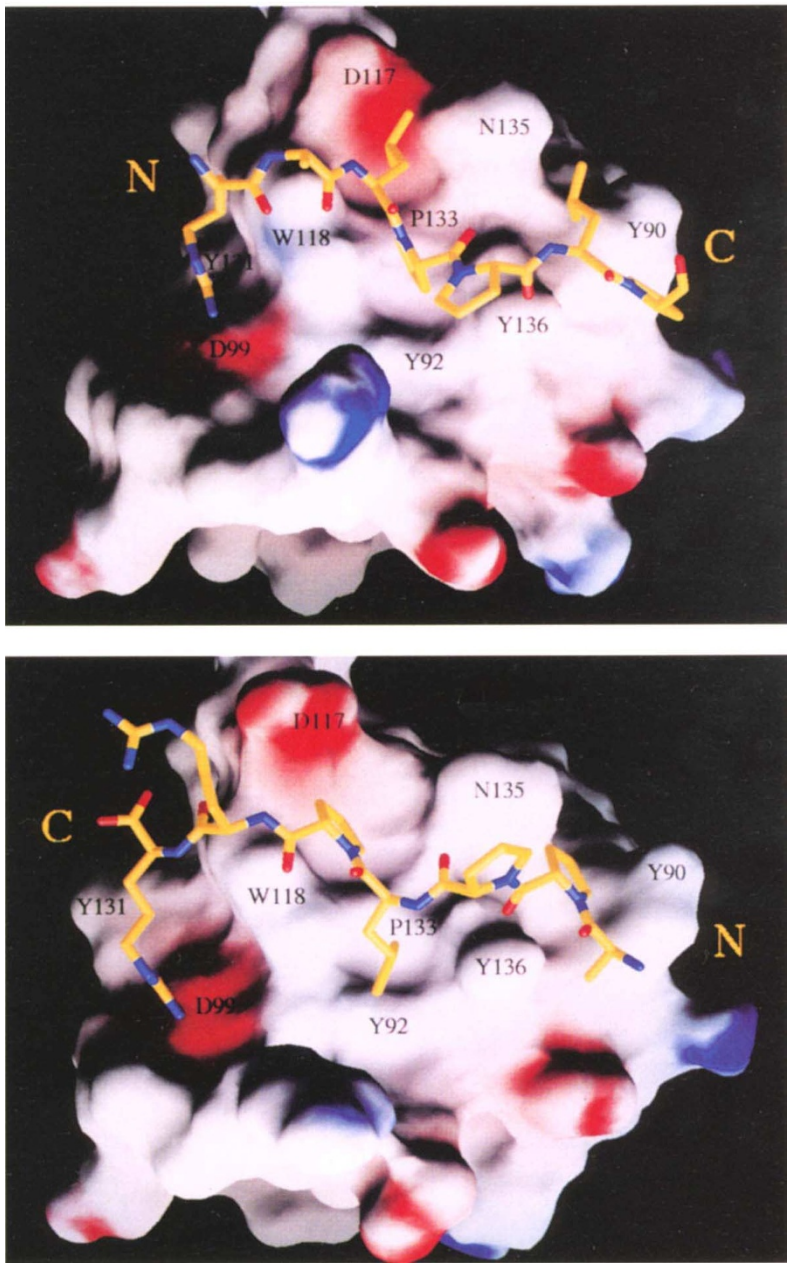
Heads you bind, tails you bind



SH3-domains are common features of a number of proteins involved in intra-cellular signalling and cytoskeletal architecture, mediating protein-protein interactions by their binding of proline rich peptides. Over the last year a number of structures of SH3-domains from different proteins, with bound peptide have been derived by both X-ray crystallography and NMR-spectroscopy (see *News & Views* by Saraste M. & Mussachio A. in last months Nature Structural Biology). All these report the bound peptide in a left-handed poly-proline type II configuration fitted into a cleft on the SH3-domain. The orientations of the bound peptides were very different; depending on the protein studied; the peptides fitted in one of two orientations at 180° to each other.

This dichotomy has been further demonstrated by a recent paper in Science (Feng, S., Chen, J.K., Yu, H., Simon, J.A. & Schreiber, S.L. Science 266 1241-1247). Different peptides have been shown to bind to the same SH3-domain (that from the tyrosine kinase Src) in different orientations. The positioning of arginine residues at either the beginning or the end of the peptides RALPPLPRY (top in figure) and AFAPPLPRR (bottom in figure) appears to be the crucial determinant of the peptide orientation. Both peptides bind with this residue close to the same aspartic acid on the binding cleft forcing the inverted orientations of the peptides.

CS