Molecular Modeling with PyMOL

PyMOL software is distributed under a license that permits use by Professor Nowick and his students for research and teaching purposes. Students of Professor Nowick may contact him for a link to download PyMOL.

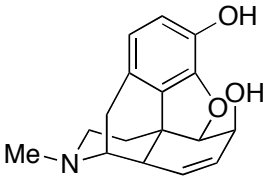
PyMOL can perform *molecular mechanics* calculations to generate realistic molecular models of molecules with common types of atoms and functional groups. Molecular mechanics uses a force field to calculate the steric energy of the molecule and then adjusts the conformation of the molecule to minimize the steric energy. A force field is set of parameters for the bond lengths, angles, torsional parameters, electrostatic properties, van der Waals interactions, etc. PyMOL uses the Merck Molecular Force Field (MMFF), which accurately accommodates a variety of atom types and functional groups.

The conformation generated by molecular mechanics is a *local minimum*. A local minimum is a conformation at the bottom of an energy well (i.e., a conformer). It is not necessarily the lowest energy conformer (i.e., the global minimum). If you start near gauche butane, you will generate gauche butane as a local minimum; if you start near anti butane, you will generate anti butane as a local minimum that is also the global minimum. If you start with a boatlike conformation of cyclohexane, you will end up with a twist-boat conformer; if you start with a chairlike conformation of cyclohexane, you will end up with a chair conformer.

The lowest-energy conformer (global minimum) many be identified by various strategies. With simple molecules and small ring sizes, this is often best done by manually adjusting the structure and re-minimizing the structure. Manual adjustments can consist of rotating about bonds (e.g., turning a gauche-like structure to an anti-like structure) or flipping rings (e.g., a ring flip of cyclohexane). The lowest-energy conformer of molecules containing large rings is often best found by automated conformational searching procedures that are implemented in full-featured molecular mechanics programs such as MacroModel.

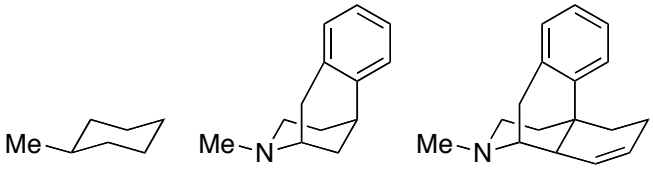
Molecular mechanics calculations are an appropriate method to model molecules containing common structures and functional groups, such as morphine and strychnine. For molecules containing arrangements of atoms and functional groups, reactive intermediates, or transition metals, electronic structure calculations are often more appropriate. Structures such as oxocarbenium ions, organopalladium compounds, or the transition state for an aza-Cope rearrangement best modeled with electronic structure calculations in programs such as Spartan, Gaussian, or TURBOMOLE.

Exercise 1, Morphine



morphine

In this exercise, we are going to build a minimum energy structure of morphine and create a PyMOL file morphine.pse and a .pdb coordinate file morphine.pdb. We are going to build up the structure in a series of steps, making models morph_A, morph_B, and morph_C along the way.



morph_A morph_B morph_C

A. Use the builder module of PyMOL (Windows) or PyMOLX11Hybrid (Mac) to make intermediate structure morph_A. First use the cyclohexane template to make a cyclohexane ring. Then use the CH_4 template to add a methyl group. Use the pulldown menu (File-Save Session As) to save the structure as morph_A.pse .

B. Continue building to make intermediate structure morph_B. Convert the tertiary carbon atom to a nitrogen. Add the axial phenyl group. Rotate about the phenyl group into position using the right mouse button and the control key to pick the torsion bond (PkTB) and then the left mouse button and the control key to rotate the phenyl group (TorF). Use the CH_4 template to add an axial methyl group. Use Bonds-Create button to create a bond between the methyl group and the phenyl ring. Use the Model-Clean button to minimize the structure. Use the pulldown menu to save the structure (File-Save Session).

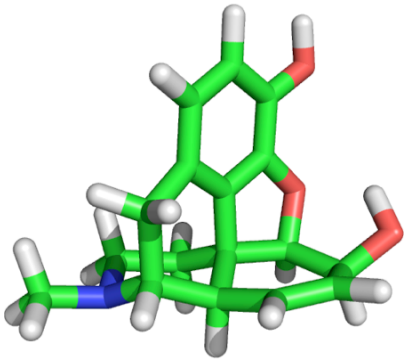
C. Continue building to make intermediate structure morph_C. Use the C=C template to add a vinyl group. Use the CH_4 template to add the two remaining carbons of the cyclohexene ring. Use Bonds-Create button to close the cyclohexene ring. Use the Model-Clean button to minimize the structure. Use the pulldown menu to save the structure (File-Save Session).

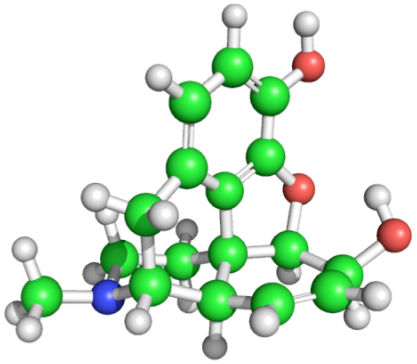
D. Complete the construction and minimization of morphine. Add the oxygen atoms. Use Bonds-Create button to close the dihydofuran ring. Use the Model-Clean button to minimize the structure. Use the pulldown menu to save the structure as morphine.pse (File-Save Session As). Use the pulldown menu to export the structure in the .pdb file format as morphine.pdb (File-Save Molecule).

Generate a .png image of the molecule as a sticks drawing. Rotate the molecule into an appropriate orientation. Use the side menu (S) to show the molecule as sticks (Show-sticks). Use

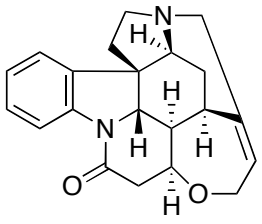
the pulldown menu hide double bonds (Display- uncheck Show Valences). Use the pulldown menu to display the molecule in maximum quality with (Display-Quality-Maximum Quality). Use the pulldown menu to make the background white (Display-Background-White). Use the Ray button on the upper right hand corner to render the image. Use the pulldown menu to save the image in the .png file format as morphine-sticks.png (File-Save Image As-PNG).

Generate a .png image of the molecule as a ball-and-stick drawing. Use the side menu (A) to show the molecule as ball and stick (Actions-presets-ball and stick). Use the pulldown menu show double bonds (Display-Show Valences). Use the Ray button on the upper right hand corner to render the image. Use the pulldown menu to save the image in the .png file format as morphine-ball-and-stick.png (File-Save Image As-PNG).



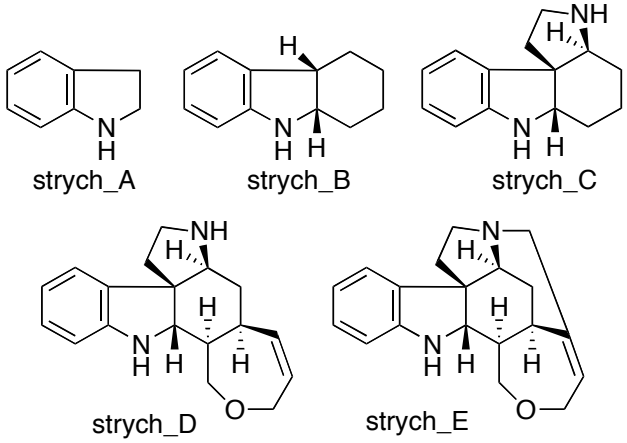


Exercise 2, Strychnine



strychnine

In this exercise, we are going to build a minimum energy structure of strychnine and create a PyMOL file strychnine.pse and a .pdb coordinate file strychnine.pdb. We are going to build up the structure in a series of steps, making models strych_A, strych_B, strych_C, strych_D, and strych_E along the way. This exercise builds on what we have learned in the previous exercise and thus provides less detailed instructions. Please refer to the previous exercise if you have trouble with the details.



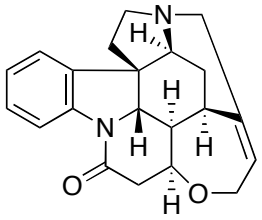
A. Use the builder module of PyMOL (Windows) or PyMOLX11Hybrid (Mac) to make intermediate structure strych_A. Either use the phenyl template, CH_4 template, Bonds-Create button, and nitrogen atom to build the structure, or use the indane template and nitrogen atom. Use the Model-Clean button to minimize the structure. Use the pulldown menu (File-Save Session As) to save the structure as strych_A.pse .

B. Continue building to make intermediate structure stych_B. Use the CH_4 template and Bonds-Create button to make the additional ring. Minimize the structure with the Model-Clean button. Save the structure as strych_B.pse .

C. Continue building to make intermediate structure stych_C. Build and minimize the structure as above. Save the structure as strych_C.pse .

D. Continue building to make intermediate structure stych_D. Build and minimize the structure as above. Save the structure as strych_D.pse .

E. Continue building to make intermediate structure stych_E. Build and minimize the structure as above. Save the structure as strych_E.pse .



strychnine

F. Complete the construction of strychnine. Use the C=O and CH_4 templates and Bonds-Create button to make the additional ring. Minimize the structure. Save the structure as strychnine.pse and export the structure in the .pdb file format as strychnine.pdb .

Generate a .png image of the molecule as a sticks drawing. Save the image as strychnine-sticks.png .

Generate an .png image of the molecule as a ball-and-stick drawing. Save the image as strychnine-ball-and-stick.png.