MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS 1963-A
To date, using high-resolution X-ray crystallography, we have determined the structures of 10 small molecule ligands or inhibitors to the serine protease, porcine pancreatic elastase. These complexes reveal details of binding or steps on the catalytic pathway (Michaelis complex, acyl intermediate, transition state intermediate) that now can be used to design novel, more specific inhibitors or intermediates. Keywords: Enzyme inhibitors.
1. Project Goals

A. Test the enzyme mechanism: The tetrapeptide, Pro-Ala-Pro-Tyr bound to porcine pancreatic elastase (PPE), has been studied (J. Mol. Biol. (1986) 190, 259-267). A sequel study is now in progress; "forward" binding in the active site is found.

B. Test the enzyme mechanism: The azapeptide, Suc-Ala-Ala-Pro-azaAla, did not bind to PPE due to blockage at the S4 site. Further study will be made with a shortened azapeptide; this should help capture a reaction intermediate.

C. Inhibitor binding: Several studies of newer isocoumarins have been made using low-resolution diffractometer as well as high-resolution film data. In all cases either the PPE active site was "empty" or else the low electron density indicated statistical disorder. Prof. Powers has found an approximate 50:50 distribution of two competing reactions (nucleophile = His 57 or OH-) over a broad pH range (Biochem. (1985) 24, 7200-7213). Some inhibitors are too insoluble in aqueous buffers to yield complexes, in the face of competing reactions (e.g., hydrolysis).

D. Inhibitor binding: Insufficient resources (data collection, manpower) have kept us from studying 3-benzyl-ynene-enol-butyrolactone.

E. Inhibitor binding: A low-resolution data set of the ketoester showed no binding, presumably because of blockage at the S4 site. A shorter ketoester was made available to us very recently. Synthesis of a shorter inhibitor is now in progress.

F. The structure of human leucocyte elastase (HLE) has been solved (EMBO Journal (1986) 5, 2453-2458); preliminary structural data are being used to study differential binding of inhibitors between PPE and HLE.
4. Synopsis
   a) List of publications


b) Major Presentations

