The addition of a nucleophile to the fumarate double
bond is an SN2 type addition. There is a close
intermolecular contact between the C23 carbon of the
fumarate double bond in β-FNA and the O3-phenolic
oxygen on a neighboring β-FNA molecule, which can serve
as a model for nucleophilic attack on the fumarate
group. After a least-squares fit of the fused ring
moieties of α- and β-FNA, the C23 of the α-epimer is
more than 2A away from the C23 of the β-compound, too
far away and in the wrong orientation for alkylation to
take place.
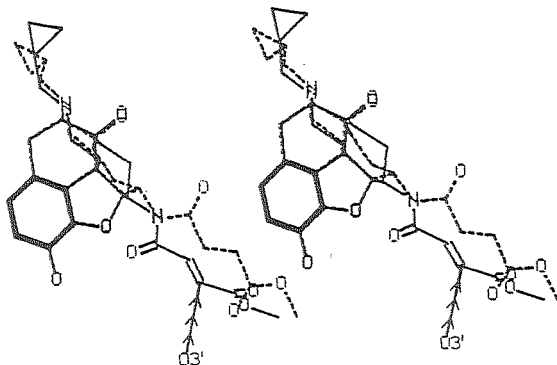
(iii) The use of distance-matrices (2) to define the sub-
strate conformations and orientations which are compati-
ble with the geometrical features previously defined for
the receptor sites.
Some examples of the docking of polypeptide substrates
into the active sites of enzymes of known structures are
given.

(1) BUSETTA,B., TICKLE,I.J. & BLUNDELL,T.L. (1983), J.
     Appl.Cryst. 16, 432–437.

(2) HAVEL,T.F., KUNTZ,I.D. & CRIPPEN, G.M. (1983), Bull
     Math.Biol. 45, 665–720.

**03.4—7   DOCKER : AUTOMATIC ALGORITHMS FOR SIMULATING
PROTEIN RECEPTOR AND SUBSTRATE INTERACTIONS.**

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If interactive computer graphics programs seem to be the
best approach to study the docking of flexible substrates
into a protein receptor of known three-dimensional struc-
ture (1), they cannot be limited the geometric operations
and facilities in refining conformational energies. Auto-
matic algorithms must be designed to avoid fastidious and
somewhat subjective manipulations so as to make the users'
task easier and more reliable.

To correlate the results of the conformational analysis
at the level of the receptor sites, with the biological
observations a complete inspection of the different pos-
sible interactions must be assumed.A three-step algorithm
to perform an automatic study of the docking of a flexi-
ble substrate is proposed with :

(i) A bitwise use of the computer memory to represent
the three-dimensional accessible volume of the receptor
site as a fine grid sampled at regular small intervals
and a subsequent partition of the set of these accessi-
ble points into "hydrophobic" pockets and "hydrophilic"
zones.

(ii) The generation of all the possible "ab initio" con-
formations of the flexible substrate. For sequential sub-
strates such as peptides, nucleic acids, polysaccharides
this task may be done once only, and preserved in a fast
accessible data bank.

**03.4—8   SMALL MOLECULE + ELASTASE BINDING
AS MODELS FOR DRUG + RECEPTOR INTERACTIONS:
METHODS AND RESULTS** By E. Meyer G.Cole,
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Due to the sum of weak forces on the resulting
structural and functional specificity of
drug+receptor interactions, it is essential
that the receptor architecture be known to the
highest resolution possible, that the ubiqui-
tous water molecule be included appropriately,
that the internal flexibility of functional
groups be considered and that the composite
picture be evaluated quantitatively. While mo-
lecular modelling via computer graphics makes
much of the above both possible and even com-
prehensible, it is overly subjective.
In order to put such studies on a solid basis
and better define the spatial geometry of a re-
ceptor, crystallographic investigations have
been initiated: the 2.5A resolution structure
of porcine pancreatic elastase (PPE Sawyer, et
al., JMB(1978)118,137) has been extended to
1.65A resolution (R=0.18).
Next, a crystal of PPE was given excess sub-
strate (Ac-AlaProAla-pNA) and the reaction al-
lowed to reach equilibrium; 1.65A resolution
data sets at pH 5.0 and 7.5 were measured and
refined (currently, R=.19, pH5). A comparison
of the results of the refined structures will
be presented.
In order further to probe the model of binding
of inhibitors, crystals of PPE have been soaked
in solutions of select compounds and
low-resolution (4.5A) data used for difference
Fourier calculations to establish binding prior
to high--resolution studies. Concurrently,
these compounds have been graphically modelled