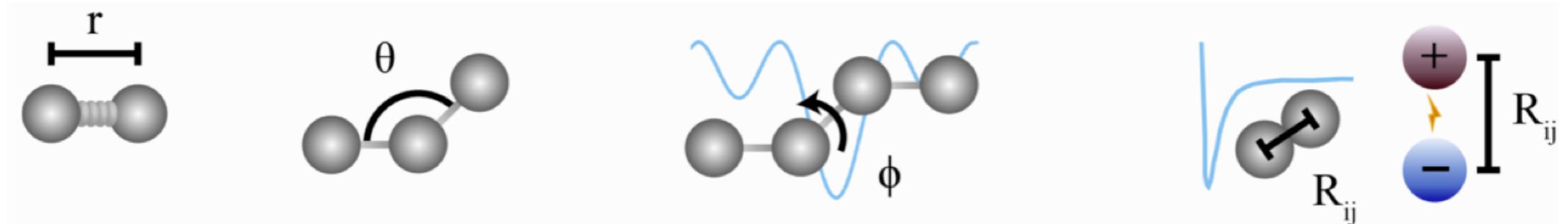


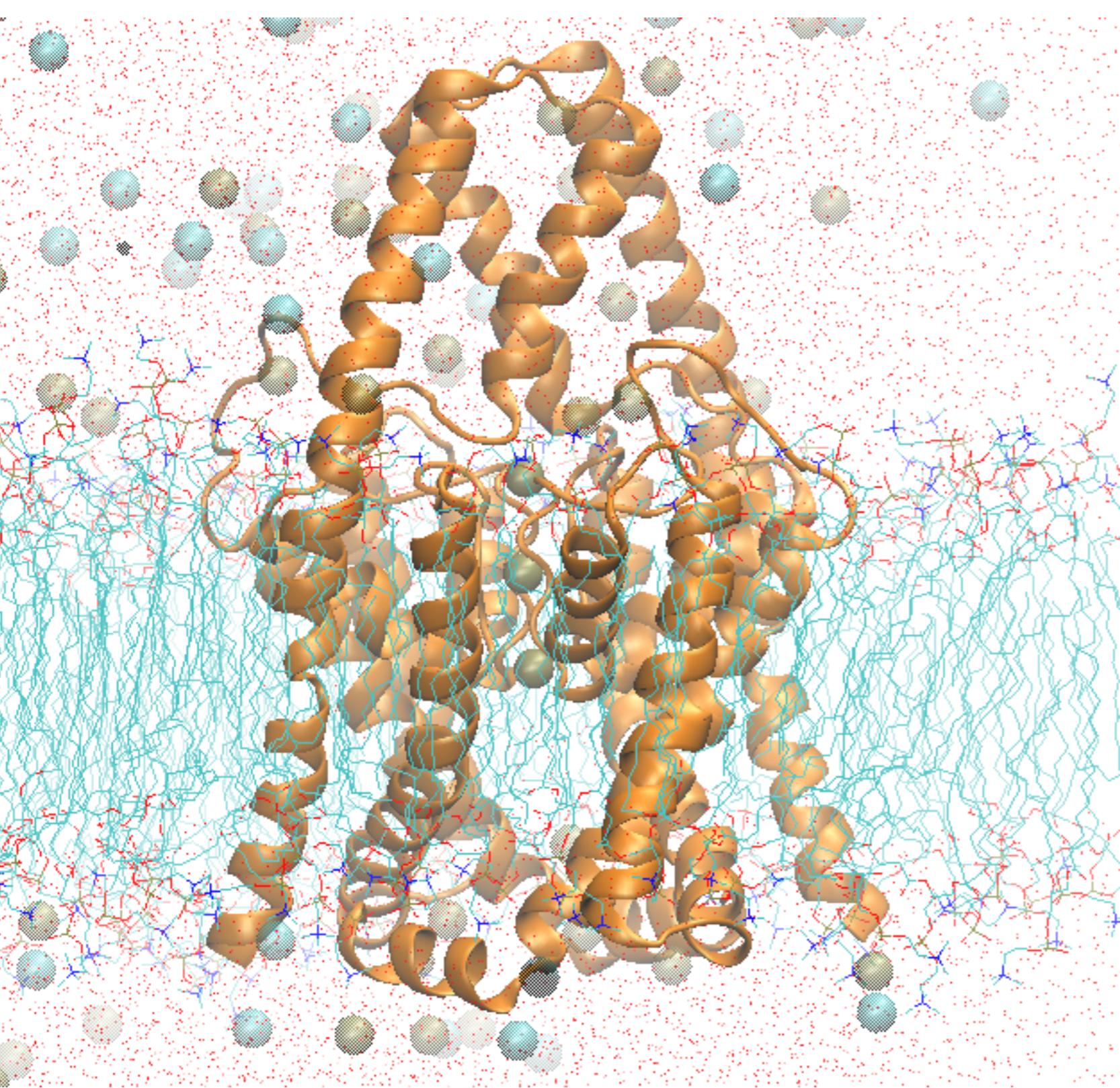
# Dinámica Molecular (DM)

Se pretende integrar las ecuaciones de movimiento de Newton en cada paso de simulación para cada una de las partículas/átomos que integran el sistema. Dadas las posiciones y velocidades iniciales, es posible determinar los valores de dichas variables en un instante de tiempo  $t$  dependiendo de las fuerzas con que actúan los átomos.

Se debe calcular la energía total sobre cada partícula mediante **Mecánica Molecular**, estas contribuciones son integradas en un campo de fuerza así:

$$E_{total} = \underbrace{\sum_{enlaces} K_r(r - r_{eq})^2 + \sum_{ángulos} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedros} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)]}_{Enlazantes} + \underbrace{\sum_{i < j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]}_{No-enlazantes}$$





$\approx 65.000$  átomos

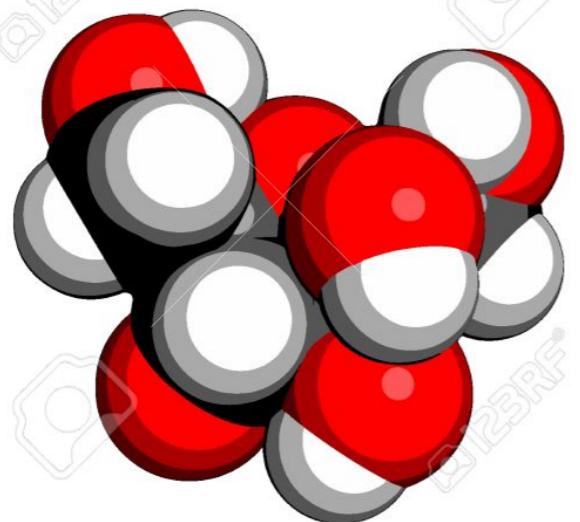
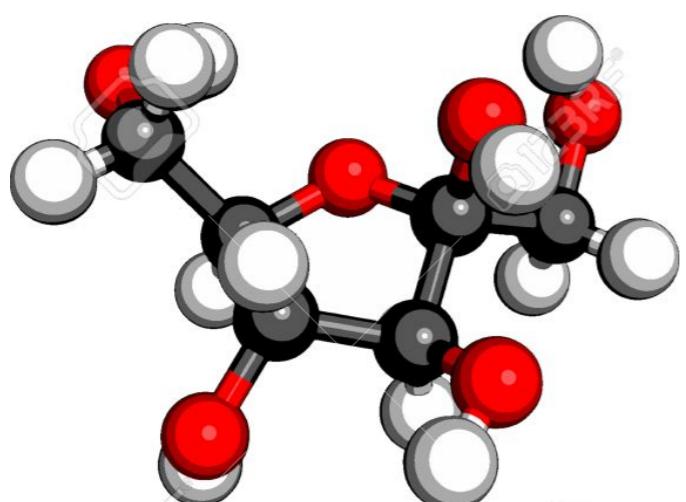
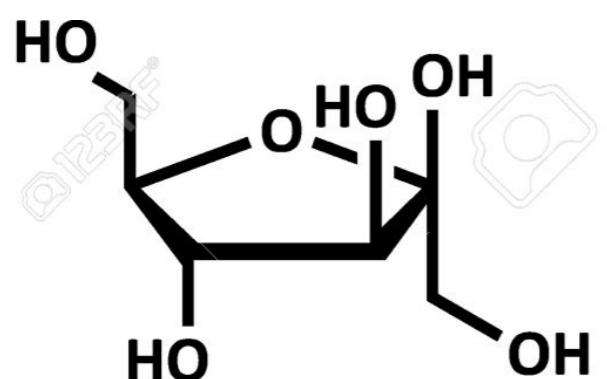
[ ]<sub>sal</sub> = 0.096 M KCl

Filtro de Selectividad  
 $K^+$  en  $S_0, S_2$  y  $S_4$   
 $H_2O$  en  $S_1$  y  $S_3$

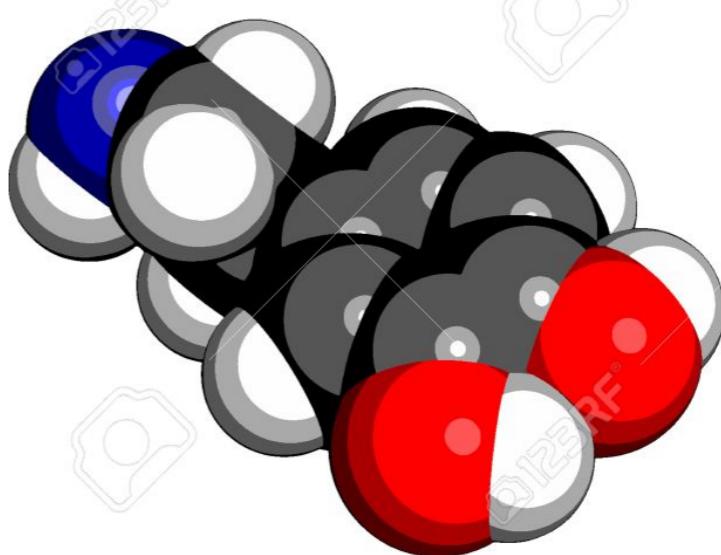
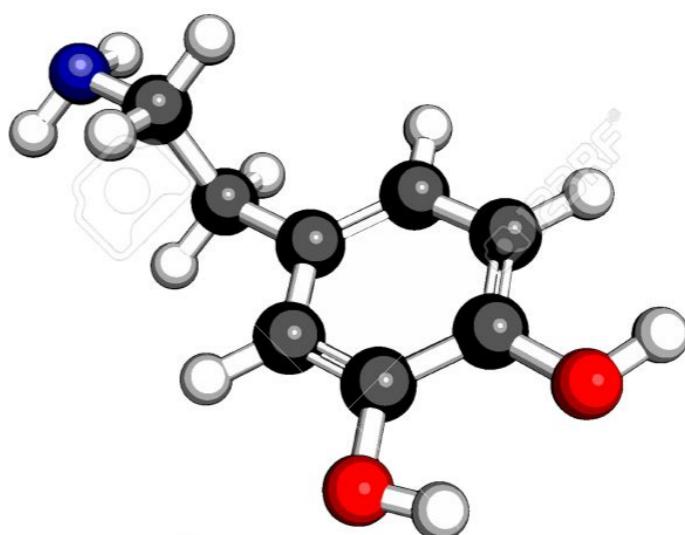
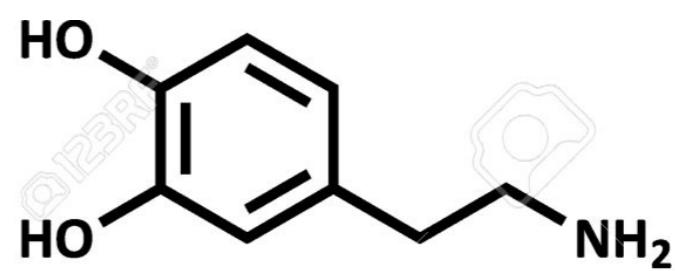
Membrana POPC (diacilglicerol +  
fosfolipido) (*1-palmitoil-2-oleoil-glicerol-3-fosfocloruro*)

Solvatación: Caja ortorrómbia con  
agua SPC

Software: Desmond (ff: OPLS-2005)



Fructosa



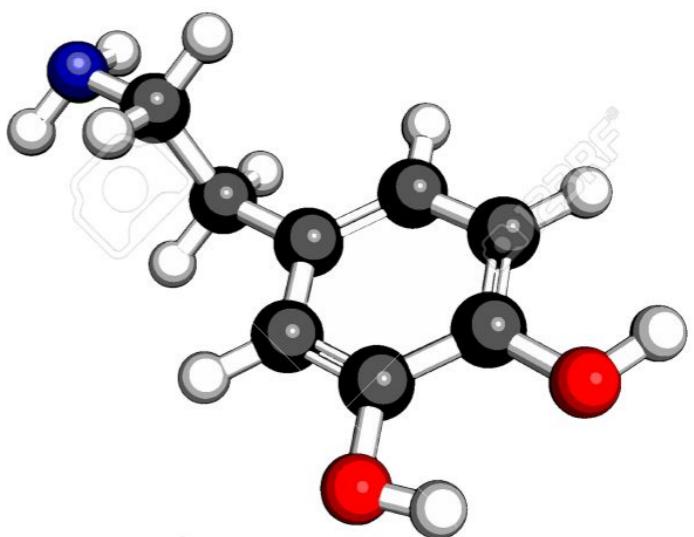
Dopamina

# ¿Qué hay detrás de las representaciones 3D?

```

1 @<TRIPOS>MOLECULE
2 Structure1
3 22 22 1
4 SMALL
5 USER_CHARGES
6
7
8 @<TRIPOS>ATOM
9   1 C1      -4.0122  0.4661  1.3885 C.ar    1 **** 0.0000
10  2 C2     -4.7588  1.6612  1.4171 C.ar    1 **** 0.0000
11  3 C3     -6.1452  1.6187  1.6525 C.ar    1 **** 0.0000
12  4 C4     -6.7810  0.3806  1.8730 C.ar    1 **** 0.0000
13  5 C5     -6.0338 -0.8152  1.8548 C.ar    1 **** 0.0000
14  6 C6     -4.6386 -0.7797  1.6126 C.ar    1 **** 0.0000
15  7 H7     -2.9512  0.5108  1.1938 H       1 **** 0.0000
16  8 H8     -4.2687  2.6107  1.2556 H       1 **** 0.0000
17  9 H9     -7.8448  0.3329  2.0568 H       1 **** 0.0000
18 10 O10    -6.8608  2.7821  1.6680 O.3     1 **** 0.0000
19 11 H11    -7.7851  2.6524  1.8133 H       1 **** 0.0000
20 12 O12    -6.6866 -1.9933  2.0676 O.3     1 **** 0.0000
21 13 H13    -6.1322 -2.7516  1.9834 H       1 **** 0.0000
22 14 C14    -3.7964 -2.0517  1.5786 C.3     1 **** 0.0000
23 15 H15    -4.4241 -2.9079  1.3307 H       1 **** 0.0000
24 16 H16    -3.0771 -1.9787  0.7605 H       1 **** 0.0000
25 17 C17    -3.0565 -2.3298  2.8997 C.3     1 **** 0.0000
26 18 H18    -2.5822 -3.3102  2.8570 H       1 **** 0.0000
27 19 H19    -3.7578 -2.3508  3.7356 H       1 **** 0.0000
28 20 H20    -1.5496 -1.4986  4.0126 H       1 **** 1.2070
29 21 N21    -2.0248 -1.3343  3.1361 N.3     1 **** -0.3216
30 22 H22    -2.4442 -0.4160  3.2061 H       1 **** -0.1028
31 @<TRIPOS>BOND
32   1   1   2 ar
33   2   1   6 ar
34   3   1   7 1
35   4   2   3 ar
36   5   2   8 1
37   6   3   4 ar
38   7   3  10 1
39   8   4   5 ar
40   9   4   9 1
41  10   5   6 ar
42  11   5  12 1
43  12   6  14 1
44  13  10  11 1
45  14  12  13 1
46  15  14  15 1
47  16  14  16 1
48  17  14  17 1
49  18  17  18 1
50  19  17  19 1
51  20  17  21 1
52  21  20  21 1
53  22  21  22 1
54 @<TRIPOS>SUBSTRUCTURE
55   1 **** 1 GROUP 0 **** 0 ROOT

```



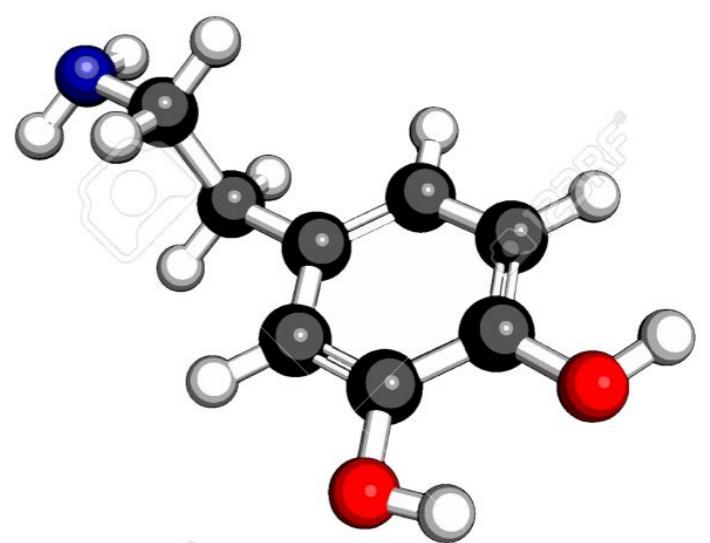
dopamine.mol2

# ¿Qué hay detrás de las representaciones 3D?

```

1 REMARK 4      COMPLIES WITH FORMAT V. 3.0, 1-DEC-2006
2 REMARK 888
3 REMARK 888 WRITTEN BY MAESTRO (A PRODUCT OF SCHRODINGER, LLC)
4 TITLE Structure1
5 MODEL    1
6 HETATM   1  C1  UNK    1    -4.012   0.466   1.389  1.00  0.00      C
7 HETATM   2  C2  UNK    1    -4.759   1.661   1.417  1.00  0.00      C
8 HETATM   3  C3  UNK    1    -6.145   1.619   1.653  1.00  0.00      C
9 HETATM   4  C4  UNK    1    -6.781   0.381   1.873  1.00  0.00      C
10 HETATM   5  C5  UNK    1    -6.034   -0.815   1.855  1.00  0.00      C
11 HETATM   6  C6  UNK    1    -4.639   -0.780   1.613  1.00  0.00      C
12 HETATM   7  O1  UNK    1    -6.861   2.782   1.668  1.00  0.00      O
13 HETATM   8  O2  UNK    1    -6.687   -1.993   2.068  1.00  0.00      O
14 HETATM   9  C7  UNK    1    -3.796   -2.052   1.579  1.00  0.00      C
15 HETATM  10  C8  UNK    1    -3.057   -2.330   2.900  1.00  0.00      C
16 HETATM  11  N1  UNK    1    -2.025   -1.334   3.136  1.00  0.00      N
17 HETATM  12  H1  UNK    1    -2.951   0.511   1.194  1.00  0.00      H
18 HETATM  13  H2  UNK    1    -4.269   2.611   1.256  1.00  0.00      H
19 HETATM  14  H3  UNK    1    -7.845   0.333   2.057  1.00  0.00      H
20 HETATM  15  H4  UNK    1    -7.785   2.652   1.813  1.00  0.00      H
21 HETATM  16  H5  UNK    1    -6.132   -2.752   1.983  1.00  0.00      H
22 HETATM  17  H6  UNK    1    -4.424   -2.908   1.331  1.00  0.00      H
23 HETATM  18  H7  UNK    1    -3.077   -1.979   0.760  1.00  0.00      H
24 HETATM  19  H8  UNK    1    -2.582   -3.310   2.857  1.00  0.00      H
25 HETATM  20  H9  UNK    1    -3.758   -2.351   3.736  1.00  0.00      H
26 HETATM  21  H10 UNK    1    -1.550   -1.499   4.013  1.00  0.00      H
27 HETATM  22  H11 UNK    1    -2.444   -0.416   3.206  1.00  0.00      H
28 CONECT   1    2    6    12
29 CONECT   1    2
30 CONECT   2    1    3    13
31 CONECT   2    1
32 CONECT   3    2    4    7
33 CONECT   3    4
34 CONECT   4    3    5    14
35 CONECT   4    3
36 CONECT   5    4    6    8
37 CONECT   5    6
38 CONECT   6    1    5    9
39 CONECT   6    5
40 CONECT  12    1
41 CONECT  13    2
42 CONECT  14    4
43 CONECT   7    3    15
44 CONECT  15    7
45 CONECT   8    5    16
46 CONECT  16    8
47 CONECT   9    6    17    18    10
48 CONECT  17    9
49 CONECT  18    9
50 CONECT  10    9    19    20    11
51 CONECT  19   10
52 CONECT  20   10
53 CONECT  21   11
54 CONECT  11   10    21    22
55 CONECT  22   11
56 ENDMDL
57 END
58

```

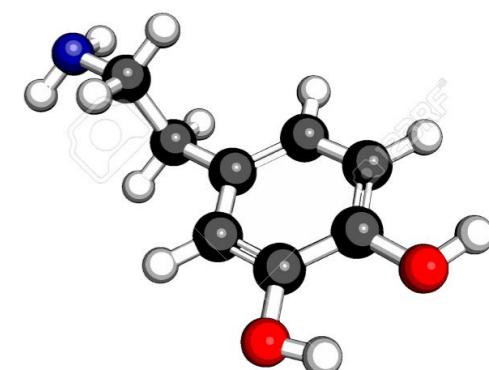


dopamine.pdb

# Ejercicio 1: Optimizando la geometría de la Dopamina

## List of commercial software and web servers:

Softwares	Description
AMBER	Assisted Model Building with Energy Refinement (AMBER) is the molecular dynamics software package that measures force fields. It also used in geometry optimization of chemical structures.
GROMOS	IT is a molecular dynamics simulation package used for simulation and geometry optimization.
VLifeMDS	It is advanced chemoinformatics tool offering Molecular docking, QSAR, 2D QSAR, 3D QSAR, Molecular modeling, Homology modeling and structure optimization.
YASARA	Yet Another Scientific Artificial Reality Application (YASARA) is a molecular visualisation, optimization, modelling, and dynamics program.
TREMOLO-X	A Molecular Dynamics Software tool used in simulation, modeling and structure optimization.
MOE	It is chemoinformatics package used in Molecular Mechanics, Molecular Dynamics, optimization, Visualization, Automatic Pharmacophore Generation etc.
ICM	It is used in Molecular modeling and simulations, Homology and loop modeling, Protein-protein docking, Small molecule docking and screening and lead optimization.

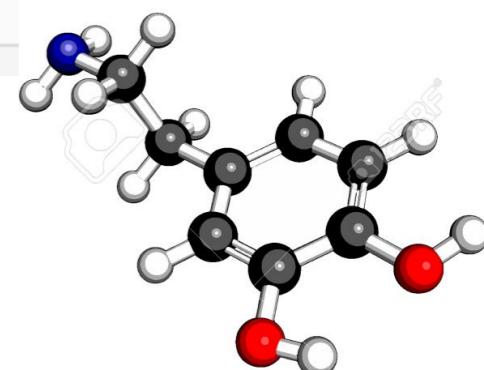


## Ejercicio 1: Optimizando la geometría de la Dopamina

### List of software and web servers used for structure optimization of molecules:

Softwares	Description
Openbabel	Openbabel is a free software, used in the inter-conversion of chemical structure/conformers (2D/3D) and different chemical file formats, substructure search, force field calculation, extraction of stereochemical information and fingerprint calculation.
SMI23D	SMI23D (3D Coordinate Generation) program converts one or more SMILES strings into 3D.
FROG	FROG (FRee Online druG) is a molecule conformation generation tool for small molecules starting from their 1D or 2D descriptions.
TINKER	It is molecular modeling software having several features such as molecular dynamics, minimization and conformational sampling. It generates structure conformers by unconstrained molecular dynamics and each conformer is simulated and energy minimized.
MOPAC	Molecular Orbital PAckage (MOPAC) is an open source semi-empirical quantum chemistry program that is used to study molecular structures and reactions.
Balloon	It generates 3D atomic coordinates using molecular connectivity via distance geometry.
Cyndi	It is based on the multi-objective evolution algorithm which is capable of generating geometrically diverse conformers at the large scale.
DG-AMMOS	It used to generation of the 3D conformation of small molecules using distance geometry and their energy minimization.

FROG: <http://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::Frog2>



## Ejercicio 1: Optimizando la geometría de la Dopamina

**Frog2** 

Free Online drug conformation generation.

**\* Input drug description**

\* Input type  3D 

\* Input drug description  mol2 

\* Query 

**paste** **upload** **EDIT** **CLEAR**

Enter your data below:

## Ejercicio 1: Optimizando la geometría de la Dopamina

**Frog2** 

FFree Online drug conformation generation.

**Input drug description**

\* Input type  3D 

\* Input drug description  mol2 

\* Query 

paste upload  

Seleccionar archivo No se eligió archivo  select

```
@<TRIPOS>MOLECULE
Structure1
22 22 1
SMALL
USER_CHARGES

@<TRIPOS>ATOM
 1 C1   -4.0122  0.4661  1.3885 C.ar  1 ****  0.0000
 2 C2   -4.7588  1.6612  1.4171 C.ar  1 ****  0.0000
 3 C3   -6.1452  1.6187  1.6525 C.ar  1 ****  0.0000
 4 C4   -6.7810  0.3806  1.8730 C.ar  1 ****  0.0000
 5 C5   -6.0338 -0.8152  1.8548 C.ar  1 ****  0.0000
```

Input -> Dopamina.mol2

## Ejercicio 1: Optimizando la geometría de la Dopamina

▼ Calculation parameters

\* Output format

\* Disambiguate

\* Minimize

\* Produce

\* #conf

\* E max

\* #mc steps

\* Energy Window

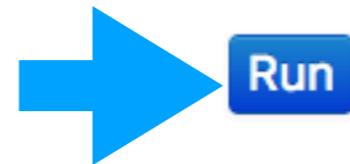
## Parametros del cálculo

## Ejercicio 1: Optimizando la geometría de la Dopamina

Correr el cálculo

Frog2 

Free Online drug conformation generation.



Run

Reset

### Input drug description

\* Input type  3D 

\* Input drug description  mol2 

\* Query 

paste

upload

EDIT

CLEAR

Seleccionar archivo No se eligió archivo  select

```
@<TRIPOS>MOLECULE
Structure1
22 22 1
SMALL
USER_CHARGES

@<TRIPOS>ATOM
 1 C1    -4.0122  0.4661  1.3885 C.ar  1 ****  0.0000
 2 C2    -4.7588  1.6612  1.4171 C.ar  1 ****  0.0000
 3 C3    -6.1452  1.6187  1.6525 C.ar  1 ****  0.0000
 4 C4    -6.7810  0.3806  1.8730 C.ar  1 ****  0.0000
 5 C5    -6.0338 -0.8152  1.8548 C.ar  1 ****  0.0000
```

# Ejercicio 1: Optimizando la geometría de la Dopamina

Welcome      Forms      Data Bookmarks      **Jobs**      Tutorials

Overview      Frog2 - 07/07/17 19:41:49 

✓ <http://mobyle.rpbs.univ-paris-diderot.fr/data/jobs/Frog2/J09798858350039>

get help      back to form      remove job      download

results

▼ Results

Unambiguous smiles (Drug \_3DStructure)

► Frog.smiles (smiles) 

Mol2 file (Drug \_3DStructure)

▼ Frog.mol2 (mol2) 

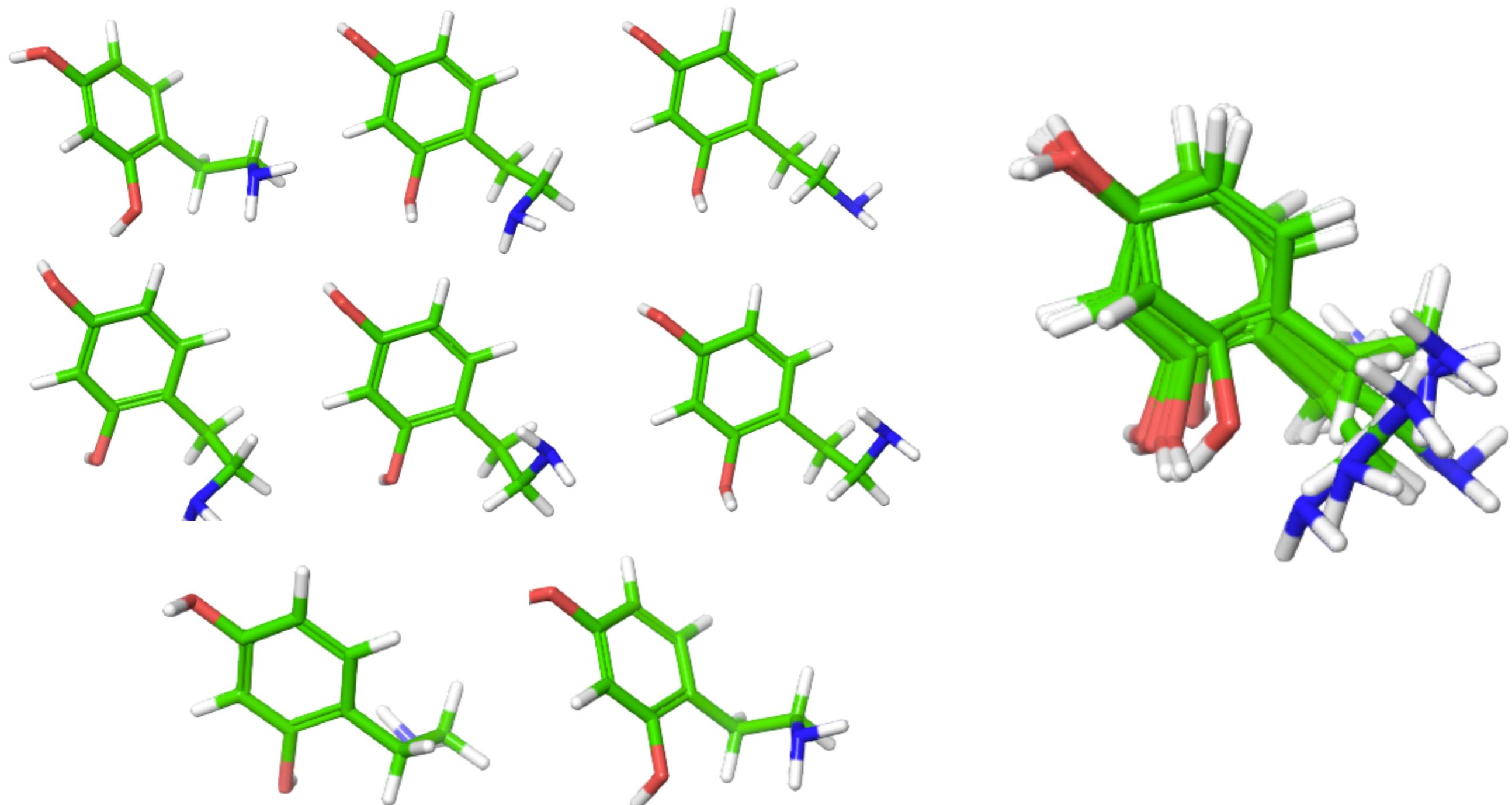
```
17 14 17 1
18 17 18 1
19 17 19 1
20 17 21 1
21 20 21 1
22 21 22 1
@<TRIPOS>MOLECULE
Structure1_3
22 22 0 0 0
SMALL
```

full screen      openastex      marvinview      jmol      bookmark as  or  further analysis

▼ Frog.log 

```
disambiguation      : True, nb max conformations   : 50, per isomer          : False
energetic threshold : 50.0, bad energy threshold    : 100.0, stage 2 Monte Carlo : False
minimize            : True
```

Id 1: Structure1  
8 conformation(s) calculated.



# ¿Qué hay detrás de las representaciones 3D?

## Ejercicio 2

1. Descargar del PDB ([www.rcsb.org/pdb/home/home.do](http://www.rcsb.org/pdb/home/home.do)) la MAO-B en complejo con el ligando 6-hydroxy-N-propargyl-1(R)-aminoindan (Crystal structure of MAOB in complex with 6-hydroxy-N-propargyl-1(R)-aminoindan- PDB id: 1S3E)

Structure Summary    3D View    Annotations    Sequence    Sequence Similarity    Structure Similarity    Experiment    Literature

**Biological Assembly 1 ?**

**1S3E**

Crystal structure of MAOB in complex with 6-hydroxy-N-propargyl-1(R)-aminoindan

DOI: [10.22110/pdb1s3e/pdb](https://doi.org/10.22110/pdb1s3e/pdb)

Classification: [OXIDOREDUCTASE](#)

Deposited: 2004-01-13 Released: 2004-03-30

Deposition author(s): [Binda, C.](#), [Hubalek, F.](#), [Li, M.](#), [Herzig, Y.](#), [Sterling, J.](#), [Edmondson, D.E.](#), [Mattevi, A.](#)

Organism: [Homo sapiens](#)

Expression System: *Pichia pastoris*

**Experimental Data Snapshot**

Method: X-RAY DIFFRACTION  
 Resolution: 1.6 Å  
 R-Value Free: 0.216  
 R-Value Work: 0.198

**wwPDB Validation**

Metric	Percentile Ranks	Value
Rfree	2	0.217
Clashscore	2	2
Ramachandran outliers	0	0
Sidechain outliers	2.6%	2.6%
RSRZ outliers	25.1%	25.1%

Legend: Worse Percentile relative to all X-ray structures Better Percentile relative to X-ray structures of similar resolution

**Literature**

[Download Primary Citation](#)

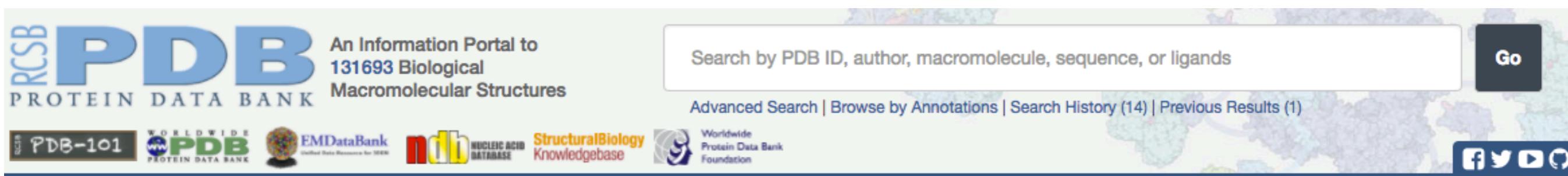
**View in 3D:** [NGL](#) or [JSmol](#) or [PV](#) (in Browser)

**Standalone Viewers**

[Simple Viewer](#)   [Protein Workshop](#)  
[Ligand Explorer](#)   [Kiosk Viewer](#)

# ¿Qué hay detrás de las representaciones 3D?

## 2. Abrir archivo PDB en editor de texto (de preferencia block de notas)



## PDB File Format

The Protein Data Bank (PDB) format provides a standard representation for macromolecular structure data derived from X-ray diffraction and NMR studies. This representation was created in the 1970's and a large amount of software using it has been written.

Documentation describing the PDB file format is available from the wwPDB at <http://www.wwpdb.org/documentation/file-format.php>.

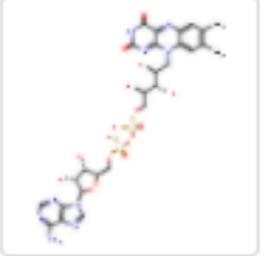
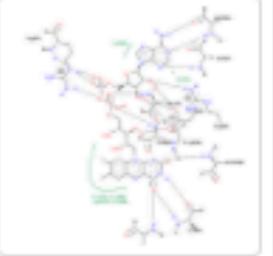
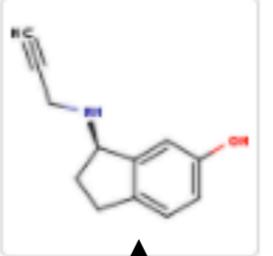
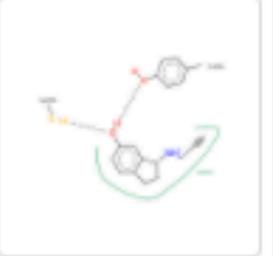
Historical copies of the PDB file format from 1992\* and 1996\* are available.

1	HEADER	OXIDOREDUCTASE	13-JAN-04	1S3E
2	TITLE	CRYSTAL STRUCTURE OF MAOB IN COMPLEX WITH 6-HYDROXY-N-		
3	TITLE	2 PROPARGYL-1(R)-AMINOINDAN		
4	COMPND	MOL_ID: 1;		
5	COMPND	2 MOLECULE: AMINE OXIDASE [FLAVIN-CONTAINING] B;		
6	COMPND	3 CHAIN: A, B;		
7	COMPND	4 SYNONYM: MONOAMINE OXIDASE, MAO-B;		
8	COMPND	5 EC: 1.4.3.4;		
9	COMPND	6 ENGINEERED: YES		
10	SOURCE	MOL_ID: 1;		
11	SOURCE	2 ORGANISM_SCIENTIFIC: HOMO SAPIENS;		
12	SOURCE	3 ORGANISM_COMMON: HUMAN;		
13	SOURCE	4 ORGANISM_TAXID: 9606;		
14	SOURCE	5 GENE: MAOB:		

						<b>x</b>	<b>y</b>	<b>z</b>		
720	ATOM	1	N	ASN	A	3	65.689	122.554	6.206	1.00 53.34 N
721	ATOM	2	CA	ASN	A	3	65.021	121.234	6.391	1.00 53.05 C
722	ATOM	3	C	ASN	A	3	64.995	120.765	7.854	1.00 52.49 C
723	ATOM	4	O	ASN	A	3	64.022	121.020	8.560	1.00 52.44 O
724	ATOM	5	CB	ASN	A	3	65.645	120.175	5.471	1.00 53.57 C
725	ATOM	6	CG	ASN	A	3	64.731	118.981	5.243	1.00 54.54 C
726	ATOM	7	OD1	ASN	A	3	63.555	119.132	4.902	1.00 56.25 O
727	ATOM	8	ND2	ASN	A	3	65.272	117.783	5.429	1.00 55.74 N
728	ATOM	9	N	LYS	A	4	66.058	120.100	8.309	1.00 51.46 N
729	ATOM	10	CA	LYS	A	4	66.081	119.508	9.652	1.00 50.56 C
730	ATOM	11	C	LYS	A	4	66.894	120.320	10.661	1.00 49.47 C
731	ATOM	12	O	LYS	A	4	68.018	120.738	10.374	1.00 49.49 O
732	ATOM	13	CB	LYS	A	4	66.587	118.058	9.602	1.00 50.98 C
733	ATOM	14	CG	LYS	A	4	65.731	117.135	8.740	1.00 52.32 C
734	ATOM	15	CD	LYS	A	4	65.895	115.670	9.121	1.00 54.56 C
735	ATOM	16	CE	LYS	A	4	65.077	114.778	8.194	1.00 55.55 C
736	ATOM	17	NZ	LYS	A	4	65.000	113.373	8.684	1.00 56.60 N
737	ATOM	18	N	CYS	A	5	66.309	120.540	11.841	1.00 47.89 N
738	ATOM	19	CA	CYS	A	5	66.953	121.294	12.921	1.00 46.41 C
739	ATOM	20	C	CYS	A	5	66.455	120.844	14.300	1.00 45.24 C
740	ATOM	21	O	CYS	A	5	65.632	119.927	14.399	1.00 45.24 O
741	ATOM	22	CB	CYS	A	5	66.728	122.800	12.732	1.00 46.47 C
742	ATOM	23	SG	CYS	A	5	64.993	123.318	12.817	1.00 46.43 S
743	ATOM	24	N	ASP	A	6	66.963	121.481	15.356	1.00 43.52 N
744	ATOM	25	CA	ASP	A	6	66.524	121.193	16.721	1.00 42.05 C
745	ATOM	26	C	ASP	A	6	65.224	121.923	17.067	1.00 40.71 C
746	ATOM	27	O	ASP	A	6	64.284	121.314	17.584	1.00 40.46 O
747	ATOM	28	CD	ASP	A	6	67.600	121.565	17.744	1.00 40.46 C

<http://www.wwpdb.org/documentation/file-format>

## Small Molecules

Ligands <span style="background-color: #f0f0f0; border-radius: 10px; padding: 2px 5px;">2 Unique</span>				
ID	Chains	Name / Formula / InChI Key	2D Diagram & Interactions	3D Interactions
FAD <a href="#">Query on FAD</a>	A, B	<b>FLAVIN-ADENINE DINUCLEOTIDE</b> C <sub>27</sub> H <sub>33</sub> N <sub>9</sub> O <sub>15</sub> P <sub>2</sub> VWWQXMAJTJZDQX-UYBVJOGSSA-N	 	<a href="#">Ligand Explorer</a> <a href="#">NGL</a> <a href="#">Binding Pocket (JSmol)</a> <a href="#">Electron Density (JSmol)</a>
RHP <a href="#">Query on RHP</a>	A, B	(3R)-3-(PROP-2-YNYLAMINO)INDAN-5-OL <b>5-HYDROXY-N-PROPARGYL-1(R)-AMINOINDAN</b> ( <i>Synonym</i> ) C <sub>12</sub> H <sub>13</sub> N O NRSDGDXUWMMUEV-GFCCVEGCSA-N	 	<a href="#">Ligand Explorer</a> <a href="#">NGL</a> <a href="#">Binding Pocket (JSmol)</a>

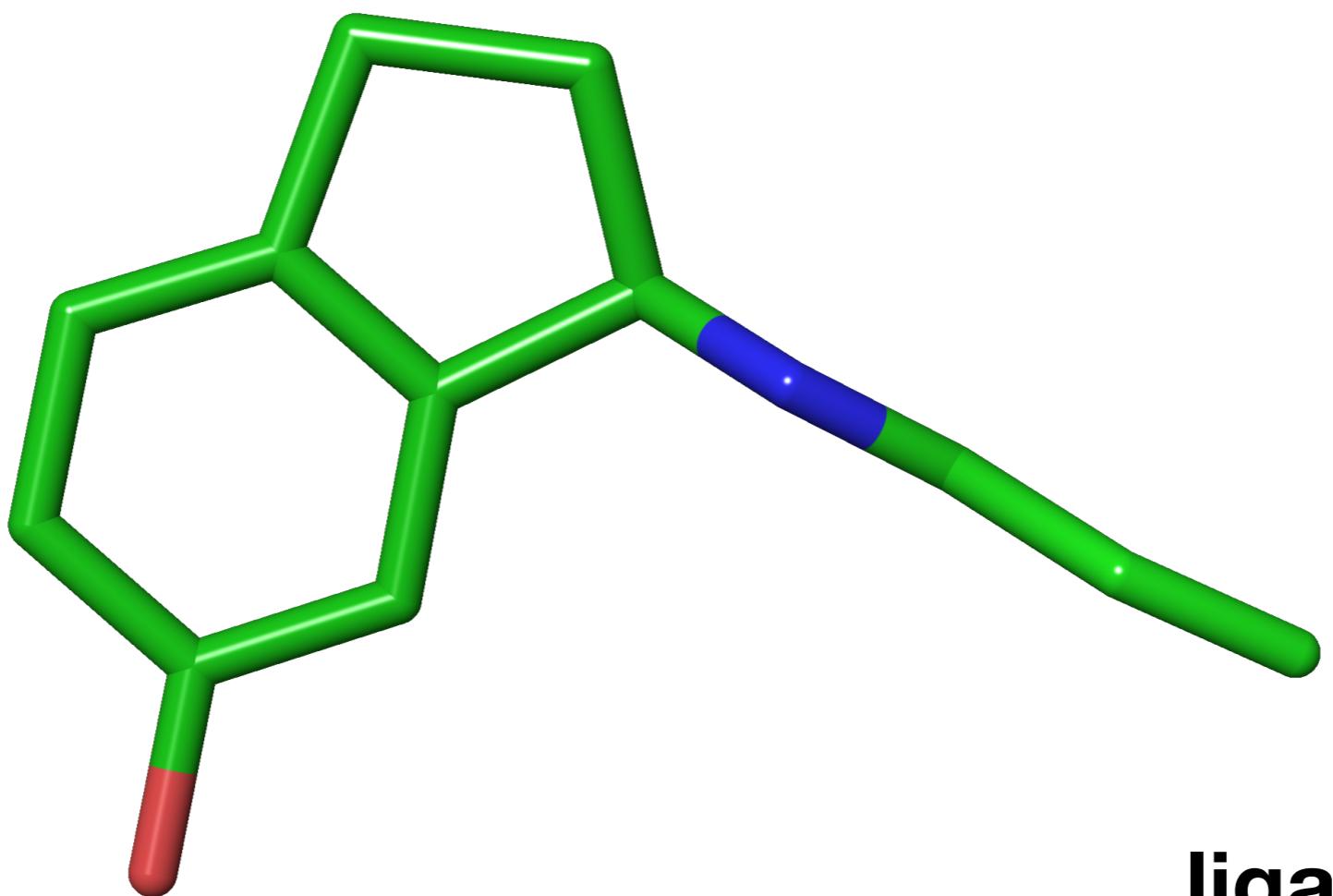
External Ligand Annotations	
ID	Binding Affinity (Sequence Identity %)
RHP	IC50: 230 nM (88) <a href="#">BindingDB</a> Ki: 17000 nM (100) <a href="#">BindingDB</a>  N/A in BindingMoad N/A in PDBbind



### 3. Seleccionar el ligando RHP y copiarlo a un nuevo documento PDB (ligando-RHP.pdb)

8683	HETATM	7964	O5'	FAD	A	600	57.482	141.727	19.902	1.00	28.95	O
8684	HETATM	7965	P	FAD	A	600	57.073	140.201	19.616	1.00	29.40	P
8685	HETATM	7966	O1P	FAD	A	600	58.265	139.491	19.105	1.00	29.23	O
8686	HETATM	7967	O2P	FAD	A	600	56.433	139.551	20.849	1.00	30.64	O
8687	HETATM	7968	O3P	FAD	A	600	55.937	140.235	18.478	1.00	29.41	O
8688	HETATM	7969	C13	RHP	A	601	54.491	152.119	22.060	1.00	38.65	C
8689	HETATM	7970	C12	RHP	A	601	54.583	152.796	23.166	1.00	41.75	C
8690	HETATM	7971	C11	RHP	A	601	53.531	153.774	23.710	1.00	42.52	C
8691	HETATM	7972	N10	RHP	A	601	53.759	154.449	24.783	1.00	44.16	N
8692	HETATM	7973	C9	RHP	A	601	52.734	155.364	25.276	1.00	44.52	C
8693	HETATM	7974	C1	RHP	A	601	53.274	156.782	25.505	1.00	44.79	C
8694	HETATM	7975	C2	RHP	A	601	52.674	157.310	26.825	1.00	45.38	C
8695	HETATM	7976	C3	RHP	A	601	52.224	156.056	27.498	1.00	44.61	C
8696	HETATM	7977	C8	RHP	A	601	52.274	154.987	26.651	1.00	44.91	C
8697	HETATM	7978	C7	RHP	A	601	51.905	153.729	27.075	1.00	44.94	C
8698	HETATM	7979	C4	RHP	A	601	51.815	155.927	28.812	1.00	45.14	C
8699	HETATM	7980	C5	RHP	A	601	51.443	154.662	29.256	1.00	45.50	C
8700	HETATM	7981	C6	RHP	A	601	51.490	153.575	28.391	1.00	45.49	C
8701	HETATM	7982	O6	RHP	A	601	51.119	152.321	28.832	1.00	46.50	O
8702	HETATM	7983	PA	FAD	B	600	29.119	126.431	8.952	1.00	29.45	P
8703	HETATM	7984	O1A	FAD	B	600	30.078	126.712	10.046	1.00	29.89	O
8704	HETATM	7985	O2A	FAD	B	600	28.082	125.346	9.250	1.00	29.01	O
8705	HETATM	7986	O5B	FAD	B	600	29.899	126.017	7.619	1.00	29.39	O

1	HETATM	7969	C13	RHP	A	601	54.491	152.119	22.060	1.00	38.65	C
2	HETATM	7970	C12	RHP	A	601	54.583	152.796	23.166	1.00	41.75	C
3	HETATM	7971	C11	RHP	A	601	53.531	153.774	23.710	1.00	42.52	C
4	HETATM	7972	N10	RHP	A	601	53.759	154.449	24.783	1.00	44.16	N
5	HETATM	7973	C9	RHP	A	601	52.734	155.364	25.276	1.00	44.52	C
6	HETATM	7974	C1	RHP	A	601	53.274	156.782	25.505	1.00	44.79	C
7	HETATM	7975	C2	RHP	A	601	52.674	157.310	26.825	1.00	45.38	C
8	HETATM	7976	C3	RHP	A	601	52.224	156.056	27.498	1.00	44.61	C
9	HETATM	7977	C8	RHP	A	601	52.274	154.987	26.651	1.00	44.91	C
10	HETATM	7978	C7	RHP	A	601	51.905	153.729	27.075	1.00	44.94	C
11	HETATM	7979	C4	RHP	A	601	51.815	155.927	28.812	1.00	45.14	C
12	HETATM	7980	C5	RHP	A	601	51.443	154.662	29.256	1.00	45.50	C
13	HETATM	7981	C6	RHP	A	601	51.490	153.575	28.391	1.00	45.49	C
14	HETATM	7982	O6	RHP	A	601	51.119	152.321	28.832	1.00	46.50	O



ligando-RHP.pdb

# Representación, visualización y modelamiento molecular (3D).



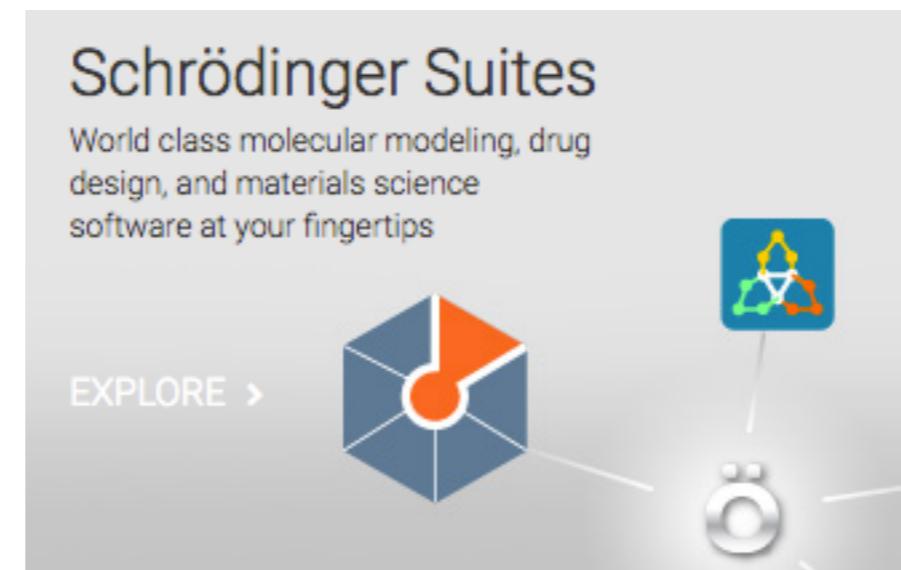
[www.pymol.org](http://www.pymol.org)

Python



[www.ks.uiuc.edu/Research/vmd/](http://www.ks.uiuc.edu/Research/vmd/)

Tcl

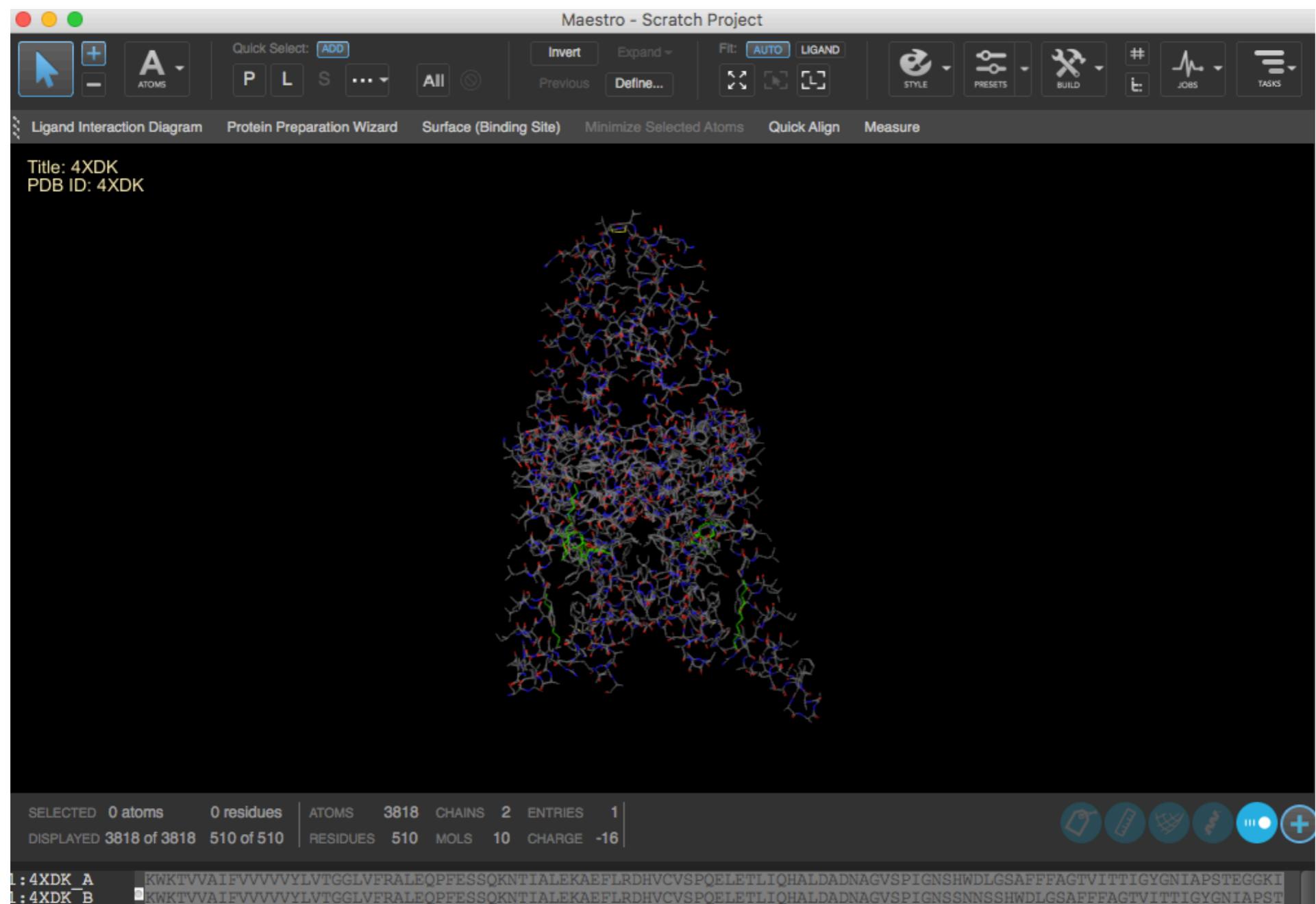


<https://www.schrodinger.com/>

Python

Schrödinger Suites  
[www.schrodinger.com](http://www.schrodinger.com)

→ Free maestro 11



<https://www.youtube.com/watch?v=NyeJsKzzxak>



# Schrödinger Suites

Maestro - Scratch Project

Quick Select: **ADD**    Invert    Expand **LIGAND**    Fit: **AUTO**    Previous    Define...    **STYLE**    **PRESETS**    **BUILD**    **#**    **JOB**    **TASKS**

Ligand Interaction Diagram    Protein Preparation Wizard    Surface (Binding Site)    Minimize Selected Atoms    Quick Align    Measure

Workspace Navigator

ENTRY LIST

Row	In	Title
-----	----	-------

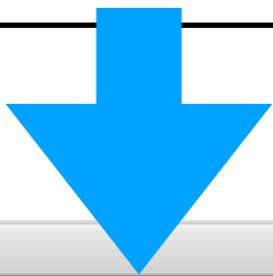
STRUCTURE HIERARCHY

- Current Selection

SELECTED 0 atoms 0 residues    ATOMS 0 CHAINS 0 ENTRIES 0  
DISPLAYED 0 of 0 0 of 0    RESIDUES 0 MOLS 0 CHARGE 0

Entries: 0 total, 0 selected, 0 included    Groups: 0 total, 0 selected

(?)





Maestro - Scratch Project

Quick Select: ADD    Invert    Expand    Fit: AUTO LIGAND    STYLE    PRESETS    BUILD

Ligand Interaction Diagram    Protein Preparation Wizard    Surface (Binding Site)    Minimize Selected Atoms    Quick Align    Measure

Workspace Navigator

ENTRY LIST

Row	In	Title
1	1	Scratch Project

STRUCTURE HIERARCHY

- Current Selection

SELECTED 0 atoms 0 residues    ATOMS 0 CHAINS 0 ENTRIES 0  
DISPLAYED 0 of 0 0 of 0    RESIDUES 0 MOLS 0 CHARGE 0

Entries: 0 total, 0 selected, 0 included  
Groups: 0 total, 0 selected

3D Builder

Move    Add Fragments    Draw

Organic    Metal Centers

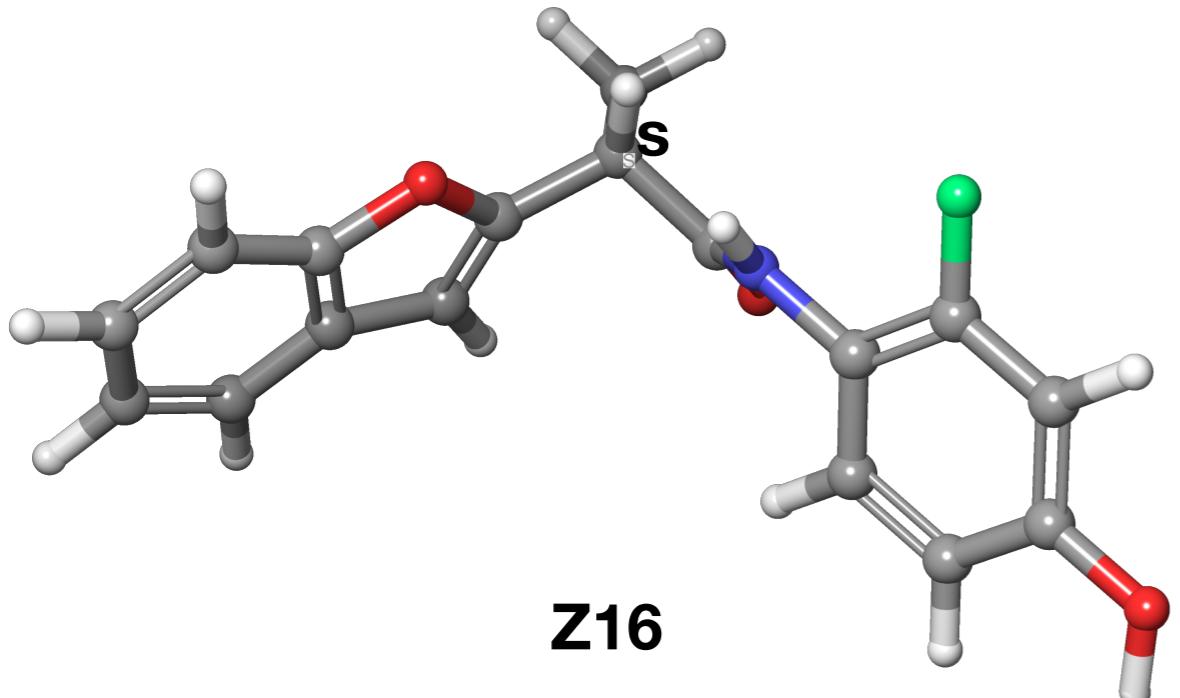
<chem>H-O-H</chem>	<chem>H-N-H</chem>	<chem>O=S(=O)(H)H</chem>	<chem>HC=O</chem>
<chem>H3C</chem>			More...

Create Enumerated Entries...

## Ejercicio 3. Modelando moléculas pequeñas

### 1. Modelar Z16 y 5 derivados:

02\_Session -> 04\_Molecules\_Modeling -> 16\_Series.pdf



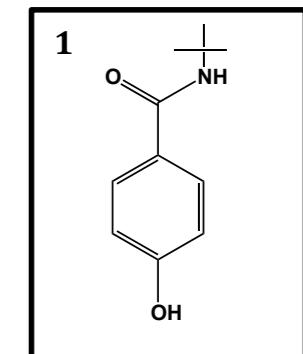
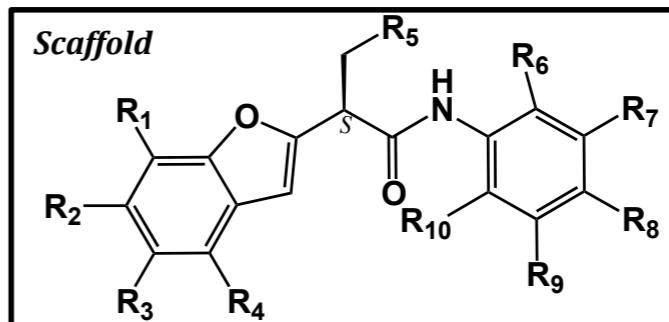
### 2. Asignar parámetros a las moléculas

Edit -> Assign -> Partial charges

STYLE -> Apply Labels -> Partial charges

### 3. Exportar los archivos a formato .mol2

Project table -> export -> Z16.mol2

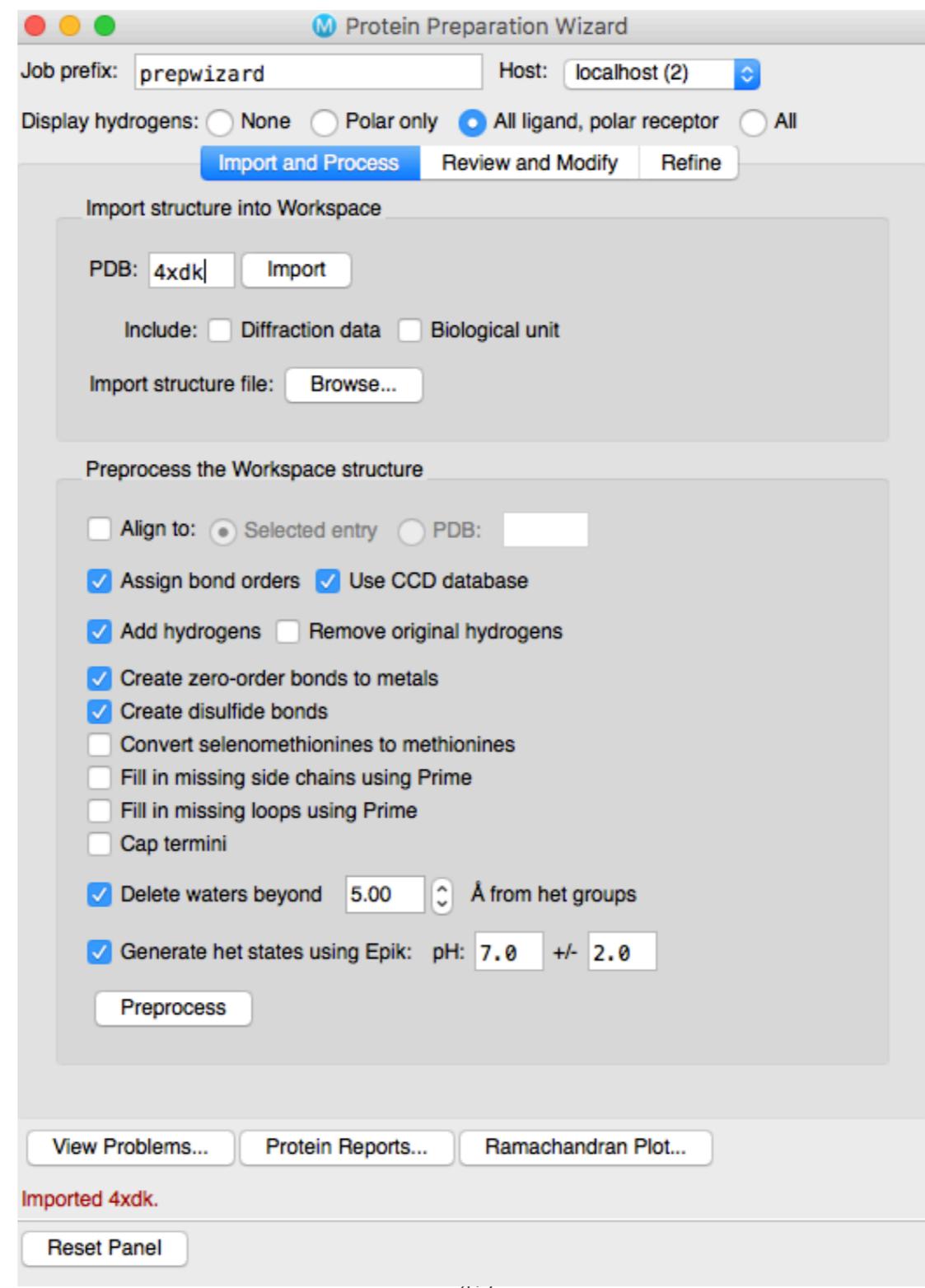


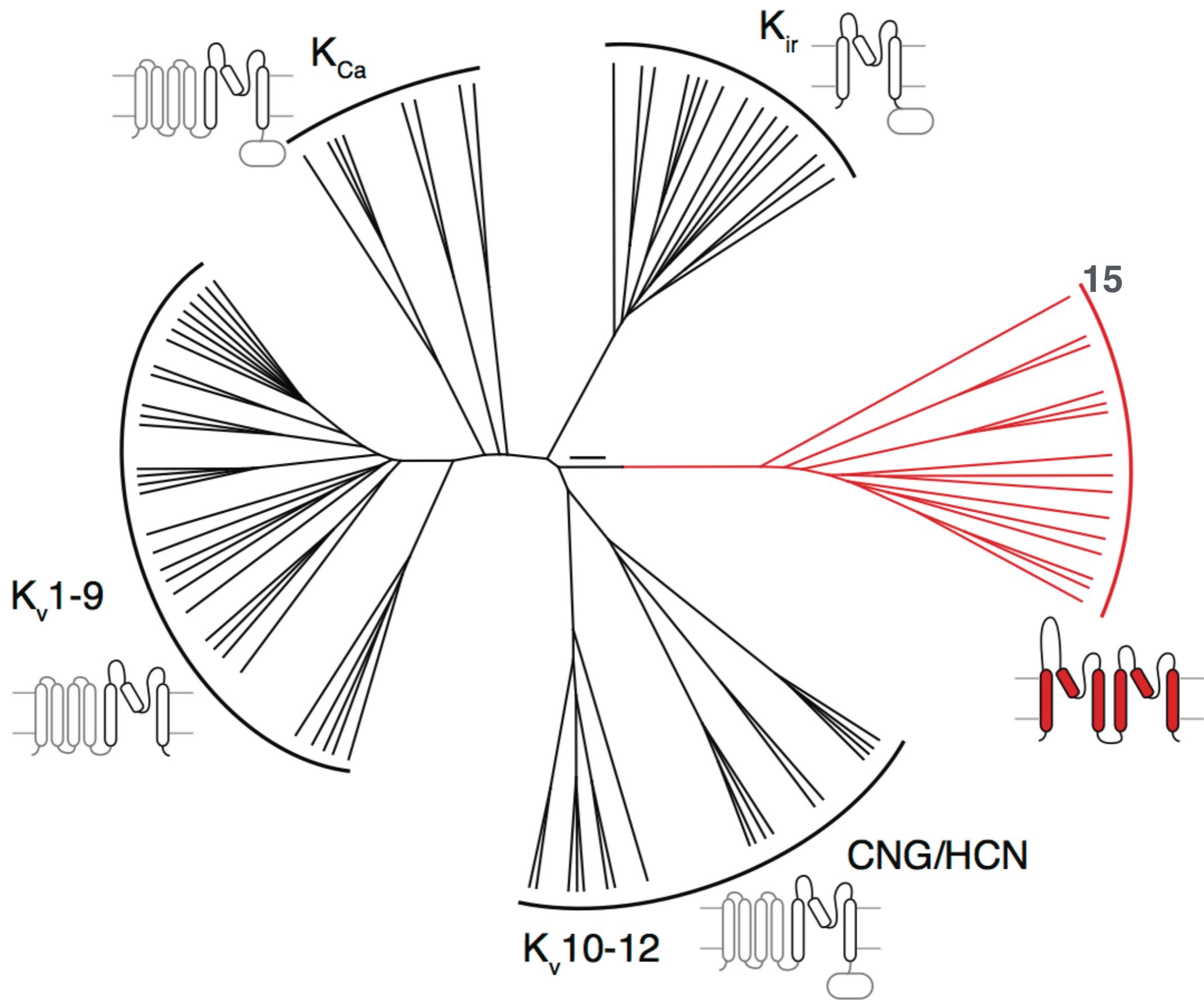
Series	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>	R <sub>10</sub>
<b>Z16</b>	H	H	H	H	H	H	H	OH	H	F
<b>2</b>	H	H	H	H	H	H	H	F	H	OH
<b>3</b>	H	H	H	H	H	F	H	OH	H	OH
<b>4</b>	H	H	H	H	H	OH	H	F	H	OH
<b>5</b>	H	H	H	H	H	F	OH	H	OH	H
<b>6</b>	1	H	H	H	H	H	H	OH	H	F
<b>7</b>	H	1	H	H	H	H	H	OH	H	F
<b>8</b>	H	H	1	H	H	H	H	OH	H	F
<b>9</b>	H	H	H	1	H	H	H	OH	H	F
<b>10</b>	1	H	H	H	H	H	H	F	H	OH
<b>11</b>	H	1	H	H	H	H	H	F	H	OH
<b>12</b>	H	H	1	H	H	H	H	F	H	OH
<b>13</b>	H	H	H	1	H	H	H	F	H	OH
<b>14</b>	1	H	H	H	H	F	H	OH	H	OH
<b>15</b>	H	1	H	H	H	F	H	OH	H	OH
<b>16</b>	H	H	1	H	H	F	H	OH	H	OH
<b>17</b>	H	H	H	1	H	F	H	OH	H	OH
<b>18</b>	1	H	H	H	H	OH	H	F	H	OH
<b>19</b>	H	1	H	H	H	OH	H	F	H	OH
<b>20</b>	H	H	1	H	H	OH	H	F	H	OH
<b>21</b>	H	H	H	1	H	OH	H	F	H	OH
<b>22</b>	1	H	H	H	H	F	OH	H	OH	H
<b>23</b>	H	1	H	H	H	F	OH	H	OH	H
<b>24</b>	H	H	1	H	H	F	OH	H	OH	H
<b>25</b>	H	H	H	1	H	F	OH	H	OH	H
<b>26</b>	H	H	H	H	CH <sub>3</sub>	H	H	OH	H	F
<b>27</b>	H	H	H	H	OCH <sub>3</sub>	H	H	OH	H	F
<b>28</b>	H	H	H	H	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	OH	H	F
<b>29</b>	1	H	H	H	CH <sub>3</sub>	H	H	OH	H	F
<b>30</b>	H	1	H	H	CH <sub>3</sub>	H	H	OH	H	F
<b>31</b>	H	H	1	H	CH <sub>3</sub>	H	H	OH	H	F
<b>32</b>	H	H	H	1	CH <sub>3</sub>	H	H	OH	H	F
<b>33</b>	1	H	H	H	OCH <sub>3</sub>	H	H	OH	H	F
<b>34</b>	H	1	H	H	OCH <sub>3</sub>	H	H	OH	H	F
<b>35</b>	H	H	1	H	OCH <sub>3</sub>	H	H	OH	H	F
<b>36</b>	H	H	H	1	OCH <sub>3</sub>	H	H	OH	H	F
<b>37</b>	1	H	H	H	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	OH	H	F
<b>38</b>	H	1	H	H	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	OH	H	F
<b>39</b>	H	H	1	H	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	OH	H	F
<b>40</b>	H	H	H	1	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	OH	H	F

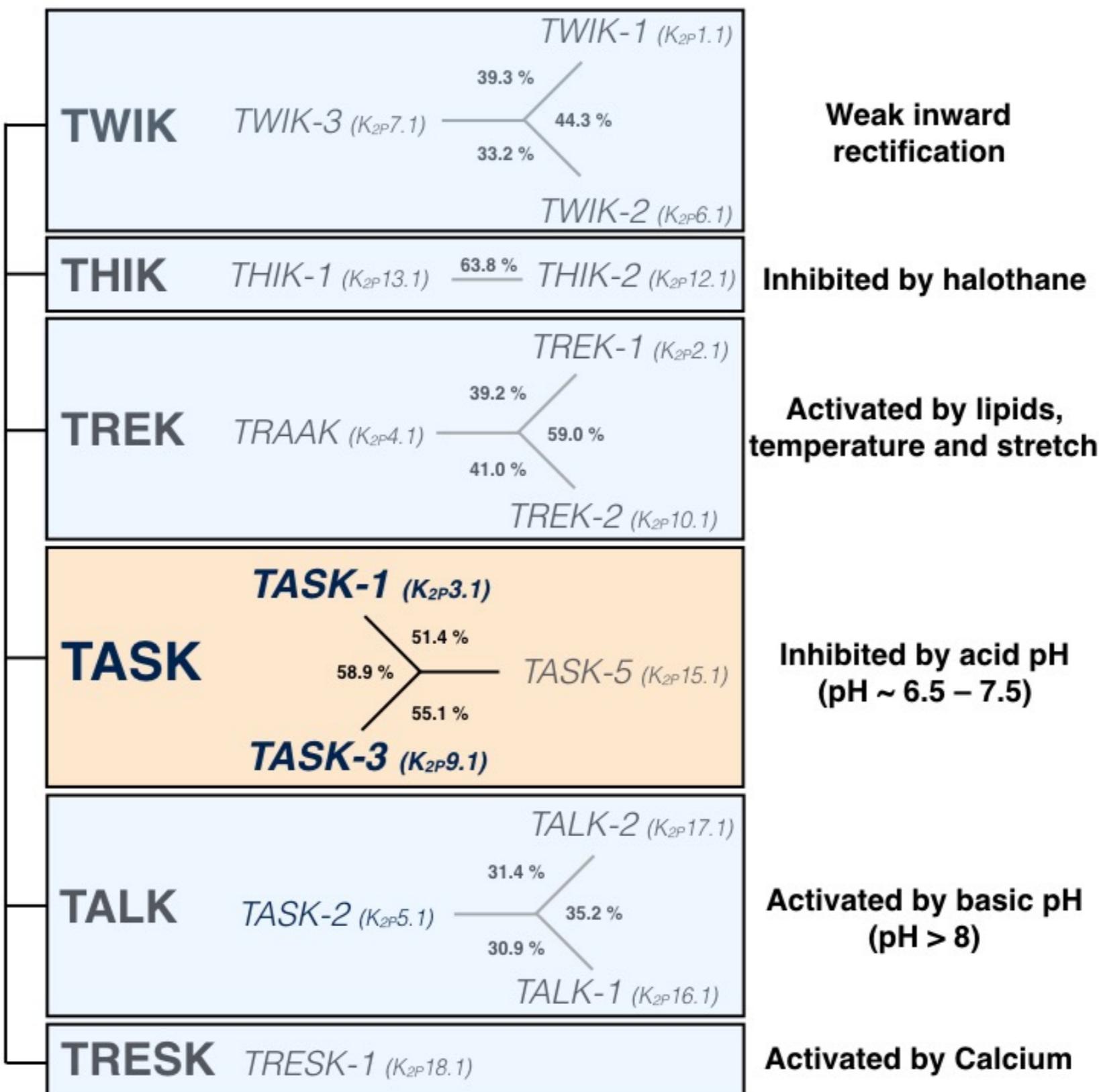
## Ejercicio 4. Trabajando con macromoléculas

### 1. Importar canal de potasio de dos dominios de poro TREK-2 (PDB id: 4XDK):

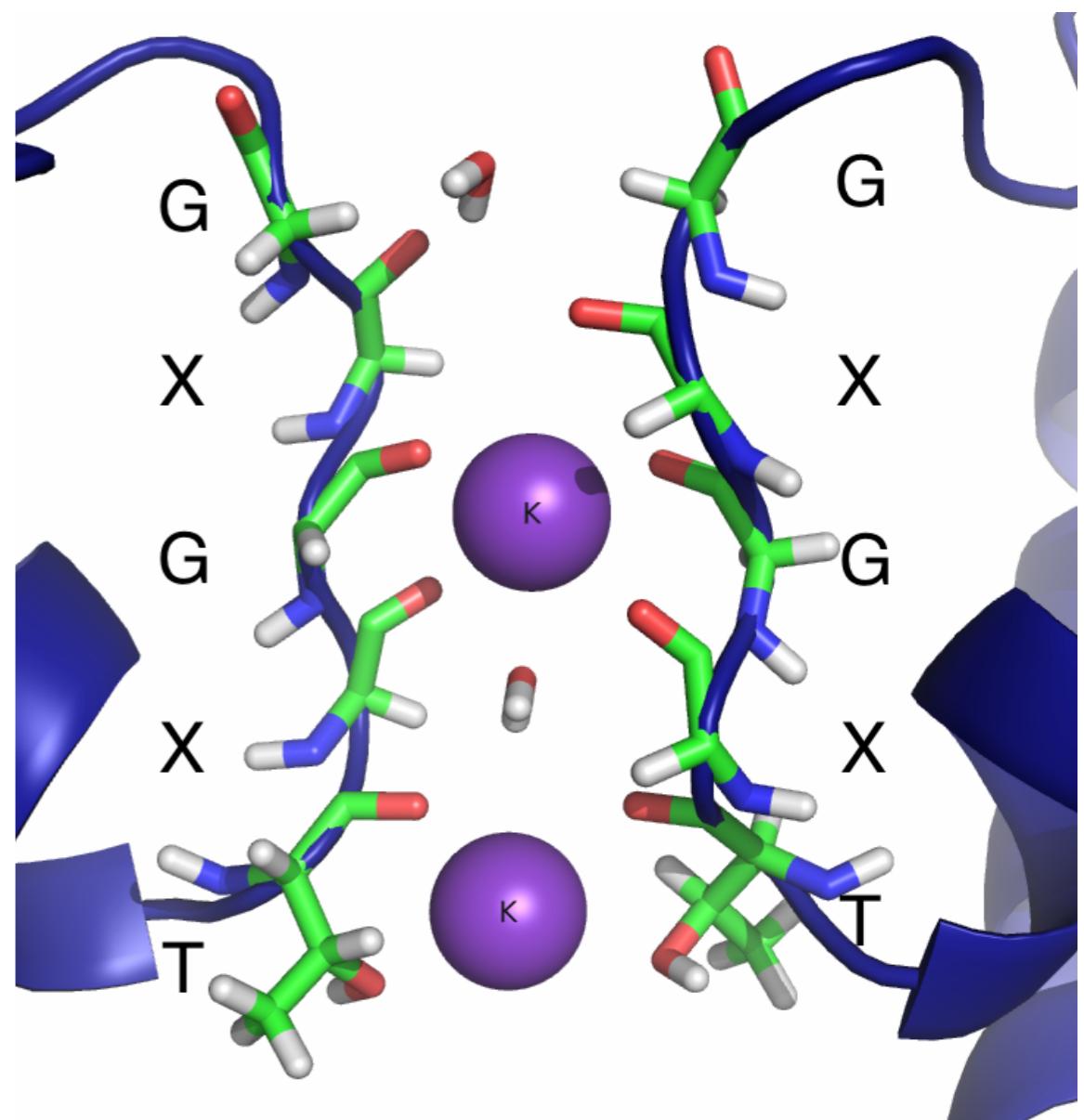
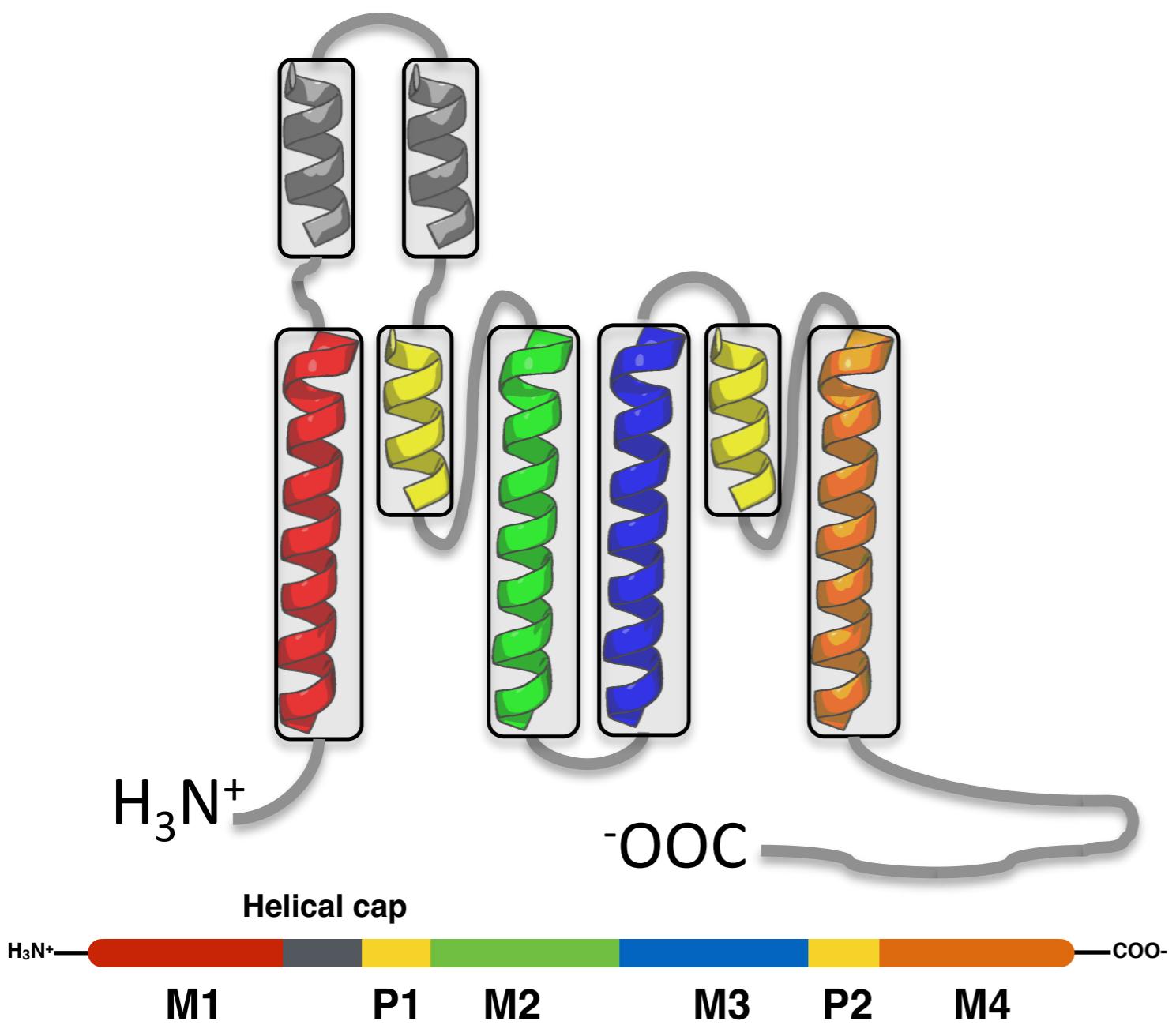
Protein Preparation Wizard



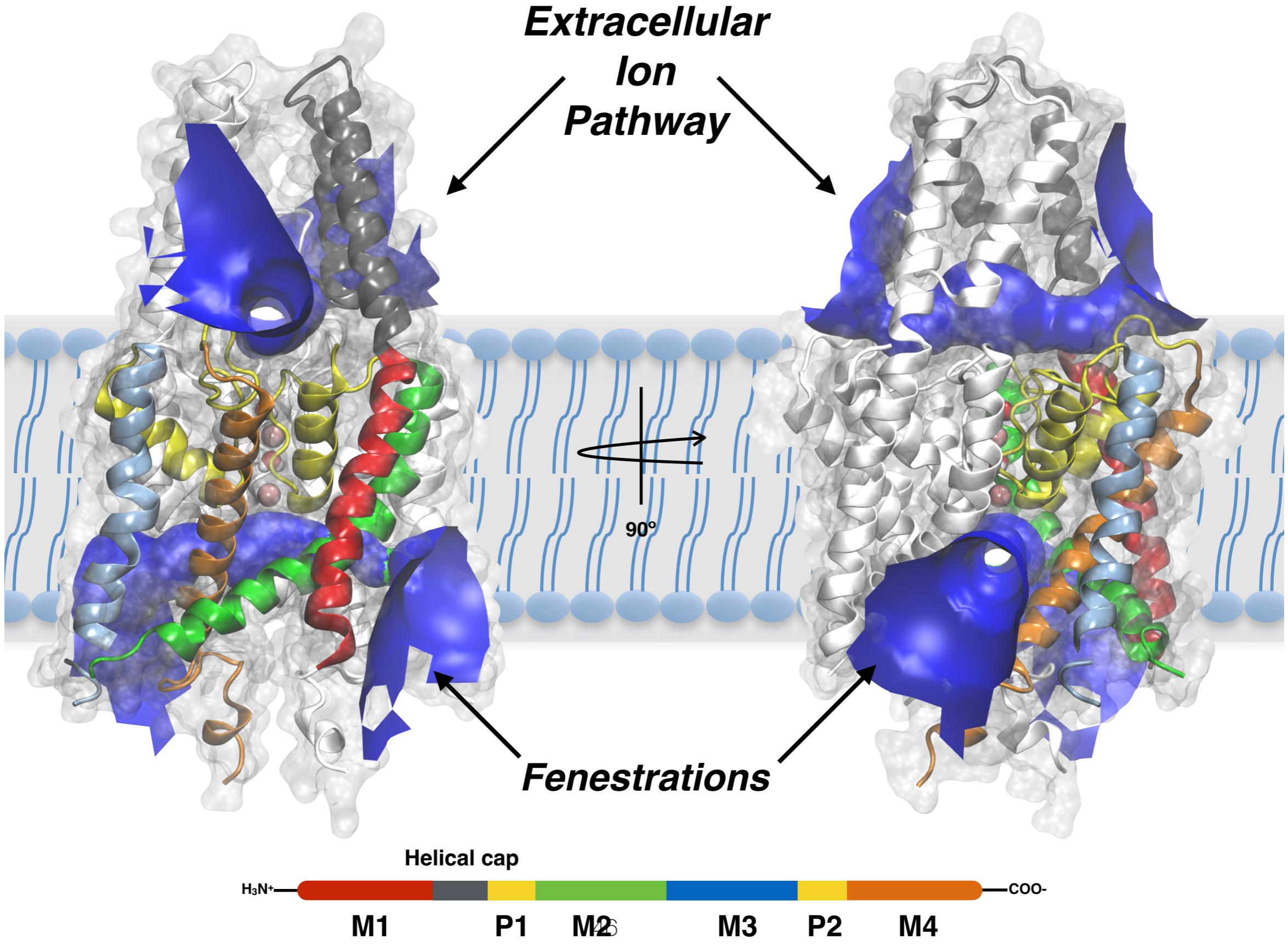




# Topology



# Structure





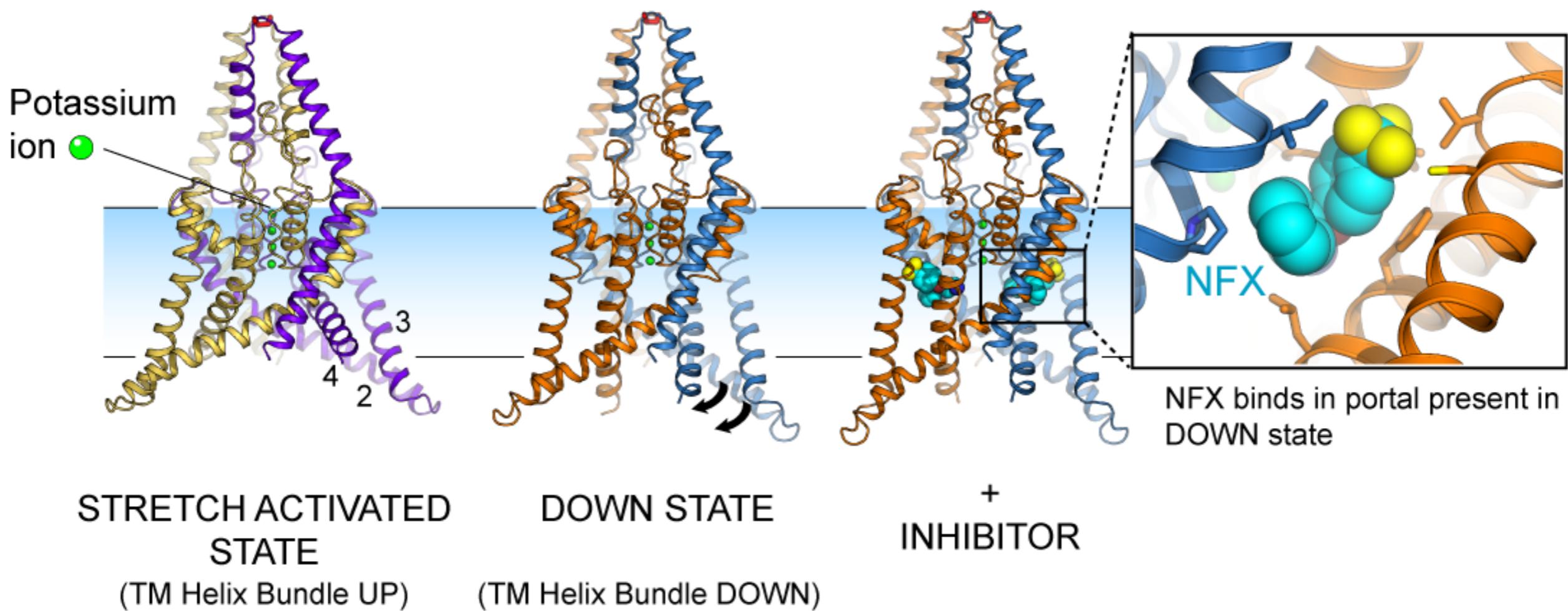
## K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac

Yin Yao Dong *et al.*

*Science* **347**, 1256 (2015);  
DOI: 10.1126/science.1261512

PDB ID	Title	Macromolecule Name
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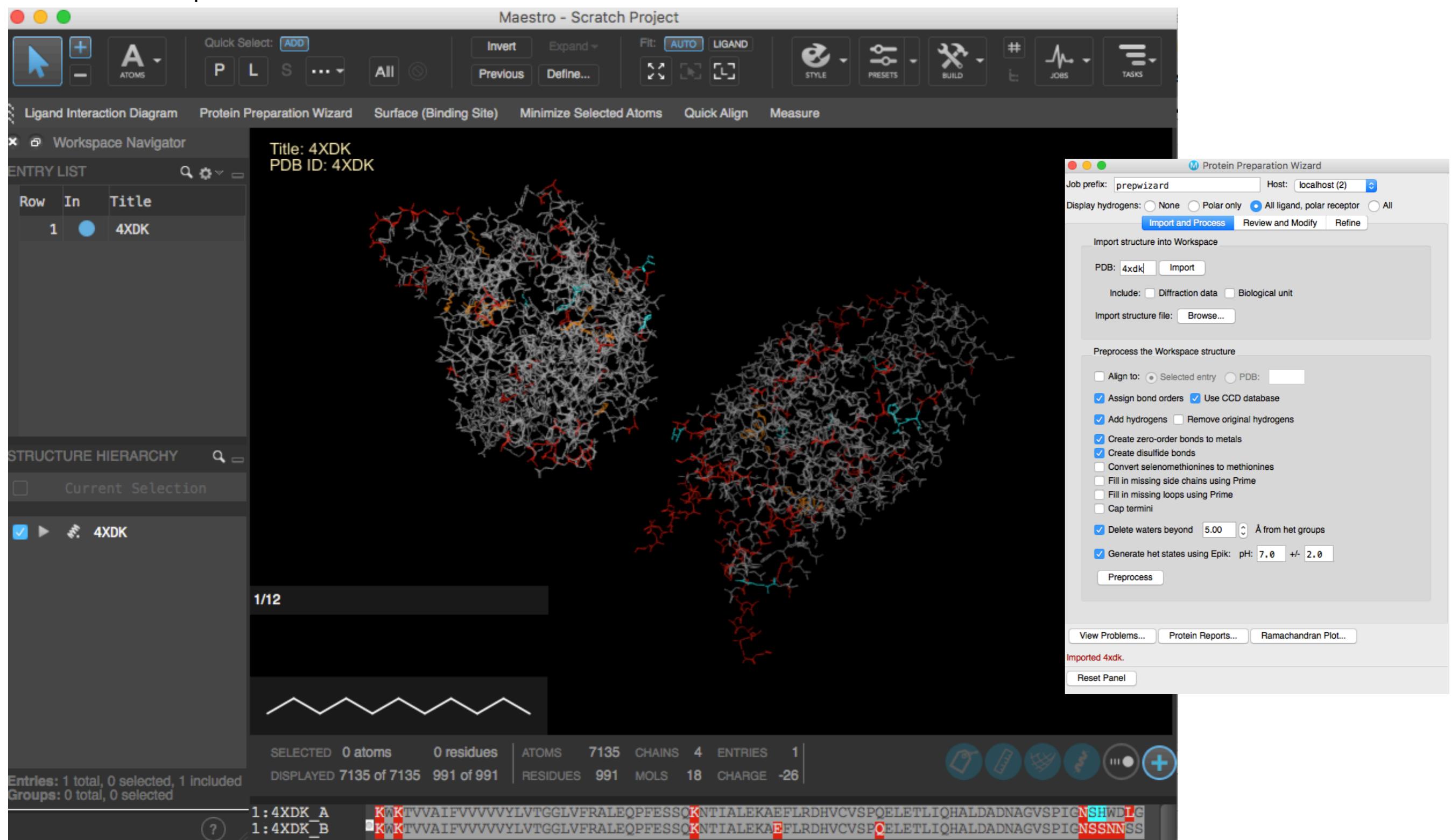
<input checked="" type="checkbox"/> <b>4BW5</b>	Crystal structure of human two pore domain potassium ion channel TREK2 (K2P10.1)	POTASSIUM CHANNEL SUBFAMILY K MEMBE...
<input checked="" type="checkbox"/> <b>4XDK</b>	Crystal structure of human two pore domain potassium ion channel TREK2 (K2P10.1) in complex with norfluoxetine	Potassium channel subfamily K membe...
<input checked="" type="checkbox"/> <b>4XDL</b>	Crystal structure of human two pore domain potassium ion channel TREK2 (K2P10.1) in complex with a brominated fluoxetine	Potassium channel subfamily K membe...
<input checked="" type="checkbox"/> <b>4XDJ</b>	Crystal structure of human two pore domain potassium ion channel TREK2 (K2P10.1) in an alternate conformation (FORM 2)	POTASSIUM CHANNEL SUBFAMILY K MEMBE...



## Ejercicio 2. Trabajando con macromoléculas

### 1. Importar canal de potasio de dos domos de poro TREK-2 (PDB id: 4XDK):

Protein Preparation Wizard



## Ejercicio 2. Trabajando con macromoléculas

### 2. Arreglar la proteína. (Eliminar segundo canal, otros compuestos que no son ligando, lípidos, etc.):

- Protein Preparation Wizard -> Review and Modify -> Analyze Workspace
- Select Chains C & D -> Delete selected chains
- Select Het No. 4, 5, 6, 9, 10 & 11 -> Delete selected residues  
Así se eliminan los ligados que no hacen parte del complejo TREK-2 – Norfluoxetine (ver PDB info)
- Preparar el complejo: Protein Preparation Wizard -> Import and Process -> Preprocess
- Visualizar la proteína en representación **Cartoon**, los ligados en **sticks** y los K<sup>+</sup> en **VDW**.



Maestro - Scratch Project

Quick Select: **ADD**   **P** **L** **S** **...** **All**   **Invert** **Expand** **Fit: AUTO LIGAND**   **Previous** **Define...**   **Atoms** **Style** **Presets** **Build**   **#** **JOBS** **TASKS**

Ligand Interaction Diagram   Protein Preparation Wizard   Surface (Binding Site)   Minimize Selected Atoms   Quick Align   Measure

**Workspace Navigator**

Title: 4XDK  
PDB ID: 4XDK

ENTRY LIST

Row	In	Title
1	○	4XDK
2	●	<b>4XDK</b>

STRUCTURE HIERARCHY

Current Selection

4XDK

1/2

SELECTED 0 atoms 0 residues   ATOMS 7494 CHAINS 2 ENTRIES 1  
DISPLAYED 84 of 7494 10 of 504   RESIDUES 504 MOLS 9 CHARGE -14

Entries: 2 total, 1 selected, 1 included  
Groups: 0 total, 0 selected

2:4XDK\_A   KWKTIVVAIFVVVVVYLVTGLVFRALLEQPFESSQKNTIALEKAELRDHVCVSPQELETLIQHALDADNAGVSPIGNSHWDLG  
2:4XDK\_B   KWKTIVVAIFVVVVVYLVTGLVFRALLEQPFESSQKNTIALEKAELRDHVCVSPQELETLIQHALDADNAGVSPIGNSSNNSS

Toolbar icons: Selection tools, Style, Presets, Build, Measure, Align, Fit, Surface, Ligand, Invert, Expand, Previous, Define, Atoms, Style, Presets, Build, #, JOBS, TASKS.

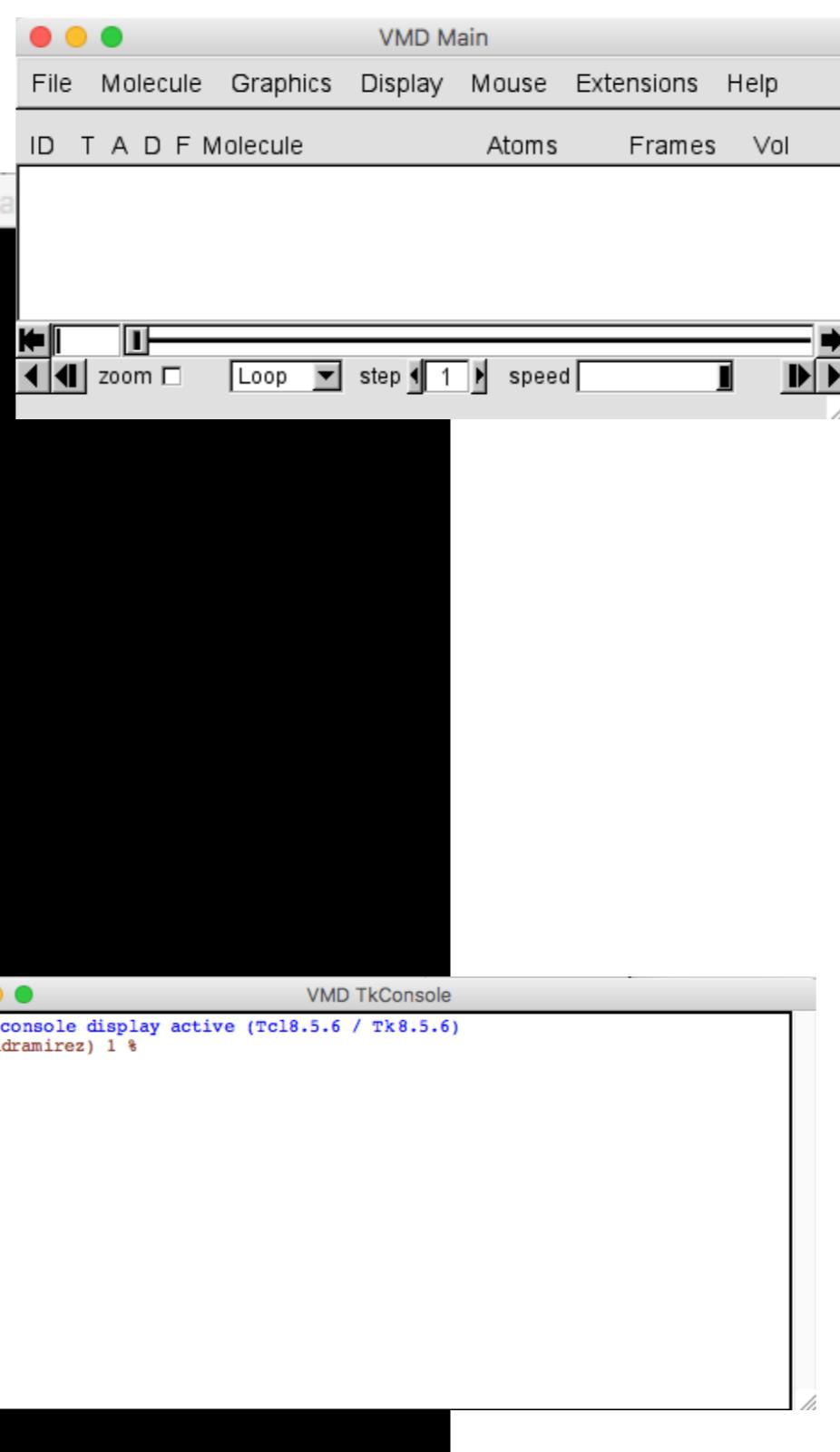
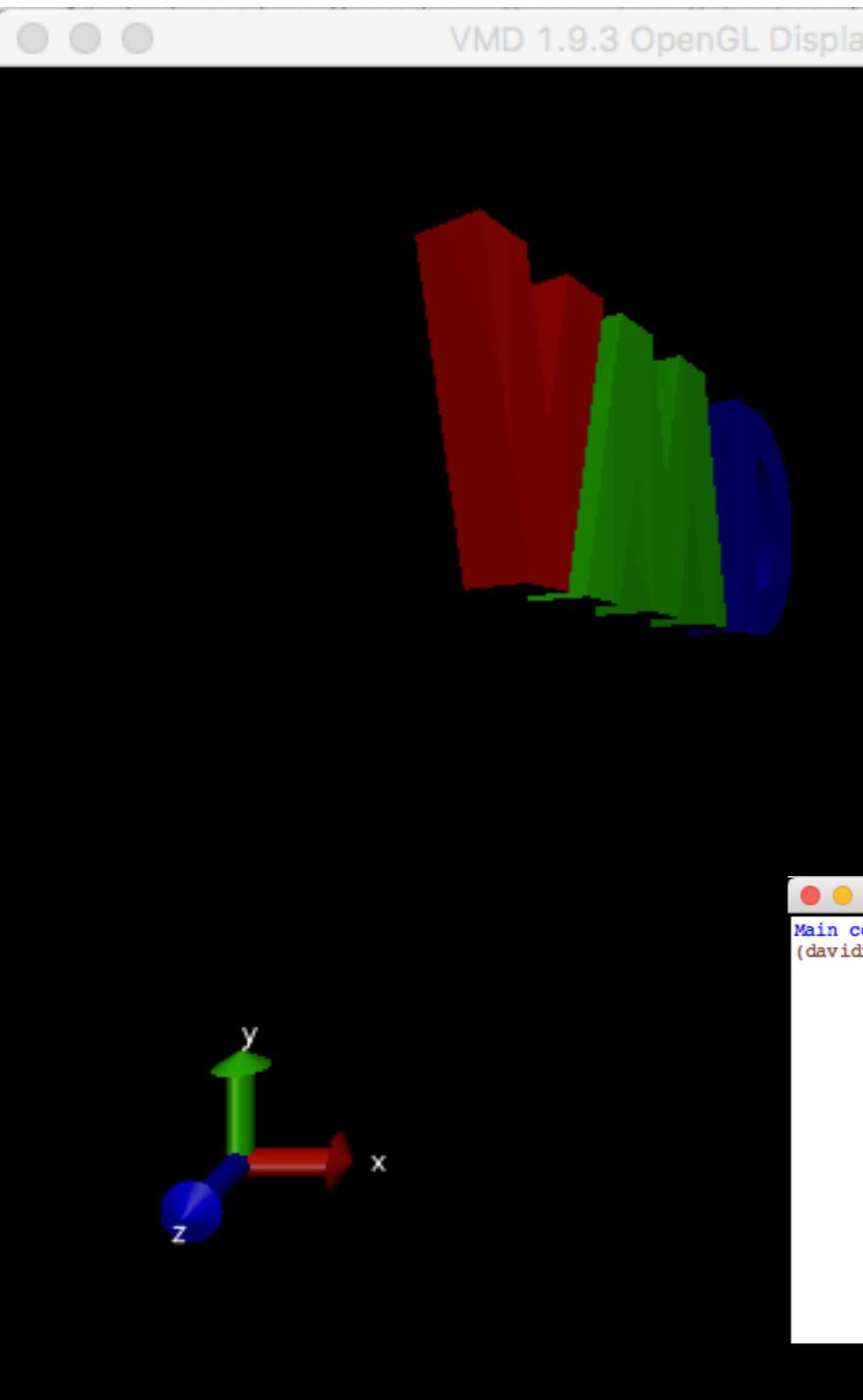
### 3. Guardar el complejo.

- **Seleccionar el complejo en el Project Table:** Export -> 4xdk\_modificated.mol2
- **Seleccionar el complejo en el Project Table:** Export -> 4xdk\_modificated.pdb
- **Seleccionar el complejo en el Project Table:** Export -> 4xdk\_modificated.mae



# VMD

Visual Molecular Dynamics



Graphical Representations

Selected Molecule

Create Rep Delete Rep

Style Color Selection

Selected Atoms

Draw style Selections Trajectory Periodic

Coloring Method Material

Name Opaque

Drawing Method Default

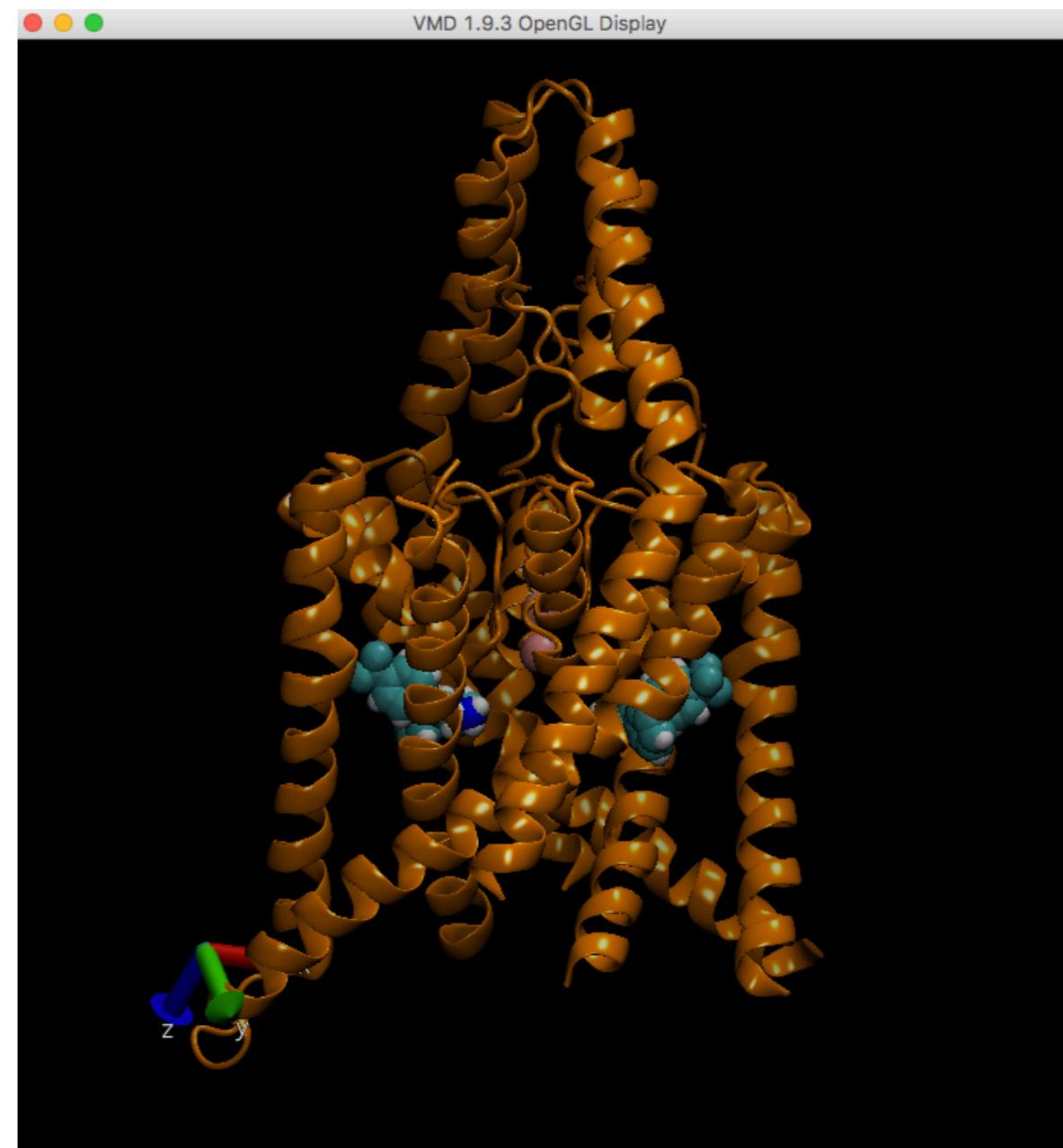
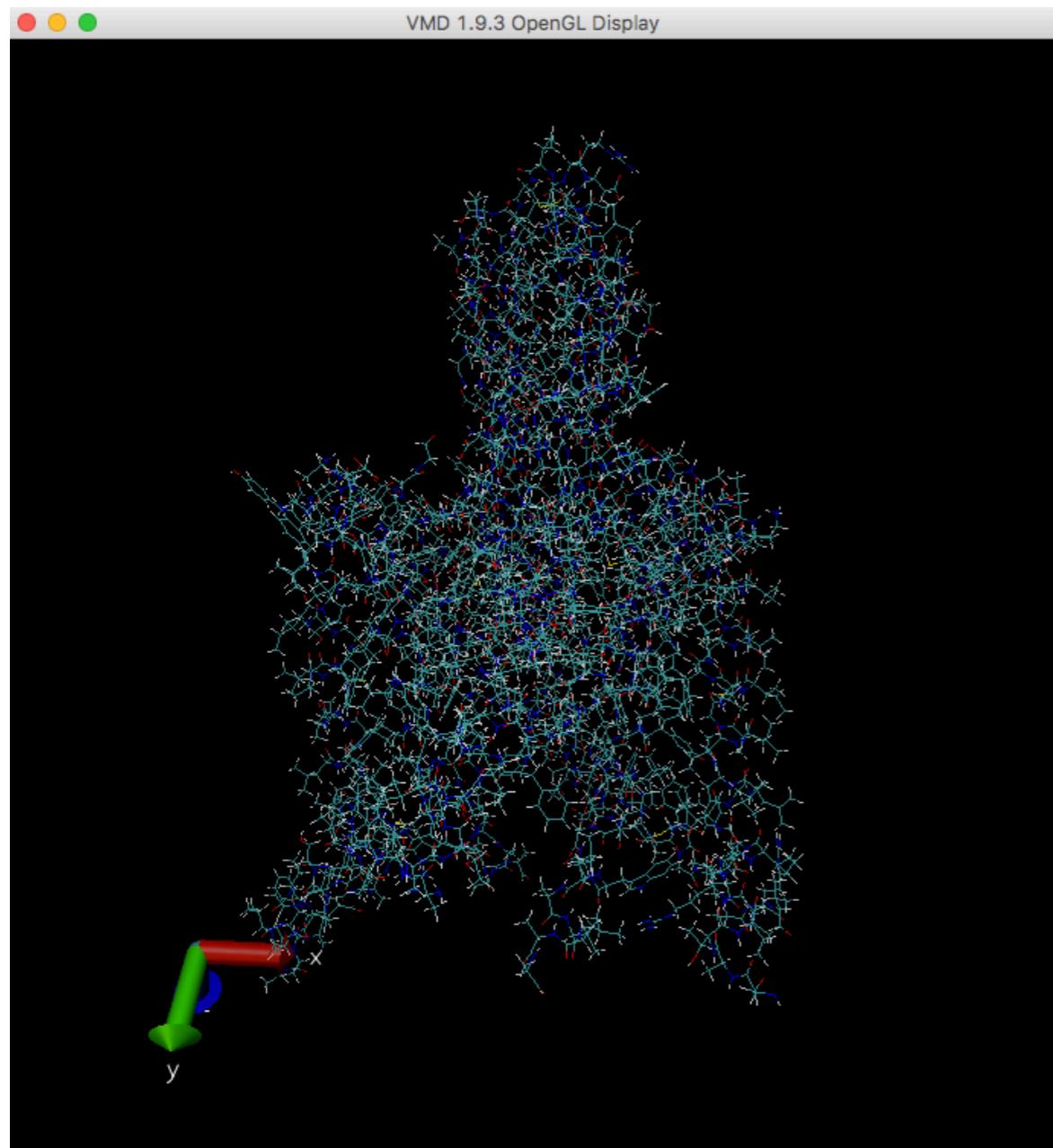
Thickness 1

◆ Apply Changes Automatically Apply

This panel contains several configuration sections: "Create Rep" and "Delete Rep" buttons, "Style", "Color", and "Selection" dropdowns, a "Selected Atoms" list, and tabs for "Draw style", "Selections", "Trajectory", and "Periodic". It also includes "Coloring Method" and "Material" dropdowns, "Name" and "Opaque" options, "Drawing Method" and "Default" options, and a "Thickness" slider set to 1. At the bottom are "Apply Changes Automatically" and "Apply" buttons.

## 1. Importar el complejo a VMD.

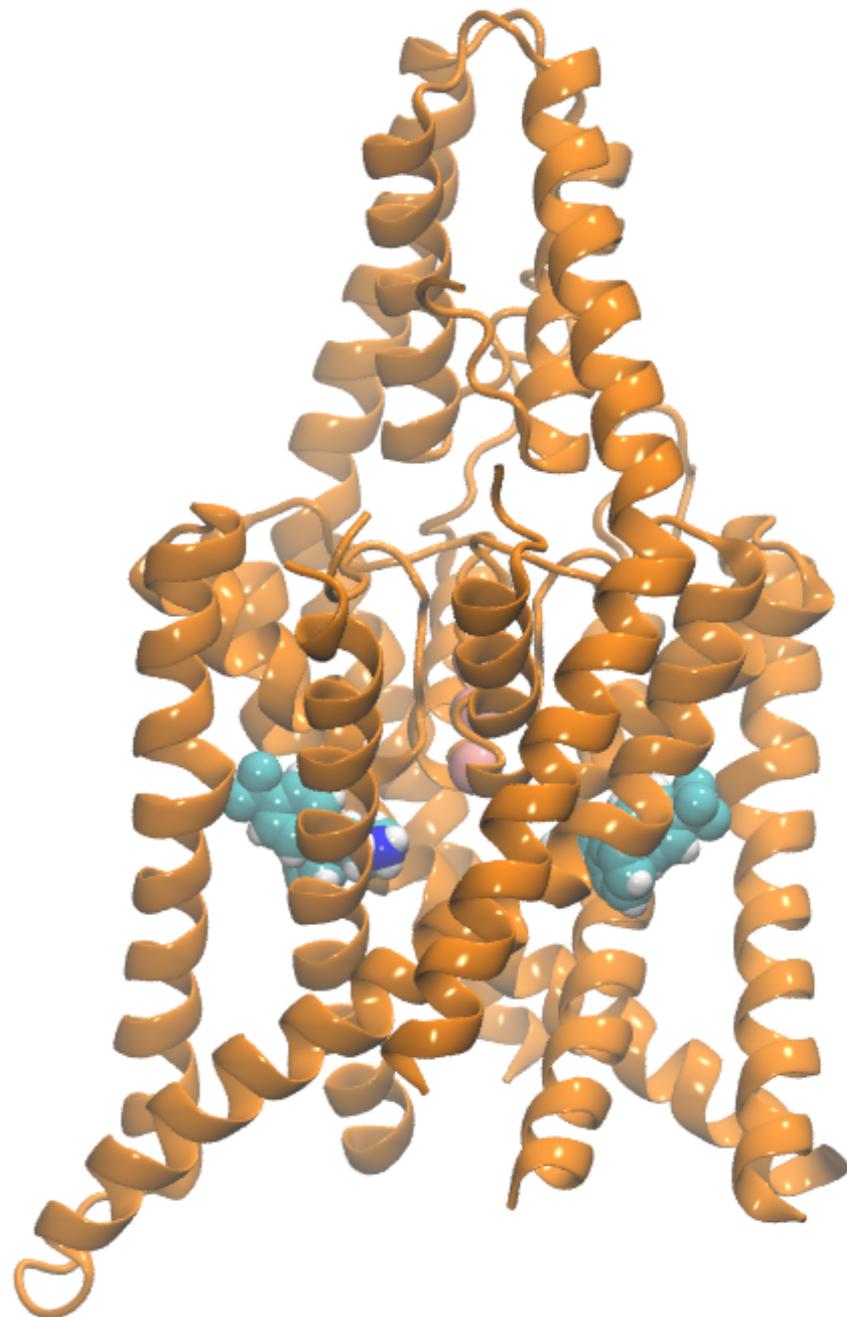
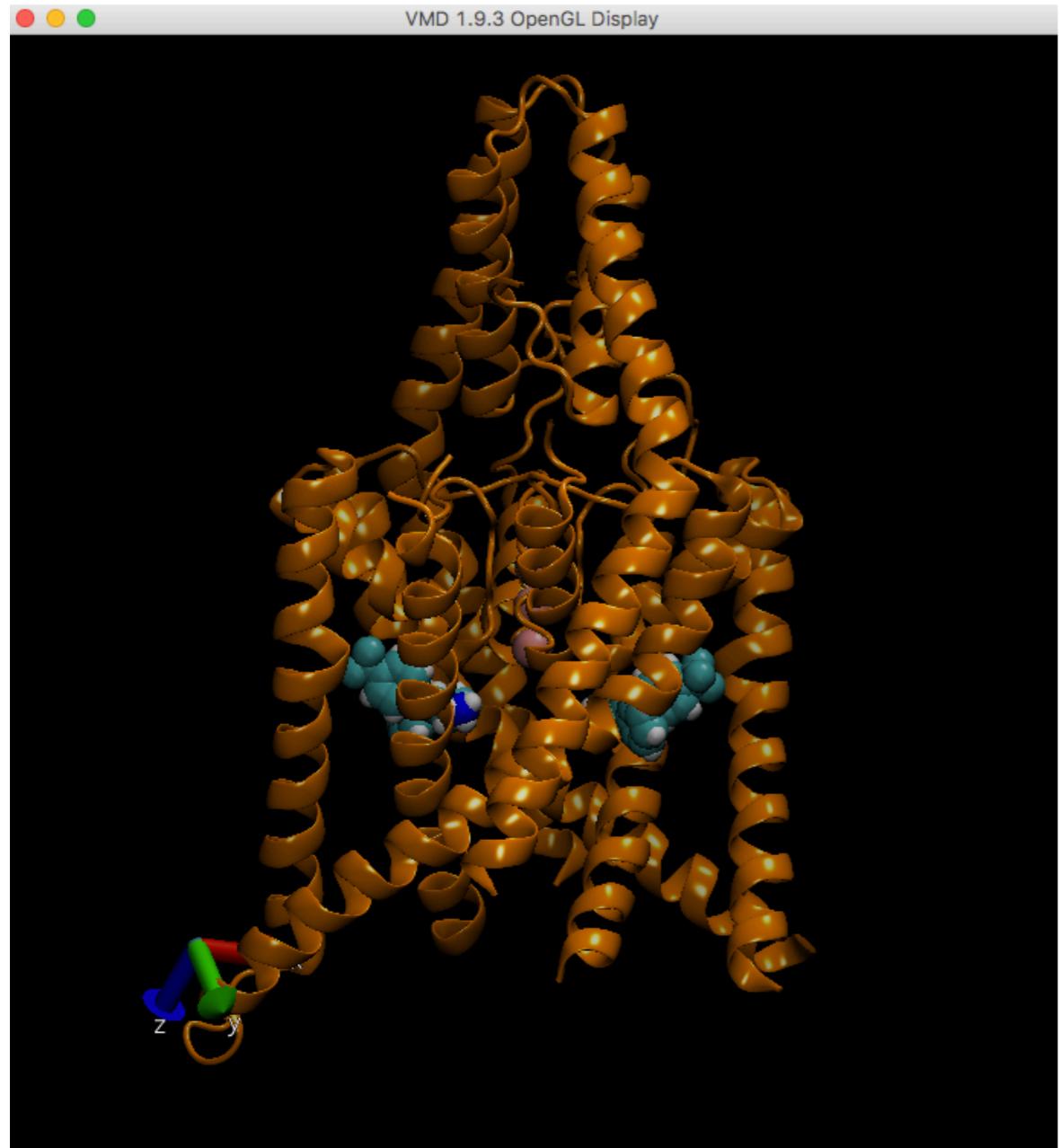
- En **VMD main**: File -> New Molecule -> Browse -> /PATH/TO/FILES/4xdk\_modified.pdb -> Load



Usando la ventana de Graphical Representation

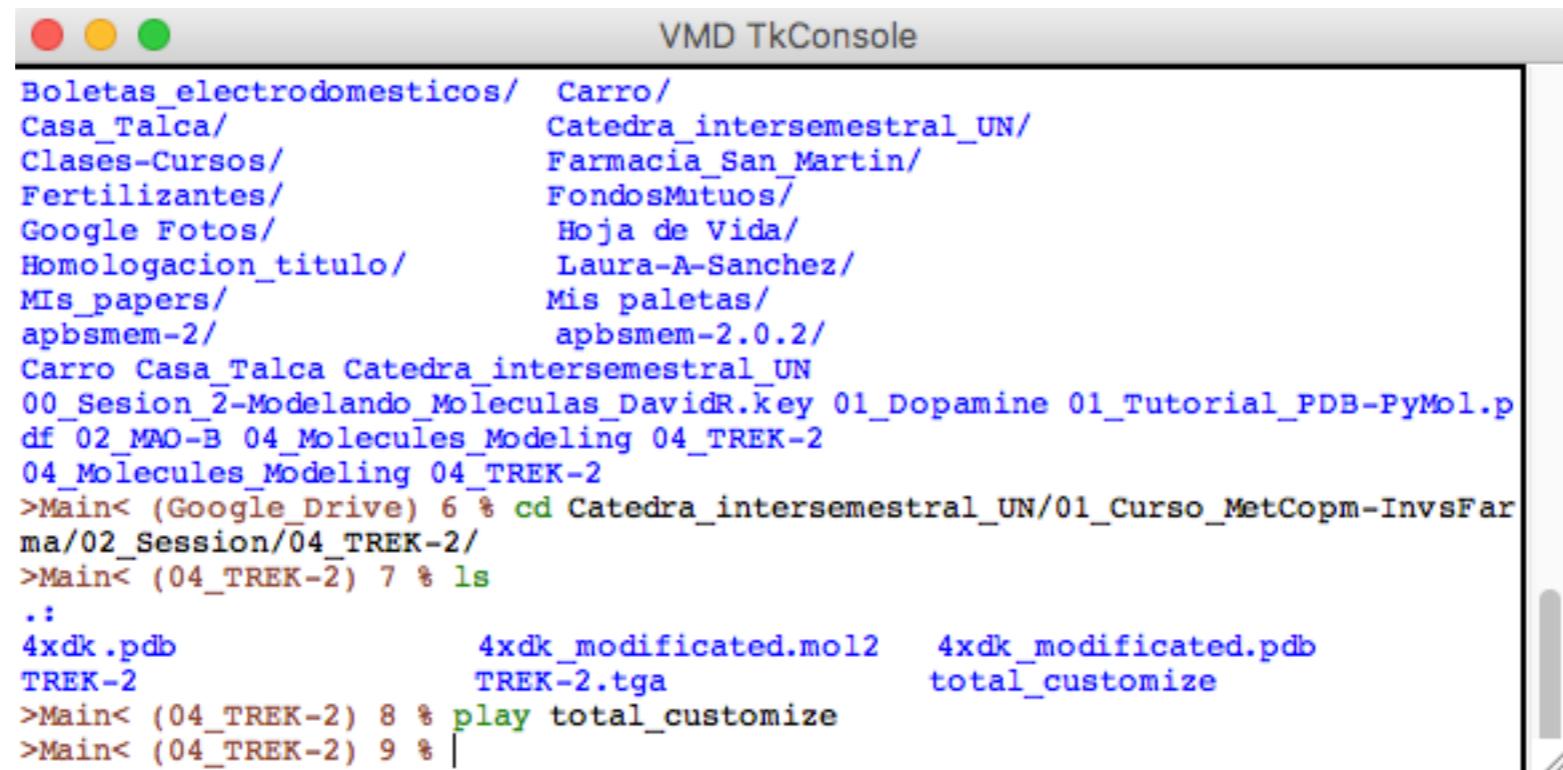
## 2. Guardando imágenes en VMD.

- En **VMD main**: File -> Render -> Tachyon -> Filename:Browse -> Start Rendering



### 3. Ejecutado Scripts en VMD.

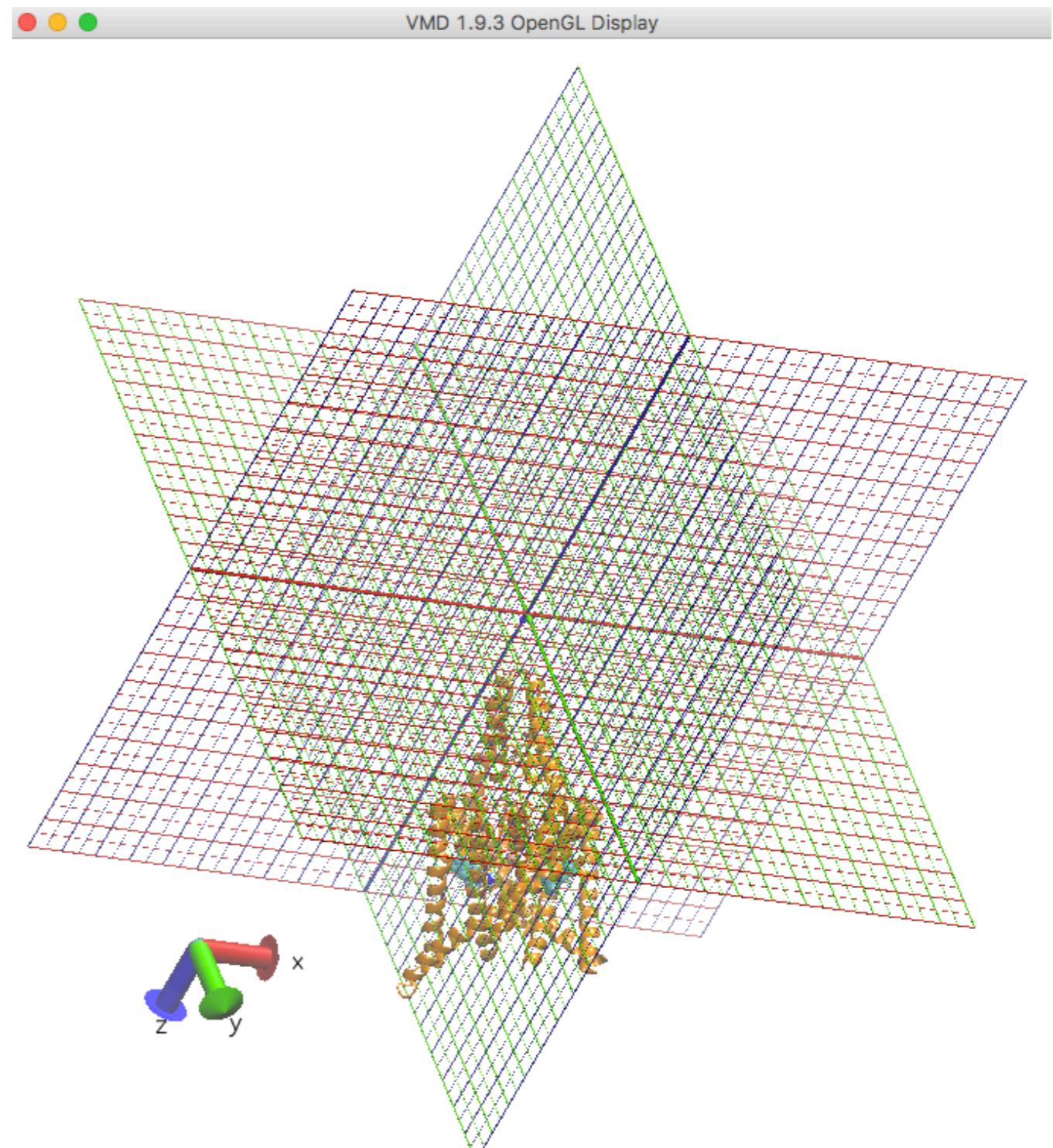
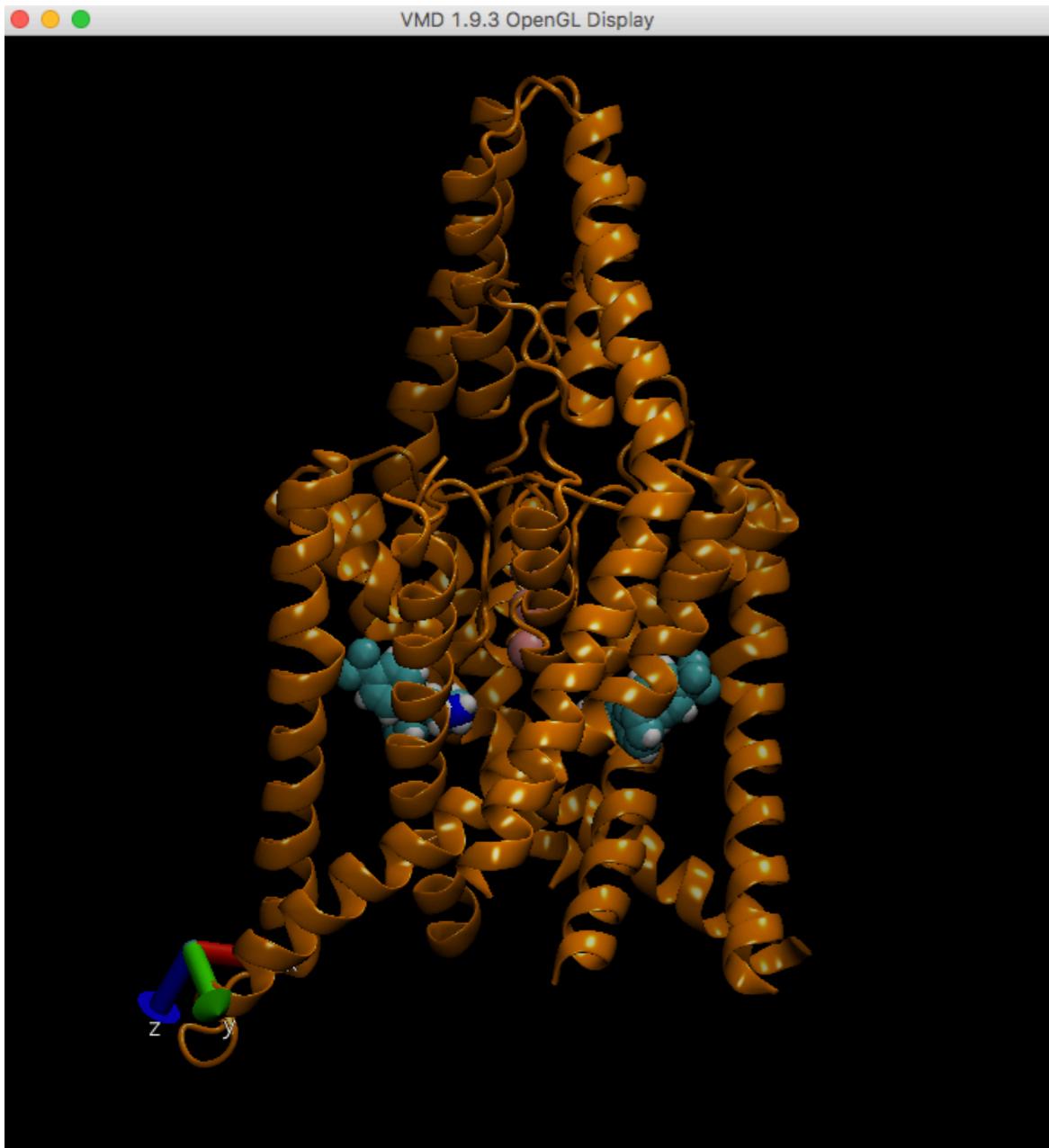
- En **VMD main:** Extensions-> Tk Console
  - **Dirigirse al directorio de trabajo:** cd /Directorio/De/Trabajo/
  - **Copiar script total\_customize al directorio de trabajo y luego cargarlo:** play total\_customize



The screenshot shows a terminal window titled "VMD TkConsole". The session starts with a list of directory contents, followed by a series of commands in a shell-like environment. The commands include navigating to a directory, listing files, and running a script named "total\_customize".

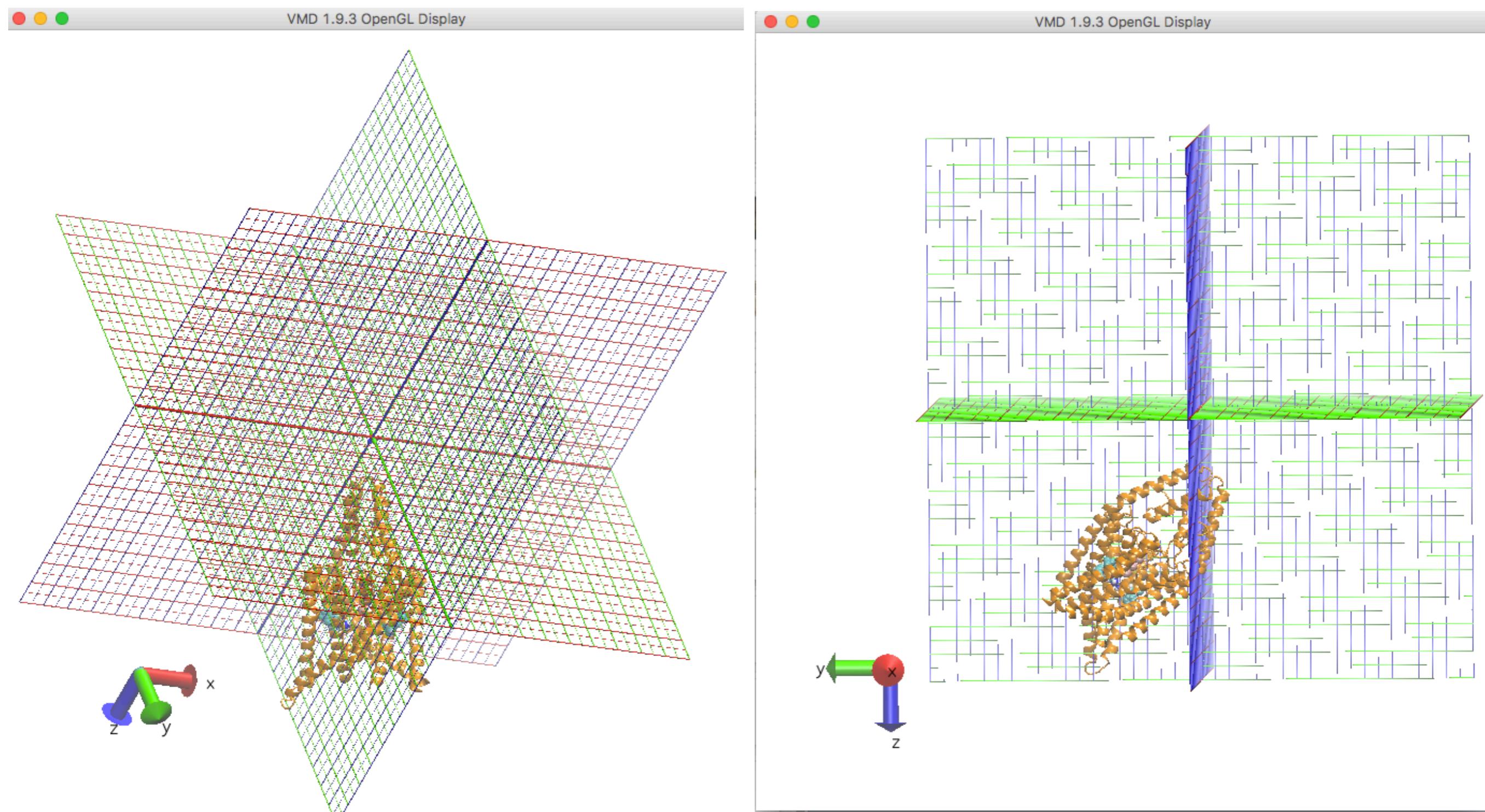
```
Boletas_electrodomesticos/ Carro/
Casa_Talca/ Catedra_intersemestral_UN/
Clases-Cursos/ Farmacia_San_Martin/
Fertilizantes/ FondosMutuos/
Google Fotos/ Hoja_de_Vida/
Homologacion_titulo/ Laura-A-Sanchez/
MIs_papers/ Mis_paletas/
apbsmem-2/ apbsmem-2.0.2/
Carro Casa_Talca Catedra_intersemestral_UN
00_Sesion_2-Modelando_Moleculas_DavidR.Key 01_Dopamine 01_Tutorial_PDB-PyMol.p
df 02_MA0-B 04_Molecules_Modeling 04_TREK-2
04_Molecules_Modeling 04_TREK-2
>Main< (Google_Drive) 6 % cd Catedra_intersemestral_UN/01_Curso_MetCopm-InvsFar
ma/02_Session/04_TREK-2/
>Main< (04_TREK-2) 7 % ls
.:
4xdk.pdb 4xdk_modificated.mol2 4xdk_modificated.pdb
TREK-2 TREK-2.tga total_customize
>Main< (04_TREK-2) 8 % play total_customize
>Main< (04_TREK-2) 9 %
```

### 3. Ejecutado Scripts en VMD.



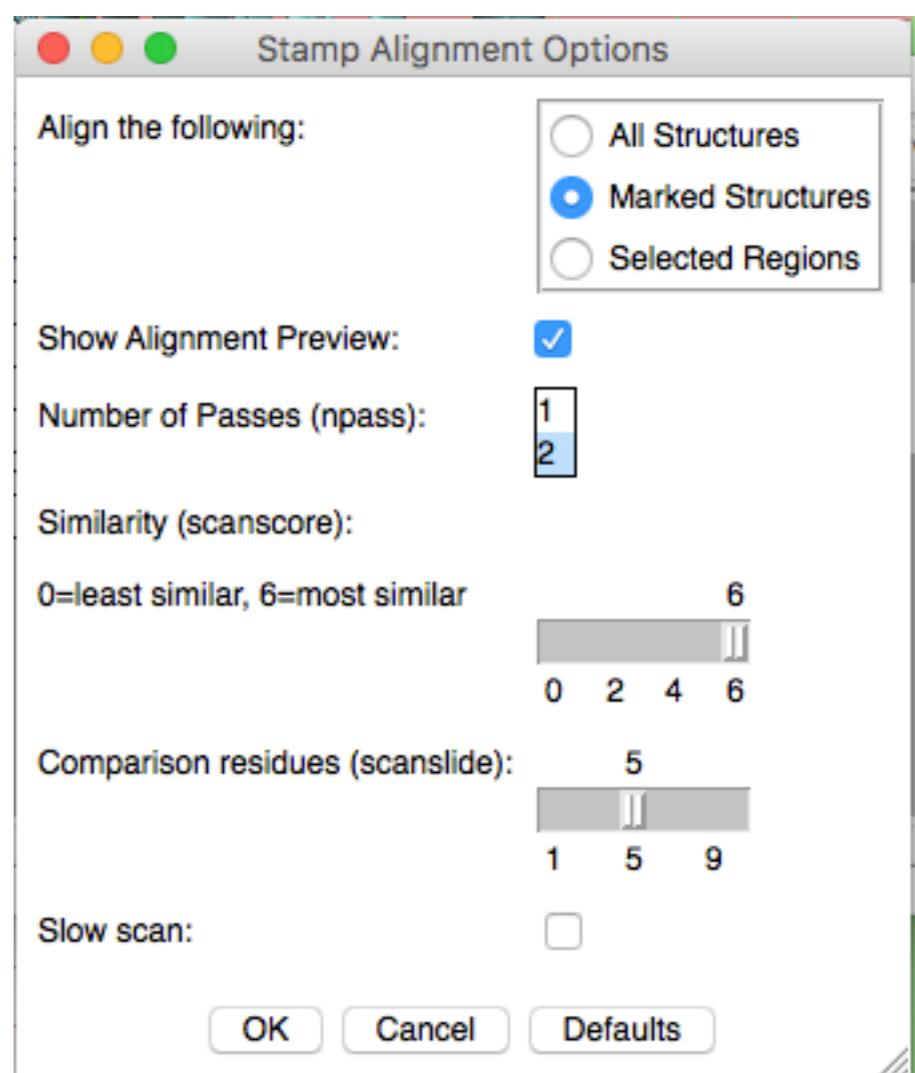
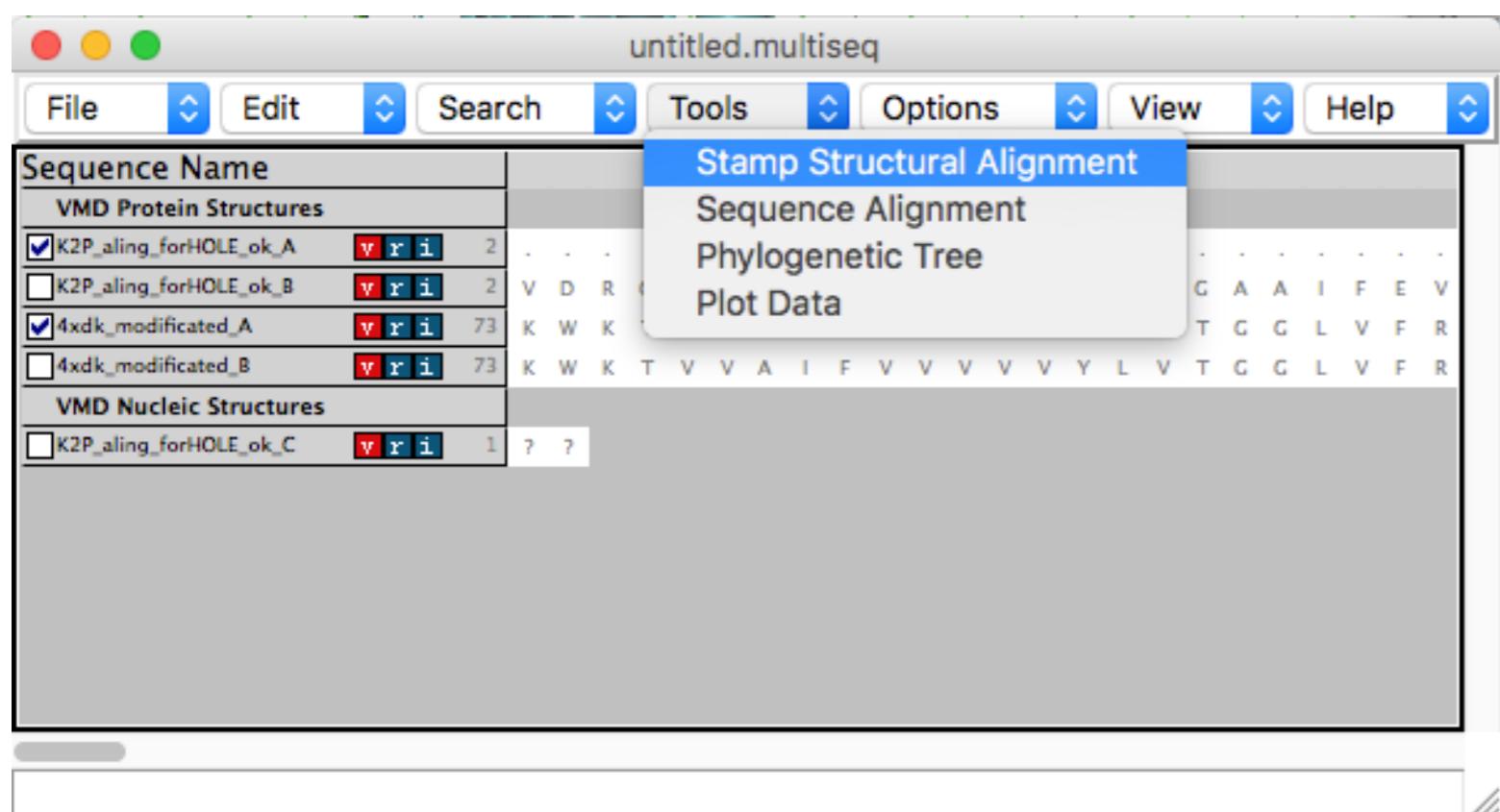
Grid: En VMD Open GL Display -> G

### 3. Ejecutado Scripts en VMD.

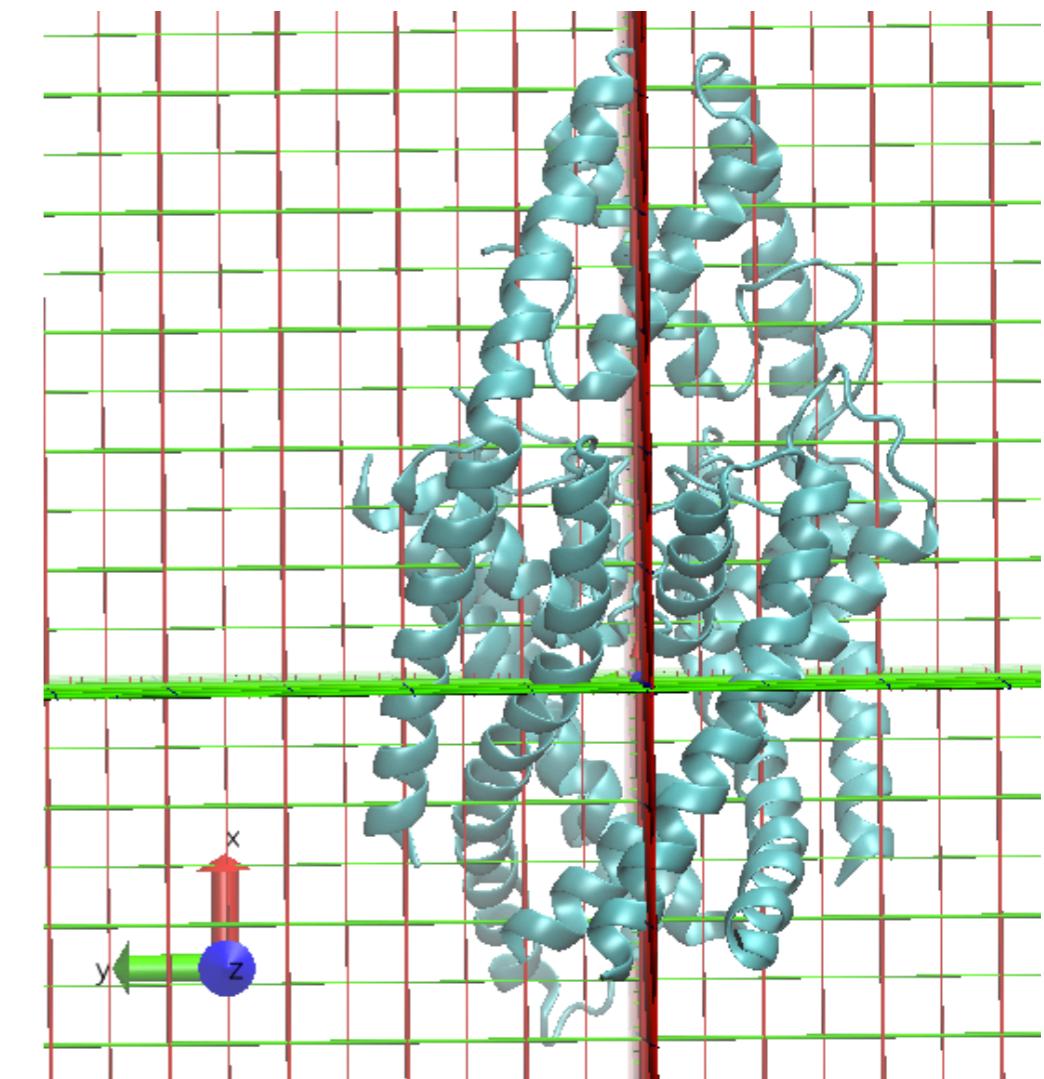
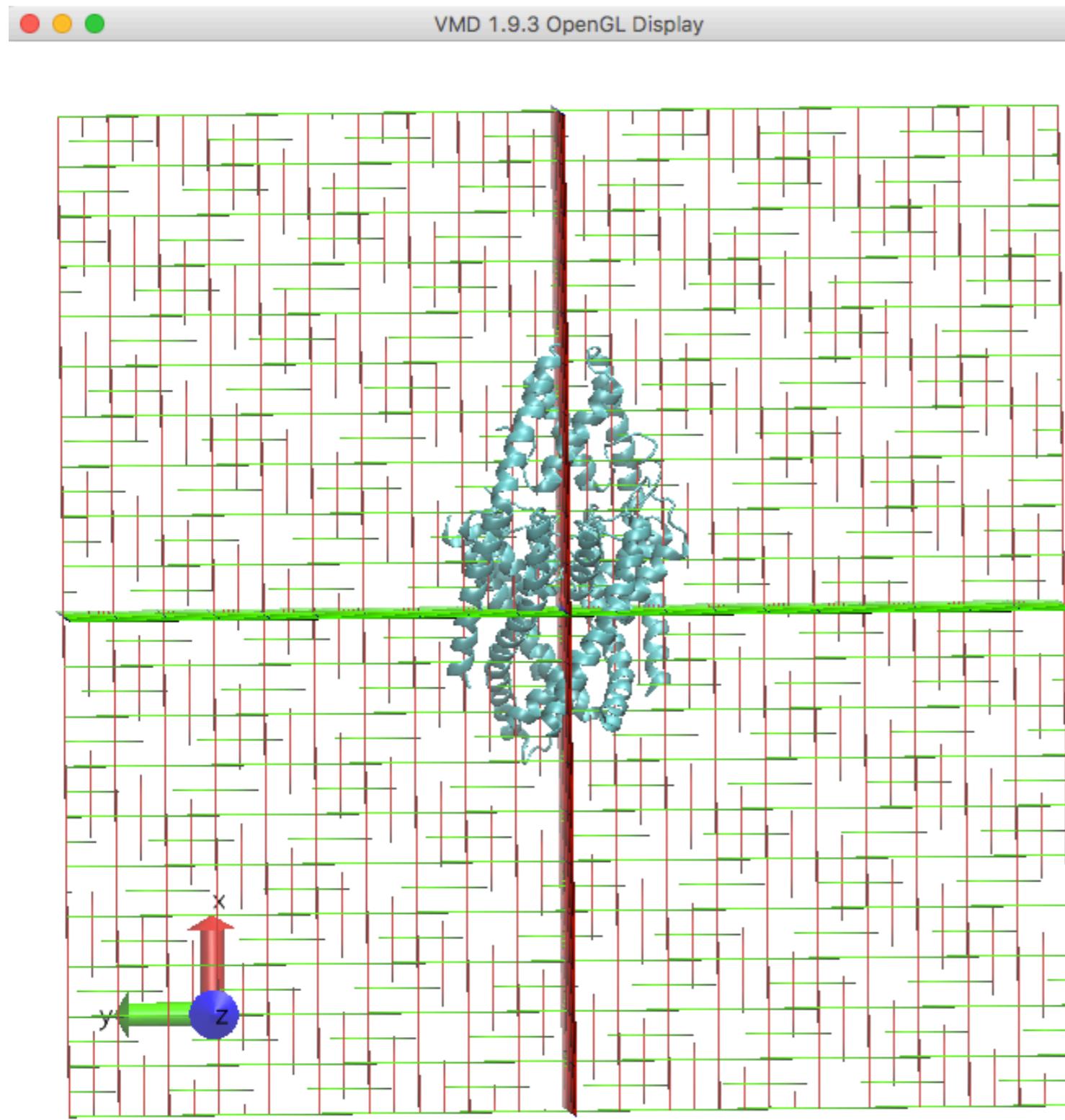


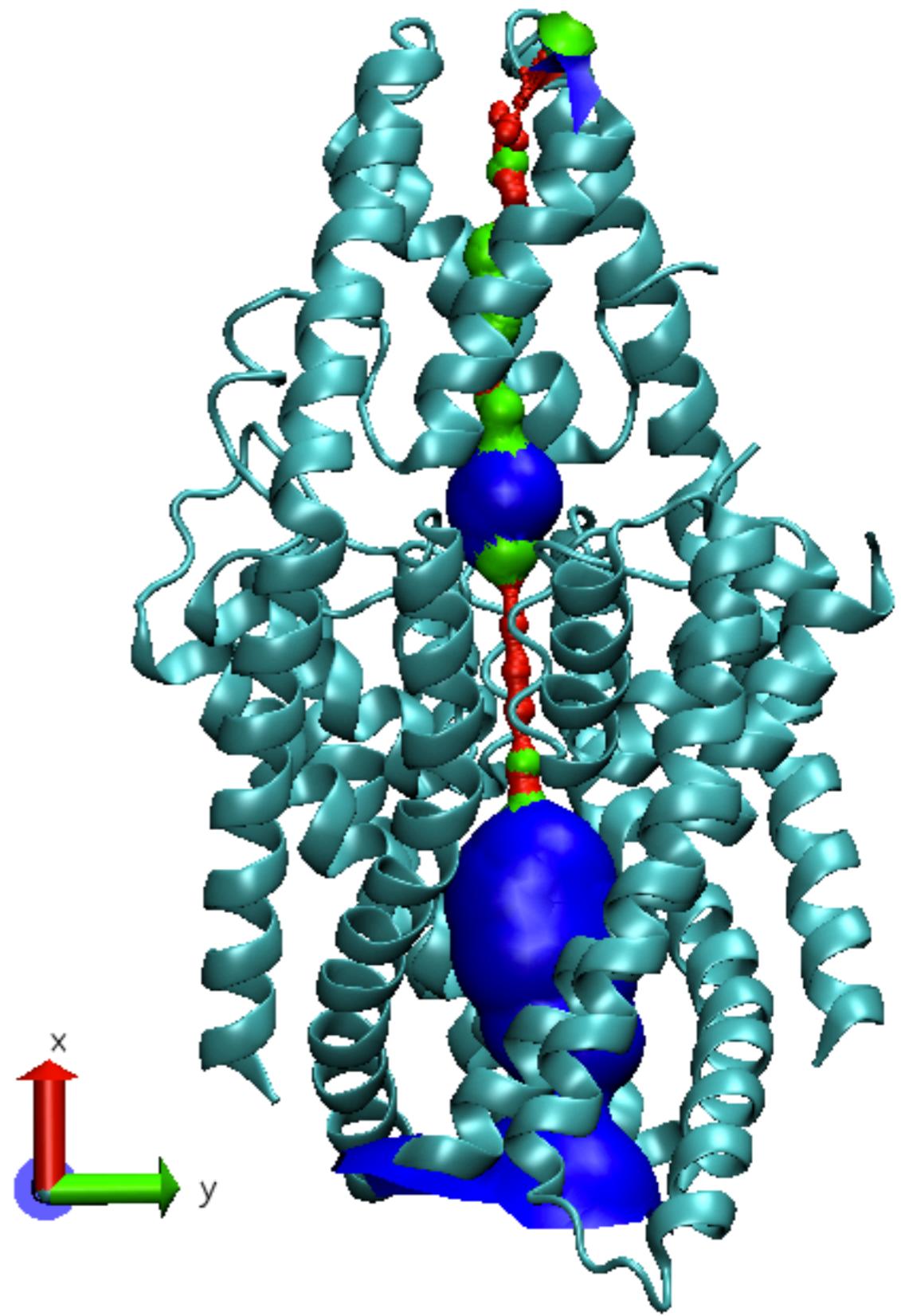
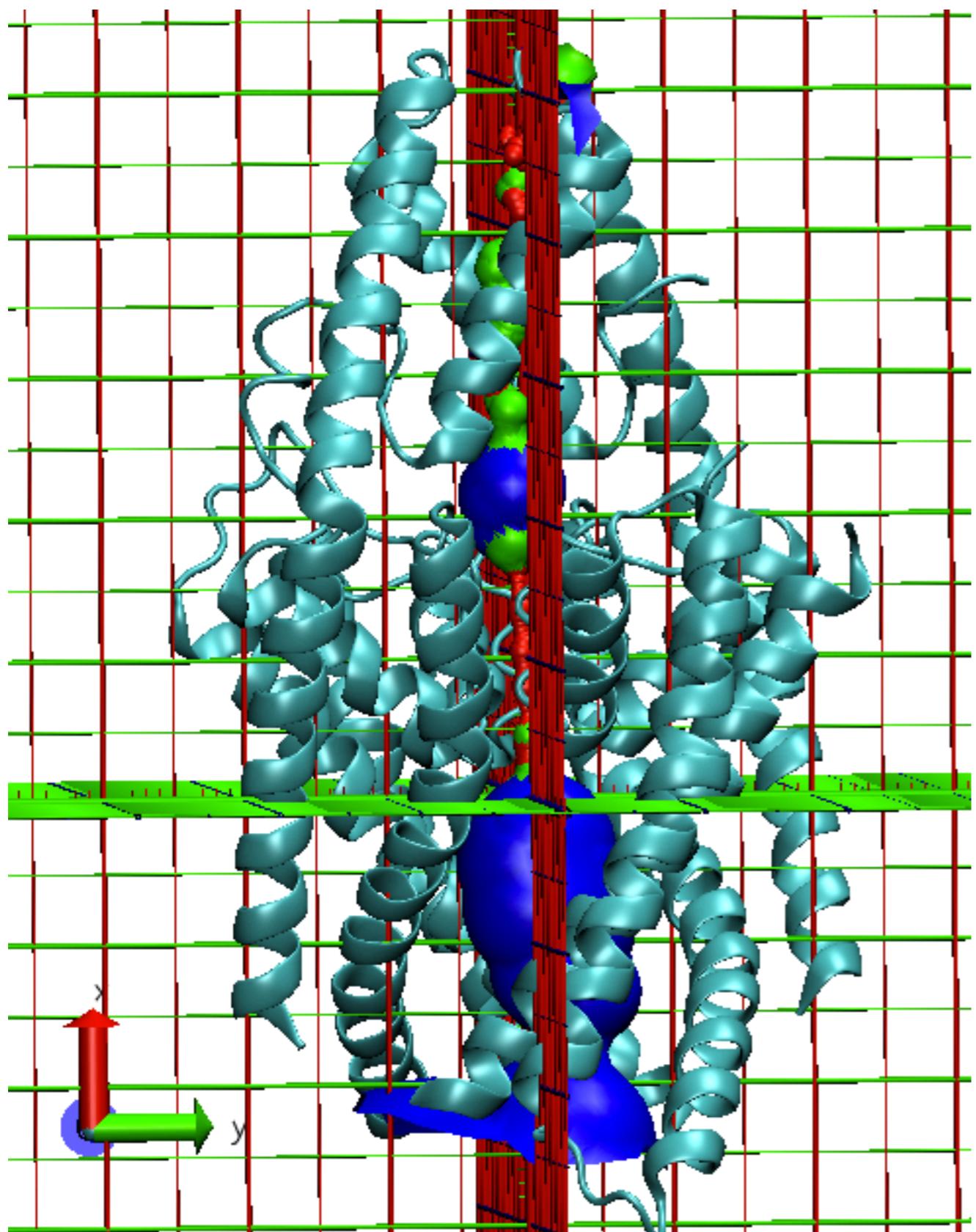
## 4. Alineando estructuras.

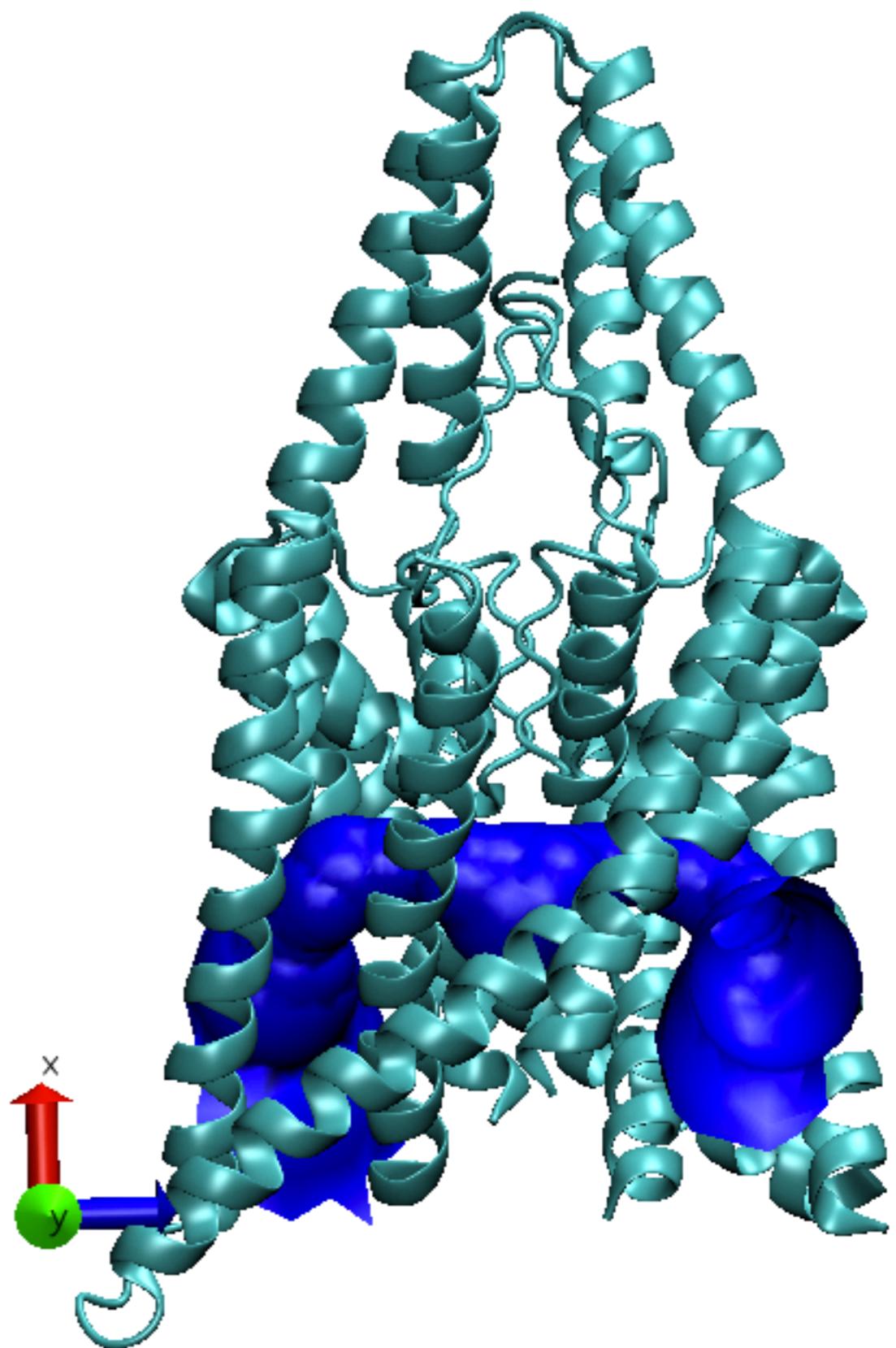
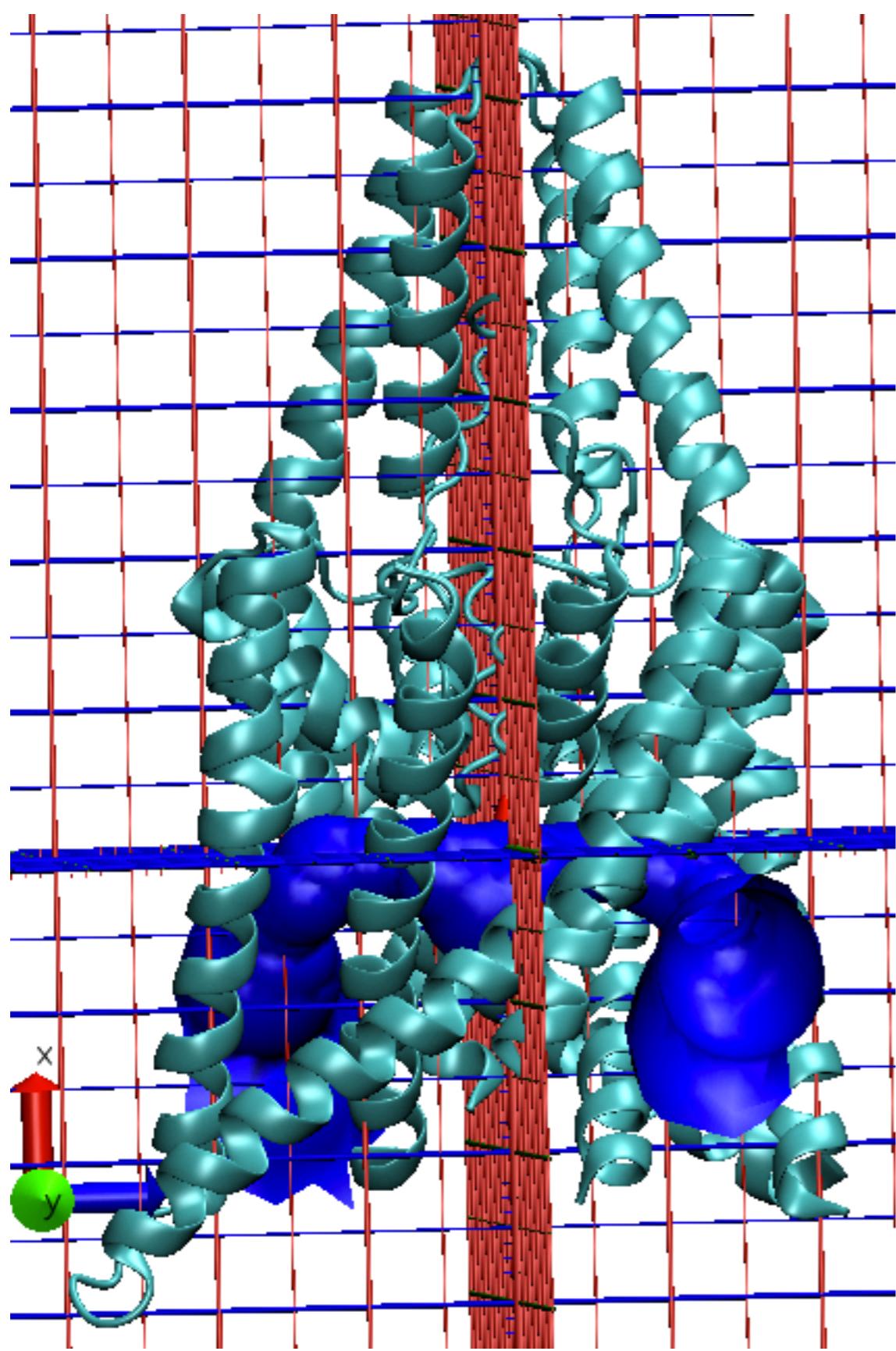
- Borre la estructura 4xdk\_modified.pdb; En VMD main: Select the Molecules -> (right clic) delete molecule
- Cargue el archivo K2P\_aling\_forHOLE\_ok.pdb
- Cargue el archivo 4xdk\_modified.pdb
- En VMD main: Extensions -> Analysis -> MultiSeq -> Choose a directory -> Select NO for database
- En untitled.multiseq: Select K2P\_aling\_forHOLE\_ok\_A and 4xdk\_modified\_A -> tools -> Stamp Structure Alignment Marked Structures -> OK



### 3. Alineando estructuras.





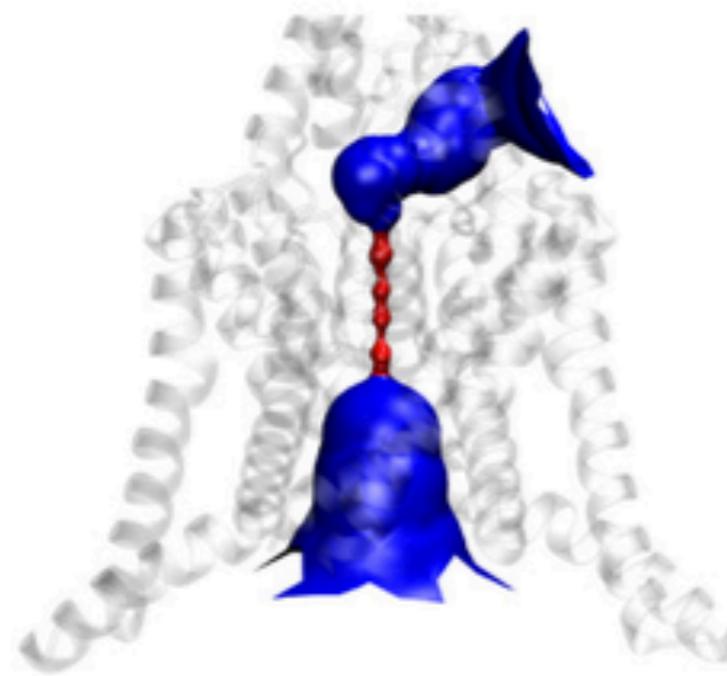
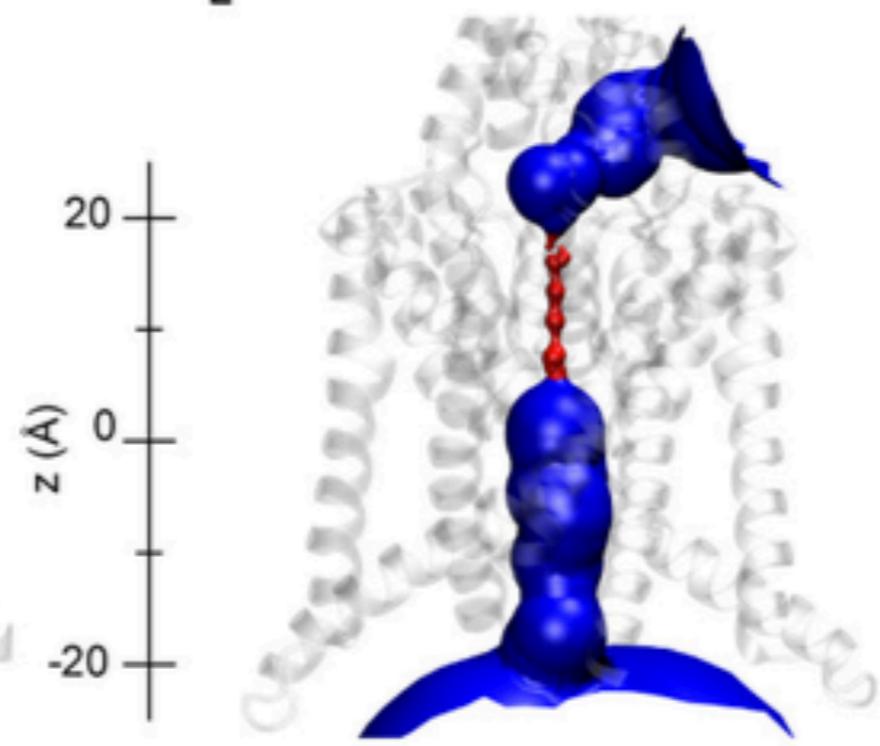
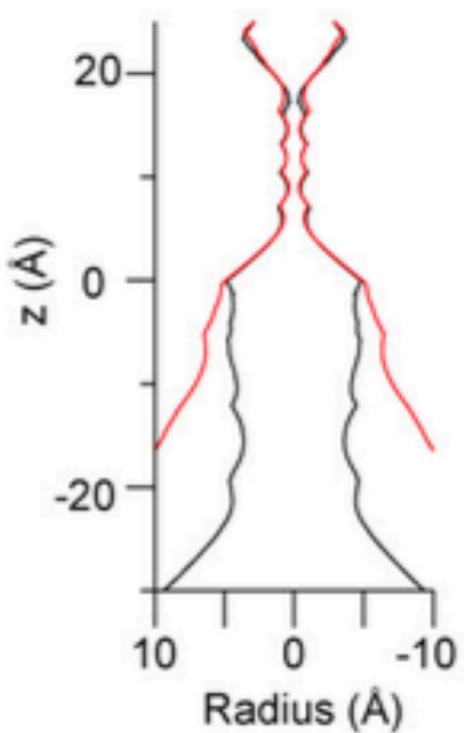


## Supplementary Materials for

**K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac**

Yin Yao Dong, Ashley C. W. Pike, Alexandra Mackenzie, Conor McClenaghan, Prafulla Aryal, Liang Dong, Andrew Quigley, Mariana Grieben, Solenne Goubin, Shubhashish Mukhopadhyay, Gian Filippo Ruda, Michael V. Clausen, Lishuang Cao, Paul E. Brennan, Nicola A. Burgess-Brown, Mark S. P. Sansom, Stephen J. Tucker,\* Elisabeth P. Carpenter\*

\*Corresponding author. E-mail: liz.carpenter@sgc.ox.ac.uk (E.P.C.); stephen.tucker@physics.ox.ac.uk (S.J.T.)

**D****E****F**

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# Trabajando con Moléculas, ligandos y proteínas.

## Representación, visualización y modelamiento molecular (3D).

## HomeWork

### 1. Realizar el tutorial de PyMol

1. 01\_Tutorial\_PDB-PyMol.pdf

### 2. Revisar páginas de interés.

- 1: [https://pymolwiki.org/index.php/Main\\_Page](https://pymolwiki.org/index.php/Main_Page)
2. <http://www.ks.uiuc.edu/Training/Tutorials/vmd/tutorial-html/>
3. <https://www.schrodinger.com/training/tutorials>
4. <https://www.schrodinger.com/videos>

### 3. Los software usados en esta sesión pueden ser descargados de manera gratuita de:

- 1: Free Maestro: <https://www.schrodinger.com/>
2. VMD: <http://www.ks.uiuc.edu/Development/Download/download.cgi?PackageName=VMD>
3. PyMol: <https://www.pymol.org/>