

New vistas in anti-retroviral HIV drug design

HIV-1 protease is an enzyme which is essential for the replication of HIV, the retrovirus that causes AIDS. **The enzyme is a key drug target** for HIV/AIDS therapy; understanding its structure and function at the atomic level, including **the location and movement of hydrogen atoms, is vital for understanding drug resistance and guiding rational drug design.**

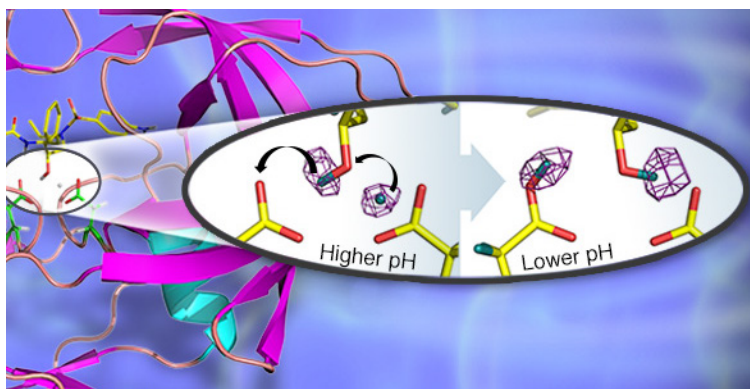


Fig. 1 - A 3D structure of the HIV-1 protease in cartoon representation with bound clinical drug darunavir (shown as sticks). The catalytic site contains two closely positioned aspartic acid residues. The insert depicts the hydrogen transfer reaction in the catalytic site, captured for the first time by neutron crystallography. Credit Jill Hemman and Andrey Kovalevsky (Oak Ridge National Laboratory).

The use of X-ray crystallography to study the structures of HIV-1 protease and drug complexes has led to the design of effective, commercially available drugs, but x-rays cannot determine the positions of mobile hydrogen atoms and protons. Neutron crystallography, however, can reveal these hydrogen-bonding interactions, which play a key role in how effectively a drug binds to its target.

Researchers used neutron crystallography to probe the structure of HIV-1 protease in complex with the clinical inhibitor darunavir, allowing details of the hydrogen-bonding interactions in the active site to be determined and revealing ways to enhance drug-binding and reduce drug-resistance. The group was also able to shed light on the sensitivity to pH of the enzyme's catalytic activity. These details will help in the design of new more effective antiretroviral therapy drugs.

➔ These results highlight that neutrons represent a unique probe to obtain structural details for proton transfer reactions in biological systems.

REFERENCE

Long-Range Electrostatics-Induced Two-Proton Transfer Captured by Neutron Crystallography in an Enzyme Catalytic Site, Gerlits et al., *Angewandte Chemie International Edition* 55, 4924-4927, 2016 and ILL news.

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