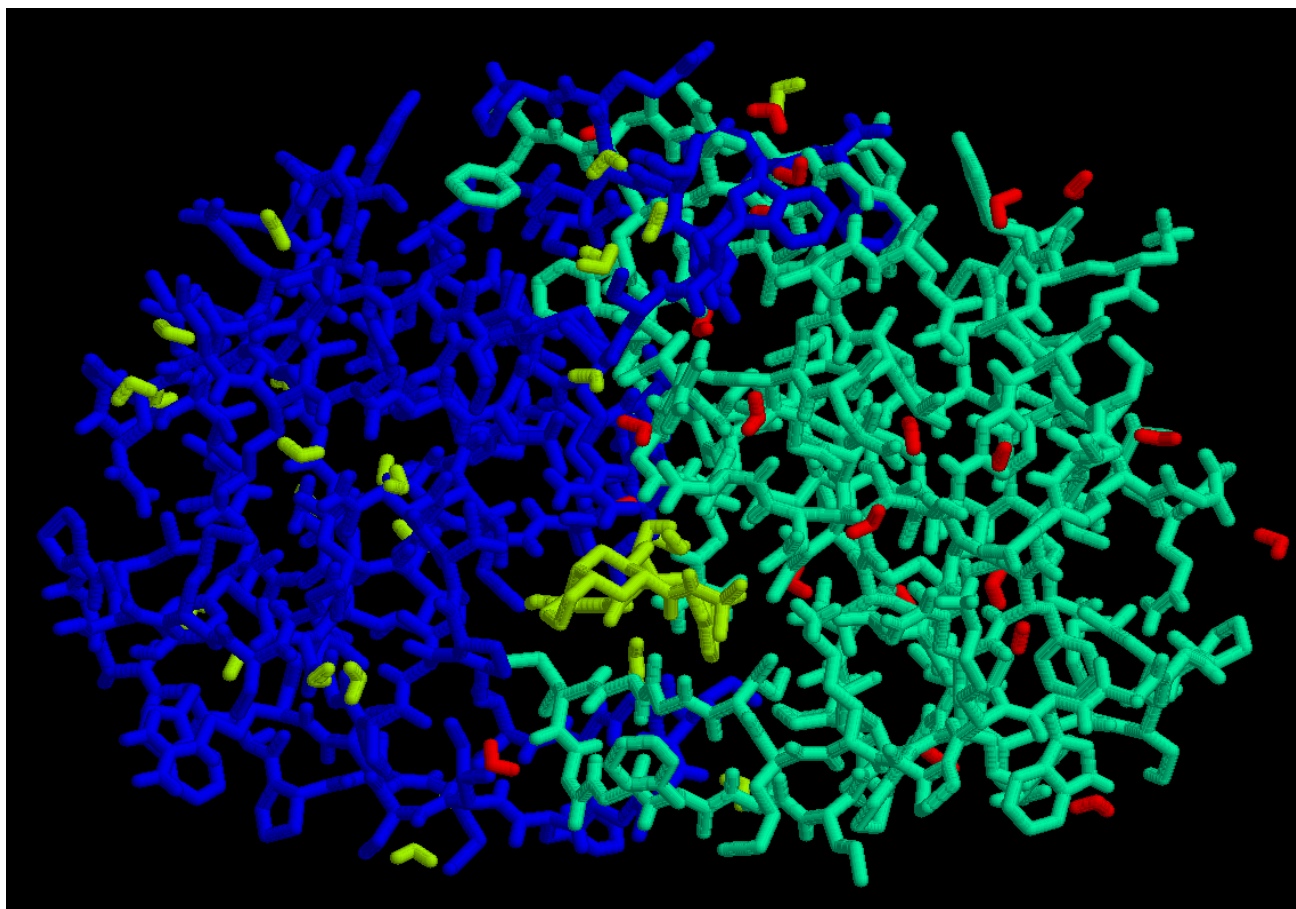


## Why Structure is Important in CHM 109

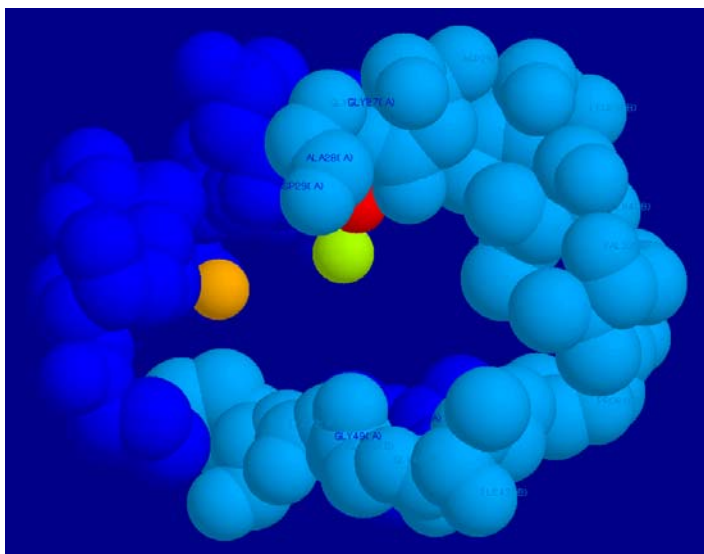
Students are sometimes surprised that they must know about chemical structures to be able to understand biochemistry and pharmacology (the study of drugs and their actions). The importance of structure in these fields is readily shown by looking at the protease inhibitor class of anti-HIV (AIDS) drugs. Many of these drugs were developed using primarily structural approaches. The structure of the active site of the HIV protease was determined by x-ray crystallography, and molecules were then designed to have appropriate fit and binding properties to this active site. Shown below is an x-ray crystal structure of the HIV protease complexed (bound) to the drug Nelfinavir (which you may know as Veracept. See Wikipedia if needed.). Nelfinavir is shown in bright green in the lower-central part of the structure. The two subunits of the protease are shown in blue (left) and seafoam green (right).



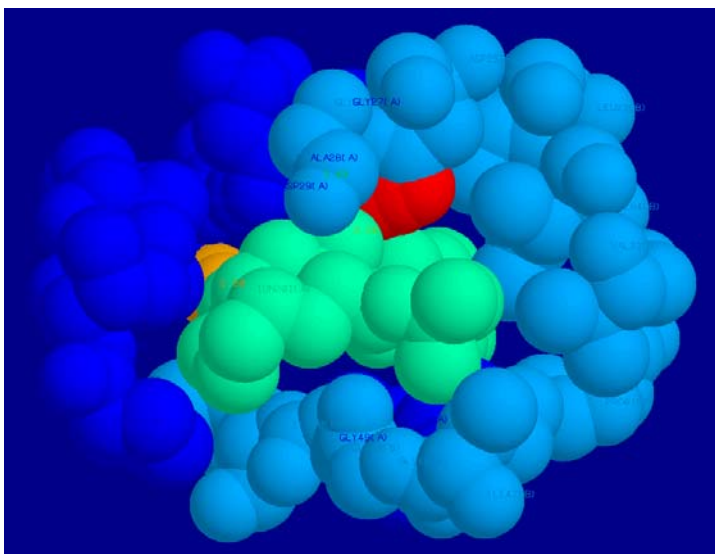
*Figure 1. HIV Protease-Nelfinavir (Viracept) Complex. This is a RasMol representation of Protein Data Bank file 1ohr <http://www.rcsb.org/pdb/explore.do?structureId=1ohr>*

The complex in Figure 1 is shown in “stick” mode to make it easier for you to distinguish Nelfinavir from the protease. If you are not used to looking at molecular structures it is easy to misinterpret them. Because the structure in Figure 1 is shown in “stick” mode, it may look like there is lots of open space and like the drug does not fit tightly into the active site of the protease. In fact, the drug fits the active site relatively tightly. This is shown below in Figure 2, where just the active site parts of the protease are shown binding to Nelfinavir in “space filling” mode. The space filling mode gives a much more accurate representation of a molecule’s actual shape than the stick mode.

HIV Protease Active Site



HIV Protease Active Site-Nelfinavir Complex



*Figure 2. HIV Protease Active Site-Nelfinavir (Viracept) Complex. This was prepared using a RasMol representation of pdb file 1ohr from the Ligands function of the PDB Sum web site:*

<http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=1ohr&template=ligands.html&l=1.1>

The color scheme in Figure 2 is different than in Figure 1. The two protease subunits in Figure 2 are shown in dark blue (left) and light blue (right), while the drug (Nelfinavir) is shown in seafoam green. Don't worry about the orange, red, and yellowish atoms right now. The right-hand panel of Figure 2 shows the crystal structure of the active site with the drug bound. The left-hand panel is derived from the same structure (1ohr), but the atoms of Nelfinavir were deleted from the structure. The orientation of the drug and active site of the protease are approximately the same in Figures 1 & 2.

In addition to the drug being the right size and shape to fit into the active site of the protease, it must also have appropriately positioned functional groups if it is to bind tightly to the active site. While we do not have enough chemical background to examine the nature of the binding groups right now, we will before the semester is over.

The example shown above relates to a xenobiotic (not biologically produced) molecule binding to an active site. The same principles that account for binding of drugs like Nelfinavir to the active site of HIV protease can also be used to study the interaction of natural substrates with their enzymes (phenylalanine with PAH), hormones with their receptors (estrogen with the estrogen receptor), and antibodies with antigens. You can see therefore that we will use molecular structure to analyze many important, naturally occurring molecular processes associated with living things.