02.1-20 HUMAN CARBONIC ANHYDRASE I - IODIDE COMPLEX: STRUCTURE AND INHIBITION MECHANISM. By Vinay Kumar, Padma Satyamurthy and K.K. Kannan, Neutron Physics Division, Bhabha Atomic Research Centre, Bombay 400 085, India.

Iodide like other anions (CN^-, SH^- etc) is a competitive inhibitor of HCO_3^- reaction and an uncompetitive inhibitor of CO_2 hydration reaction of carbonic anhydrase isozymes. Crystals of Human carbonic anhydrase I isozyme (HCAI) were soaked in a solution of 0.2M NH_4I in 2.5M $(NH_4)_2SO_4$ pH = 8.5. Three-dimensional intensity data for HCAI-I^- crystals was collected to a resolution of 2.5Å on an Arndt-Wonacott oscillation camera. Data processing was done on a Scandig-3 microdensitometer controlled by a PDP 11/34 computer (P.K. Pal et al., Int. Sum. School on Cryst. Comp., 1983, Kyoto Japan) followed by 3-dimensional scaling. 48159 reflections were scaled to get 10150 unique reflections. The overall R-factor on F_{obs} was 11.7%. Phases were determined from the refined structure of HCAI (K.K. Kannan et al., Ann. New York Academy of Sciences, 1984, 429, 49-60) with 197 solvent molecules included. (2Fo-Fc) and (Fo-Fc) Fourier maps were computed wherein the Iodide (I^-) position was located and included in the structure. This structure was refined using the restrained least squares (J.H. Konnert, Acta Cryst., 1976, A32, 614-617) method and model building interactive graphics. The initial R-factor was 30.3%. The R-factor after 12 cycles of refinement and one model fitting on a Vector General 3400 graphics system using Frodo (T.A. Jones, J. Appl. Cryst., 1978, 11, 268) programme is 20%. RMS delta and sigma values for covalent bond distances are 0.014 and 0.020, for planar torsion angles 2.5° and 15.0° and for main chain bonded thermal values (B) is 1.3Å^2 and 1.00Å^2 respectively. Refined occupancy and B values of I^- ion are 69% and 11.4Å^2. I^- is inhibiting the enzyme by replacing the catalytically important solvent molecule and is at a distance of 2.57Å from Zn^{2+} ion (Fig. 1). There seem to be two more low occupancy I^- sites with

respective occupancies and B values of 45%, 23.7Å² and 27%, 12.2Å² bound in regions of the molecule other than the active site. Also, there is an undefined large peak in the electron density map near SG of Cys 212 residue.

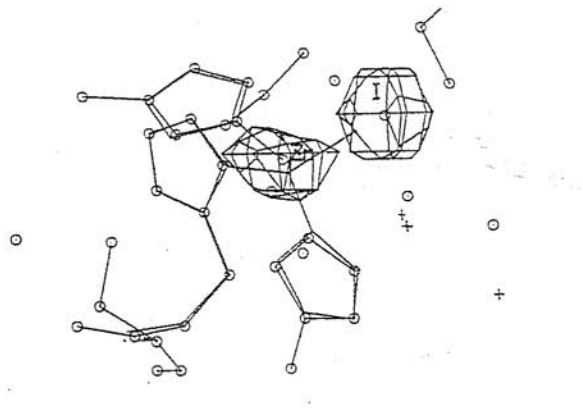

FIG. 1. Zn^{2+} AND I^- IN THE ACTIVE SITE OF HCAI