MOLECULAR PRESENTATIONS

Carboxypeptase A - Hydration-Directed Catalytic Function

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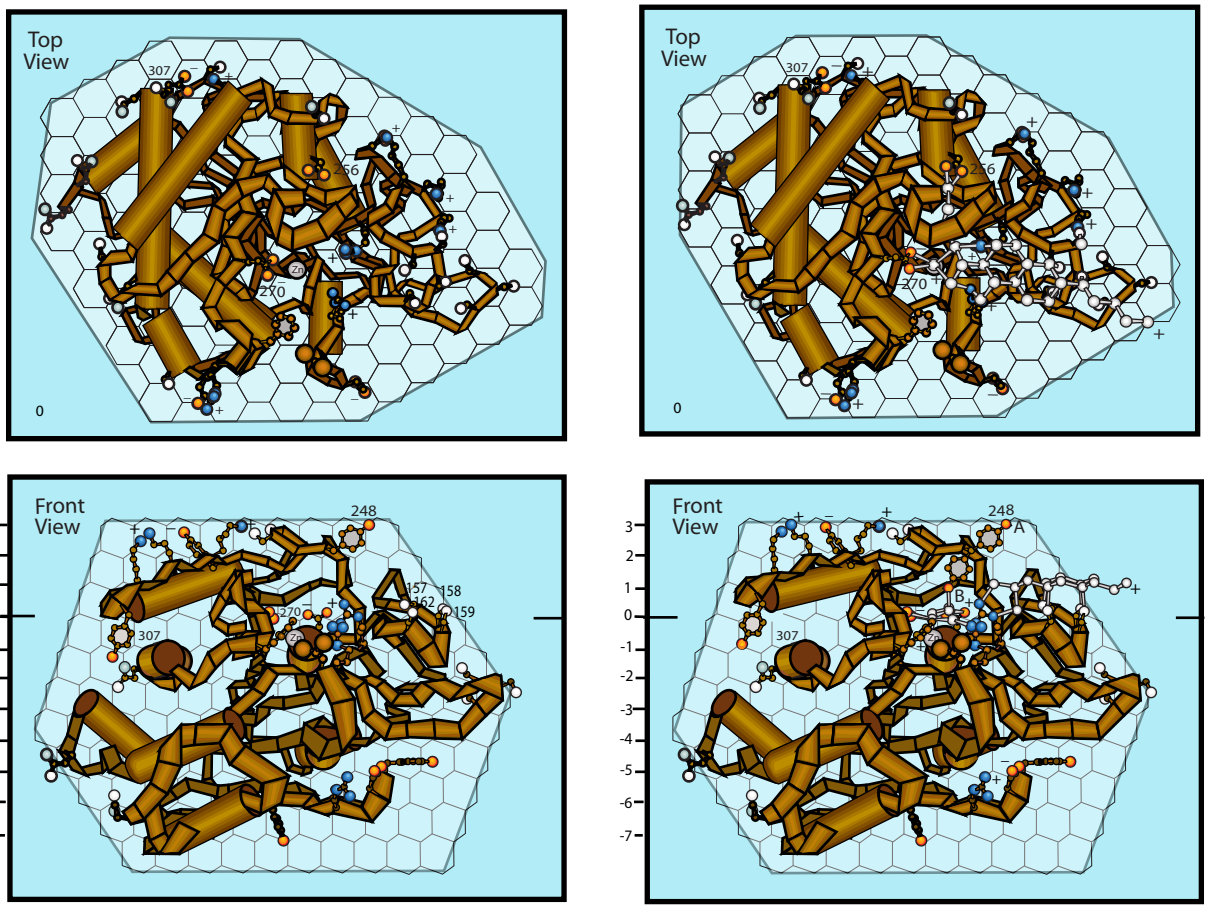
Dedicated to the late Professors Carl Djerassi and William S. Johnson of Stanford University.

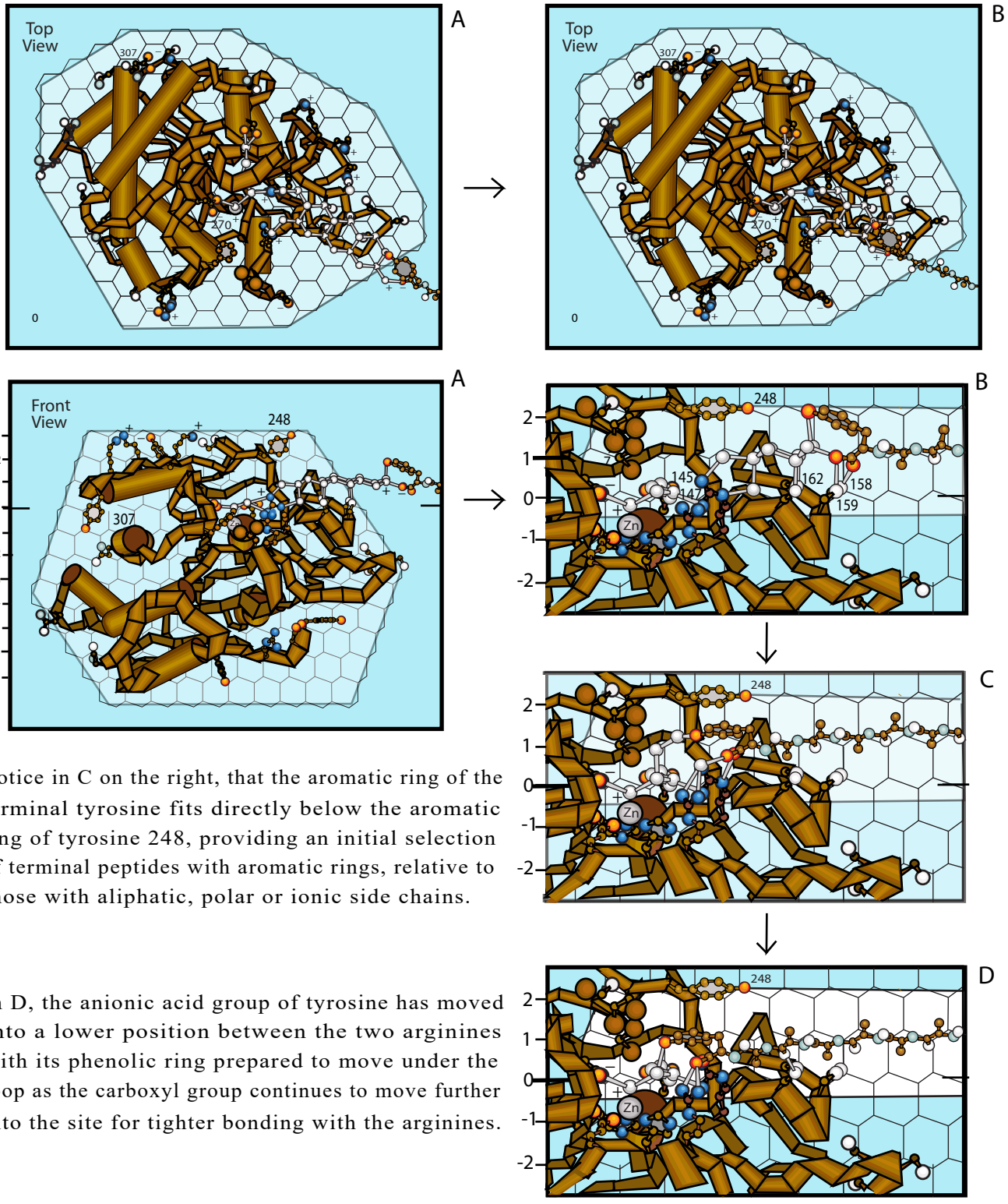
As a continuation of the presention in www.cubichydration.com, the carboxypeptidase A enzyme is displayed on the left in its crystalline form.[1] The gray zinc ion in the center, with two blue cationic arginines on the right and the anionic glutamate at 270 on the left, is the cataltic reaction site. Although peptides in the central core of the protein are held in relatively ridged positions, most of those on the surface which hydrogen bond directly with surface water, have a degree of freedom.



However, the four serines at positions 157, 158, 159 and 162 play a critical role in the function of the enzyme. Since, as shown on the right, they are resting on the core, they have lttle freedom to move vertically but, as shown on the right, by rotating only slightly, are in positions to hold water molecules above them at level 1 in low-energy linear and hexagonal forms which extend out from the molecule to direct the anionic ends of polypeptides into the binding site for cleavage.[3] Although a continuous line of ordered water molecules are shown in the figure on the right, at any instant, only short linear segments of order are present in those probability positions.[4]

Notice that the coils on the upper left have rotated upward slightly so that charges on the ionic ends of their side chains can be stabilized by hydration in layers 3 and 4 of surrounding water.[4] Also notice that the aromatic ring of tyrosine 248 can rotate down to hydrogen bond with water and substrate molecules in the reaction site.

As the terminal tyrosine peptide on a polypeptide approaces the enzyme, it is drawn by transient linear elements of hydration propagating out from the catalytic site into line as shown in Figures A below. By displacing water molecules in preferred linear positions, the polypeptide is drawn into direct binding with serines 158 and 159, as shown in B and then into direct binding with atoms in the binding site as shown in C. By following the postitive charge tunneling from the binding site in these preferred linear elements of hydration, the polypeptide is drawn by permitted steps into the site.

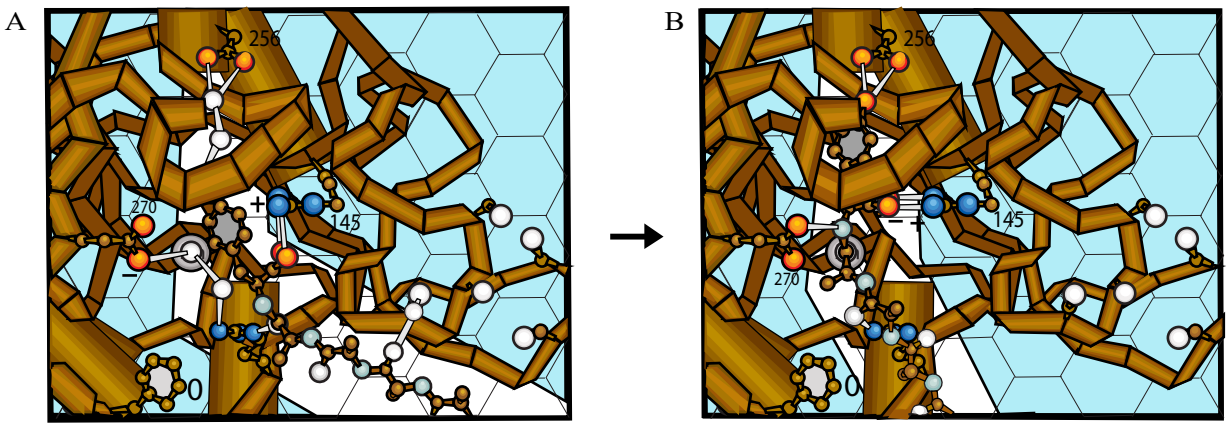


Notice in C on the right, that the aromatic ring of the terminal tyrosine fits directly below the aromatic ring of tyrosine 248, providing an initial selection of terminal peptides with aromatic rings, relative to those with aliphatic, polar or ionic side chains.

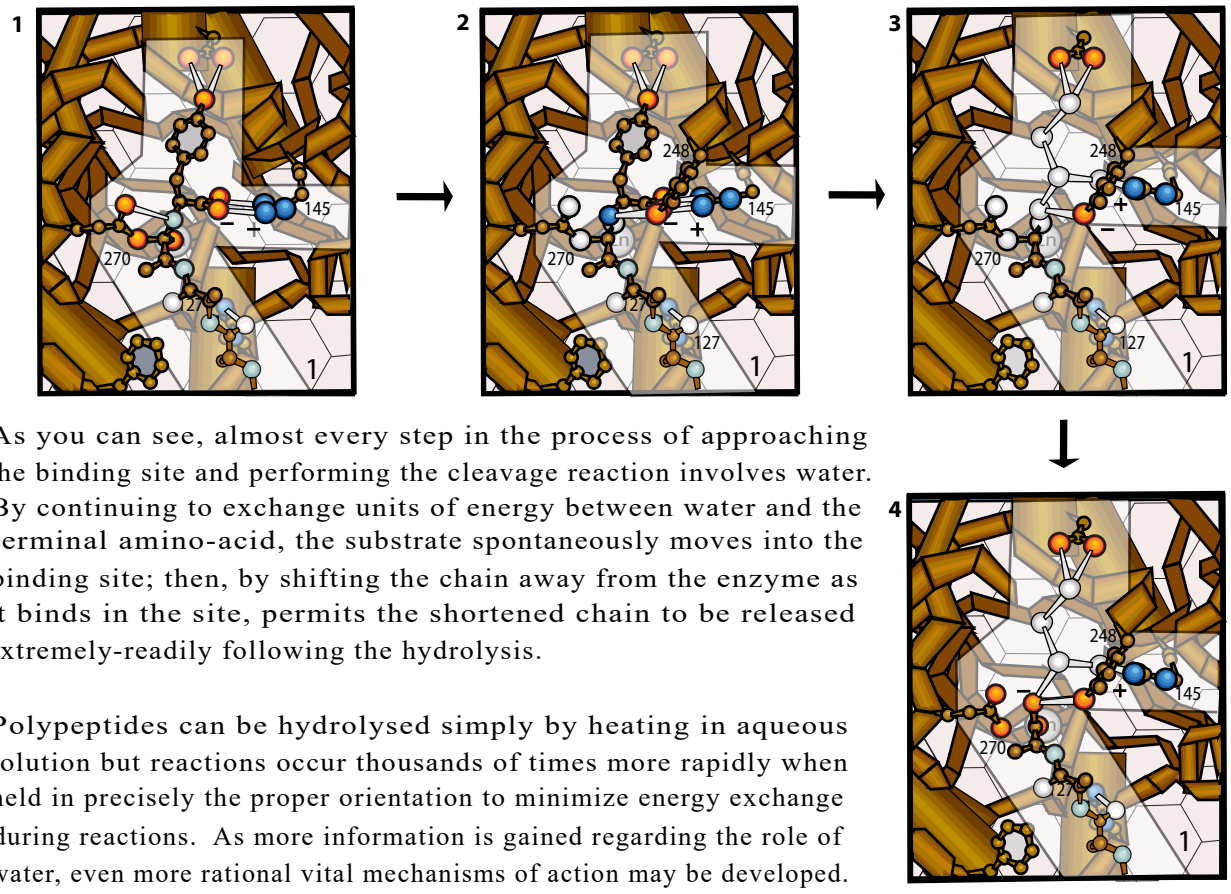
In D, the anionic acid group of tyrosine has moved into a lower position between the two arginines with its phenolic ring prepared to move under the loop as the carboxyl group continues to move further into the site for tighter bonding with the arginines.

In A, as the anionic end of the polypeptide chain moves in to begin bonding with arginine 145 and the aromatic phenolic ring moves into the hydration space below the loop, water continually moves from order toward disorder to drive the movement. Finally, in B, essentially all water has been displaced and the tyrosine peptide oxygen is bound to the zinc ion.

Top Views



With the loop removed, as in 1 below, you can see that the carboxylate of glutamate 270 is in precisely the proper position to bond with the tyrosine carbonyl carbon, break the amide bond, form an anydride and release the terminal tyrosine, as in 2.[4] In Figure 2, tyrosine 248 on the upper loop is shown rotated down to hydrogen-bond with the nitrogen of the released tyrosine amino-acidc to escort it out from below the loop. As water moves into the open space, tyrosine 248, as shown in 3, holds a water molecule in precisely the proper position to bond with the anhydride, break the bond with glutamate 270 and, as in 4, escort the chain out of the site.



As you can see, almost every step in the process of approaching the binding site and performing the cleavage reaction involves water. By continuing to exchange units of energy between water and the terminal amino-acid, the substrate spontaneously moves into the binding site; then, by shifting the chain away from the enzyme as it binds in the site, permits the shortened chain to be released extremely-readily following the hydrolysis.

Polypeptides can be hydrolysed simply by heating in aqueous solution but reactions occur thousands of times more rapidly when held in precisely the proper orientation to minimize energy exchange during reactions. As more information is gained regarding the role of water, even more rational vital mechanisms of action may be developed.

Although detailed studies of the reaction described above have been reported in the literature,[5] the possible role of water, as presented above, has not been included.[4] Time will tell whether the interpretation presented here are valid or not.

References

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