J Biol Inorg Chem (2011) 16:819–820
DOI 10.1007/s00775-011-0816-5

COMMENTARY

Ab initio wavefunctions in bioinorganic chemistry: More than a *succès d'estime*?

Abhik Ghosh

Received: 30 June 2011 / Accepted: 30 June 2011 / Published online: 14 July 2011

Ab initio wavefunction theory (WFT[1]), often billed as affording "the right answer for the right reason," was the darling of the 1980s. WFT, however, was and continues to be notoriously difficult to apply to transition metal systems, where an accurate description of the electronic structure frequently involves multiple Slater determinants. As recently as 5 years ago [1], I felt obliged to describe WFT as a *succès d'estime*,[2] as far as bioinorganic chemistry was concerned, i.e., a critically acclaimed but unpopular success. Against this backdrop came density functional theory (DFT), a single-determinant, essentially ground-state method that provided relatively high ab-initio-level accuracy, but at a fraction of the cost. The spin-unrestricted form of DFT, where up-spin and down-spin electrons occupy different spatial orbitals, proved spectacularly successful for transition metals and took bioinorganic chemistry by storm. By 1990–1991, hemes and other important bioinorganic structures had been fairly adequately explored by DFT [2]. In the next few years, entire mechanistic pathways of key metalloenzymes, including reactive intermediates and transition states, were likewise mapped out with DFT calculations [3]. Even today, spin-unrestricted DFT is the unrivaled method of choice for a typical application involving open-shell transition metal species. Ab initio theorists by and large did not participate in this theoretical-bioinorganic revolution, complaining that DFT was a quick and dirty, semiempirical method and stating they would really prefer to wait till they could do more "honest" calculations. Pragmatic chemists and biochemists, needless to say, had no such qualms and by 2000 DFT had become a fixture in all major chemistry journals, whereas WFT was relegated to specialized journals devoted to chemical physics (for an early account of the role of WFT in bioinorganic chemistry, see [4]).

To understand why practitioners of WFT by and large did not study important bioinorganic problems, we must necessarily enter the realm of speculation. Foremost among their problems is certainly the sheer difficulty of developing WFT methods for large open-shell transition metal systems. There are, however, other factors as well. Key interpretational tools such as qualitative molecular orbital theory, notably ligand field theory, have often been viewed with a certain disdain by the ab initio community; "molecular orbitals don't exist," for example, has been a common refrain. Other analytical tools such as Mulliken population analyses, energy decomposition analyses of bonding, and nucleus-independent chemical shifts as a measure of aromaticity have all attracted their share of censure. Without the benefit of simple chemical models, practitioners of WFT have understandably found transition metal chemistry a hopelessly complex area, far outside their comfort zone.

Whatever the failings of the ab initio enterprise until now, WFT cannot be dismissed out of hand, for the simple reason that DFT is far from perfect. For open-shell

Dedicated to the memory of Björn Roos (1937–2010), one of the fathers of modern multiconfigurational quantum chemistry, who also cared deeply about chemical applications, and a fun and inspiring friend to countless theoretically oriented chemists.

A. Ghosh (✉)
Department of Chemistry and Center for Theoretical and Computational Chemistry,
University of Tromsø, 9037 Tromsö, Norway
e-mail: abhik@chem.uit.no

[1] WFT is not a standard abbreviation.

[2] The French expression, used more commonly for literary and artistic contributions, has also been translated, tongue in cheek, as "a success that has run out of steam."

transition metal systems, DFT performs well in many cases. A key weakness is that different exchange–correlation functionals often provide widely divergent descriptions of the spin-state energetics of transition metals, a problem that is particularly acute for iron and hence also much of bioinorganic chemistry. A related weakness involves antiferromagnetic coupling; transition metal nitrosyls provide a good illustration of this problem, with different functionals often providing very different spin-density profiles [1]. Despite general apathy, a select few WFT practitioners have devoted significant effort to developing high-quality methods suitable for transition metal systems. The multideterminantal complete active space self-consistent field (CASSCF)/complete active space second-order perturbation theory (CASPT2) methods, pioneered by Roos [5] and continually improved over the years, are perhaps preeminent in this regard. Mention might also be made of the related second-order *n*-electron valence state perturbation theory (NEVPT2) method [6], which circumvents some of CASPT2's pitfalls. Recent developments in multireference coupled-cluster (MRCC) theory are also exciting in this connection, even though they are yet to find application in bioinorganic chemistry. Mukherjee's state-specific MRCC theory [7, 8], for example, might prove applicable to systems as large as (unsubstituted) metalloporphyrins and related systems.

Thus, at long last WFT seems poised to take on real-life bioinorganic problems. I have been fortunate in participating in the solution of a few such problems, of which a couple of examples might serve to illustrate the potential use of WFT in bioinorganic chemistry. CASSCF/CASPT2 calculations performed in collaboration with Roos proved conclusively that chloroiron corrole is best described as $Fe^{III}(S = 3/2)$–$corrole^{\cdot 2-}$, as opposed to Fe^{IV}–$corrole^{3-}$, ending a protracted controversy that DFT could not conclusively resolve [9]. In another study, in collaboration with Peter Taylor, we predicted on the basis of CASPT2 calculations that difluoroiron(IV) porphyrin could not exist as a ground-state species [10]; instead, such a species was better described as Fe^{III}–$porphyrin^{\cdot -}$. Gratifyingly, Ikezaki et al. [11] have recently obtained clear NMR and Mössbauer confirmation of this prediction. Obviously, ligand noninnocence is a major issue for heme protein intermediates such as compounds I and II [12] and we can only predict that multideterminantal methods will play a major role in elucidating the nature of these remarkable species [13].

In this section, three carefully chosen commentaries explain in nonmathematical terms the potential role of WFT in bioinorganic chemistry. The opening commentary by Neese et al. [14] provides a general introduction to the field, with emphasis on newer variants of coupled-cluster methods that promise to be applicable to real-life bioinorganic systems. The second commentary, by Harvey [15], provides a more in-depth introduction to coupled-cluster methods, including CCSD(T), which is often viewed as the gold standard of single-reference coupled-cluster methods. The third commentary, by Shaik and Chen [16], focuses on oxyheme, a long-standing electronic-structural problem that these authors solved satisfactorily with CASSCF/CASPT2 calculations. Of particular note is the insight they derived from valence-bond-style reading of the complex multiconfigurational wavefunction in terms of localized orbitals, an approach that we also adopted in our study of chloroiron corrole [9].

I believe that we have progressed to the point where WFT can begin to address problems of genuine interest to the bioinorganic community. I would thus suggest that WFT today is more than a *succès d'estime*. Will WFT ever rival DFT as far as bioinorganic applications are concerned? Not any time soon. Rivalry, however, is not the right word for describing the relation between WFT and DFT. Today the two approaches are truly synergistic, with frequent and productive cross-pollination. But enough said—do read on and judge for yourself!

References

1. Ghosh A (2006) J Biol Inorg Chem 11:712–724
2. Ghosh A (2001) J Biol Inorg Chem 6:739–752
3. Bassan A, Blomberg MRA, Borowski T, Siegbahn PEM (2006) J Inorg Biochem 100:727–743
4. Ghosh A, Taylor PR (2003) Curr Opin Chem Biol 7:113–124
5. Roos BO (1999) Acc Chem Res 32:137–144
6. Angeli C, Cimiraglia R, Malrieu JP (2002) J Chem Phys 117:9138–9153
7. Datta D, Mukherjee D (2011) J Chem Phys 134:054122
8. Mahapatra US, Datta B, Mukherjee D (1999) J Chem Phys 110:6171–6188
9. Roos BO, Veryazov V, Conradie J, Taylor PR, Ghosh A (2008) J Phys Chem B 112:14099–14102
10. Ghosh A, Taylor PR (2005) J Chem Theory Comput 1:597–600
11. Ikezaki A, Takahashi M, Nakamura M (2011) Dalton Trans. doi: 10.1039/C1DT10561B
12. Rittle J, Green MT (2010) Science 330:933–937
13. Shaik S, Hirao H, Kumar D (2007) Acc Chem Res 40:532–542
14. Neese F, Liakos DG, Ye S (2011) J Biol Inorg Chem. doi: 10.1007/s00775-011-0787-6
15. Harvey (2011) J Biol Inorg Chem. doi:10.1007/s00775-011-0786-7
16. Shaik S, Chen H (2011) J Biol Inorg Chem. doi:10.1007/s00775-011-0763-1