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Intermediate Results in Computational Biology: Can they be the Realities during Biological Processes?

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Molecular modeling is an important technique used in Biological Research Studies in various contexts. The molecular modeling involves computer simulation techniques, and software has now been designed for finding solutions to problems in biological research. Most often, it is the end result of the simulation studies which is considered for progressing further on the considerations of Biological Systems.

To be more specific, the quantum chemical molecular orbital calculations are inherent in most of the molecular modeling simulations in Biology. These calculations invariably use geometry optimization procedures with appropriate geometry constraints acquired from experiments. These optimizations proceed by repeating the energy calculation by making small corrections to the structure parameter, at every stage of iteration. These corrections are based on the principles of energy minimization. The evaluation of the extent of corrections at each stage is done by the algorithms based on mathematical principles for optimization. Even when the potential energy profile during a chemical reaction is calculated as the reaction proceeds each intermediate situation would be an optimized situation.

Energy minimization principle is such a sound criterion that most of the situations results in a convergence to an end result which is relatable to the end result of a chemical reaction. Then, does that mean all the intermediate structures that are encountered in the optimization procedure during a calculation have a real existence as intermediate stage in chemical reaction? Then if there are different kinds of mathematical algorithms for geometry optimization, then the path of the optimization can be different even if end results are comparable. Then which of the algorithm would be closer to what happens in chemical laboratory? An algorithm which is computationally fast and accurate may not have an authenticity that the path during these efficient mathematical procedures consists of chemically realizable intermediate structures.

The above considerations would be dealt with as much as possible with the examples of computational results and the chemical intuitions. It is intended to highlight how these considerations affect the reconciliation of the Biological macro structures, and, the micro level bio-molecular structure details. In particular, in view of the fact that NMR spectroscopy is taking strides to gain in importance, as much as X-ray techniques, in macromolecular structure determination it is intended to find how the Calculated NMR chemical shifts of structures corresponding to the intermediate stages during the Geometrical optimization can be useful in influencing the considerations on experimentally obtainable NMR spectra(1,2,3).

1. "http://aravamudhan-s.ucoz.com/nmr_article.html"
2. http://www.ugc-inno-nehu.com/ToxicHE.html
3. http://www.ugc-inno-nehu.com/the_gamess.html

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http://www.ugc-inno-nehu.com/crsi_13nsc_nmrs2011.html#CRSI-13NSC

Illustrating an Elementary Approach by Cluster Calculations for Structure, Dynamics and Reactions

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There has been much interest in studying the structures and spectroscopy of solvent-solute clusters, consisting of ions (either cations or anions) or neutral species, which are solvated by neutral molecules (usually water) or rare gas atoms. It is hoped that these studies will enable a better understanding of the fundamentals of structure, dynamics and reactions of ions and molecules in bulk solutions[1].

As it stands stated in the above excerpt, there have been several efforts[2] to study the systems of cluster by quantum chemical calculations of structures and energies. These efforts have been mostly to obtain the optimized, end-structure-parameters and energies. Starting with the given input structure of the cluster, structure sequences are generated during the optimization procedures at various steps till the end. And enquiring into the structural details and the sequences of structures obtained during the Geometry Optimization can be providing indications to the various pathways of interactions of cluster components. This approach is a much simpler approach for beginners to inquire about the mechanistic aspects of reactions than a potential energy surface calculations and trying to relate to reaction coordinates.

In this abstract this approach is reported as a feasible methodology. An illustrative set of calculations using computational chemistry tools are the basis for such conclusion and in particular a calculation on the isolated molecule alpha amino acid [Glycine] substantiates a remark made on the acid base characteristics of such amino acids elegantly bringing out the intra-molecular proton transfer from one of the equilibrium structure to result in another. The roles of water molecules present in the neighborhood can be shown to influence this intra molecular transfer to become water mediated inter molecular transfer of protons. The importance of hydronium ion ($[H_3O]^+$) formation is also evidenced. The equilibrium characteristics of zwitterions form and the unionized form of the amino acid also could be well discerned and such results seem to be indicating details which were not thought of as possibilities for study by such simple calculations.

An effort also would be made to provide references of previous related studies when the results are discussed[2].

Reference:

1. "*Atomic and Molecular Clusters",* Roy L. Johnston, Taylor Francis (Year 2002), Sec.3.5, p73.
2. http://www.ugc-inno-nehu.com/crsi_13nsc.html

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http://www.ugc-inno-nehu.com/crsi_13nsc_nmrs2011.html#NMRS-2011

Theoretically Possible Structures and the Averaging; Calculated Chemical Shifts and Simulated NMR Spectra: And, Comparison with Experimental Spectra.

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This contribution would have reference to this author's previous contributions (1) to the Annual Meetings of the Indian Biophysics Society. The effort had been to illustrate the kind of averaging techniques useful for averaging the chemical shift values corresponding to the confirmation changes during a fluctuation of a given structure. As per what is now known, the advantages of the NMR technique in comparison with Xray technique are that the solution structures can be determined by NMR. However, it is also necessary to consider the determination of the Macromolecular structure in Solution by NMR methods entails obtaining the several contributing structures for a given Biological macromolecule while the x-Ray method would be resulting in a single conformation as the structural investigation.

If a given solution structure obtained by NMR is a superposition of several structures, then each contributing structure must be recognized as a MEAN structure exhibiting fluctuations from the mean thus each of the contributing structure must be subjected to fluctuation characteristics while processing.

Thus when a molecule is having several confirmations in equilibrium, arriving at the effective structure accounting for the experimental NMR features would depend upon the appropriate characteristic times, and it may either require summing the experimental spectra or averaging the chemical shift values and then constructing a single spectrum corresponding to the experimental spectrum.

It does not simple enough to envisage how the theoretically calculated chemical shifts corresponding to contributing structures can be used to average the theoretical (*optimized / can there be more than one?*) structures, average the calculated chemical shifts and simulate the spectrum to be compared with the experimental spectra. This calculation and simulation results would be discussed in the presentation.

References:

1. **a)** "http://aravamudhan-s.ucoz.com/inboxnehu_sa/IBS2006/ForIbs2006.html"
   b) "http://aravamudhan-s.ucoz.com/Posters_nsc9_nmrs2007_ibs2007.html#IBS2007"