

The Energy Components of the Extended Transition State Energy Decomposition Analysis Are Path Functions: the Case of Water Tetramer

Miquel Solà^{1,*}, Miquel Duran¹ and Jordi Poater^{2,3,*}

¹ Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, C/ Maria Aurèlia Capmany 69, 17003 Girona, Catalonia, Spain

² Departament de Química Inorgànica i Orgànica & IQTCUB, Universitat de Barcelona, Martí i Franquès 1-11, 08028 Barcelona, Catalonia, Spain

³ ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain

Mail to: miquel.sola@udg.edu, jordi.poater@ub.edu,

Abstract

A recent paper (*Phys. Chem. Chem. Phys.* 2020, 22:22459) shows that the energy components of the extended transition state energy decomposition analysis (ETS-EDA) are path functions, and, therefore, they are not uniquely defined. In this work, we apply the ETS-EDA to analyze all possible dissociation paths of the water tetramer to four free water molecules. Our results confirm that the energy components of the ETS-EDA are path functions. However, they also show that differences among energy components obtained for the different paths are relatively small, and, therefore, we conclude that the information obtained from an ETS-EDA can be used to discuss the nature of chemical bonds and analyze the origin of isomerization energies and energy barriers. However, if a given process can be attained by means of different and chemically reasonable paths, we recommend to perform the ETS-EDA of a given reaction for all different paths to confirm that energy components of the ETS-EDA do not differ very much from one path to another.

Keywords: Energy decomposition analysis; water cluster; density functional theory; hydrogen bonding; state functions; non-state functions, path functions; dissociation energy.

1. Introduction

The chemical bond is probably the most important concept in chemistry. The molecular structure, reactivity, and properties of molecules depend on the nature of the chemical bonds that hold the atoms of molecules together. As many of the concepts relevant in chemistry, the chemical bond does not have an operator in quantum mechanics and, consequently, it is not well-defined. A typical case example is N_2^{2+} .¹⁻³ This molecule is thermodynamically unstable with respect to dissociation into two N^+ ions. However, N_2^{2+} is a long-lived (of the order of several seconds) metastable species with a significant Coulombic barrier to dissociation. Therefore, one may wonder whether we have a N^+-N^+ chemical bond or not. A very powerful tool provided by quantum mechanics to discuss the nature of chemical bonds, including this N^+-N^+ bond, is the energy decomposition analysis (EDA). Depending on the nature of the underlying theories, the EDA can be classified into two groups.⁴ First, those that are based on perturbation theory that express the interaction energy in terms of corrections to a noninteracting state, the symmetry-adapted perturbation theory (SAPT) being the most representative EDA of this group.^{5, 6} And second, the variational-based methods that require the application of intermediate nonphysical states. The first variational EDA was proposed in a seminal work by Morokuma *et al.*^{7, 8} Few years later, Ziegler and Rauk^{9, 10} proposed the extended transition state (ETS) method that introduces some modifications to the Morokuma's EDA, the most important being the decomposition of the orbital interactions into the different irreducible representations Γ . In the ETS-EDA method, the dissociation energy in molecule AB is decomposed into:

$$-D_e = \Delta E_{\text{prep}} + \Delta E_{\text{int}} \quad (1)$$

In this formula, the preparation energy ΔE_{prep} (also referred as deformation or strain energies) is the amount of energy required to deform two individual (isolated) fragments A and B from their equilibrium structure to the geometry that they acquire in the overall AB molecule and to bring them to their reference electronic states. The interaction energy ΔE_{int} corresponds to the actual energy change when these geometrically deformed and electronically prepared fragments are combined to form molecule AB. It is analyzed in the framework of the Kohn-Sham Molecular Orbital (MO) model using a quantitative decomposition of the interaction into electrostatic, Pauli repulsion (or exchange repulsion), and orbital interactions (Eq. (2) and Fig. 1).

$$\Delta E_{\text{int}} = \Delta V_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} (+ \Delta E_{\text{disp}}) \quad (2)$$

The instantaneous interaction energy ΔE_{int} between two fragments A and B in a molecule AB is partitioned into three terms, namely, (1) the quasiclassical electrostatic interaction ΔV_{elstat} between the fragments; (2) the repulsive exchange (Pauli) interaction ΔE_{Pauli} between electrons of the two fragments having the same spin, and (3) the orbital (covalent) interaction ΔE_{oi} which comes from polarization and orbital mixing between the fragments. The latter term can be decomposed into contributions of orbitals with different symmetry Γ , which makes possible to distinguish between σ , π , and δ contributions to bonding ($\Delta E_{\text{oi}} = \sum \Delta E_{\Gamma}$). ΔV_{elstat} and ΔE_{oi} are associated with covalent and ionic contributions to the bonding, respectively. In this sense, EDA acts as a link between the complex results of quantum chemical calculations and the classical concepts on the nature of the chemical bond. Finally, if the density functional used in the calculations contains dispersion corrections, then in Eq. (2) there is another term, ΔE_{disp} , that takes into account the interactions due to dispersion forces. Several reviews have been published describing this methodology.¹¹⁻¹⁵

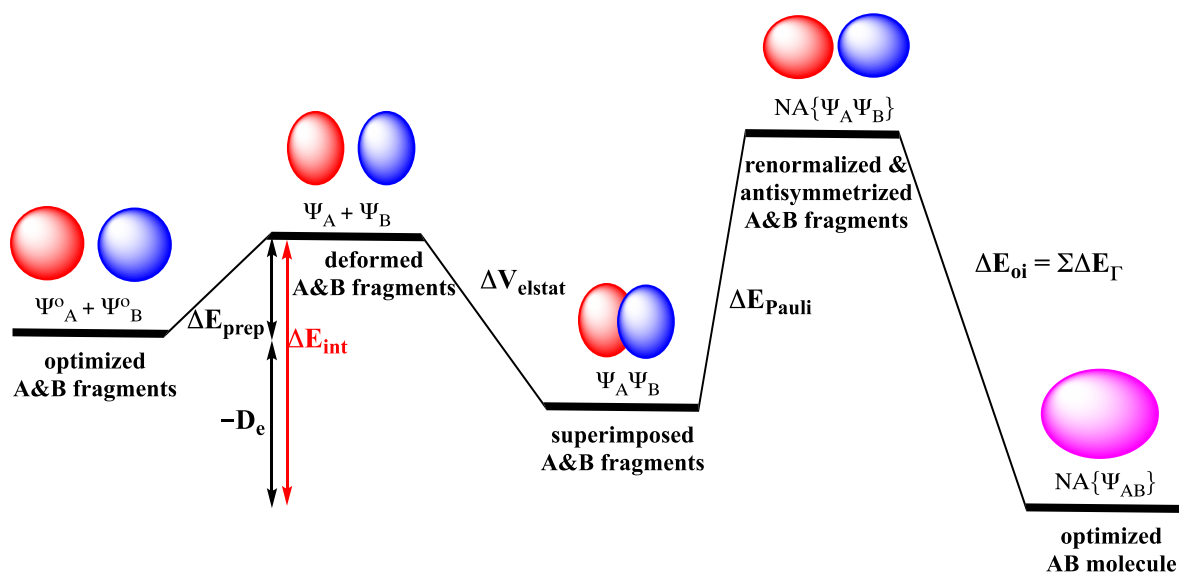


Figure 1. Schematic representation of the different steps in the Ziegler-Rauk energy decomposition analysis for the formation of a molecule AB from two fragments A and B.

The ETS-EDA method satisfies the five conditions that EDA procedures have to fulfill according to Frenking,¹⁶ namely, 1) it is based on accurate quantum chemical calculation; 2) it is mathematically unambiguously defined; 3) the results are largely independent of the level of calculation; 4) the different terms have a physical meaning; and 5) it is useful to analyze chemical problems.¹⁶ However, the ETS-EDA method fails to obey a last condition, which is that the energy components of an EDA should be ideally state functions. Very recently, Andrada and Foroutan-Nejad¹⁷ in a ground-breaking work have shown that, whereas the dissociation energy, the interaction energy, and the preparation energy of Eq. (1) are state functions, the ΔE_{Pauli} , ΔV_{elstat} , and $\Delta E_{\text{o}\iota}$ energy components of the interaction energy in Eq. (2) are not. The reason is the presence of nonphysical intermediate states in the procedure (superimposed A&B fragments in Fig. 1). Because ΔE_{Pauli} , ΔV_{elstat} , and $\Delta E_{\text{o}\iota}$ are path functions and non-observables, they are not uniquely defined, and, consequently, Andrada

and Foroutan-Nejad¹⁷ concluded that care has to be exercised when defining the nature of a chemical bond based on these arbitrary energy components.

In this work, we aim to analyze how different are the results of an ETS-EDA depending on the dissociation path considered. Hydrogen bonded water clusters have been frequently adopted as a theoretical test model for the purpose of evaluating the performance of new EDA. We have considered the water tetramer¹⁸⁻²¹ as the smallest cluster that can be dissociated into free water molecules following a number of different schemes. Our results confirm that the energy components of the EDA are path functions, but they also show that the differences among energy components obtained for the different paths is relatively small (not more than 5 kcal mol⁻¹ of change).

2. Computational Details

DFT calculations were carried out using the ADF (Amsterdam Density Functional) program.^{22, 23} Geometries of water tetramers and water molecule were optimized without any constraints using BLYP functional^{24, 25} with D3(BJ)²⁶⁻²⁸ correction and TZ2P basis set.²⁹ Vibrational frequency analysis was performed for all optimized species to confirm that were minima. ETS-EDA^{9, 10} were also carried out with the ADF program. Although the counterpoise method of Boys and Bernardi³⁰ to estimate the basis set superposition error (BSSE) enters the ETS-EDA procedure naturally,³¹ it has been found that the energy components exhibit little dependence on BSSE if the basis set is large enough.³² For this reason, we have not included the BSSE in our analysis.

3. Results and discussion

This section is divided into two sections. In the first, we discuss the structure of the water tetramer, and, in the second we perform EDA of the dissociation energy of the water tetramer into four free water molecules following different paths.

3.1. Structural details

The water tetramer has at least eight possible conformations.¹⁹ At low temperature, the water tetramer is cyclic with the four oxygen atoms almost in the same plane.^{18, 20} Each water molecule has one bonded hydrogen that lies in the plane defined by the oxygen atoms and is hydrogen bonded to an oxygen atom of a neighbor water, and another free hydrogen atom. The most stable isomer of the water tetramer according to our calculations is the one with two of the free hydrogens above the OOOO plane and two below in an up, down, up, down pattern (**udud**, see Fig. 2).^{18, 20} Our BLYP-D3(BJ)/TZ2P calculations agree with CCSD(T) results that also predict the **udud** isomer as the most stable.¹⁸ The next isomer (**uudd**) has the free hydrogens in an up, up, down, down pattern. It is higher in energy than the **udud** by only 0.9 kcal mol⁻¹. The **uuud** isomer is almost degenerate with the **uudd**, only 0.1 kcal mol⁻¹ higher. Finally, the relative energy of the **uuuu** isomer with respect to the **udud** is 2.3 kcal mol⁻¹. For our ETS-EDA, only the most stable **udud** isomer of the water tetramer was considered.

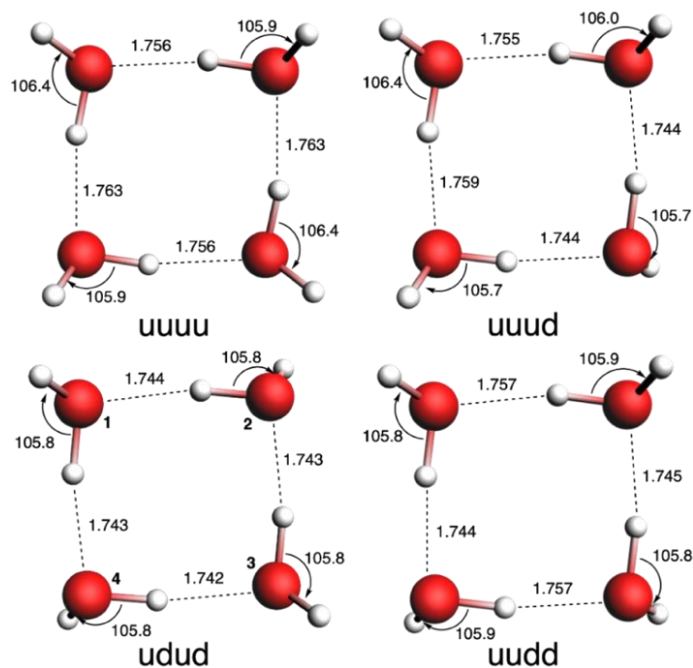


Figure 2. The four most stable configurations for the water tetramer with relevant distances (in Å) and angles (in degrees).

3.2. Energy decomposition analysis

The labels of the different water molecules in the **udud** isomer of the water tetramer are given in Fig. 2. In this section, we analyze only the interaction energy. Therefore, the geometries of the fragments are kept frozen at the geometry they have in the water tetramer. Table 1 contains the result of the ETS-EDA of different fragments of the **udud** water tetramer. For instance, **1-2** analyzes the interaction energy between water molecules **1** and **2** in the geometry they have in the water **udud** tetramer. Or **123-4** corresponds to the ETS-EDA of the interaction of molecule **4** with the water trimer **123**. Since the preparation (or deformation) energy is small (about $0.4 \text{ kcal mol}^{-1}$ per water molecule), the absolute value of the interaction energy is a good approximation to the dissociation energy.

For the **1-2** system, the interaction energy ($-4.8 \text{ kcal mol}^{-1}$) corresponds to the formation of a hydrogen bond and the result obtained is similar to that found in previous studies.³³

According to the present and previous results,³³ both covalent (represented by ΔE_{oi}) and electrostatic interactions (measured by ΔV_{elstat}) contribute substantially to the interaction energy between water molecules. Although the electrostatic interaction is the most important component of the attractive interactions, the hydrogen bond has a partial covalent character.³³ For the **1-3** system, the interaction energy ($-1.6 \text{ kcal mol}^{-1}$) is much lower and corresponds to a through space dipole-dipole interaction. For comparison, the interaction in **1-23** is stronger ($-8.5 \text{ kcal mol}^{-1}$) because one hydrogen bond and one dipole-dipole interactions are formed at the same time. The **12-34** and **123-4** yield similar results because in both interaction schemes two hydrogen bonds are formed. The higher value of the interaction energy in the **12-34** ($-22.0 \text{ kcal mol}^{-1}$) as compared to the **123-4** dissociation ($-18.3 \text{ kcal mol}^{-1}$) is attributed to the fact that two dipole-dipole interactions are formed in the former and only one in the latter. And this is the reason why in **13-2** the interaction is even weaker ($-11.7 \text{ kcal mol}^{-1}$), as also two hydrogen bonds are formed, but no dipole-dipole interaction. Finally, **13-2-4** has the largest interaction energy ($-30.0 \text{ kcal mol}^{-1}$) because it involves the formation of four hydrogen bonds and two dipole-dipole interactions. System **13-24** presents a similar value ($-28.4 \text{ kcal mol}^{-1}$), as four hydrogen bonds are also formed, but no dipole-dipole one. The interaction energies of the **13-24** and **13-2-4** systems are more than four times that of the **1-2** species due to the well-known cooperative effects in the formation of hydrogen bonded clusters.^{21, 34-39}

Table 1. ETS-EDA of the interaction energy in the water tetramer and some of their components (kcal/mol) computed at the BLYP-D3(BJ)/TZ2P level of theory.

Interaction	ΔE_{int}	ΔE_{Pauli}	ΔV_{elstat}	ΔE_{oi}	ΔE_{disp}	interactions ^a
1-2	-4.8	15.6	-12.2	-7.3	-0.9	1hb
1-3	-1.6	0.3	-1.4	-0.2	-0.3	1dd
12-34	-22.0	31.4	-31.7	-19.3	-2.4	2hb+2dd
13-24	-28.4	62.6	-50.7	-36.7	-3.5	4hb
1-23	-8.5	15.2	-14.2	-8.3	-1.2	1hb+1dd
13-2	-11.7	31.1	-24.9	-16.2	-1.8	2hb
12-3-4	-26.8	46.9	-41.5	-28.9	-3.3	3hb+2dd
13-2-4	-30.0	62.5	-51.1	-37.5	-3.8	4hb+2dd
123-4	-18.3	31.6	-28.8	-19.0	-2.1	2hb+1dd

^a Interactions formed: hb stands for hydrogen bond, whereas dd stands for dipole-dipole.

The seven possible ways to dissociate a water tetramer into four free water molecules are schematized in Figure 3. ETS-EDA of the different paths are collected in Table 2. To obtain each component in path 2, for instance, we have summed the results of the ETS-EDA in Table 1 of **12-34** plus two times **1-2**. Path 1 corresponds to the dissociation of the water tetramer into four free water molecules.

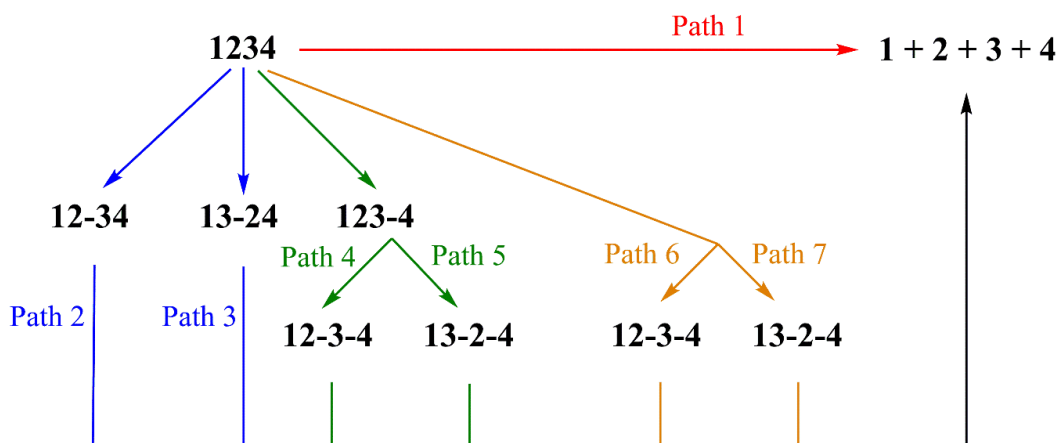


Figure 3. The seven different paths for the dissociation of the water tetramer into four free water molecules. For instance, Path 2: $1234 \rightarrow 12-34 \rightarrow 1+2+3+4$ means that there is, first, a dissociation of the tetramer into two dimers **12** and **34**, and, second, a dissociation of the dimers into monomers. Or Path 4: $1234 \rightarrow 123-4 \rightarrow 12-3-4 \rightarrow 1+2+3+4$ involves a first dissociation of the tetramer into a trimer and a monomer, followed by a dissociation of the former into a dimer and a monomer, to finally get the four monomers.

For paths **12-34** and **13-24**, one could expect different Pauli, electrostatic (different orientation of dipoles) and orbital interaction (different bond broken) terms but for the whole paths **1234** \rightarrow **12-34** \rightarrow **1+2+3+4** and **1234** \rightarrow **13-24** \rightarrow **1+2+3+4** one would expect no differences in ΔE_{int} , ΔE_{Pauli} , ΔV_{elstat} , ΔE_{oi} , and ΔE_{disp} . However, results in Table 2 confirm that, whereas ΔE_{int} and ΔE_{disp} are state functions, the ΔE_{Pauli} , ΔV_{elstat} , ΔE_{oi} energy components of ΔE_{int} change for the different paths. It is worth noting that, if we consider path 1 as the reference, results of path 3 differ less than those of path 2. The reason is that in the first step of path 3, all hydrogen bonds are broken as in path 1 and only the **13** and **24** dipole-dipole interactions remain. So, path 3 is more similar to path 1 than path 2. In this last path one breaks two hydrogen bonds in the first step and two more in the second one. For the same reason, path 7 is closer to path 1 than path 6.

What is important, however, is that differences in ΔE_{Pauli} , ΔV_{elstat} , ΔE_{oi} for the seven paths are not important enough to change the conclusion about the nature of the chemical bond in the water tetramer. In all cases, we can conclude that the bonding is predominantly electrostatic (55-60%) with an important covalent contribution (36-41%) and a less significant dispersion term (4.4%). Whether the electrostatic component is 55% or 60% is not particularly relevant. What is important is that, qualitatively, the hydrogen bond is mainly electrostatic in nature with a meaningful but minor covalent character.

Table 2. ETS-EDA of the different paths for the dissociation (Fig. 3) of the water tetramer (kcal/mol) computed at the BLYP-D3(BJ)/TZ2P level of theory. The percentage of attractive interactions for each path is given in parenthesis.

Dissociation Path	ΔE_{int}	ΔE_{Pauli}	ΔV_{elstat}	ΔE_{oi}	ΔE_{disp}
1	-31.6	62.4	-51.6 (54.8%)	-38.3 (40.7%)	-4.1 (4.4%)
2	-31.6	62.6	-56.1 (59.6%)	-33.9 (36.0%)	-4.1 (4.4%)
3	-31.6	63.2	-53.5 (56.4%)	-37.2 (39.2%)	-4.1 (4.4%)
4	-31.6	62.3	-55.1 (58.7%)	-34.6 (36.9%)	-4.1 (4.4%)
5	-31.6	63.0	-55.0 (58.2%)	-35.4 (37.5%)	-4.1 (4.4%)
6	-31.6	62.5	-53.7 (57.1%)	-36.2 (38.5%)	-4.1 (4.4%)
7	-31.6	62.8	-52.5 (55.6%)	-37.7 (40.0%)	-4.1 (4.4%)

Chemical bonding is a very complex phenomenon that can be analyzed from different perspectives with a number of tools. The results of the application of these tools allow to classify the chemical bond in different categories (repulsive, covalent, ionic, metallic, noncovalent...). As Bergmann⁴⁰ said in the concluding remarks of the Proceedings of an International Symposium held in Jerusalem in 1970: “Classification and theory are not ends in themselves. If they generate new experimental work, new compounds, new processes, new methods - they are good; if they are sterile - they are bad”. In our opinion, the results derived from the application of the ETS-EDA (and related EDA), despite the use of unphysical and non-observable intermediate states, provide a deep and useful knowledge on the nature of the chemical bonds and their classification. Moreover they help to understand the origin of isomerization energies with the turn-upside-down approach^{41, 42} and energy barriers with the activation strain model.⁴³⁻⁴⁵ Of course, it is crucial to know the limitations of the methods

used and, because of that, it is important to emphasize that ΔE_{Pauli} , ΔV_{elstat} , ΔE_{oi} in ETS-EDA are path functions.¹⁷ Knowing this limitation, our recommendation is to perform the ETS-EDA for a given bond or reaction for as many paths as possible to confirm that energy components of the ETS-EDA do not differ very much from one path to another. In many situations, however, there is only one chemically reasonable path. For instance, if one analyzes the hydrogen bond of the water dimer, the path corresponding to the dissociation of the water dimer into two free water molecules in one step seems to be the most rational one. As a whole, we can conclude that EDA does not only depend on the fragments used but also on the path considered. Both have to be clearly provided by the authors of EDA if we aim the readers to reproduce the results.

4. Conclusions

The methods and tools of analysis of the wavefunction and the electron density, and the energy decomposition analyses (EDA) provide a bridge between quantum chemistry and classical chemistry. Most of these methods present shortcomings that make them useless (or even worse, cause misunderstandings) in the analysis of certain chemical problems. One of the important tasks of computational and theoretical chemists is to uncover the limitations of the methods used to analyze the results provided by calculations based on quantum mechanics. In the present work, we confirm a limitation of the energy decomposition analysis based on Morokuma's partition of the energy, which is the fact, already reported by Andrada and Foroutan-Nejad,¹⁷ that the three components of the interaction energy in the extended transition state EDA (ETS-EDA), namely, the electrostatic interaction, the Pauli repulsion, and the orbital interactions are path functions. As a case example, we focus our work in the

different paths that transform the water tetramer into four free water molecules. The performed ETS-EDA demonstrate that different results for the electrostatic interaction, the Pauli repulsion, and the orbital interactions terms are obtained depending on the path followed for the dissociation. However, they also show that the differences among these energy components obtained for the different paths are relatively small. For this reason, we conclude that the information obtained from an ETS-EDA is useful to analyze the nature of chemical bonds as well as the origin of isomerization energies and energy barriers. However, if a given chemical process can be attained by means of different and chemically reasonable paths, we recommend to perform the ETS-EDA of a given reaction for these different paths to be sure that energy components of the ETS-EDA do not differ very much from one path to another. Finally, further work needs to be done to establish whether for some particular systems with similar ΔV_{elstat} and ΔE_{oi} or systems with large deformation energies, the conclusions about the nature of the chemical bond may change depending on the path considered.

Acknowledgments

This work has been supported by the Ministerio de Economía y Competitividad (MINECO) of Spain (Projects CTQ2017-85341-P, PID2019-106830GB-I00, and MDM-2017-0767) and the Generalitat de Catalunya (projects 2017SGR39 and 2017SGR348). Excellent service by the Supercomputer center of the Consorci de Serveis Universitaris de Catalunya (CSUC) is gratefully acknowledged. This work is dedicated to Prof. Ramon Carbó-Dorca as a proof of our admiration for his brilliant contributions to chemistry.

Supporting Information

Cartesian coordinates (in Å) and electronic energies (in kcal mol⁻¹) of the water tetramers conformations taken into study.

5. References

1. Vaughan AL. Mass Spectrograph Analyses, and Critical Potentials for the Production of Ions by Electron Impact, in Nitrogen and Carbon Monoxide. *Phys. Rev.* 1931, 38:1687-1695.
2. Mathur D. Structure and dynamics of molecules in high charge states. *Phys. Rep.* 2004, 391:1-118.
3. Fletcher JD, Parkes MA, Price SD. Bond-forming reactions of N_2^{2+} with C_2H_4 , C_2H_6 , C_3H_4 and C_3H_6 . *Int J. Mass Spectrom.* 2015, 377:101-108.
4. Phipps MJS, Fox T, Tautermann CS, Skylaris C-K. Energy decomposition analysis approaches and their evaluation on prototypical protein–drug interaction patterns. *Chem. Soc. Rev.* 2015, 44:3177-3211.
5. Szalewicz K, Jeziorski B. Symmetry-adapted double-perturbation analysis of intramolecular correlation effects in weak intermolecular interactions. *Mol. Phys.* 1979, 38:191-208.
6. Jeziorski B, Moszynski R, Szalewicz K. Perturbation Theory Approach to Intermolecular Potential Energy Surfaces of van der Waals Complexes. *Chem. Rev.* 1994, 94:1887-1930.
7. Kitaura K, Morokuma K. A New Energy Decomposition Scheme for Molecular Interactions within the Hartree-Fock Approximation. *Int. J. Quantum Chem.* 1976, 10:325-340.
8. Morokuma K. Why Do Molecules Interact? The Origin of Electron Donor-Acceptor Complexes, Hydrogen Bonding and Proton Affinity. *Acc. Chem. Res.* 1977, 10:294-300.
9. Ziegler T, Rauk A. On the calculation of Bonding Energies by the Hartree Fock Slater Method. *Theor. Chim. Acta* 1977, 46:1-10.
10. Ziegler T, Rauk A. A theoretical study of the ethylene-metal bond in complexes between copper(1+), silver(1+), gold(1+), platinum(0) or platinum(2+) and ethylene, based on the Hartree-Fock-Slater transition-state method. *Inorg. Chem.* 1979, 18:1558-1565.
11. Bickelhaupt FM, Baerends EJ. Rev. Comput. Chem. In: Lipkowitz KB, Boyd DB, eds. Vol. 15. New York: Wiley-VCH; 2000, 1-86.
12. Frenking G, Bickelhaupt FM. The EDA Perspective of Chemical Bonding. In: Frenking G, Shaik S, eds. *The Chemical Bond*. Weinheim: Wiley; 2014, 121-157.
13. Bickelhaupt FM, Houk KN. Analyzing Reaction Rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem. Int. Ed.* 2017, 56:10070-10086.
14. Fernández I. Understanding the Reactivity of Fullerenes Through the Activation Strain Model. *Eur. J. Org. Chem.* 2018, 2018:1394-1402.
15. Zhao L, von Hopffgarten M, Andrada DM, Frenking G. Energy decomposition analysis. *WIREs Comput. Mol. Sci.* 2018, 8:e1345.
16. Andrés J, Ayers PW, Boto RA, Carbó-Dorca R, Chermette H, Cioslowski J, Contreras-García J, Cooper DL, Frenking G, Gatti C, et al. Nine questions on energy decomposition analysis. *J. Comput. Chem.* 2019, 40:2248-2283.
17. Andrada DM, Foroutan-Nejad C. Energy components in energy decomposition analysis (EDA) are path functions; why does it matter? *Phys. Chem. Chem. Phys.* 2020, 22:22459-22464.

18. Pérez JF, Hadad CZ, Restrepo A. Structural studies of the water tetramer. *Int. J. Quantum Chem.* 2008, 108:1653-1659.
19. Vitek A, Kalus R, Paidarová I. Structural changes in the water tetramer. A combined Monte Carlo and DFT study. *Phys. Chem. Chem. Phys.* 2010, 12:13657-13666.
20. Ceponkus J, Uvdal P, Nelander B. Water Tetramer, Pentamer, and Hexamer in Inert Matrices. *J. Phys. Chem. A* 2012, 116:4842-4850.
21. Cruzan JD, Braly LB, Liu K, Brown MG, Loeser JG, Saykally RJ. Quantifying Hydrogen Bond Cooperativity in Water: VRT Spectroscopy of the Water Tetramer. *Science* 1996, 271:59-62.
22. Baerends EJ, Autschbach J, Bérces A, Bickelhaupt FM, Bo C, de Boeij PL, Boerrigter PM, Cavallo L, Chong DP, Deng L, et al. ADF2007.01, Amsterdam, 2007.
23. te Velde G, Bickelhaupt FM, Baerends EJ, Fonseca Guerra C, van Gisbergen SJA, Snijders JG, Ziegler T. Chemistry with ADF. *J. Comput. Chem.* 2001, 22:931-967.
24. Becke AD. Density-Functional Exchange-Energy Approximation with Correct Asymptotic-Behavior. *Phys. Rev. A* 1988, 38:3098-3100.
25. Lee C, Yang W, Parr RG. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* 1988, 37:785-789.
26. Grimme S, Antony J, Ehrlich S, Krieg H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* 2010, 132:154104.
27. Grimme S, Ehrlich S, Goerigk L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* 2011, 32:1456-1465.
28. Becke AD, Johnson ER. Exchange-hole dipole moment and the dispersion interaction revisited. *J. Chem. Phys.* 2007, 127:154108.
29. Van Lenthe E, Baerends EJ. Optimized Slater-type basis sets for the elements 1–118. *J. Comput. Chem.* 2003, 24:1142-1156.
30. Boys SF, Bernardi F. The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol. Phys.* 1970, 19:553-566.
31. Solà M, Lledós A, Duran M, Bertrán J, Ventura ON. Ab initio study of substituent effect on the addition of hydrogen fluoride to fluoroethylenes. *J. Comput. Chem.* 1990, 11:170-180.
32. Glendening ED, Streitwieser A. Natural energy decomposition analysis: An energy partitioning procedure for molecular interactions with application to weak hydrogen bonding, strong ionic, and moderate donor–acceptor interactions. *J. Chem. Phys.* 1994, 100:2900-2909.
33. Poater J, Fradera X, Solà M, Duran M, Simon S. On the electron-pair nature of the hydrogen bond in the framework of the atoms in molecules theory. *Chem. Phys. Lett.* 2003, 369:248-255.
34. Song H-J, Xiao H-M, Dong H-S. Cooperative effects, strengths of hydrogen bonds, and intermolecular interactions in circular *cis*, *trans*-cyclotriazane clusters (n=3–8). *J. Chem. Phys.* 2006, 125:074308.
35. Guevara-Vela JM, Chávez-Calvillo R, García-Revilla M, Hernández-Trujillo J, Christiansen O, Francisco E, Martín Pendás Á, Rocha-Rinza T. Hydrogen-Bond Cooperative Effects in Small Cyclic Water Clusters as Revealed by the Interacting Quantum Atoms Approach. *Chem. Eur. J.* 2013, 19:14304-14315.

36. Fonseca Guerra C, Zijlstra H, Paragi G, Bickelhaupt FM. Telomere Structure and Stability: Covalency in Hydrogen Bonds, Not Resonance Assistance, Causes Cooperativity in Guanine Quartets. *Chem. Eur. J.* 2011, 17:12612-12622.
37. Nochebuena J, Cuautli C, Ireta J. Origin of cooperativity in hydrogen bonding. *Phys. Chem. Chem. Phys.* 2017, 19:15256-15263.
38. Wolters LP, Smits NWG, Guerra CF. Covalency in resonance-assisted halogen bonds demonstrated with cooperativity in N-halo-guanine quartets. *Phys. Chem. Chem. Phys.* 2015, 17:1585-1592.
39. Paragi G, Fonseca Guerra C. Cooperativity in the Self-Assembly of the Guanine Nucleobase into Quartet and Ribbon Structures on Surfaces. *Chem. Eur. J.* 2017, 23:3042-3050.
40. Bergmann ED. Aromaticity, Pseudo-Aromaticity and Anti-Aromaticity. In: Bergmann ED, Pullman B, eds. *Proc. of the Int. Symposium, Jerusalem, 1970*. Jerusalem: The Israel Academy of Science and Humanities; 1971, 392.
41. El-Hamdi M, Tiznado W, Poater J, Solà M. An Analysis of the Isomerization Energies of 1,2-/1,3-Diazacyclobutadiene, Pyrazole/Imidazole, and Pyridazine/Pyrimidine with the Turn-Upside-Down Approach. *J. Org. Chem.* 2011, 76:8913-8921.
42. El Bakouri O, Solà M, Poater J. Correction: Planar vs. three-dimensional X_6^{2-} , $X_2Y_4^{2-}$, and $X_3Y_3^{2-}$ (X, Y = B, Al, Ga) metal clusters: an analysis of their relative energies through the turn-upside-down approach. *Phys. Chem. Chem. Phys.* 2018, 20:3845-3846.
43. Wolters LP, Bickelhaupt FM. The activation strain model and molecular orbital theory. *WIREs Comput. Mol. Sci.* 2015, 5:324-343.
44. Fernández I, Bickelhaupt FM. The activation strain model and molecular orbital theory: understanding and designing chemical reactions. *Chem. Soc. Rev.* 2014, 43:4953-4967.
45. Vermeeren P, van der Lubbe SCC, Fonseca Guerra C, Bickelhaupt FM, Hamlin TA. Understanding chemical reactivity using the activation strain model. *Nat. Protoc.* 2020, 15:649-667.

FOR TABLE OF CONTENTS

