How long will the Concertedness of Chemical Reactions Stand the Test of Time?

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There are numerous articles published in the organic/computational chemistry interface that are proving/disproving the concertedness of popular chemical reactions such as the Diels-Alder reaction[1] (fortunately, the majority are still concerted!). In some cases, the current state-of-the-art has revealed that with certain reactants, what was once considered concerted and obeying the Woodward-Hoffmann rules is actually non-concerted[2-7] when its transition state (TS) was successfully located by DFT calculations[1] (B3LYP, M06-2X, CASSCF(8,8) etc.) and 3D visualisation. The TS is also known as the saddle point on the potential energy surface (PES). Domingo has also suggested the *molecular electron density theory* (MEDT)[8], a modern view of reactivity for organic chemistry.

Would it be fair to suggest that while some are concerted (with an aromatic TS), while others are not and stepwise[2] (e.g. diradical/pseudoradical)? I'm not making any sweeping statements here or disproving the historically established, but expressing curiosity! Also, for some reactants, under what experimental conditions (e.g. choice of solvent or catalyst) could the reaction choose either mechanistic pathway, if theoretically feasible?

Such calculations are computationally expensive requiring geometry-optimised structures and a cluster of computer hardware in supercomputing centres involving parallel computing. Popular basis sets are often chosen to strike a balance between program running time and accuracy. I hope, one day, research hasn't progressed so that it doesn't require only the world's best supercomputers and only a handful of research groups can actually use them (to reduce even more approximations for the exchange-correlation energy functional in the calculations) for more complex structures.

Perhaps, one day, if smaller devices could harness such powerful technology in one device, even students of organic chemistry could reliably achieve the same using a sophisticated app on devices such as tablets (or even mobile phones) without the need for any powerful back-end servers and have data suitable for publication. In the meantime, a cluster of rooted student mobile devices (RenderScript kernel), wirelessly and securely performing the background SCF convergence and other calculations (e.g. follow-up IRC reaction pathway) might be more realistic or the use of powerful cloud computing technology. A recent practical development[9] of a mobile cluster has been achieved using compiled MPICH for the ARM architecture and other software (e.g. Buildroot). Alternatively, there are high-performance mobile devices with NVIDIA multicore GPUs (e.g. Tegra 4) that could be used for MP4 calculations (as an example). You would probably also need options to investigate non-covalent interactions (NCI) and the gradient field of electron localisation function (ELF).

Clearly, the app user must be able to provide the correct geometries for reactants (or product or any predicted TS - if required) prior to a TS search. Hopefully the next

generation, in several decades time or hopefully far sooner, will be able to do just that.

It would be great if open-source code (e.g. Apache 2.0 license) becomes widely available for the scientific community to experiment with and uses industry-standard precision. Interpretation of the mathematical theories behind all this is certainly not for the faint-hearted.

We are seeing a dawn in a new age of experimental/commercial quantum computers[10], with, hopefully, probable potential to reach the masses in the future sometime (as has often been the case), if the quantum systems involved can be 'controlled' and scaled up with exceptionally high precision and is practically feasible, as the materials currently used require near absolute zero temperatures. Quantum computers and quantum mechanics for computational chemistry: an uncanny natural match!? Just imagine the huge potential for high-performance computing and Big Data with those computers/networks. I doubt they'll bundle it into the next generation Quantum Nexus or iPhone, but certainly in cloud-based applications.

I wonder what other quantum-mechanical theories might have come along by then (if at all possible) that are even more accurate than DFT[11] and much less computationally expensive for smaller device use? By-passing the Kohn-Sham equations with machine learning[11] is currently being investigated for improved accuracy and lower computational cost in DFT calculations.

TS theory is also central in the design and development of suitable enzyme inhibitors (TS analogues) for medicinal chemistry, e.g. the competitive neuraminidase inhibitor, oseltamivir/Tamiflu, an antiviral (influenza A and B) prodrug or the origins of chemical reaction enantioselectivity, so has widespread application.

1. See the following for theoretical studies (concerted/non-concerted): M. Linder, T. Brinck, *Phys. Chem. Chem. Phys.*, 2013, **15**, 5108-5114; https://dx.doi.org/10.1039/C3CP44319A.

2. Non-concerted: L.R. Domingo, *J. Chil. Chem Soc.*, 2014, **59**, 2615-2618; https://dx.doi.org/10.4067/S0717-97072014000300019.

3. E. Jasińska, A.S.A. Tarnów, E. Dresler, A. Łapczuk-Krygier, A. Kącka, T. Kościuszko, E. Nowakoska-Bogdan, R. Jasiński, *Chemik*, 2015, **69**, 395-400;

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4. H.V. Pham, D.B.C. Martin, C. Vanderwal, K.N. Houk, *Chem. Sci.*, 2012, **3**, 1650-1655; https://dx.doi.org/10.1039/C2SC01072K.

5. Zwitterions and unobserved intermediates have also been found in organocatalytic Diels-Alder reactions: A. Dieckmann, M. Breugst, K.N. Houk, *J. Am. Chem. Soc.*, 2013, **135**, 3237-3242; https://dx.doi.org/10.1021/ja312043g.

6. You might also be interested in other reactions such as 1,3-dipolar cycloaddition reactions (concerted vs. non-concerted): A. Darù, D. Roca-López, T. Tejero, P. Merino, *J. Org. Chem.*, 2016, **81**, 673-680; https://dx.doi.org/10.1021/acs.joc.5b02645.

7. For a theoretical investigation, see: J. Miller, 2017, *Theoretical studies involving two Diels-Alder reactions under solvent-free conditions*, Harvard Dataverse, V6; https://dx.doi.org/10.7910/DVN/E3LY2H.

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9. D.E. Attia, A. M. ElKorany, A.S. Moussa, *Int. J. Adv. Comp. Sci. Appl.,* 2016, **7**, 99-103; https://dx.doi.org/10.14569/IJACSA.2016.070913.

10. S. Boixo, S.V. Isakov, V.N. Smelyanskiy, R. Babbush, N. Ding, Z. Jiang, J.M. Martinis, H. Neven, *Characterizing Quantum Supremacy in Near-Term Devices*, arxiv.org/abs/1608.00263; http://arxiv.org/abs/1608.00263.

11. Challenges for Density Functional Theory (despite its success story): A. J. Cohen, P. Mori-Sánchez, W. Yang, *Chem. Rev.*, 2012, **112**, 289-320; https://dx.doi.org/10.1021/cr200107z.

12. F. Brockherde, L. Li, K. Burke, K.-R. Müller, *By-passing the Kohn-Sham equations with machine learning*, arxiv.org/abs/1609.02815; http://arxiv.org/abs/1609.02815.