What is required for solving chemical problems on a quantum computer?

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K. Bourzac, C&EN, 2017, 95 (43), pp 27-31, October 30, 2017

So, what are the problems that might be solved?

Depends on the quantum algorithms that allow for exponential or high-order polynomial speed-up ...

Density matrices are not easily accessible

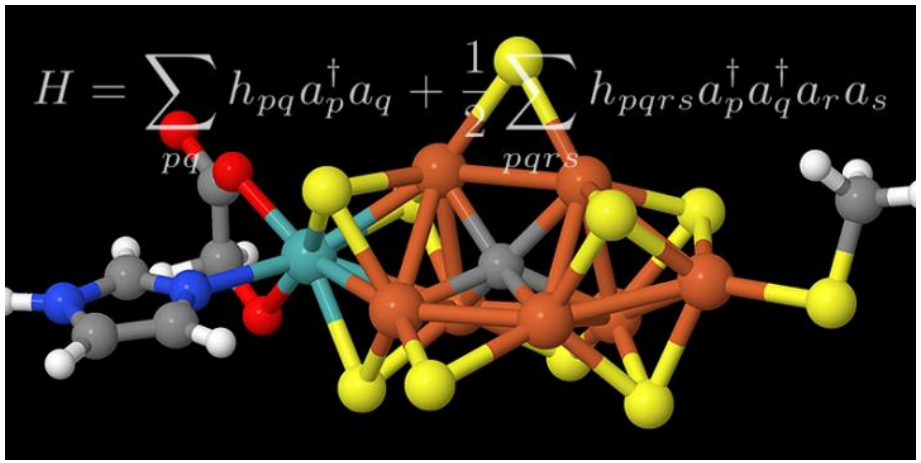
$\rightarrow$ focus on energies for the time being
(specifically, trotterization on universal quantum computer)

$\Rightarrow$ study reaction mechanisms and questions of molecular design
(provided that molecular structures can be obtained from somewhere - usually DFT optimizations)

Elucidating reaction mechanisms on quantum computers

In 2014, Matthias Troyer stepped into my office: Are there applications of moderately sized quantum computers (say, 200 logical qubits for state representation) in chemistry? $\rightarrow$ static electron correlation

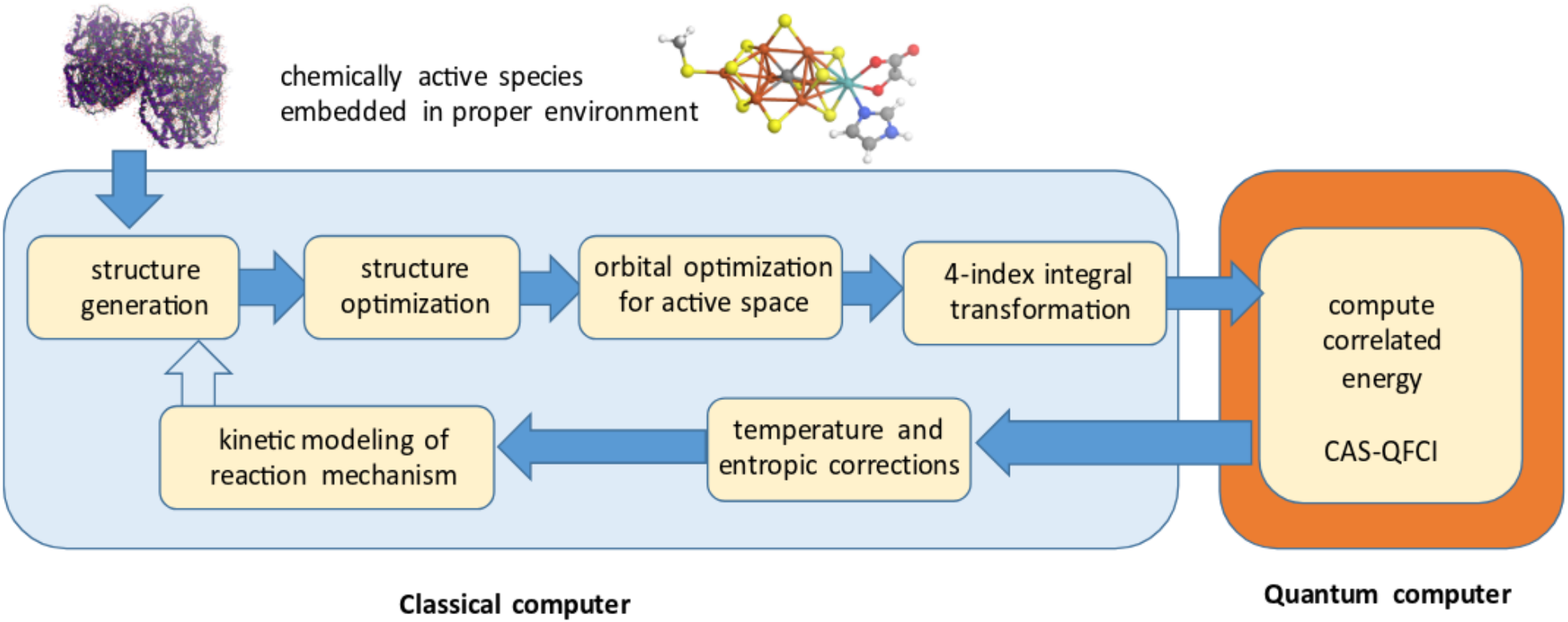
My choice was the iron-sulfur active site of nitrogenase:



Rigorous resource estimates (excluding state preparation):
For this model structure of the resting state, we obtained integrals to parametrize the second-quantized Coulomb Hamiltonian for some electronic states in a Hartree-Fock orbital basis.

M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.

QComputing replaces the exact diagonalization step



M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.

Elucidation of Nitrogenase's mode of action

from air accessible to plants, the mechanism of nitrogen fixation at FeMoco is not known. Experiments have not yet been able to provide sufficient details on the chemical mechanism, and theoretical attempts are hampered by intrinsic methodological limitations of traditional quantum chemical methods.

Quantum Chemical Methods for Mechanistic Studies

At the heart of any chemical process is its mechanism, the elucidation of which requires the identification of all relevant stable intermediates and transition states. In general, a multitude of charge and spin states need to be explicitly calculated in search of the relevant ones that make the whole chemical process viable. Such a mechanistic exploration can lead to thousands of elementary reaction steps (25) whose reaction energies must be reliably calculated. In the case of nitrogenase, numerous protonated intermediates of dinitrogen-coordinating FeMoco and subsequently reduced intermediates in different charge and spin states are feasible and must be assessed with respect to their relative energy. Especially, kinetic modeling poses tight limits on the accuracy of activation energies entering the argument of exponentials in rate expressions.

For nitrogenase, an electrostatic quantum mechanical/molecular mechanical (QM/MM) model (26) that captures the embedding of FeMoco into the protein pocket of nitrogenase can properly account for the protein environment. Accordingly, we consider a structural model for the active site of nitrogenase (Fig. 1, *Right*) carrying only models of the anchoring groups of the protein, which represents a suitable QM part in such calculations. To study this bare model is no limitation, as it does not at all affect our feasibility analysis (because electrostatic QM/MM embedding will not change the number of orbitals considered for the wave function construction). We carried out (full) molecular structure optimizations with DFT methods of this FeMoco model in different charge and spin states to avoid basing our analysis on a single electronic structure. Although our FeMoco model is taken from the resting state, binding of a small molecule such as dinitrogen, dihydrogen, diazene, or ammonia will not decisively change the complexity of its electronic structure.

The Born–Oppenheimer approximation assigns an electronic energy to every molecular structure. The accurate calculation of this energy is the pivotal challenge, here considered by quantum computing. Characteristic molecular structures are optimized to provide local minimum structures indicating stable intermediates and first-order saddle points representing transition structures. The electronic energy differences for elementary steps that connect two minima through a transition structure enter expressions for rate constants by virtue of Eyring's absolute

M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.

Be aware of competitors in classical computing!

Exact Diagonalization Methods in Chemistry. If the frontier orbital region around the Fermi level of a given molecular structure is dense, as is the case in π-conjugated molecules or open-shell transition metal complexes (such as FeMoco), then so-called strong static electron correlation plays a decisive role already in the ground state. Static electron correlations are even more pronounced for electronically excited states relevant in photophysical and photochemical processes such as light harvesting for clean energy applications. Such situations require multiconfigurational methods of which the complete-active-space self-consistent-field (CASSCF) approach has been established as a well-defined model that also serves as the basis for more advanced approaches (29). CAS-type approaches require the selection of orbitals for the CAS, usually from those around the Fermi energy, which can be automatized (30–33). Although CAS-type methods well account for static electron correlation, the remaining dynamic correlation is decisive for quantitative results. A remaining major drawback of exact-diagonalization schemes therefore is to include the contribution of all neglected virtual orbitals.

CASSCF is traditionally implemented as an exact diagonalization method, which limits its applicability to 18 electrons in 18 (spatial) orbitals, because of the steep scaling of many-electron basis states with the number of electrons and orbitals (34). The polynomially scaling density matrix renormalization group (DMRG) algorithm (35) can push this limit to about 100 spatial orbitals; this, however, also comes at the cost of an iterative procedure whose convergence for strongly correlated molecules is, due to the matrix product state representation of the electronic wave function, neither easy to achieve nor guaranteed.

M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.

Quantitative data requires dynamics correlation!

Ways Quantum Computers Will Help Solve These Problems. Molecular structure optimizations are commonly found with standard DFT approaches. DFT-optimized molecular structures are, in general, reliable, even if the corresponding energies are affected by large uncontrollable errors. The latter problem can be solved by a quantum computer that implements a multiconfigurational wave function model to access truly large active orbital spaces. The orbitals for this model do not necessarily need to be optimized, as natural orbitals can be taken from an unrestricted Hartree–Fock (36) or small-CAS CASSCF calculation. The missing dynamic correlation can then be implemented in a "perturb-then-diagonalize" fashion before the quantum computations start or in a "diagonalize-then-perturb" fashion, where the quantum computer is used to compute the higher-order reduced density matrices required. The former approach, i.e., built-in dynamic electron correlation, is considerably more advantageous, as no wave function-derived quantities need to be calculated. One option for this approach is, for example, to consider dynamic correlation through DFT that avoids any double counting effects by virtue of range separation, as has already been successfully studied for CASSCF and DMRG (37, 38). Fig. 2 presents a flowchart that describes the steps of a quantum computer-assisted chemical mechanism exploration. Moreover, the quantum computer results can be used for the validation and improvement of parametrized approaches such as DFT to improve on the latter for the massive prescreening of structures and energies.

M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.

Recall ...

We set out to study possible applications of quantum computing on moderately sized machines
(still requiring thousands/millions physical qubits for error correction)

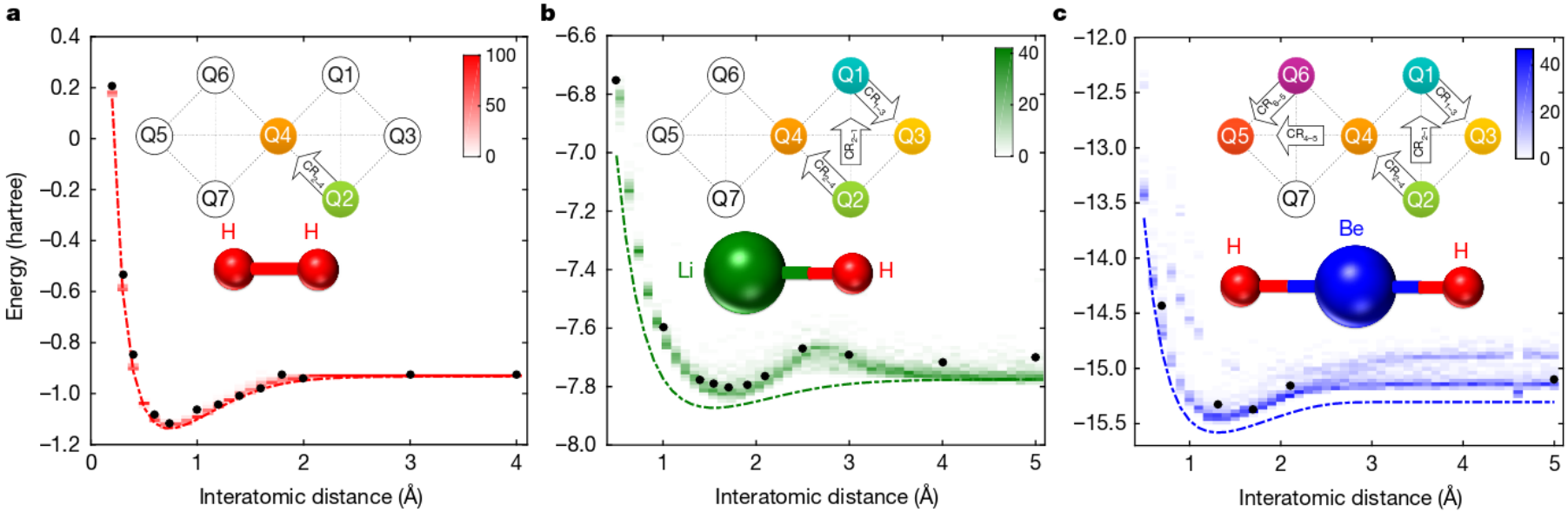
This choice introduces a distinction between static and dynamic correlation ...

$\rightarrow$ and is therefore the cause of all trouble

$\Rightarrow$ **If we would have a quantum computer with, say, a few thousands logical qubits than that would be a game changer in chemistry.**

Let's have a look at current state of experimentation

Take the IBM experiment published last year in Nature as an example ...



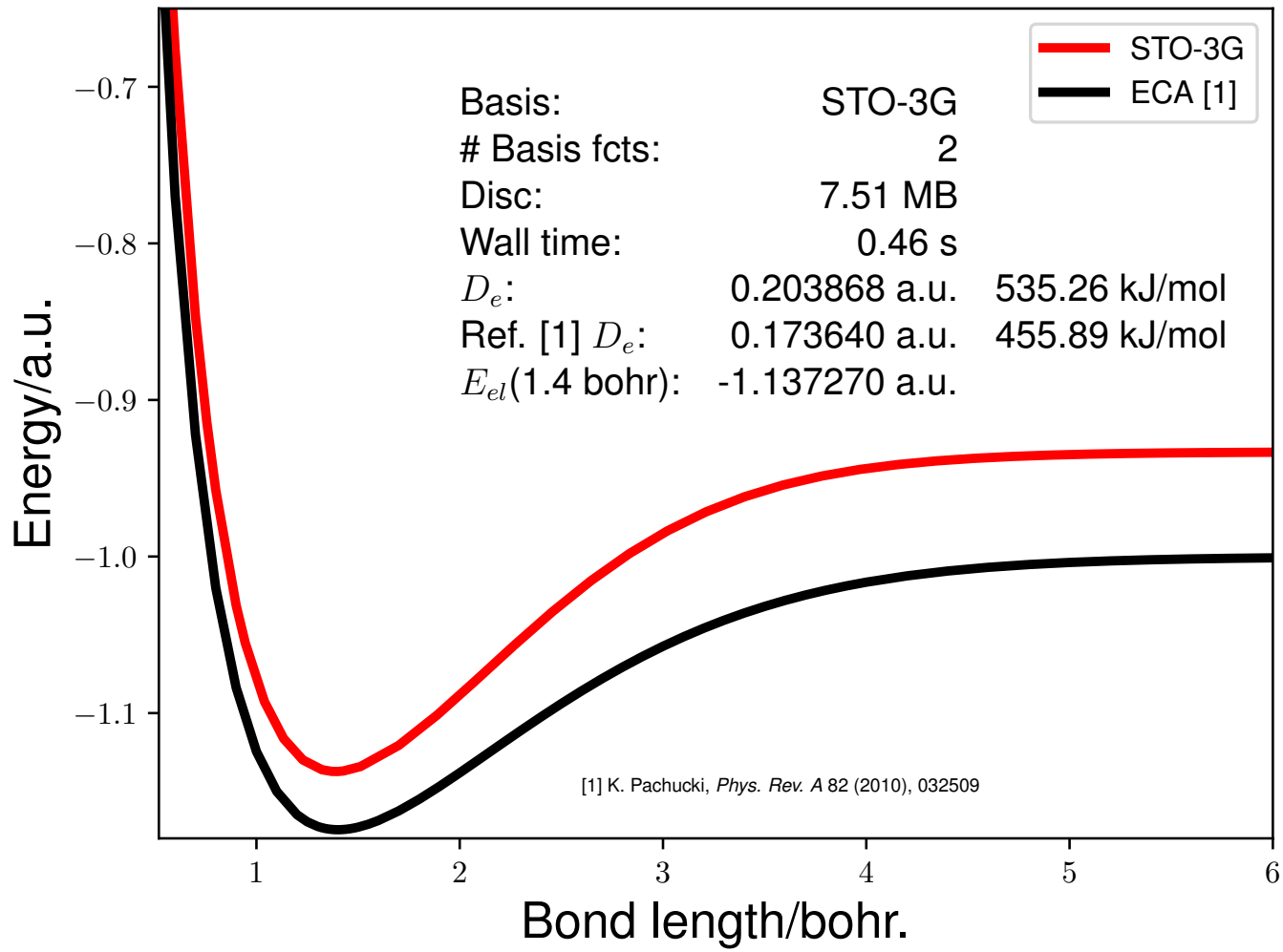
A. Kandala, A. Mezzacapo, K. Temme, M. Takita, M. Brink, J. M. Chow, J. M. Gambetta, Nature 549 (2017) 242-246.

improved data available on arXiv: arXiv:1805.04492

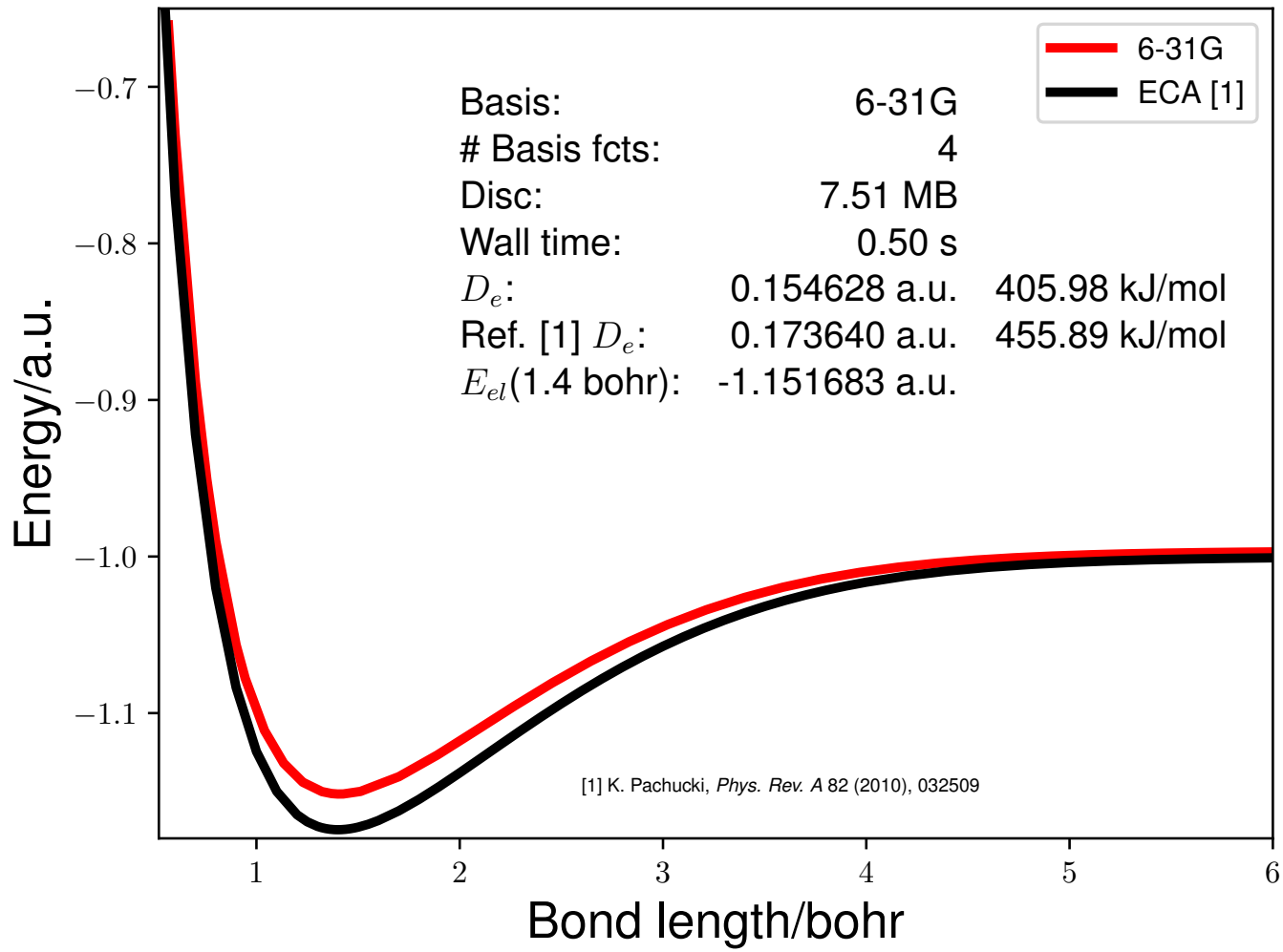
see also:

Quantum Chemistry Calculations on a Trapped-Ion Quantum Simulator, by C. Hempel et al., Phys. Rev. X 8 (2018) 031022

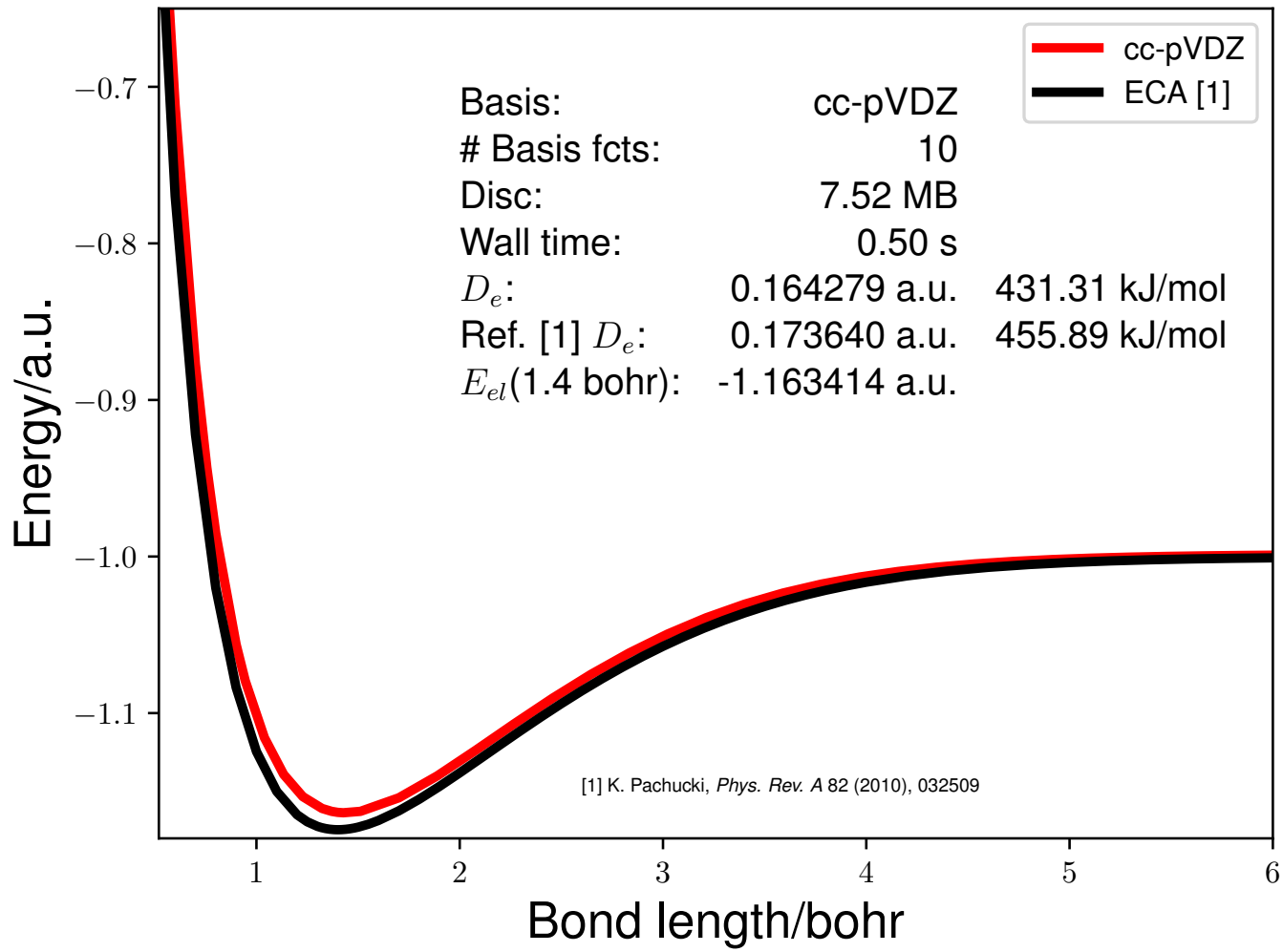
H_2 curve classical computing: minimal basis



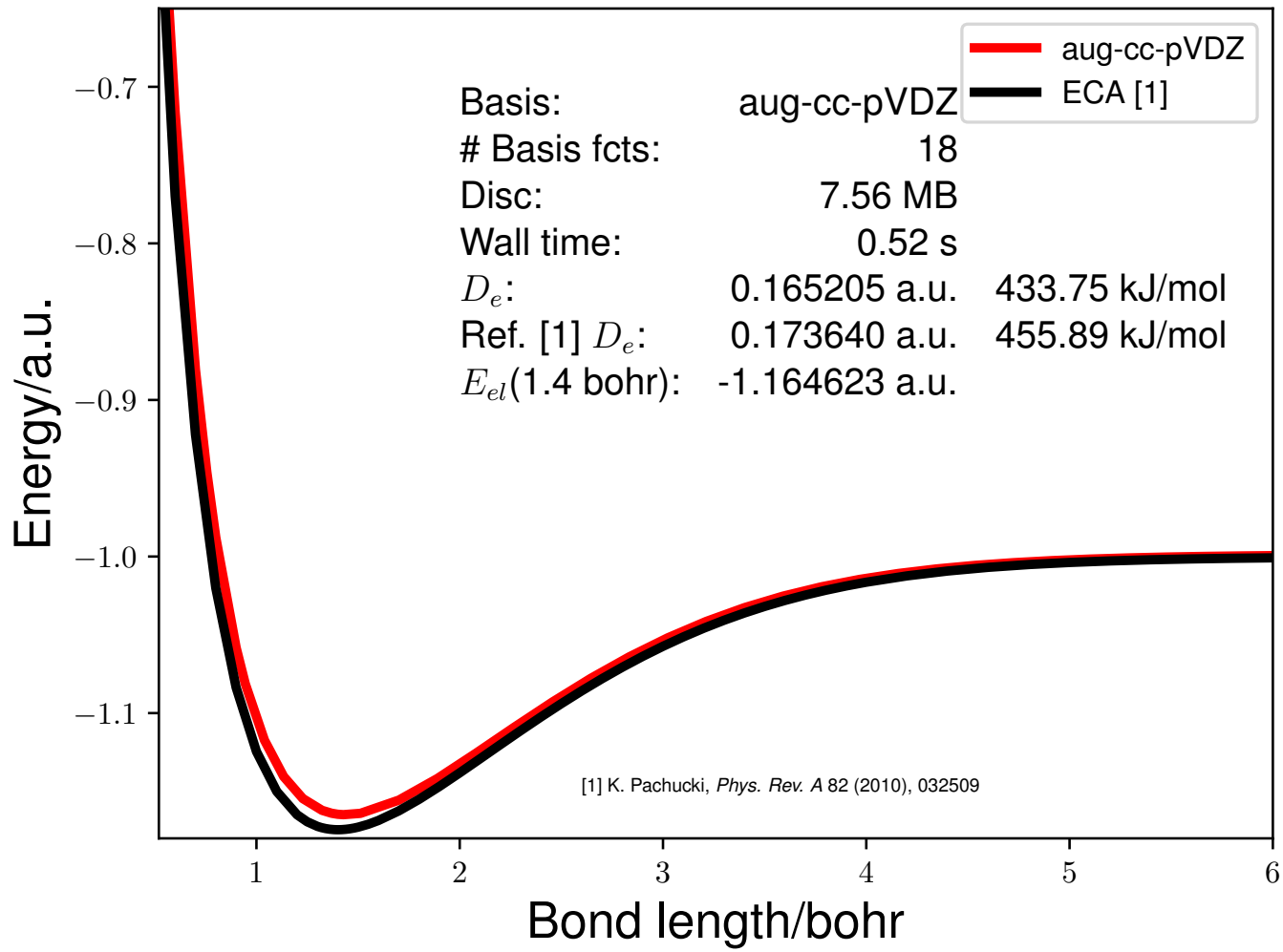
H_2 curve classical computing: small double-ζ



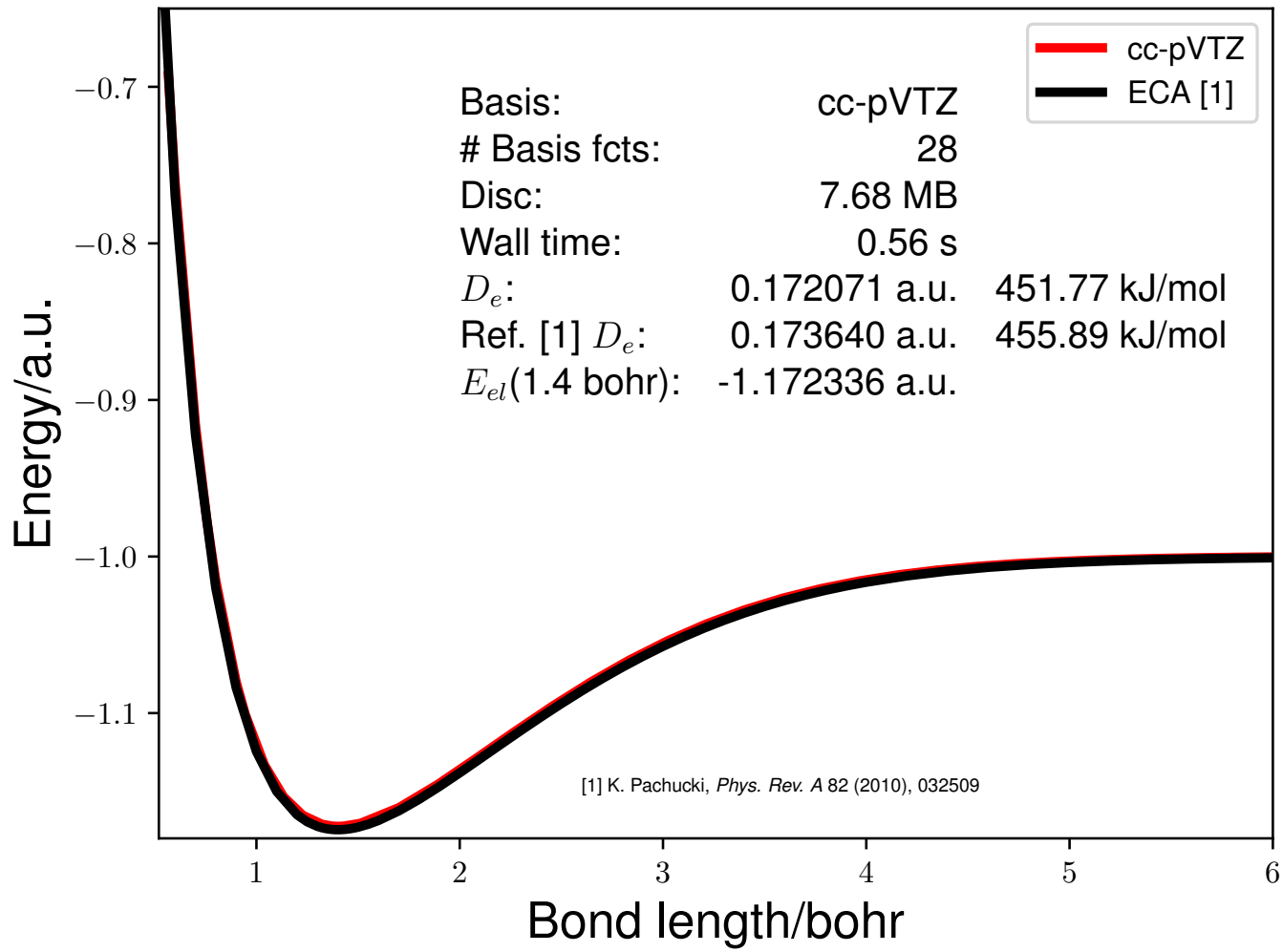
H_2 curve classical computing: larger double-ζ



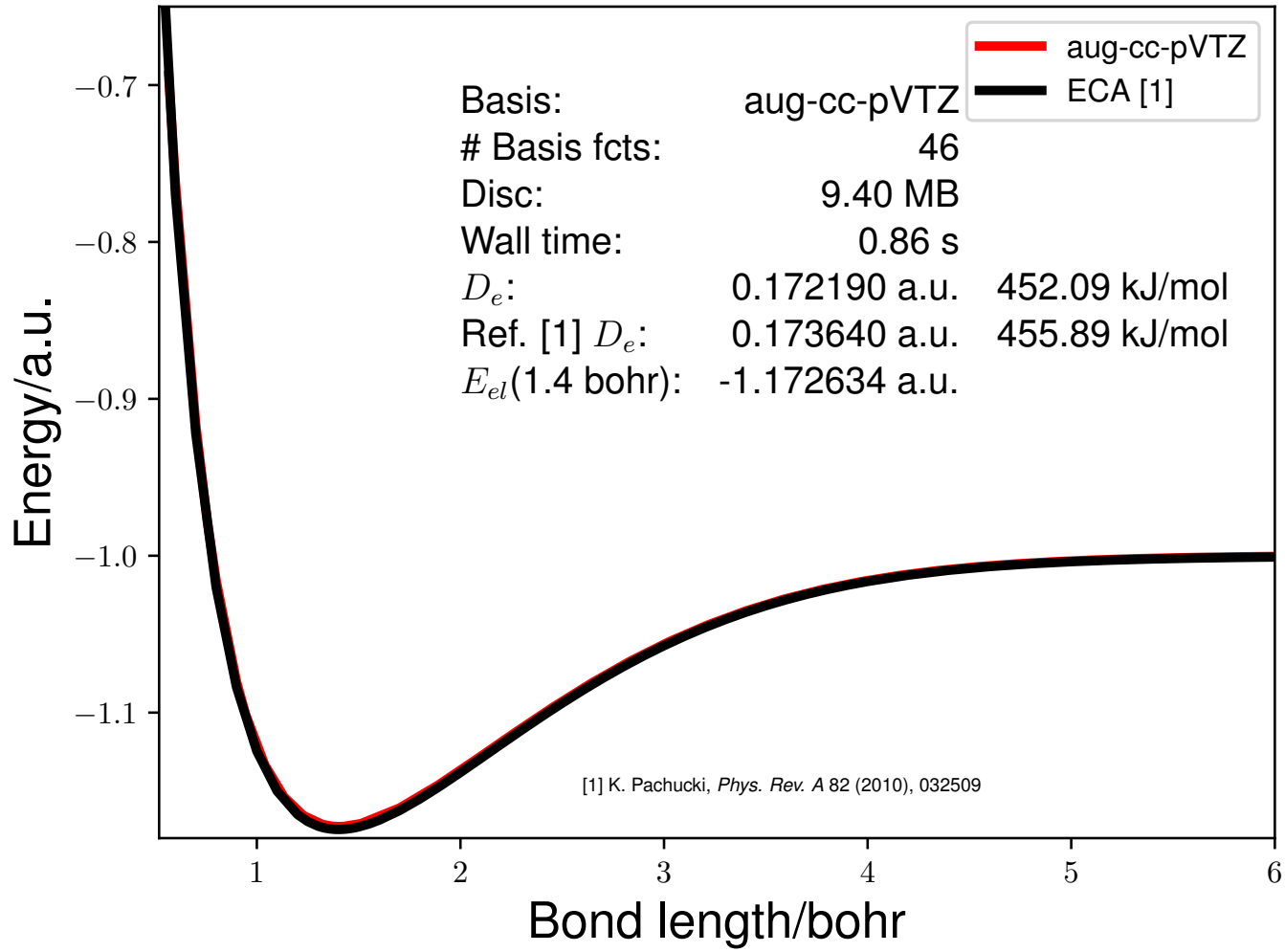
H_2 curve classical computing: even larger bases



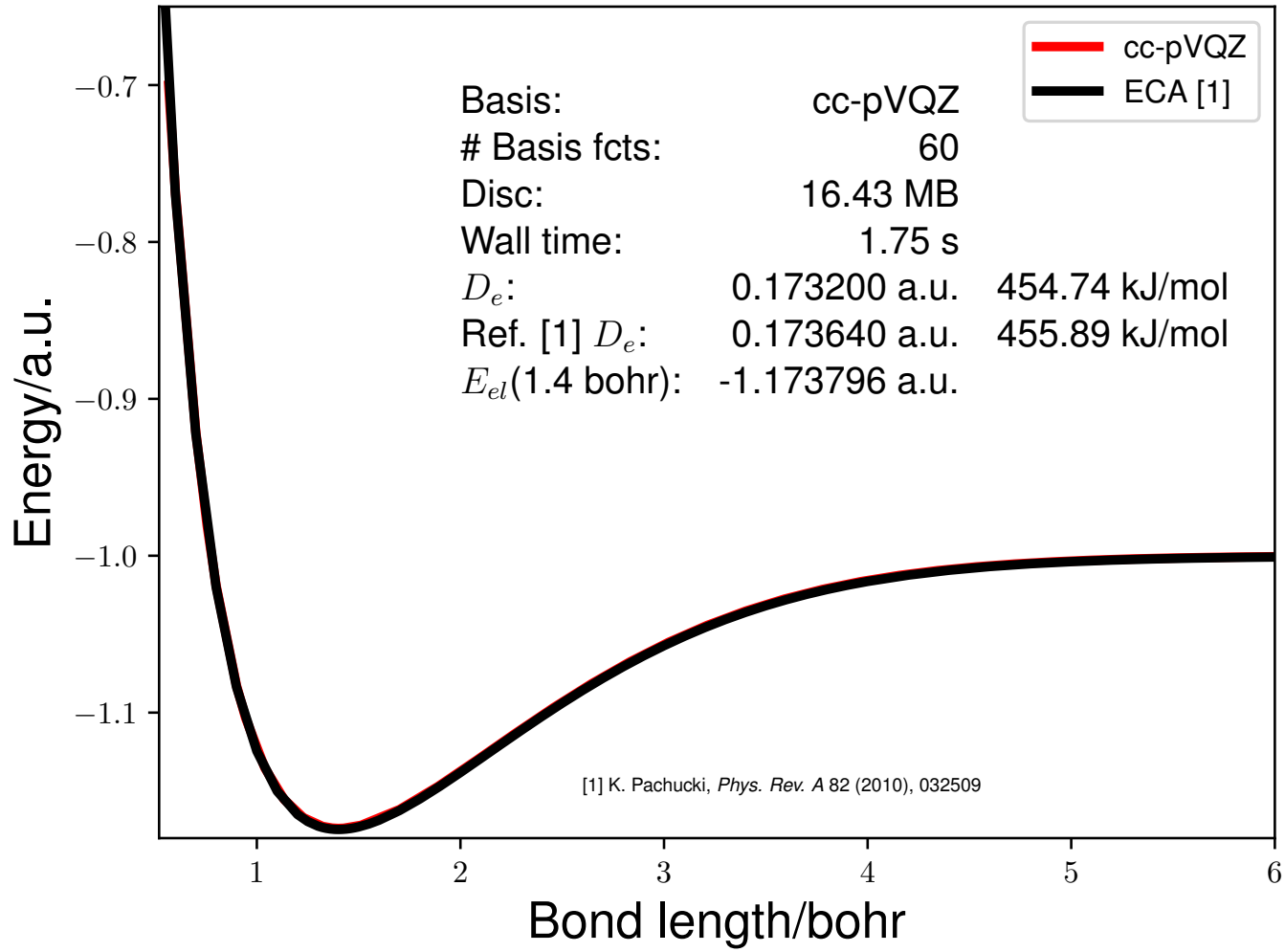
H_2 curve classical computing: even larger bases



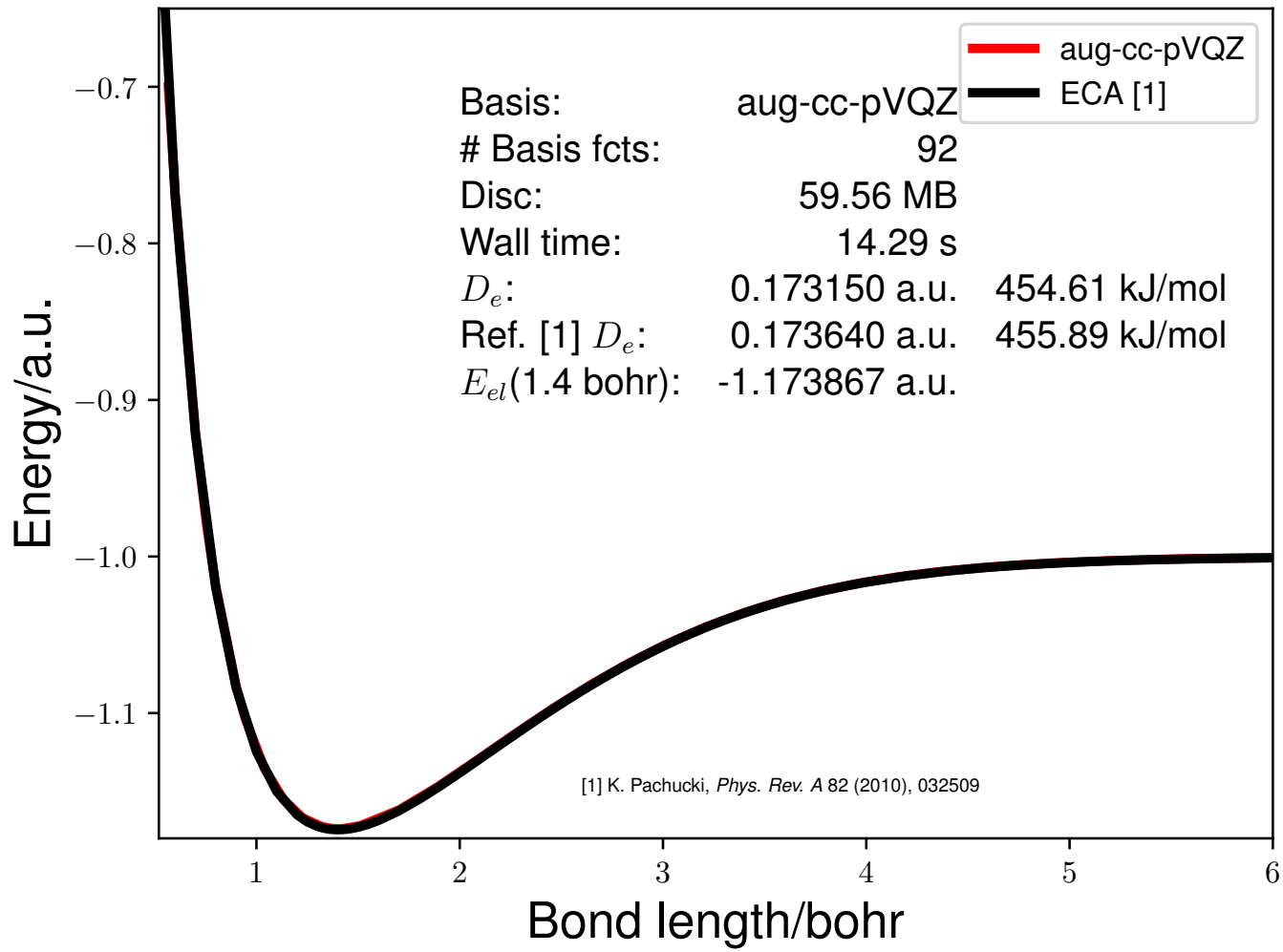
H_2 curve classical computing: even larger bases



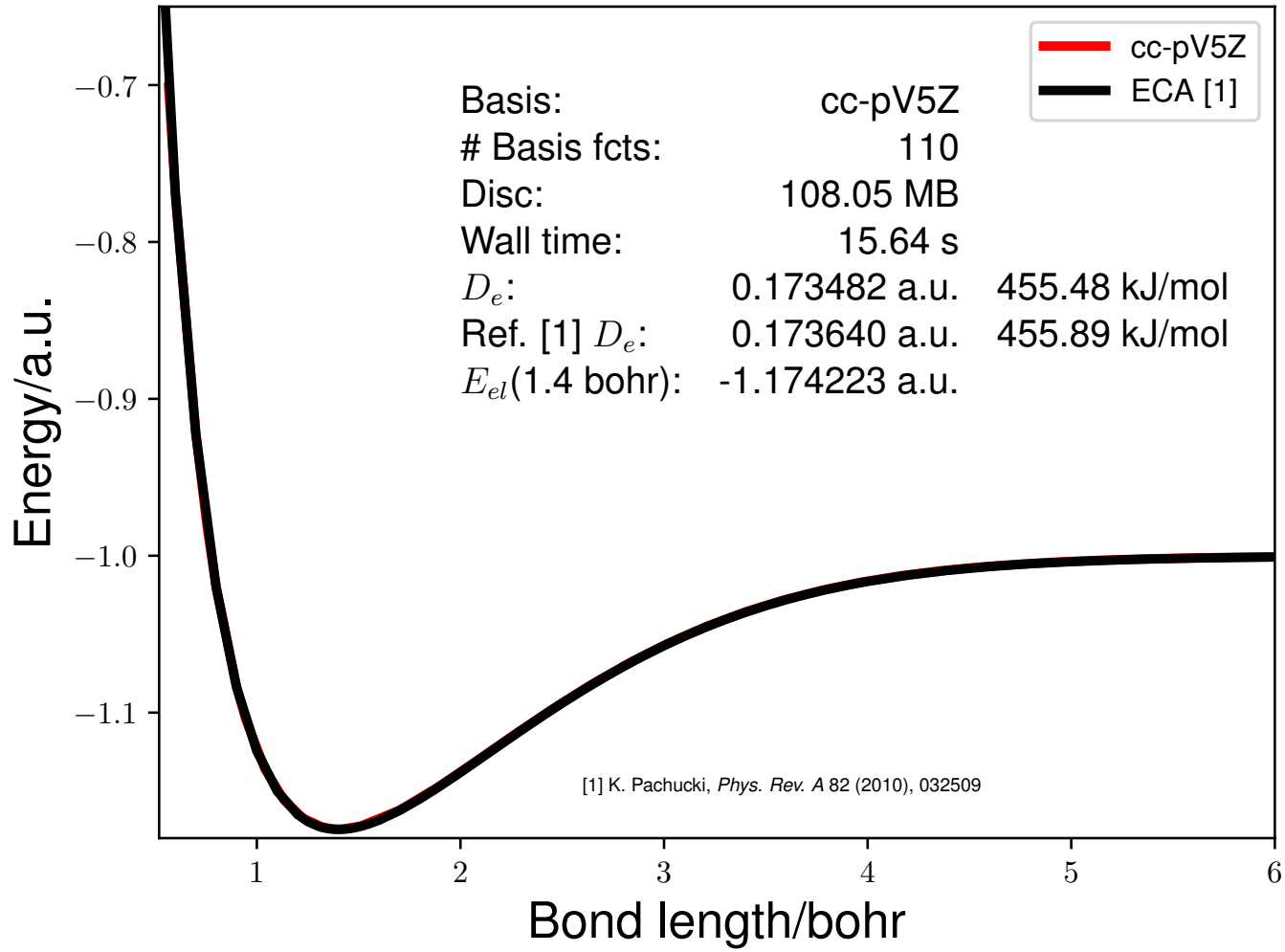
H_2 curve classical computing: even larger bases



H_2 curve classical computing: even larger bases



H_2 curve classical computing: even larger bases



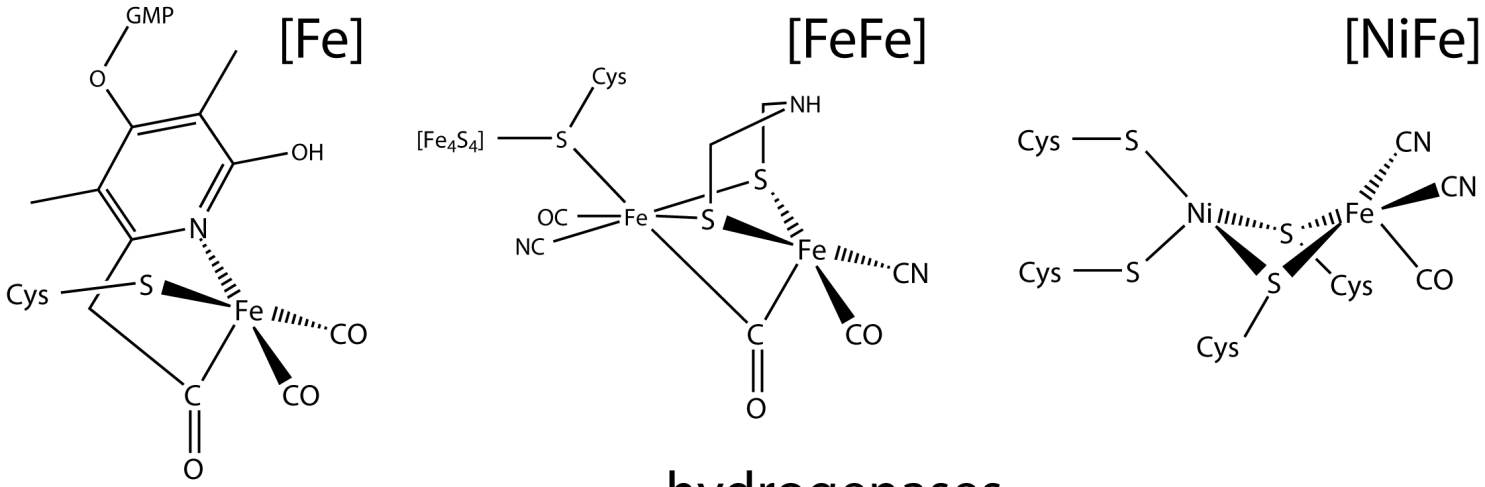
Let's get back to the question of what it actually takes to solve a chemical problem ...

... and let's not again bring up the Nitrogenase problem, which I took a an example already at this Microsoft Workshop in 2012:

https://www.microsoft.com/en-us/research/video/quantum-computation-for-quantum-chemistry-status-challenges-and-prospects-session-1

Another Real-World Example: Hydrogenases

- Catalyze the reversible oxidation of H_2, $H_2 \rightleftharpoons 2\ H^+ + 2\ e^-$.
- Three unrelated classes are known $\rightarrow$ convergent evolution.
- Common theme: Catalysis at Fe centers.



hydrogenases

P.M. Vignais, B. Billoud, *Chem. Rev.*, **2007**, *107*, 4206–4272.
K.A. Vincent, A. Parkin and F.A. Armstrong, *Chem. Rev.*, **2007**, *107*, 4366–4413.
A.L.D. Lacey, V.M. Fernandez, M. Rousset, R. Cammack, *Chem. Rev.* **2007**, *107*, 4304–4330.
W. Lubitz, H. Ogata, O. Rüdiger, E. Reijerse, *Chem. Rev.* **2014** *114*, 4081–4148.

- Intensive efforts to employ them in H_2-based clean-energy projects

  by Armstrong, Fontecilla-Camps, Friedrich, Ghirardi, Happe, Leger, Lenz, Lubitz, ...

- Most crucial obstacle: O_2 inhibition !

Focus on: Fe-only Hydrogenases

- [Fe] hydrogenases occur only in methanogenic archaea.

  $\rightarrow$ reduction of CO_2 to CH_4 with H_2.

- [FeFe] hydrogenases in anaerobic bacteria and unicellular algae.

  $\rightarrow$ formation of H_2, protons act as electron end-acceptor.

  $\rightarrow$ [FeFe] hydrogenases most efficient H_2 producers!

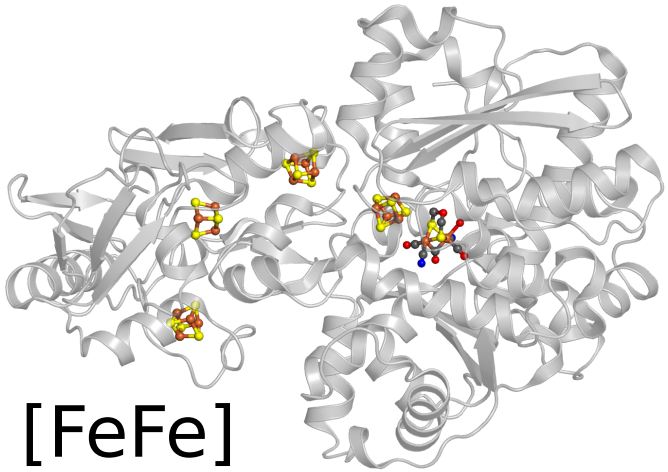
R.K. Thauer et al., *Annu. Rev. Biochem.*, **2010**, *79*, 507–536.

P.M. Vignais, B. Billoud, *Chem. Rev.*, **2007**, *107*, 4206–4272.

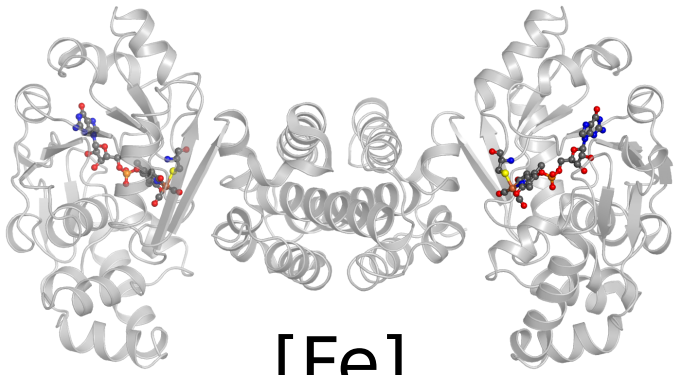
Structural characterization

[FeFe] hydrogenase structurally characterized from *Desulfovibrio* and *Clostridium* species.

[Fe] crystal structure revealed unusual coordination of central Fe atom.



[FeFe]



[Fe]

S. Shima et al., *Science*, **2008**, *321*, 572–575.
T. Hiromoto et al., *Angew. Chem. Int. Ed.*, **2009**, *48*, 6457–6460.
J.W. Peters et al., *Science*, **1998**, *282*, 1853–1858.
Y. Nicolet et al., *Structure Fold. Des.*, **1999**, *7*, 13–23.

DFT: mechanism of [FeFe] hydrogenases (selection)

Investigations into the catalytic cycle with a $[2Fe]_H$ model:

- H.-J. Fan, M.B. Hall, *J. Am. Chem. Soc.* **2001**, *123*, 3828–3829
- Z.-P. Liu, P. Hu, *J. Chem. Phys.* **2002**, *117*, 8177-8180
- G. Zampella, C. Greco, P. Fantucci, L. De Gioia, *Inorg. Chem.* **2006**, *45*, 4109–4118
- L. Yu, C. Greco, M. Bruschi, U. Ryde, L. De Gioia, M. Reiher, *Inorg. Chem.* **2011**, *50*, 3888–3900

$\Rightarrow$ Omitting the hydrogen bridges to the cyanides can change energetics

Thermodynamics of the μ-H vs. terminal-H species:

- M. Bruschi, C. Greco, M. Kaukonen, P. Fantucci, U. Ryde, L. De Gioia, *Angew. Chem. Int. Ed.* **2009**, *48*, 3503–3506

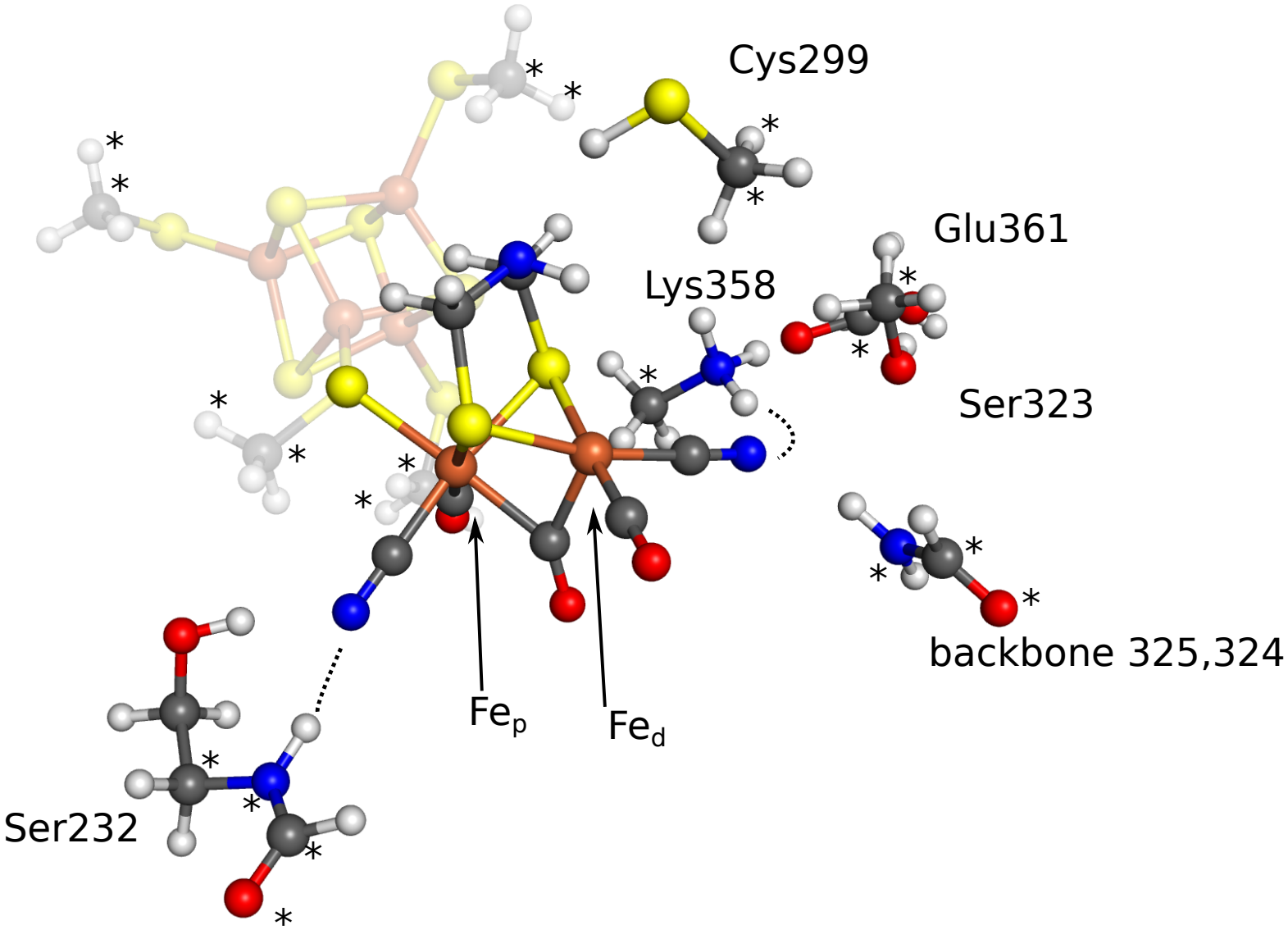
$\Rightarrow$ Relative stability of μ-H and terminal-H species only slightly affected by environment. Kinetic hindrance?

QM/MM calculations on catalytic intermediates:

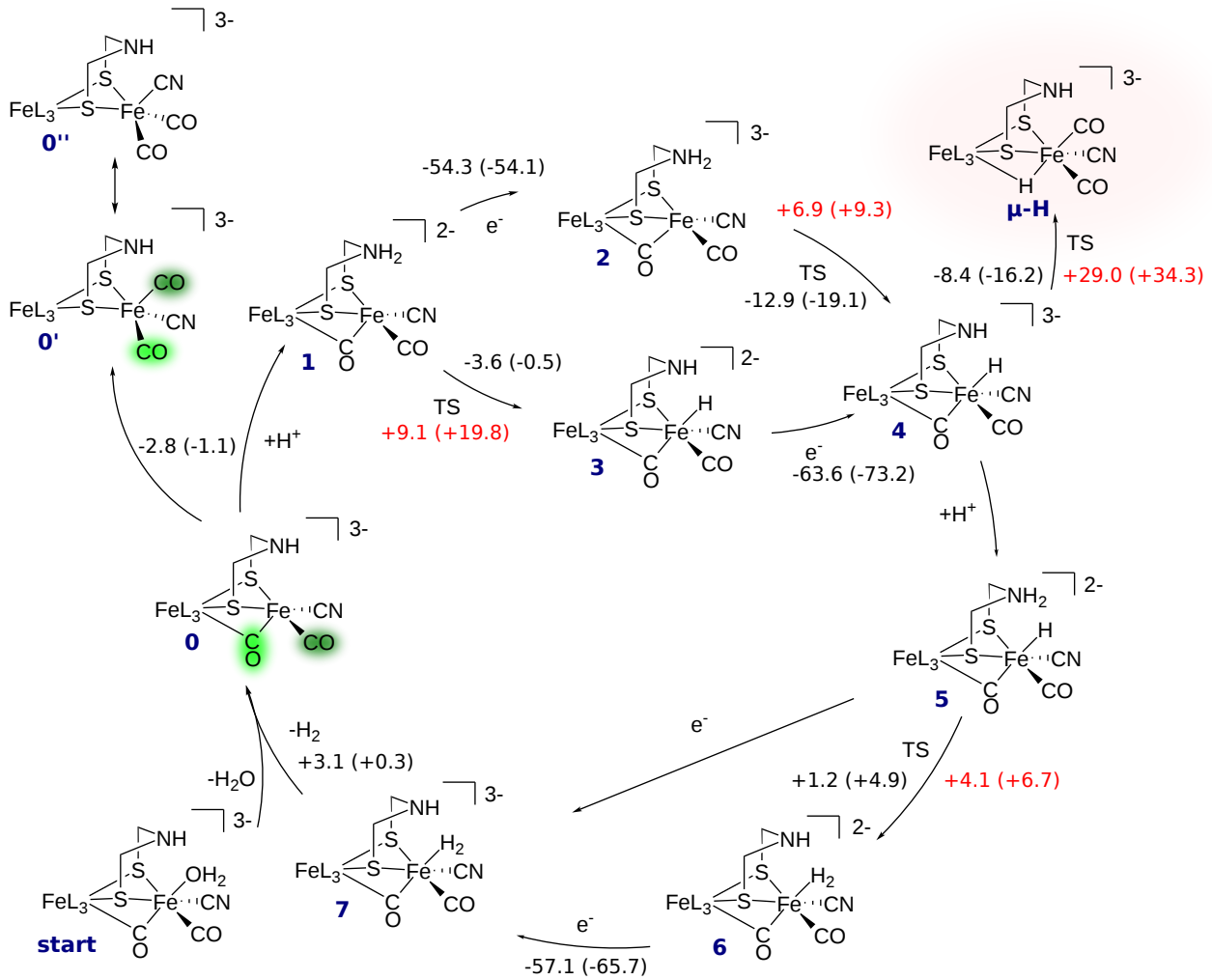
- C. Greco, M. Bruschi, L. De Gioia, U. Ryde, *Inorg. Chem.* **2007**, *46*, 5911–5921
- C. Greco, M. Bruschi, P. Fantucci, U. Ryde, L. De Gioia, *ChemPhysChem* **2011**, *132*, 3376–3382

$\Rightarrow$ Influence and interplay of cubanes on spin distribution and charges discussed in detail

Catalytic mechanism studied for large [FeFe] model



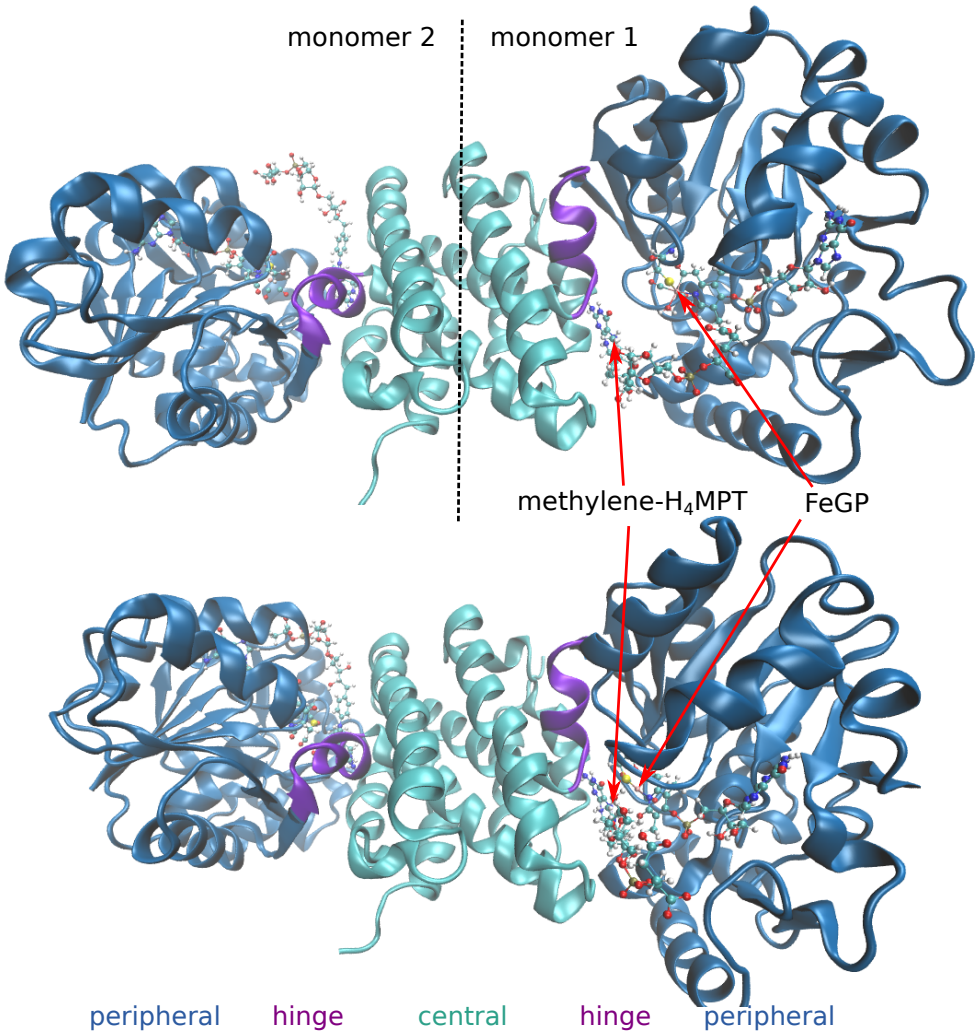
Catalytic mechanism studied for a large [FeFe] model



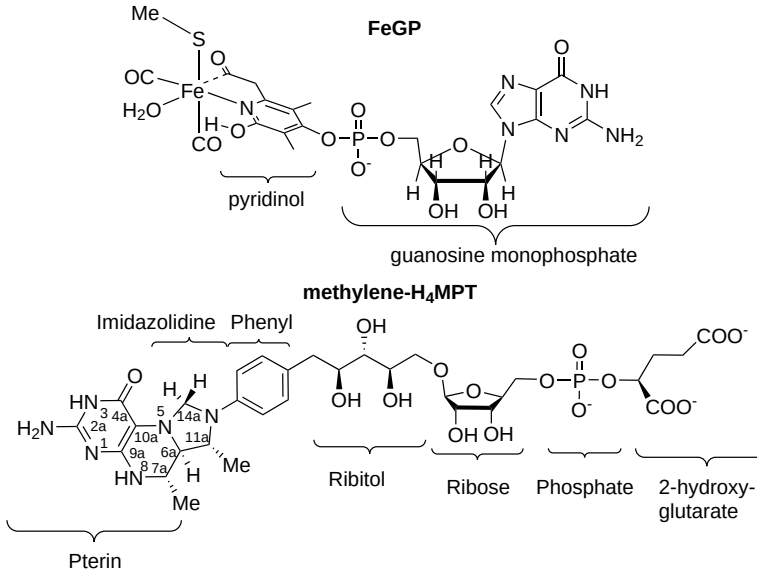
(all energies in kcal/mol)

A.R. Finkelmann, M.T. Stiebritz, M. Reiher, *Chem. Sci.* **2014**, *5*, 215–221

Structure of [Fe] Hydrogenase

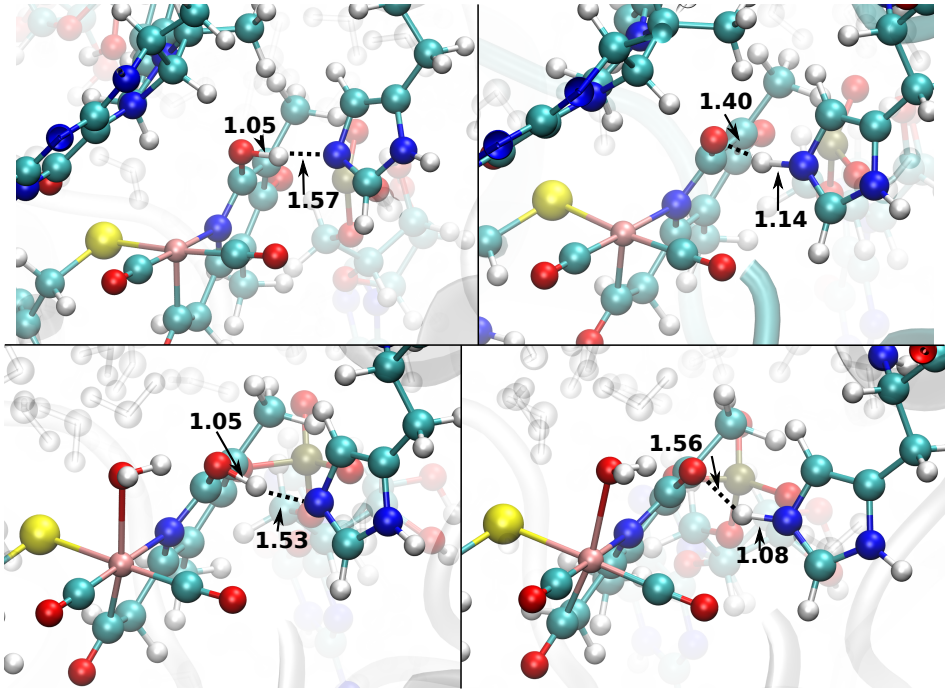


- $100/95\,\mathrm{ns}$ MD for *open* / *closed* conformation
- QM/MM calculations on representative snapshots



Protonation state of the pyridinol ligand

- In both conformations a hydrogen bond between His14 and the OH group of the hydroxyl ligand is formed frequently



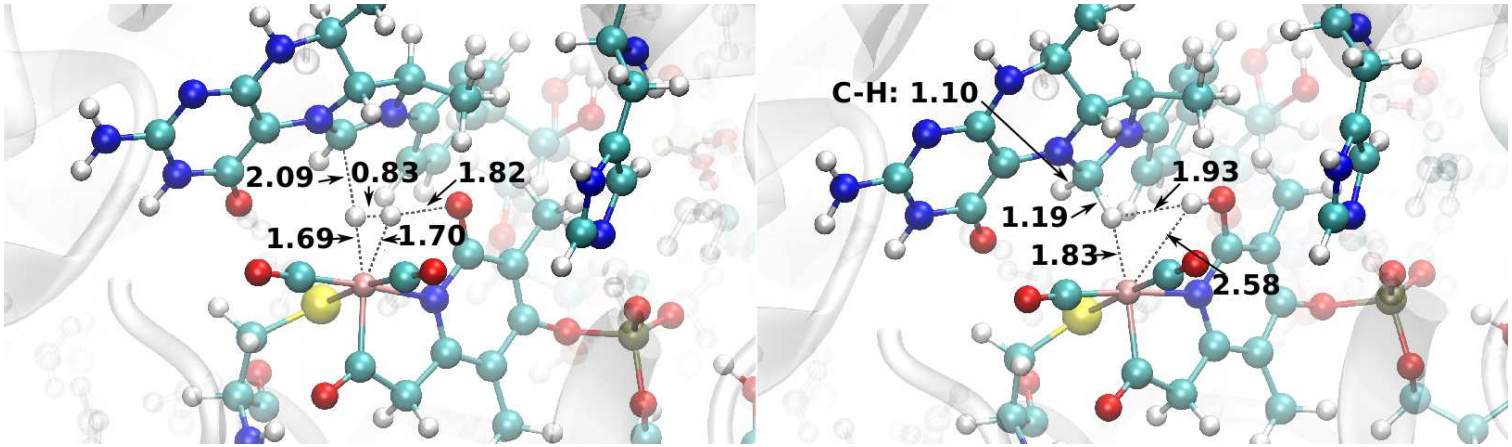
- Deprotonation of the pyridinol endothermic by only $+2.3\,\mathrm{kcal/mol}$ in the *closed* conformation and thermoneutral in the *open* conformation

$\Rightarrow$ Deprotonated form exists in significant amounts

A. R. Finkelmann, H. M. Senn, M. Reiher, *Chem. Sci.*, *5* **2014** 4474–4482.

Hydrogen cleavage

- Hydrogen coordinated to the deprotonated form can rapidly be cleaved (barrier estimated to be below $1\,\mathrm{kcal/mol}$)



- H_2 cleavage exothermic by $-18.7\,\mathrm{kcal/mol}$
- No stable hydride species can be optimized!

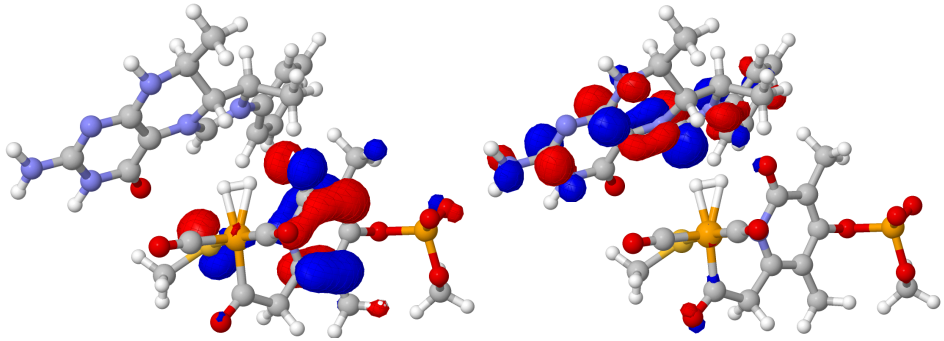
$\Rightarrow$ This mechanism complies with the criteria stated before

- If the pyridinol is not deprotonated, H_2 can still be cleaved *via* the thiolate. This reaction is, however, less favored.

A. R. Finkelmann, H. M. Senn, M. Reiher, *Chem. Sci.*, *5* **2014** 4474–4482.

New view on H_2 cleavage by [Fe] hydrogenase

- Reactive *closed* conformation constructed and simulated
- Evidence for deprotonation of FeGP *via* His14
- H_2 cleavage possible without involving a hydride species
- Low barrier of this process, hence the H_2-bound adduct need not be very stable for this rare event to occur
- Ionic and orbital push-pull mechanism
- Reaction only possible in the *closed conformation*



A. R. Finkelmann, H. M. Senn, M. Reiher, *Chem. Sci.*, *5* **2014** 4474–4482.

see also: E. D. Hedegaard et al. Angew. Chem. 127 **2015** 6344

To actually solve a chemical problem will require many calculations ...

A single quantum computation will not contribute anything to chemistry.

A parallel quantum computer will be necessary.

Parallelizing the quantum computation of the energy landscape will be crucial to providing answers within a timeframe of several days instead of several years. Bounding the number of repetitions of phase estimation needed to prepare the ground state from an initial ansatz remains an open problem (see *SI Appendix*), and parallelism may often be needed to allow us to tolerate low success probability. Quantum computers therefore must be designed with a scalable architecture in mind and also built with the realization that constructing a single quantum computer is insufficient to solve such tasks. Instead, we should aim to have quantum computers that can be built en masse, because clusters of quantum computers will be needed to scan over the many structures that need to be examined to identify and estimate all important reaction rates (25).

Finally, chemical reactions that involve strongly correlated species that are hard to describe by traditional multiconfiguration approaches are not just limited to nitrogen fixation: They are ubiquitous. They range from C–H bond activating catalysts; to those for hydrogen and oxygen production, carbon dioxide fixation, and transformation; to industrially useful compounds; to photochemical processes. Given the economic and societal impact of chemical processes ranging from fertilizer production to polymerization catalysis and clean energy processes, the importance of a versatile, reliable, and fast quantum chemical approach powered by quantum computing can hardly be overemphasized.

M. Reiher, N. Wiebe, K. M. Svore, D. Wecker, M. Troyer, PNAS 114 (2017) 7555-7560.