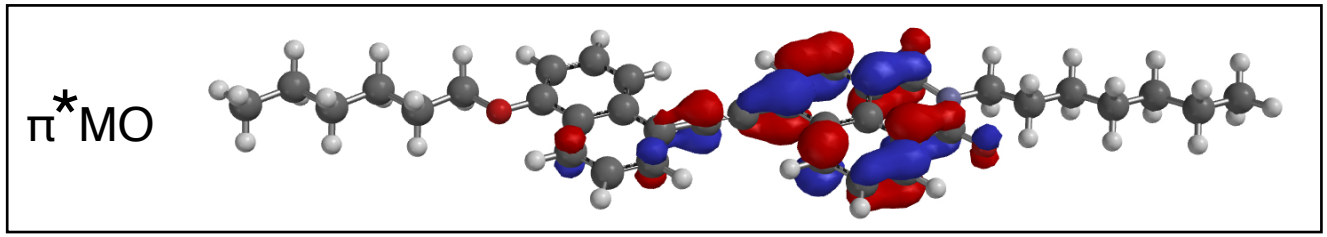
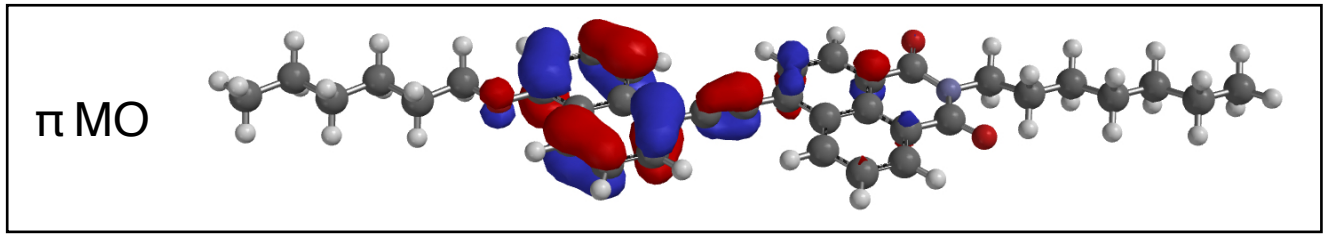
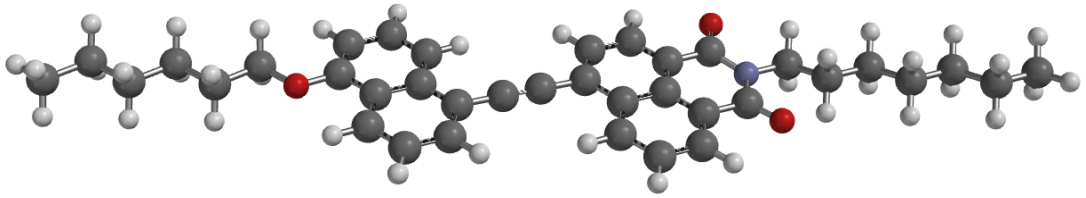
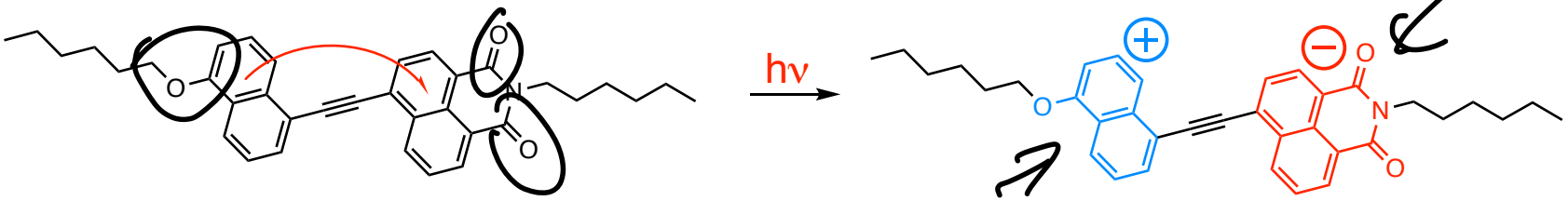


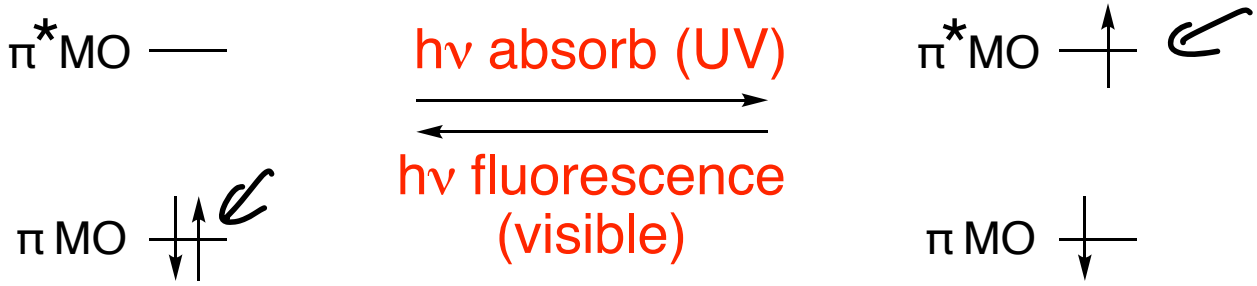


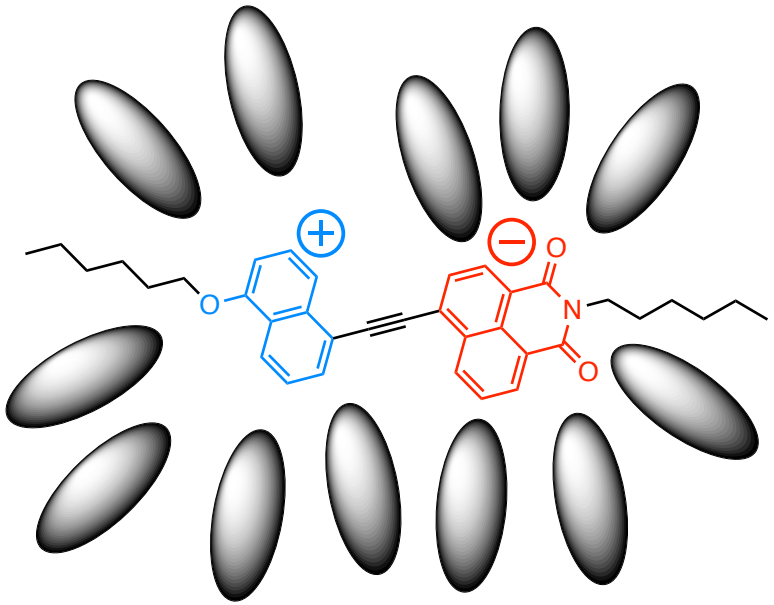


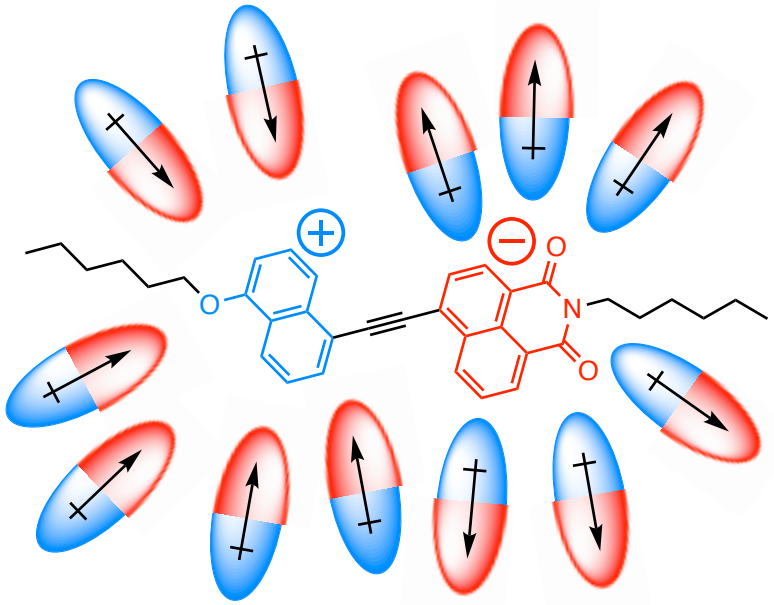
Blue Light = higher energy

Orange light = lower energy



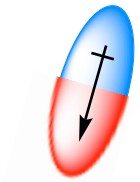






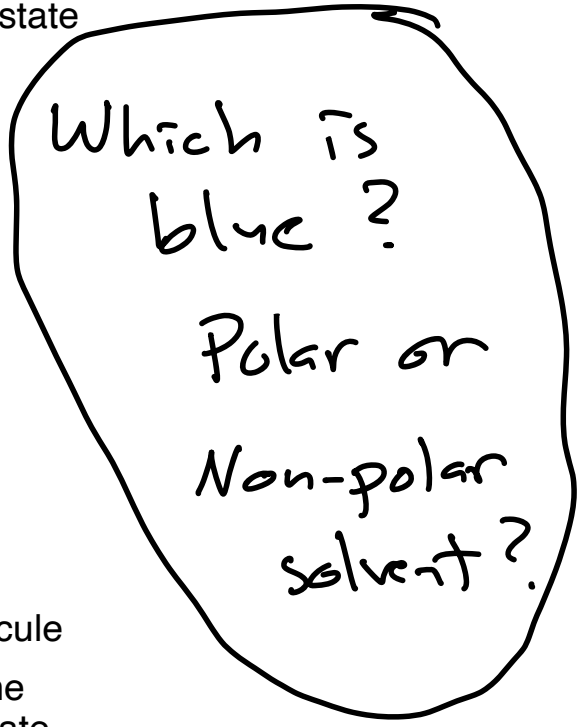
Non-polar Solvent Molecule

No stabilization of the charged excited state

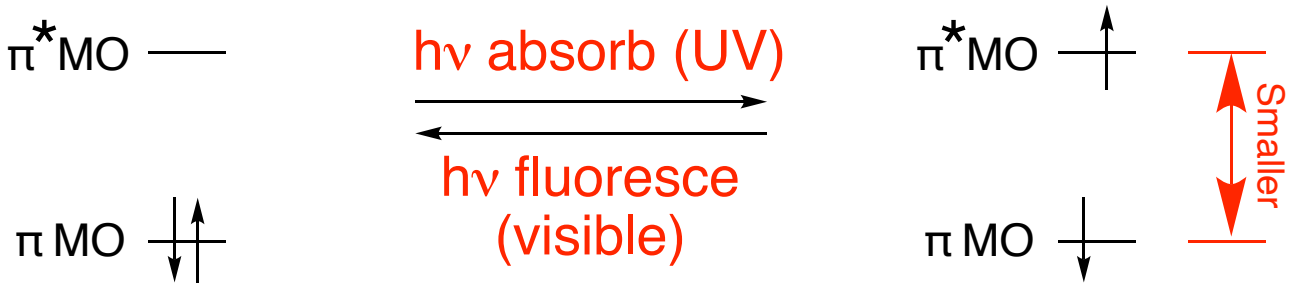


Polar Solvent Molecule

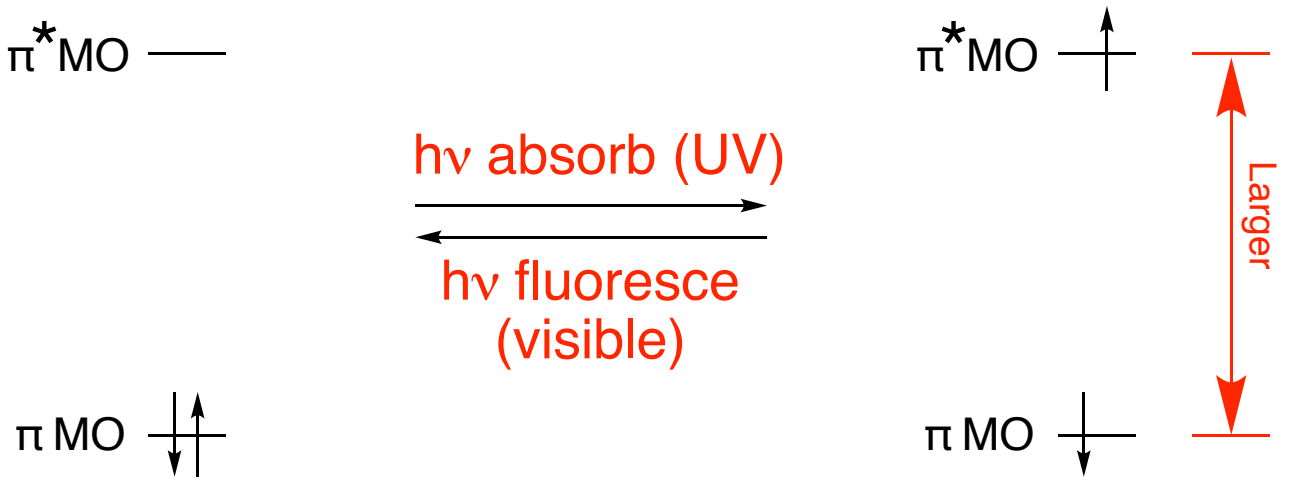
Stabilization of the charged excited state




Less Polar Solvents
More Polar Solvents



Polar Solvent - the charged excited state is well solvated because the solvent molecules have a relatively large molecular dipole that interacts favorably with the charges. There is a smaller energy difference between the ground state and excited state, corresponding to orange light

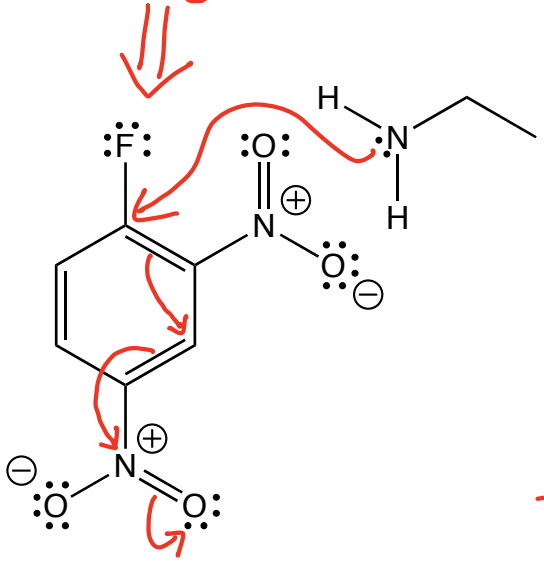


Non-polar Solvent - the charged excited state is disfavored because it is not well-solvated. There is no molecular dipole in the solvent to interact favorably with the charges.This makes the charged excited state higher in energy. There is a larger energy difference between the ground state and excited state, corresponding to blue light

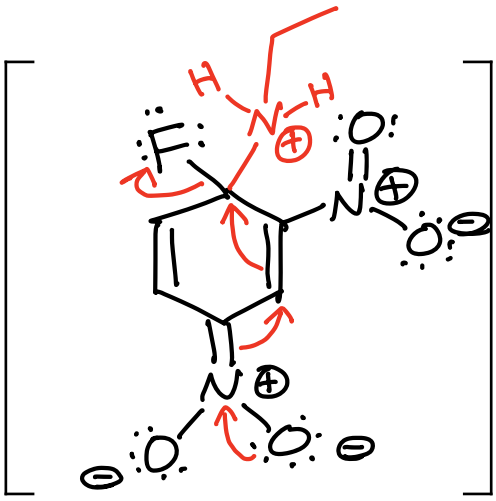
Answer to pop-quiz question

VERY electron deficient aromatic ring because of all the electron withdrawing groups

Nucleophilic Aromatic Substitution



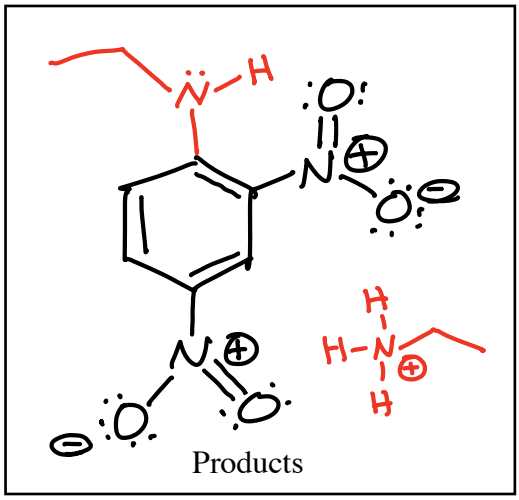
Make a bond



Meisenheimer complex

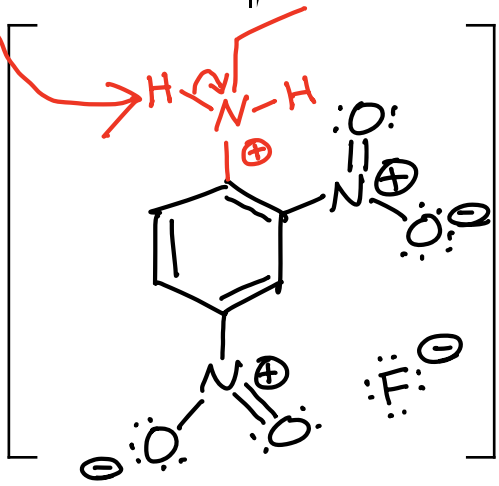
The timing of this last deprotonation step is uncertain

Break a bond



Products

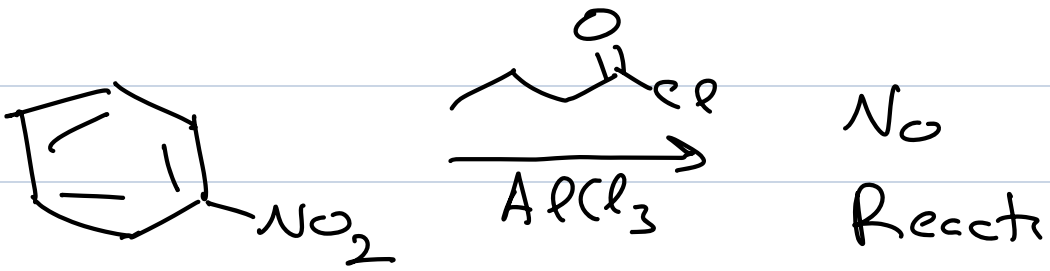
Take a Proton Away



This reaction is relatively rare, and this is the only example you will see in this class

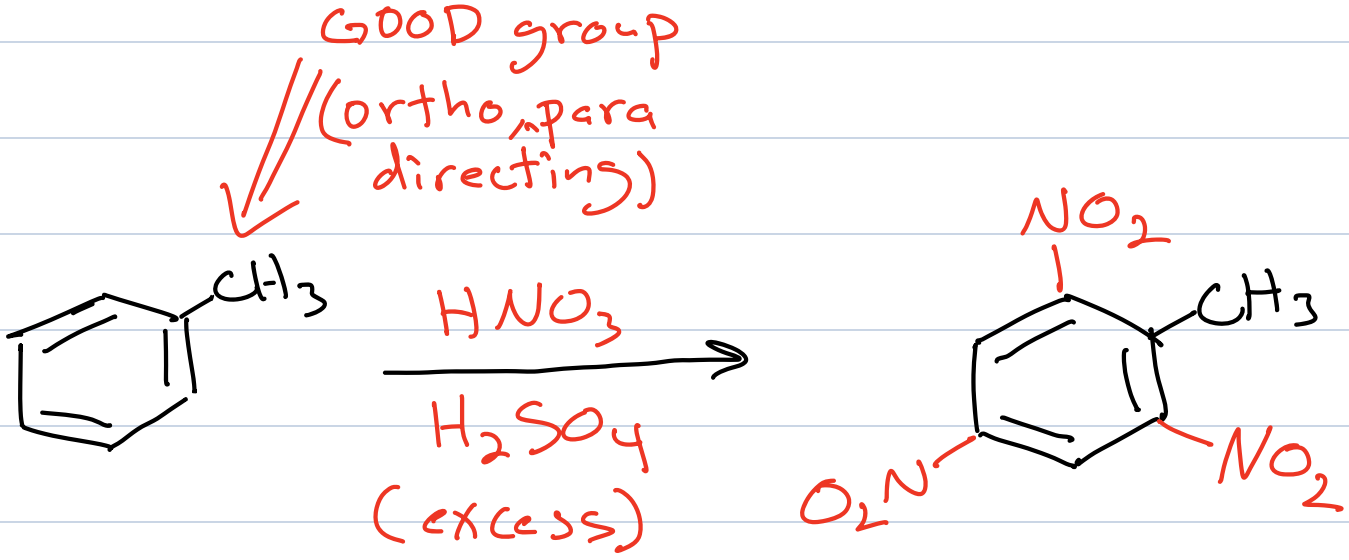
What you need to know about electrophilic aromatic substitution reactions:

1) Friedel-Crafts alkylations and acylations do not work if there is a bad group (i.e. $-NO_2$) on the ring



Conditions are not strong enough to overcome a deactivated ring

However → some reactions with harsh conditions will work:



Toluene

Solvent used in model glue

Trinitrotoluene (TNT)

Boom!

Carbohydrates

pentose

hexose

Monosaccharides → 5 or 6 carbons and are aldehydes and ketones

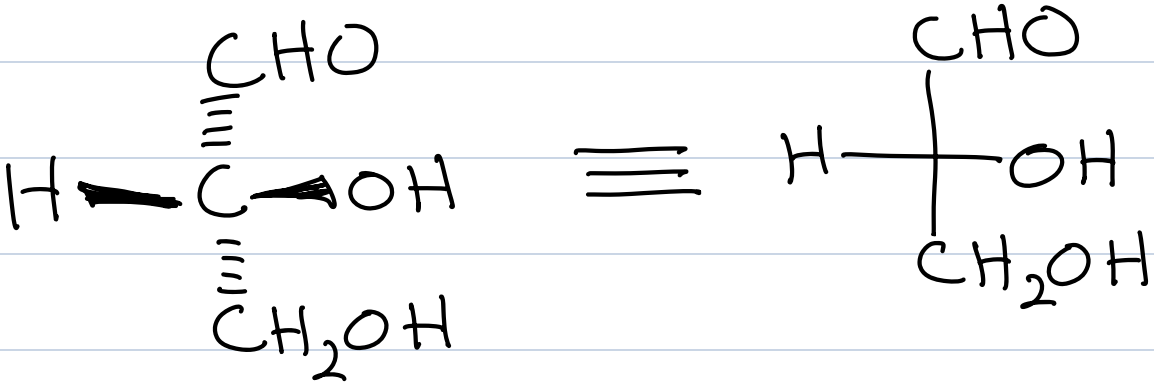
aldose

ketose

Ex.

Glucose is an aldohexose

Stereochemistry



(R)-D-Glyceraldehyde

dextrorotatory (+)

Called Fischer projection

"Like a Teddy Bear giving you a hug"

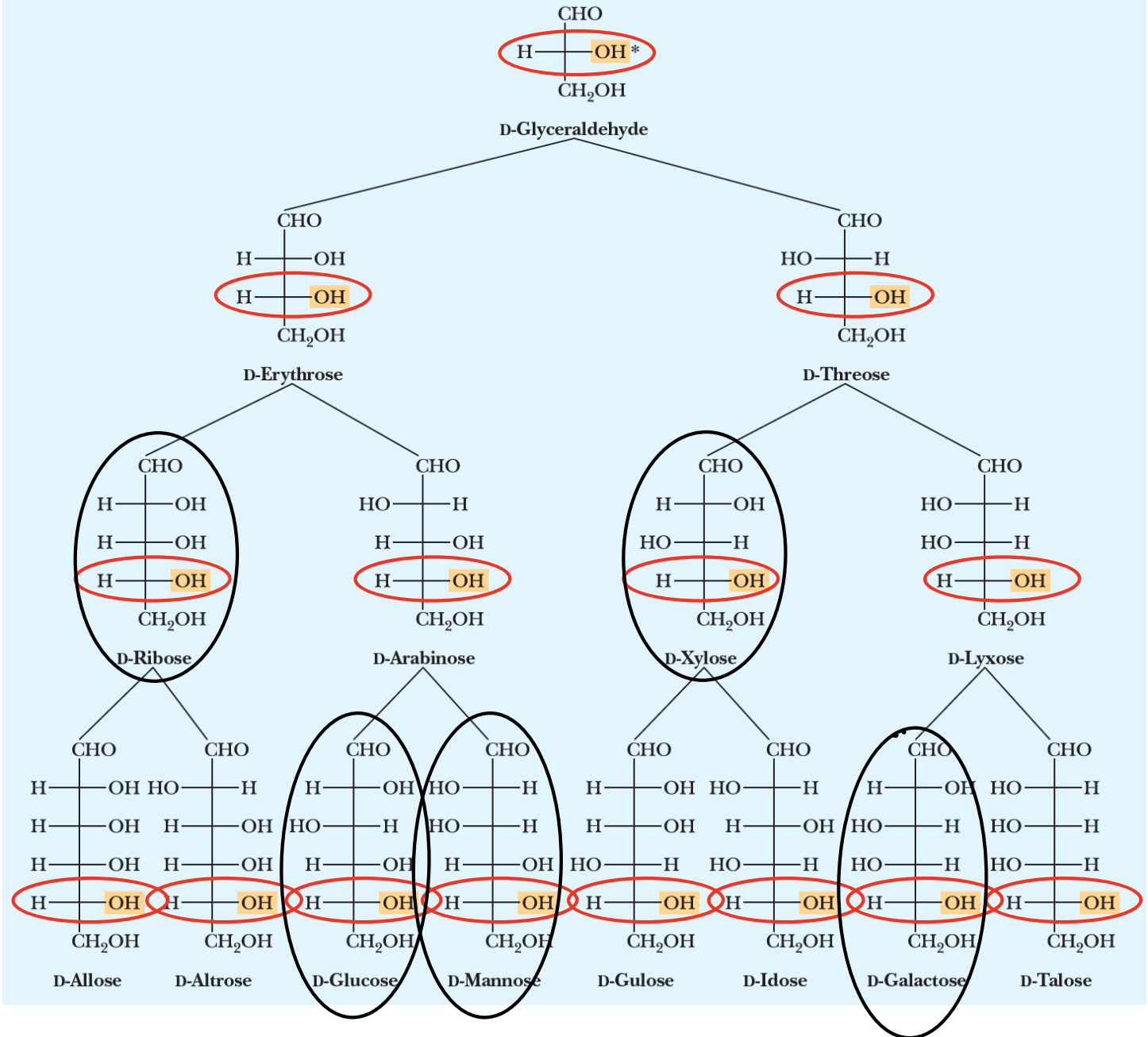

Can I have a hug please?

Stereochemistry defines the different carbohydrates

→ Due to the way carbohydrates are synthesized in cells → the common carbohydrates all have the same stereochemistry as D-glyceraldehyde at the carbon farthest from the carbonyl (aldehyde or ketone)

That is why they are called "D" carbohydrates

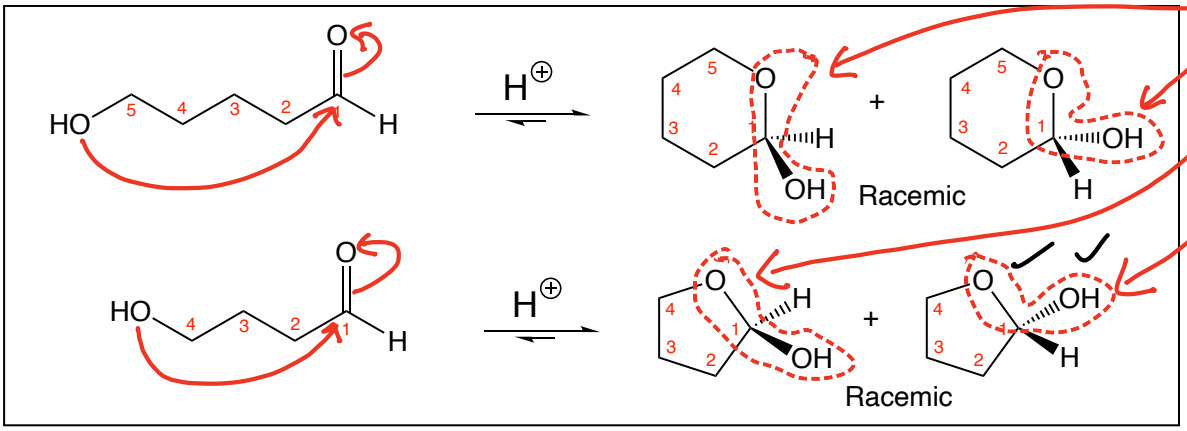
Table 25.1 Configurational Relationships Among the Isometric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses



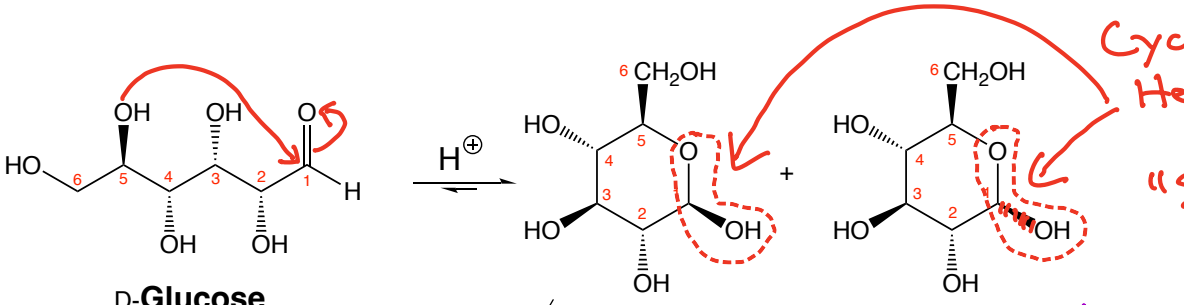
Most common carbohydrates

Cyclic Hemiacetals and Carbohydrates

Cyclic hemiacetals



The cyclic form of hemiacetals are stable-"SWEET!"
→ The chelate effect



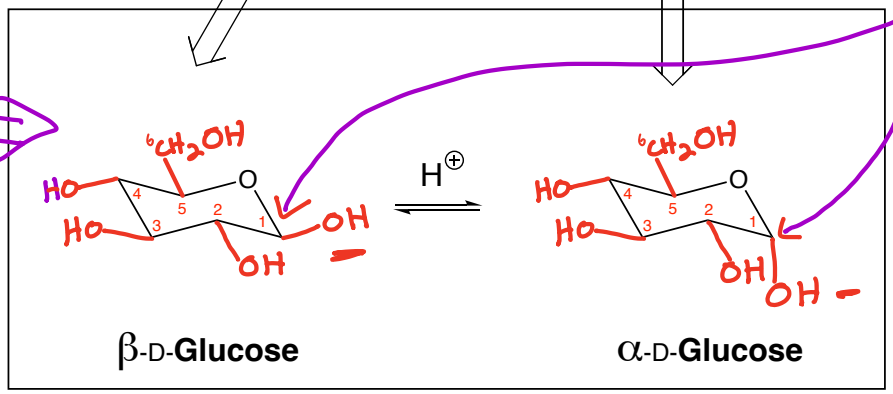
D-**Glucose**
(open chain form)

Cyclic Hemiacetals

"SWEET!"

Anomeric Carbon

This interconversion is called "mutarotation"



Biochemists call these two forms "anomers"

β-D-Glucopyranose

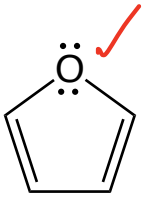
means "6-mebered ring"

More stable → every group is equatorial!

α-D-Glucopyranose

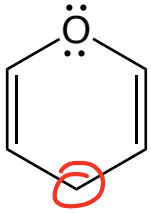
Less stable → one -OH is axial

For Glucose:
"α is axial!"



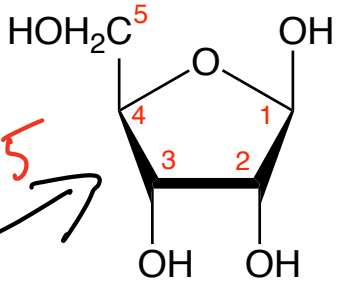
5

Furan



6

Pyran

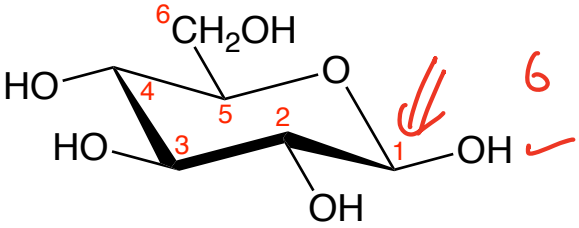


5

A furanose

β-D-Ribose

or β-D-Ribofuranose



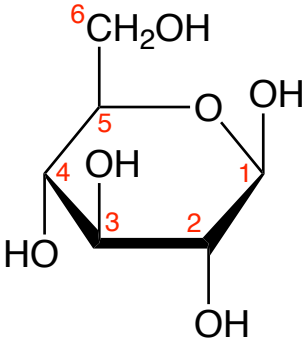
6

A pyranose

β-D-Glucose

or β-D-Glucopyranose

This is called a Haworth projection



PERSPECTIVE

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HIV-1 protease: mechanism and drug discovery

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1 Introduction

It has now been two decades since acquired immunodeficiency syndrome (AIDS) was first reported by the US Center for Diseases Control (CDC). A few years later, it was found that a retrovirus called human immunodeficiency virus (HIV) is the causative agent in AIDS.[1] In a short time, AIDS increased to epidemic proportions throughout the world, affecting more than 40 million people today and killing so far more than 22 million (UNAIDS, 2001).

Since the outbreak of the AIDS epidemic, tremendous efforts have been directed towards development of antiretroviral therapies that target HIV type 1 in particular (HIV-1). The identification of the HIV retrovirus and the accumulated knowledge about the role of the different elements in its life cycle led researchers around the world to develop inhibitors that target different steps in the life cycle of the virus. One of these targets is HIV-1 protease (HIV PR), an essential enzyme needed in the proper assembly and maturation of infectious virions. Understanding the chemical mechanism of this enzyme has been a basic requirement in the development of efficient inhibitors. In this review, we summarize studies conducted in the last two decades on the mechanism of HIV PR and the impact of their conclusions on the drug discovery processes.

2 The life cycle of HIV

HIV belongs to the class of viruses called retroviruses, which carry genetic information in the form of RNA. HIV infects T cells that carry the CD4 antigen on their surface. The infection of the virus requires fusion of the viral and cellular membranes, a process that is mediated by the viral envelope glycoprotein (gp120, gp41) and receptors (CD4 and coreceptors, such as CCR5 or CXCR4) on the target cell. As the virus enters a cell, its RNA is reverse-transcribed to DNA by a virally encoded enzyme, the reverse transcriptase (RT). The viral DNA enters the cell nucleus, where it is integrated into the genetic material of the cell by a second virally encoded enzyme, the integrase. Activation of the host cell results in the transcription of the viral DNA into messenger RNA, which is then translated into viral proteins. HIV protease, the third virally encoded enzyme, is required in this step to cleave a viral polyprotein precursor into individual mature proteins. The viral RNA and viral proteins assemble at the cell surface into new virions, which then bud from the cell and are released to infect another cell. The extensive cell damage from the destruction of the host's genetic system to the budding and release of virions leads to the death of the infected cells.

3 HIV protease

3.1 HIV protease: a logical target for AIDS therapy

Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body, which results in the weakness and destruction of the body's immune system. From the analysis of the HIV life cycle, one could conclude that there are several steps that might be interfered with, thus stopping the replication of the virus. For example, there are several commercially available drugs that inhibit the enzyme reverse transcriptase (RT). The first class of RT inhibitors is the nucleoside analogs such as AZT, ddI, ddC and d4T. These dideoxy compounds lack the 3′-hydroxy, causing DNA chain termination when they are incorporated into the growing DNA strand. The second class of inhibitors is the non-nucleoside inhibitors (NNIs); these inhibitors are known to bind in a pocket away from the polymerase active site, and are believed to cause a conformational change of the enzyme active site, and thus inhibit its action. Currently, there are three available non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine, and efavirenz) for the treatment of AIDS.

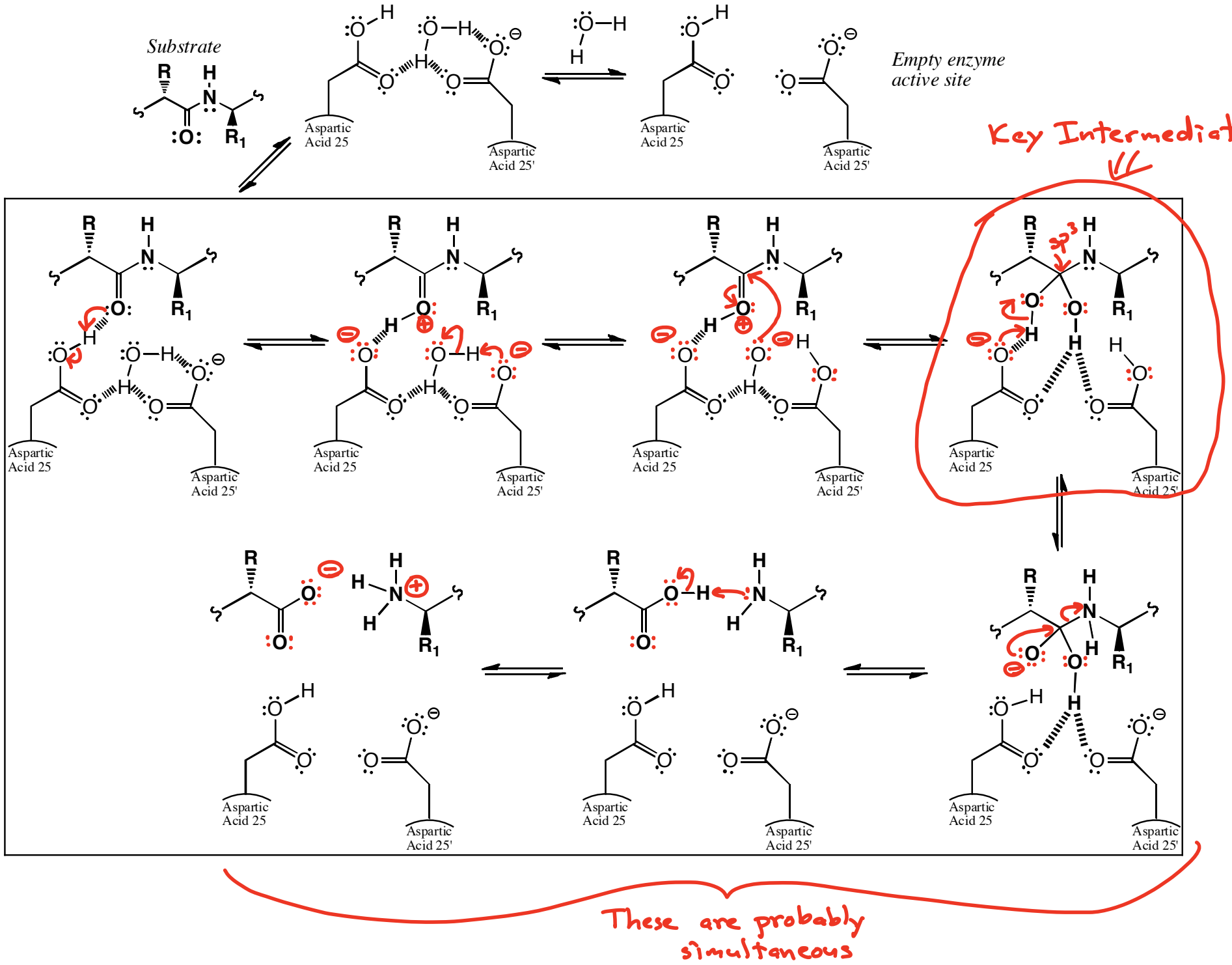
Another critical step in the life cycle of HIV is the proteolytic cleavage of the polypeptide precursors into mature enzymes and structural proteins catalyzed by HIV PR. It has been shown that budded immature viral particles that contain catalytically inactive protease cannot undergo maturation to an infective form.[2] The necessity of this enzyme in the virus life cycle makes it a promising target for therapy of the HIV infection.[3]

3.2 Structure of HIV protease

Navia *et al.* from Merck laboratories were the first group to obtain a crystal structure of HIV PR;[4] a more accurate structure was reported subsequently by Kent and coworker.[5] HIV PR is a 99 amino acid aspartyl protease which functions as a homodimer with only one active site which is C_2-symmetric in the free form. More than 140 structures of the HIV-1 PR, its mutants and enzymes complexed with various inhibitors have been reported so far. A database dedicated to providing structural information about HIV PR has been created at the National Cancer Institute (http://www-fbsc.ncifcrf.gov/HIVdb/). The enzyme homodimer complexed with TL-3[6] is shown in Fig. 1 (PDB ID: 3TLH). Each monomer contains an extended β-sheet region (a glycine-rich loop) known as the flap, that constitutes in part the substrate-binding site and plays an important role in substrate binding, and one of the two essential aspartyl residues, Asp-25 and Asp-25′ which lie on the bottom of the cavity. The substrate binds in its extended conformation, in which its interactions with the different amino

Fig. 1 Structure of HIV PR complexed with TL-3 (PDB: 3TLH).

DOI: 10.1039/b208248a


Substrate
Aspartic Acid 25
Aspartic Acid 25'
Empty enzyme active site
Key Intermediate
These are probably simultaneous

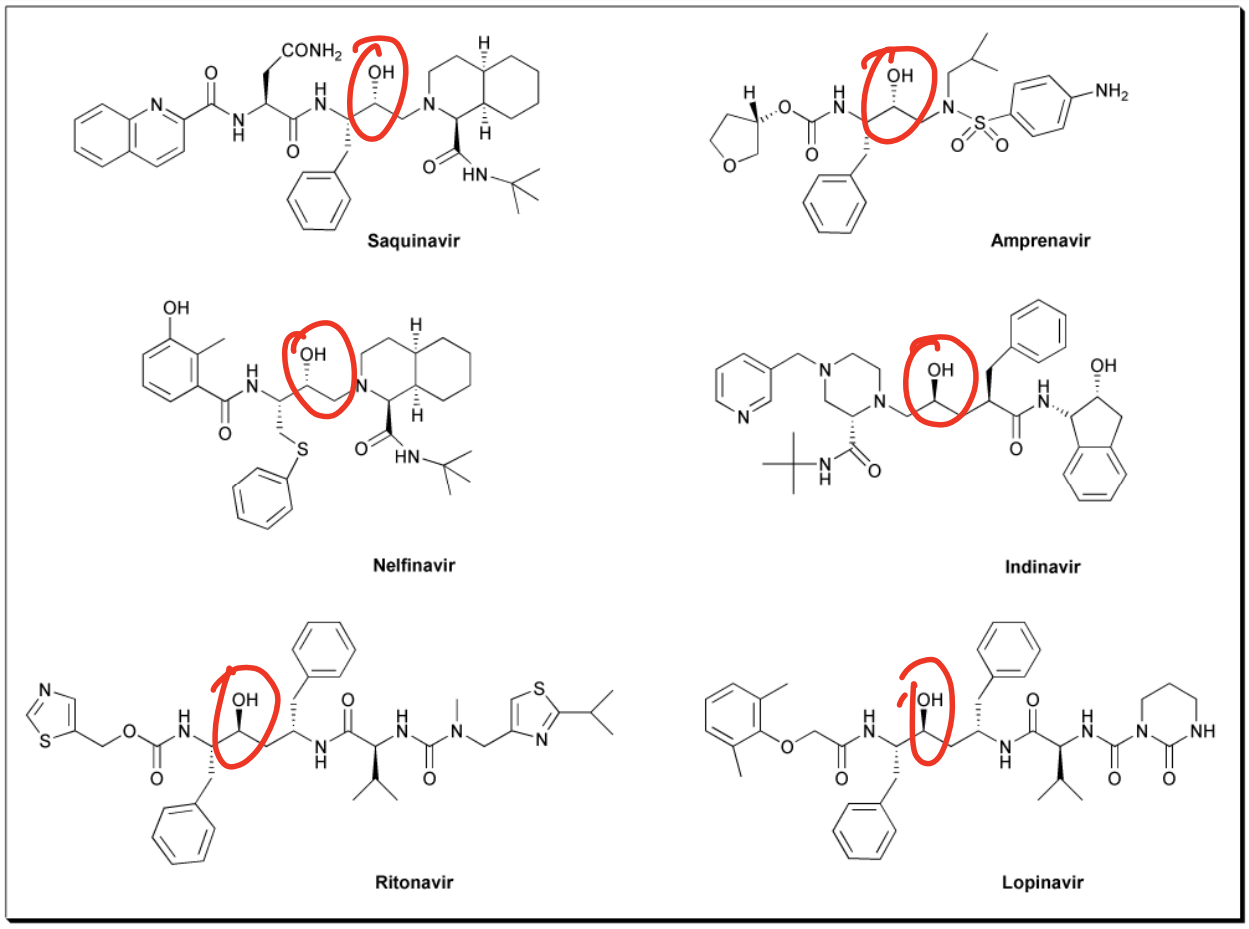


Fig. 10 FDA approved HIV-1 protease inhibitors.