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CARBOHYDRATE RESEARCH

Introduction

Three-dimensional structures of carbohydrates and how they interact with proteins (from a transcript of the opening comments)

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One of the perspectives that I bring to the present meeting on "Three-dimensional structures of carbohydrates and how they interact with proteins" now that I am in the drug design business, is a realisation that the drug design does not require high resolution models. I spent most of my academic career trying to get very precise about how we should interpret NOEs for carbohydrates, and what I am recognising is that the kind of precision we have been seeking all those years is, in a practical world, perhaps not needed. This does not mean it should not be done, but in the practical world it is not needed. There is a great deal we can do with the tools we currently have, and the real reason is that in a drug design process there is an iterative cycle that goes on and the real challenge is to come up with the conformation that is reasonably close for a compound that shows some kind of activity, and then there are well-developed methods for the refinement of that lead compound into a drug candidate. Massimo will ask discussion leaders to try to summarise the key advances in the areas and regions that needed further developments. From my own very personalised perspective I think the key advancements you will hear this morning are mainly in the areas which, I would say, are very healthy. As I said at the beginning, the mixture of experiment and theories, the cumulation of experimental data and bond conformations particularly through use of transferred NOEs, and then the use of that information to strain the modelling process, to me is a very healthy iterative cycle. I think you will see several posters — again my personal bias indicates that there have been improvements in the parameterisation of forcefields by including data from high level ab initio calculations, and there has been an increased sophistication in the development of docking algorithms in ways of trying to bring carbohydrates and proteins together. However, there is an incredible amount to be done and I would say that the major challenge that we are facing is the problem of treatment of hydrogen bonds; this is brought home because with increasing computing power we are now able to actually deal with much larger molecules, and as we do so we discover that large oligosaccharides have the capacity for large intramolecular hydrogen-bonding networks, partially excluded from solvent. Depending on how much importance you give to those hydrogen bonds, you end up with a very limited set of conformations, and that leads to problems if one tries to deal with the aqueous environment and hydrogen bonds through effective dielectric constants. How do you deal with the problem of a dielectric constant in the binding site which is going to be different from the dielectric constant in bulk solvent and so forth? Problems of geometry in the treatment of hydrogen bonds: explicit water would be the logical way to go. You now have a forcefield which has been parameterised in vacuo with ab initio calculations. All you need to do is add the solvent back in and everything should work. I have not seen John Brady here as yet but he will talk of explicit water I hope. I believe that there still is a lot of room for thermodynamics and a desire to try to get some experimental evidence on the relevance and importance of the different contribution to the en-

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tropy of binding, particularly whether solvent, after desolvation and resolvation, etc. are major factors or not.

Finally, the topic about which I wax eloquent after a few glasses of wine is the issue of time–space. Life is not an equilibrium process. Biological reactions in a cell do not carry on at equilibrium. There is a kinetic component, particularly when dealing with enzymes. What are the scales, e.g. time scales, of motions in binding sites compared to time scales for orientations of side-chains; i.e. dynamics is extremely important.