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## How good to get to know you more.....and a question in organic chemistry

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Dear George

It was a particular pleasure to get to know you better and to learn so much from you at the Morales Bay meeting. I would love to hear more and more about your Defense Department adventures (I once presented something to the board that you sat on.....in an elementary school in La Jolla around 2000, trying to sell them on ion channels as detectors). What a scene!

BUT I am actually writing about organic chemistry.

I am intimidated already writing about this to you, but will try to catch your attention and see if you can do what I can only fantasize about.

Attached is a paper showing that active sites of enzymes (with known structures, nearly perfectly known by my standards) have an enormous density of ionizable side chains, something like 20 M in chemical units. Importantly these are found in every class of enzymes and in most of those classes there are examples of 100 M densities. (These are not pathological when we look at the structures themselves). I understand perfectly well (John Edsall taught me about this in 1961, if I remember correctly) that the side chains may not all be ionized, but surely most of them are, and so the key biological point emerges.

This kind of unusual 'structural' and chemical feature has all the hallmarks of what biologists call an adaptation. I do not dare patronize you and explain what 'adaptation' means lest you already be expert in this, but I do not want to mystify either, so just ask if you want more discussion.

The question is how does the enzyme USE the adaptation?

I assert the following productive working hypothesis:

The enzymes uses the fixed (what I prefer to call permanent) charge of its glutamates, lysines, arginines, and aspartates to change the density of electrons in the outer shells of the substrates of the enzyme so the chemical reaction needed by evolution is catalyzed (i.e., has a lower 'activation' barrier and also lower kinetic limitations).

[The fancy language is that to a good first order the biological adaptation is this. The protein provides a specific inhomogeneous Neumann condition for the Poisson part of the Schroedinger equation.]

If I am right, an organic chemist should be able to pick a particular enzyme, look where it puts its permanent charges, look where the substrate is nestled in the active site, and say (i.e., guess intelligently) how the 'orbitals' of the substrate are distorted to make the reaction go.

I certainly cannot do that.

But a fine organic chemist can, I suppose.

Would you like to try?

As ever

Bob

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 **Ionizable Side Chains as published.pdf**  
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