Model of the Catalytic Mechanism of Human Aldose Reductase Based on Quantum Chemical Calculations

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Aldose reductase (ALR2; EC 1.1.1.21) is a NADPH-dependent enzyme that reduces a wide range of substrates, such as aldehydes,aldoses and corticosteroids. As it reduces D-glucose into D-sorbitol, it is believed to cause the development of severe degenerative complications of diabetes mellitus. We will describe the structure of ALR2 obtained from x-ray crystallographic data extending up to 0.62 Å and refined at 0.66 Å, the highest resolution ever recorded for an enzyme of this size. The catalytic reaction involves a hydride transfer from the NADPH and a proton donation from the enzyme. (See Fig. 1 for a difference map showing the protonation of the nicotinamide ring of NADPH.) Previous x-ray analysis, site-directed mutagenesis and modeling studies considered two possible proton donors: His110 and Tyr48. The subatomic resolution structure presented here, complexed with the inhibitor IDD594, shows many details unavailable at lower resolution, such as H-atom positions, significant deviations from standard stereochemistry, exact determination of atomic species, bond electron density, multiple conformations and detailed solvent structure. This accuracy enables the unambiguous assigning of the orientation of His110 ring around the Ca-Cb bond and the positioning of hydrogen atoms involved in catalysis, leading to a new reaction mechanism where both Tyr48 and His110 play a role. [This work has been published in the *Journal de Physique IV France* **10**, 10-3-10-13 (2000).]

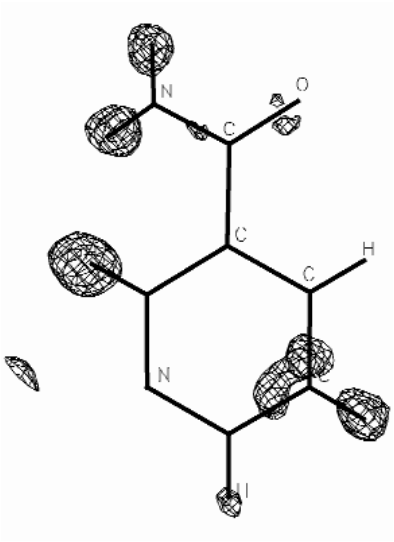

FIG. 1. Difference map showing the protonation of the nicotinamide ring of NADPH.

This work has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. NO1-CO-12400. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. W-31-109-ENG-38.