

Reliability of Interacting Quantum Atoms (IQA) Data Computed from Post-HF Densities: Impact of Approximation Used

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Abstract

The performance of BBC1, BBC2 and Müller approximations, in terms of reliability of IQA data, was investigated at CCSD, CCSD(T) and MP2 levels using glycol, as a case study, in interpreting the relative stability of its conformers, one with H-bond type intramolecular interaction and the other with a steric clash between two O-atoms. The CCSD/BBC1 level appeared to be perfectly suited as a reference needed to evaluate all possible levels of theory/approximation combinations (LoT/LoA). We found the LoT/BBC1 > LoT/BBC2 > LoT/Müller reliability trend (as well as its origin) and concluded that the Müller approximation should not be used when accuracy of IQA-defined energy terms is considered. Moreover, we have established that the requirement of reproducing, by IQA calculations, electronic energy is desirable but not a necessary requirement when a *comparative approach* is used, such as in FAMSEC-based analysis (FAMSEC = Fragment Attributed Molecular System Energy Change). A new criterion is proposed to assess quality of IQA data for comparative analyses, $\Delta E(\text{IQA}) \approx \Delta E$, where $\Delta E(\text{IQA})$ and ΔE stand for IQA and electronic energy differences, respectively, between a *fin*-state and *ref*-state of a molecular system. The closer $\Delta E(\text{IQA})$ approaches ΔE the closer FAMSEC data approaches values obtained at exceptionally well performing CCSD/BBC1 level, regardless of the LoT/LoA combination used. Importantly, MP2/BBC1 performed nearly as well as CCSD/BBC1 in comparative studies. The origin of MP2/BBC1 exceptional and MP2/Müller acceptable performance in explaining relative stability of glycol conformers has been uncovered and discussed in details.

Keywords

IQA, FAMSEC, BBC1 approximation, BBC2 approximation, Müller approximation, 2EDM

1. INTRODUCTION

The Interacting Quantum Atoms (IQA) method,¹ the energy and charge partitioning scheme for molecular systems, is a powerful tool that allows gaining an insight, on a fundamental level, on atoms' properties in terms of self-atomic energies, E_{self}^X , and the diatomic interaction energies, $E_{\text{int}}^{X,Y}$, between atoms X and Y. Arguably, from the classical chemist perspective, the most important field of application of IQA is its ability to compute interaction energies between atoms involved in intra- and intermolecular bond formation. These two physical properties, E_{self}^X and $E_{\text{int}}^{X,Y}$, are extremely useful in better understanding of variety of chemical bonds (to explore their nature) and can be used to quantify the strength of interactions/bonds and how they change when a chemical environment varies, e.g., on conformational transformations or by adding additional functionality to a molecule. All the above equally applies to an extension of IQA, namely Interacting Quantum Fragments (IQF) method,² where focus is on the chemically meaningful molecular fragments and their role in relative stability and reactivity of molecules. To this effect, the IQA and IQF concepts were applied in recently reported Fragment Attributed Molecular System Energy Change (FAMSEC)³ and Preorganized-interacting Fragment Attributed Molecular Stability (π -FARMS)^{4,5} methods, where the former was designed to characterise and quantify the strength of intramolecular interactions as well as energy contribution made by a fragment to a system, whereas the latter was designed to explain relative stability of entire molecular systems.

It is our conviction that IQA/IQF methods are not used as widely as they deserve and this can be attributed to several factors. It has been advocated^{1,6} that to generate reliable IQA data the use of the two-electron density matrix (2EDM) is required in order to compute IQA-defined V_{ee} energy contributions (intra- and interatomic, V_{ee}^X and $V_{\text{ee}}^{X,Y}$, respectively) as well as (de)localisation indices, as defined in the Bader's Quantum Theory of Atoms in Molecules (QTAIM) methodology.⁷ Exact form of 2EDM at correlated levels is well defined only for variational CI-based approaches, such as CASSCF or CISD, but it is not generally accessible in quantum chemistry packages. In the case of widely used perturbative methods (such as MP2) the form of 2EDM is not known in principle. Thus appropriate approximations for 2EDM, based on one-electron density matrix (1EDM), must be implemented.⁸⁻²² Unfortunately, the IQA calculations require extreme computational efforts, and particularly so when exact form of 2EDM is used, thus making them almost impossible to perform for post-HF correlated levels of

theory (LoT) when large(r) molecules (10 atoms plus) of e.g., biological or medicinal importance are of interest.

The most famous approximation for 2EDM was proposed by Müller,⁸ and this is the case of most commonly used AIMAll,²³ dedicated software for topological calculations, where exact 2EDM is implemented only at the HF level. For post-HF levels, the Müller functional approximates 2EDM in terms of natural orbitals of the one-electron density matrix and thus it could be used to calculate 2EDM-dependent properties. In an attempt to correct the Müller functional, two corrections were proposed by Gritchenko et al¹⁷ and they are known as BBC1 and BBC2 approximations. These two corrections and basic Müller's functional are investigated here as they have been implemented in TWOe software package developed by Polestshuk.^{24,25}

To the best of our knowledge, except one report involving small testing systems,²⁶ there has not been an extensive examination of these three approximations on the reliability of computed IQA data on more real life examples. Hence, the aim of this work is a thorough investigation of quality of the IQA data obtained from the Müller, BBC1 and BBC2 approximations at CCSD, CCSD(T) and MP2 levels using glycol's three conformers – Figure 1.

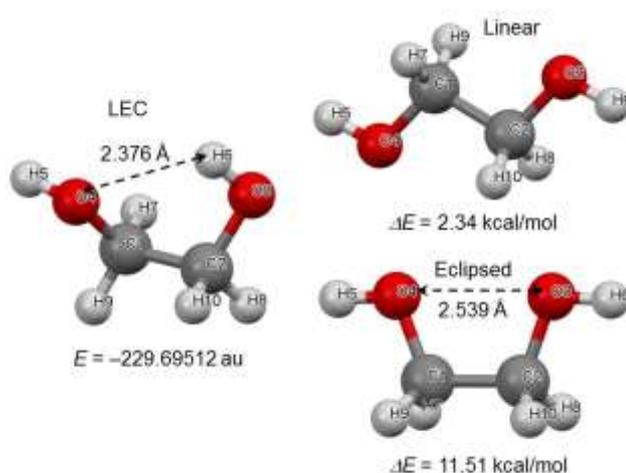


Figure 1. Ball-and-stick representation of the glycol conformers optimised at the CCSD/aug-cc-pVDZ level also showing atoms numbering, energy of the lowest energy conformer (**LEC**) as well as, relative to **LEC**, energy differences for linear and eclipsed conformers.

The linear conformer (**Lin**) has energy larger (higher) by ~ 2.3 kcal/mol than the lowest energy conformer (**LEC**), which classically would be attributed to the absence of intramolecular H-bond between O4 and H6 that is present in the **LEC**. Much larger energy increase, by ~ 11.5 kcal/mol relative to the **LEC**, was found for the eclipsed conformer (**Ecl**) which can be attributed to the steric clash between O3 and O4 atoms.

To assess a quality of the IQA data at a specific LoT and level of approximation (LoA) a reference data of high quality is required. To this effect, we have used CCSD/aug-cc-pVDZ level of theory to optimise the conformers of glycol instead of CCSD(T)/aug-cc-pVDZ because (i) the latter is prohibitively expensive and (ii) the former should, in our opinion, serve the purpose of this work well enough. In addition, we have performed single-point-calculations (SPCs) on CCSD-optimised structures at the MP2 and CCSD(T) levels with the same functional to learn about (i) performance of the two LoTs and (ii) influence of LoA on IQA data quality at these three post-HF levels of theory. Concerning IQA data, we will also examine the LoT/LoA-dependant departure of $E(\text{IQA})$, i.e., molecular energy obtained from IQA-defined components, from electronic energy E with the main focus on exploring the origin of $\Delta E_{\text{IQA},E} = E(\text{IQA}) - E \neq 0$. Finally, it was of paramount importance to explain relative stability of glycol’s conformers. To this effect, we will compare, at all LoTs and LoAs, the nature and strength of interactions as well as energy contributions made by selected molecular fragments to conformers in order to understand (or explain) their influence on relative stability of glycol’s conformers. To achieve that the FAMSEC methodology will be used employing **Lin** as a reference state of molecular system because it does not possess any specific intramolecular interactions.

2. COMPUTATIONAL METHODS

For geometry optimization and electron density generation the PRIRODA14 program of Laikov²⁷ has been employed. Three selected glycol conformer geometries were optimized at CCSD level with frozen core electrons with Dunning double zeta basis set, aug-cc-pVDZ, which is augmented by diffuse functions. To reduce computational efforts, the C_{2h} and C_{2v} symmetries, respectively, were employed for **Lin** and **Ecl**. The MP2 and CCSD(T) single point calculations have been performed on optimized geometries in order to obtain the respective natural orbitals for subsequent IQA analysis.

All topological and IQA analyses were conducted using TWOe version 14 program. Three types of 2EDM functional approximations have been selected: Müller, BBC1, and BBC2. The global precision option was selected as “norm” and for interatomic surface determination the default “Trng” method with “good” accuracy option was chosen. Due to the presence of a diffuse basis functions the maximal integration radius was increased to 12 Bohr to capture maximum electron density at atomic integration stages.

All hydrogen atoms have perfect accuracy of Zero-Flux surface determination even with assigned by default Lebedev grids. But for angular integrations of oxygen atoms the increased

Lebedev grids were selected to produce more accurate data. Tetrahedral carbons have the most difficult shapes among all atoms studied. To significantly minimize the errors in their atomic integrations the highest Lebedev and medium sized Gauss-Legendre angular grids have been chosen. All resultant atomic Laplacian $|L(\Omega)|$ values have not exceeded even 5×10^{-5} au. Typically, this is sufficient to reproduce total molecular energy components within a fraction of kcal/mol.

3. THEORETICAL BACKGROUND

3.1. Electron repulsion energy expression *via* two-electron density matrix with its functionals.

All one-electron terms (intra- and interatomic electron-nucleus V_{en} and nucleus-electron V_{ne} as well as nucleus-nucleus V_{nn} interaction energies) and kinetic energy T , can be computed in terms of a one-particle density $\rho(\mathbf{r})$, which is easily accessible to almost all levels of theory. But the huge bottleneck in evaluation of molecular energy components at post-HF levels is caused by an electron repulsion potential energy term,

$$V_{ee} = \frac{1}{2} \iint \frac{\rho_2(\mathbf{r}_1, \mathbf{r}_2)}{r_{12}} d\mathbf{r}_1 d\mathbf{r}_2 \quad (1)$$

where two-particle density matrix $\rho_2(\mathbf{r}_1, \mathbf{r}_2)$ is included. The $\rho_2(\mathbf{r}_1, \mathbf{r}_2)$ term can conveniently be partitioned into Coulombic (classical) and exchange-correlation (XC) contributions as

$$\rho_2(\mathbf{r}_1, \mathbf{r}_2) = \rho(\mathbf{r}_1)\rho(\mathbf{r}_2) - \rho_2^{xc}(\mathbf{r}_1, \mathbf{r}_2) . \quad (2)$$

Thus V_{ee} energy may be viewed as composed of Coulomb electron-electron repulsion and purely quantum XC-terms

$$V_{ee} = J + K = \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{r_{12}} d\mathbf{r}_1 d\mathbf{r}_2 - \frac{1}{2} \iint \frac{\rho_2^{xc}(\mathbf{r}_1, \mathbf{r}_2)}{r_{12}} d\mathbf{r}_1 d\mathbf{r}_2 . \quad (3)$$

In the IQA-defined partitioning scheme,¹ an atomic (or one-centre) V_{ee}^Ω and interatomic (two-centre) $V_{ee}^{\Omega_1, \Omega_2}$ contributions to V_{ee} energy have to be computed. They are obtained simply by integration over atomic basins as

$$V_{ee}^\Omega = \frac{1}{2} \int_\Omega d\mathbf{r}_1 \int_\Omega d\mathbf{r}_2 \frac{\rho_2(\mathbf{r}_1, \mathbf{r}_2)}{r_{12}} \quad (4)$$

for atomic and

$$V_{ee}^{\Omega_1, \Omega_2} = \int_{\Omega_1} d\mathbf{r}_1 \int_{\Omega_2} d\mathbf{r}_2 \frac{\rho_2(\mathbf{r}_1, \mathbf{r}_2)}{r_{12}} \quad (5)$$

for interatomic components. Thus summation of V_{ee}^{Ω} and $V_{ee}^{\Omega_1, \Omega_2}$ over all atoms and all possible atomic pairs should necessarily give total molecular V_{ee} energy:

$$V_{ee} = \sum_{\Omega} V_{ee}^{\Omega} + \sum_{\Omega_1 < \Omega_2} V_{ee}^{\Omega_1, \Omega_2} . \quad (6)$$

Unfortunately, the exact form of the $\rho_2(\mathbf{r}_1, \mathbf{r}_2)$ quantity is often inaccessible for post-HF levels, so its approximations (functionals $\zeta(n_i, n_j)$)⁹⁻²² in terms of natural orbitals $\{\chi_i(\mathbf{r})\}$ and occupation numbers $\{n_i, n_j\}$ have been proposed

$$\rho_2(\mathbf{r}_1, \mathbf{r}_2) = \sum_{ij} \zeta(n_i, n_j) [\chi_i^*(\mathbf{r}_1) \chi_j(\mathbf{r}_1) \chi_i^*(\mathbf{r}_2) \chi_j(\mathbf{r}_2)] . \quad (7)$$

The most famous functional was proposed by Müller, $\zeta^M(n_i, n_j)$,⁸ and subsequently was employed by Buijse and Baerends.^{9,16} It has a very simple form,

$$\zeta^M(n_i, n_j) = 2\sqrt{n_i n_j} . \quad (8)$$

where the multiplier 2 accounts for α and β spins within the restricted formalism (for ordinary spin-orbitals this multiplier is omitted). The energies produced with this approach are seriously overestimated (in absolute value) relative to real energy values. Some attempts to improve over-correlation of Müller functional have been made.¹¹⁻¹³ In the present work we compare two corrections to Müller functional, which were proposed by Gritchenko et al.¹⁷ The first functional was named the BBC1 approximation and it is correction to Müller basic approximation⁸ as $\zeta^M(n_i, n_j) - 4\sqrt{n_i n_j}$, $i, j > N/2$ ($i \neq j$). Thus produced functional reduces the influence of correlation originated from partially occupied orbitals,

$$\zeta^{\text{BBC1}}(n_i, n_j) = \begin{cases} -2\sqrt{n_i n_j}, & i, j > N/2 \quad (i \neq j) \\ +2\sqrt{n_i n_j}, & \text{for all other cases} \end{cases} . \quad (9)$$

The second approximation is called BBC2 and it provides, in addition to restriction incorporated in BBC1, another correction as $\zeta^{\text{BBC1}}(n_i, n_j) - 2\sqrt{n_i n_j} + 2n_i n_j$ for $i, j \leq N/2$ ($i \neq j$), thus giving

$$\zeta^{\text{BBC2}}(n_i, n_j) = \begin{cases} +2n_i n_j, & i, j \leq N/2 \quad (i \neq j) \\ -2\sqrt{n_i n_j}, & i, j > N/2 \quad (i \neq j) \\ +2\sqrt{n_i n_j}, & \text{for all other cases} \end{cases} . \quad (10)$$

More sophisticated BBC2 functional specifies contributions from different and the same occupied natural orbitals. Contrary to the Müller functional, the BBC2 functional might seriously underestimate the correlation energy due to the large contributions from the cross

products of the occupied orbitals. In this regard, one might expect that the BBC1 functional should provide more balanced correlation treatment.

3.2. Basic concepts of the FAMSEC method

The concept of FAMSEC³ was developed to explore, relative to a suitable reference state of a molecule (*ref*-state), properties of a selected n -atom molecular fragment \mathcal{F} in the final state of a molecule (*fin*-state) by making use of IQA-defined energy terms. FAMSEC has been successfully applied to explain relative stability of *cis*- and *trans*-2-butene conformers²⁸ or amino acid β -alanine lowest and highest energy conformers²⁹ in terms of quantifying energy contributions made by a selected n -atom molecular fragment \mathcal{F} as well as pointing at the origin, on the fundamental level, of the observed phenomena. First of all, we can extract global term from $E(\text{IQA})$ attributed to \mathcal{F} that is denoted as $E_{\text{attr-mol}}^{\mathcal{F}}$ quantity. It provides \mathcal{F} -fragment energy contribution to a relative stability of a molecule on a *ref*-state \rightarrow *fin*-state structural change. The $E_{\text{attr-mol}}^{\mathcal{F}}$ term is composed of two parts, namely $E_{\text{attr-loc}}^{\mathcal{F}}$ and $\Delta E_{\text{int}}^{\mathcal{F}\mathcal{F}}$ contributions,

$$E_{\text{attr-mol}}^{\mathcal{F}} = E_{\text{attr-loc}}^{\mathcal{F}} + \Delta E_{\text{int}}^{\mathcal{F}\mathcal{F}}. \quad (11)$$

The second quantity in Eq. 11 provides a measure of interfragment interaction energy change between \mathcal{F} (the fragment of interest) and \mathcal{F}^c containing all other atoms in a molecule. The first term in Eq. 11 is made of $\Delta E_{\text{self}}^{\mathcal{F}}$ and $\Delta E_{\text{int}}^{\mathcal{F}}$, standing for the change in self-fragment and intra-fragment interaction energy, respectively, Eq. 12.

$$E_{\text{attr-loc}}^{\mathcal{F}} = \Delta E_{\text{self}}^{\mathcal{F}} + \Delta E_{\text{int}}^{\mathcal{F}}. \quad (12)$$

4. RESULTS and DISCUSSION

4.1. Electronic vs. IQA molecular energy

The conformers of glycol were used here as a case study to investigate the origin of inaccuracy of computed IQA-defined two main energy terms, E_{self}^X and $E_{\text{int}}^{X,Y}$, at a specific LoT/LoA combination, because they are used to compute the molecular energy as

$$E(\text{IQA}) = \sum_X E_{\text{self}}^X + 0.5 \sum_X \sum_{Y \neq X} E_{\text{int}}^{X,Y}. \quad (13)$$

Furthermore, we wanted to establish the significance of commonly accepted criterion applied to assess quality of IQA data, namely how well $E(\text{IQA})$ is reproducing electronic energy of a molecule, E ; hence, significance of the $\Delta E_{\text{IQA},E} = E(\text{IQA}) - E$ term was also investigated. In this regard, the question one can ask is whether $\Delta E_{\text{IQA},E} \approx 0$ is a necessary and sufficient requirement to perform reliable analysis of atoms and molecular fragments' properties within the IQA and

FAMSEC schemes. It is obvious that the origin of $\Delta E_{\text{IQA,E}} \neq 0$ must be linked with the $\Delta V_{\text{ee}}^{\text{Tot}} = {}^{\text{IQA}}V_{\text{ee}}^{\text{Tot}} - {}^{\text{Exact}}V_{\text{ee}}^{\text{Tot}}$ term because the accuracy of the $V_{\text{ee}}^{\text{Tot}} = V_{\text{ee}}^{\text{X}} + \sum_{Y \neq X} V_{\text{ee}}^{\text{X,Y}}$ term depends on a specific approximation used. The value of the ${}^{\text{Exact}}V_{\text{ee}}^{\text{Tot}}$ term was obtained from total molecular energy components evaluated in the PRIRODA14 program.²⁷ Data in Table 1 shows that:

- The $|\Delta E_{\text{IQA,E}}|$ values computed using BBC1 approximation are within a few kcal/mol at the CCSD level and the following trend was found: $|\Delta E_{\text{IQA,E}}|_{\text{CCSD/BBC1}} < |\Delta E_{\text{IQA,E}}|_{\text{MP2/BBC1}} \approx |\Delta E_{\text{IQA,E}}|_{\text{CCSD(T)/BBC1}}$ from TWOe calculations of the IQA terms.
- The $|\Delta E_{\text{IQA,E}}|$ values vary with the level of approximation and the $|\Delta E_{\text{IQA,E}}|_{\text{BBC1}} < |\Delta E_{\text{IQA,E}}|_{\text{BBC2}} < |\Delta E_{\text{IQA,E}}|_{\text{Müller}}$ trend is observed at each LoT.
- The $\Delta E_{\text{IQA,E}}$ values obtained from Müller approximation are consistently two orders of magnitude larger than those from BBC1. The $E(\text{IQA})$ values from Müller are larger (more negative) than electronic molecular energies by about -170 kcal/mol at each level of theory.

Table 1. $\Delta E_{\text{IQA,E}}$ and $\Delta V_{\text{ee}}^{\text{Tot}}$ values (in kcal/mol) obtained for the indicated conformers of glycol at different levels of theory and approximation.

	LEC			Eclipsed			Linear		
LoA	CCSD	CCSD(T)	MP2	CCSD	CCSD(T)	MP2	CCSD	CCSD(T)	MP2
$\Delta E_{\text{IQA,E}} = E(\text{IQA}) - E$									
BBC1	0.4	13.6	-16.3	4.4	18.6	-13.0	6.9	20.2	-13.9
BBC2	69.6	89.9	46.2	73.9	95.5	51.2	78.5	99.3	51.1
Müller	-169.0	-172.7	-166.2	-170.9	-173.4	-167.1	-168.9	-172.0	-168.1
$\Delta V_{\text{ee}}^{\text{Tot}} = {}^{\text{IQA}}V_{\text{ee}}^{\text{Tot}} - {}^{\text{Exact}}V_{\text{ee}}^{\text{Tot}}$									
BBC1	0.2	13.6	-16.4	4.3	18.4	-13.1	6.7	20.3	-14.2
BBC2	69.4	89.9	46.1	73.8	95.3	51.0	78.3	99.3	50.8
Müller	-169.2	-172.8	-166.3	-171.1	-173.5	-167.2	-169.0	-171.9	-168.4

As expected, the origin of the $\Delta E_{\text{IQA,E}}$ values is clearly linked with inaccuracy in the computed $V_{\text{ee}}^{\text{Tot}}$ values; this is evidenced by the fact that $\Delta E_{\text{IQA,E}}$ and $\Delta V_{\text{ee}}^{\text{Tot}}$ differ, as they should, only by a fraction of a kcal/mol that is associated with the numerical integration errors.

In support of the main source of inaccuracy, it is important to stress that the T^{Tot} and $V_{\text{en}}^{\text{Tot}}$ values computed for entire molecules (as a sum of contributions made by individual atoms and interatomic components) agree with exact analytic values to a small fraction of a kcal/mol.

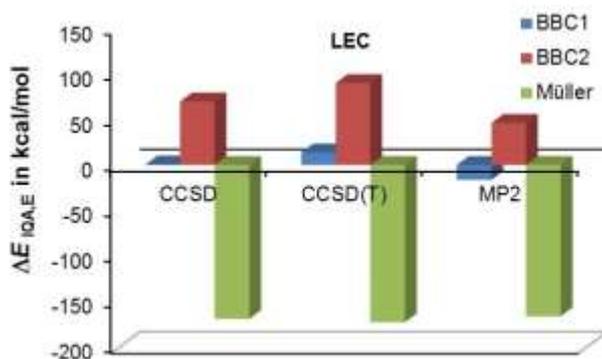


Figure 2. Pictorial presentation of the computed $\Delta E_{\text{IQA,E}}$ values for the **LEC** of glycol at the indicated levels of theory and approximation.

In general, from the $\Delta E_{\text{IQA,E}}$ perspective, only BBC1 approximation should be used in the IQA calculations when post-HF wavefunctions are considered (here CCSD, CCSD(T) and MP2) and this is nicely illustrated for the **LEC** of glycol in Figure 2 (similar trends are also observed for **Ecl** and **Lin** - see Figure S1 in the Electronic Supplementary Information, ESI). Figure 2 and Figure S1 in the ESI fully support the data obtained at the CCSD/BBC1 level of theory that was selected as a reference in our investigation.

It is important to note, however, that there is some variation in the $\Delta E_{\text{IQA,E}}$ values obtained for different conformers at the same LoT/LoA combination. For instance, $\Delta E_{\text{IQA,E}}$ values of 0.4, 4.4 and 6.9 kcal/mol were obtained, respectively, for **LEC**, **Ecl** and **Lin** from CCSD/BBC1. This clearly demonstrates that accuracy in the molecular energy values computed by use of approximated functionals also depends on the molecule and its geometry. Hence, the data in Table 1 can be used only as a convenient indicator of relative accuracy obtained at the LoA used.

To make the data in Table 1 directly comparable, one can normalise the $\Delta E_{\text{IQA,E}}$ values by expressing them as a %-fraction of molecular energy E of each conformer. Results obtained are shown in commented Figure S2 in the ESI. Importantly, very much the same trends that mimic those in Figure 2 are observed for all conformers.

4.2. Uncertainty in the total self-molecular and interaction energy terms

The computed $\Delta E_{\text{IQA,E}}$ values are informative as they pin-point at the best performing LoT/LoA combination. However, they do not provide any insight on the main contribution made to $\Delta E_{\text{IQA,E}} \neq 0$; in our opinion, finding the origin of $E(\text{IQA}) \neq E$ is of fundamental importance as it might have a decisive impact on recommending (or not) a specific LoA for a particular purpose. In the first approach we decided to evaluate the uncertainty in the computed total self-molecular energy, $E_{\text{self}}^{\text{Tot}}$, as

$$E_{\text{self}}^{\text{Tot}} = \sum_X E_{\text{self}}^X \quad (14)$$

and the total energy contribution made by all unique diatomic interactions, $E_{\text{int}}^{\text{Tot}}$, as

$$E_{\text{int}}^{\text{Tot}} = 0.5 \sum_X \sum_{Y \neq X} E_{\text{int}}^{X,Y} \quad (15)$$

because $E(\text{IQA}) = E_{\text{self}}^{\text{Tot}} + E_{\text{int}}^{\text{Tot}}$. Our aim is to establish the origin of errors contributing to $(\Delta E_{\text{IQA,E}})_{\text{LoT/LoA}} \neq 0$. To this effect, it is convenient to express $E_{\text{self}}^{\text{Tot}}$ as

$$E_{\text{self}}^{\text{Tot}} = \left(E_{\text{self}}^{\text{Tot}}\right)^{\#} + \text{err}_{\text{self}}^{\text{Tot}} = \sum_X \left(\left(E_{\text{self}}^X\right)^{\#} + \text{err}_{\text{self}}^X \right) \quad (16)$$

where $\left(E_{\text{self}}^{\text{Tot}}\right)^{\#}$ stands for the exact value of the self-molecular energy, $\text{err}_{\text{self}}^{\text{Tot}}$ is the total error in the computed self-molecular energy, $\left(E_{\text{self}}^X\right)^{\#}$ is the exact self-atomic energy of an atom X of a molecule, and $\text{err}_{\text{self}}^X$ is the error in the computed self-atomic energy of an atom X at a specific LoT/LoA combination. By analogy, we can expand the $E_{\text{int}}^{\text{Tot}}$ term as

$$E_{\text{int}}^{\text{Tot}} = \left(E_{\text{int}}^{\text{Tot}}\right)^{\#} + \text{err}_{\text{int}}^{\text{Tot}} = \sum_{X \neq Y} \left(\left(E_{\text{int}}^{X,Y}\right)^{\#} + \text{err}_{\text{int}}^{X,Y} \right) \quad (17)$$

where $\left(E_{\text{int}}^{\text{Tot}}\right)^{\#}$ is the exact total value of the contribution made by all unique interatomic interactions to the molecular energy, $\text{err}_{\text{int}}^{\text{Tot}}$ stands for the total error in the computed total interaction energy, $\left(E_{\text{int}}^{X,Y}\right)^{\#}$ represents the exact value of any diatomic interaction between atoms X and Y, and $\text{err}_{\text{int}}^{X,Y}$ describes an error in the computed value of $E_{\text{int}}^{X,Y}$. It is obvious that the $\left(E_{\text{self}}^{\text{Tot}}\right)^{\#}$ and $\left(E_{\text{int}}^{\text{Tot}}\right)^{\#}$ values (as well as $\left(E_{\text{self}}^X\right)^{\#}$ and $\left(E_{\text{int}}^{X,Y}\right)^{\#}$) are unknown; hence we used values computed at CCSD/BBC1 as best approximation available.

The main limitation in direct comparing IQA energy components computed at different LoTs is linked with differences in molecular energy values, $\Delta E_{\text{LoT,CCSD}} = E_{\text{LoT}} - E_{\text{CCSD}}$, as they will

introduce additional contribution to the computed errors of the individual IQA energy components, e.g., for the total self-molecular energy $\Delta_{\text{self}}^{\text{Tot}}$. Thus it is proposed to use rescaled values of $E_{\text{self}}^{\text{Tot}}$ and $E_{\text{int}}^{\text{Tot}}$ by re-computing them from CCSD level to another LoT. Indeed, due to the small relative differences in molecular energies, $\Delta E_{\text{LoT,CCSD}} \ll E_{\text{CCSD}}$, expanding, for example, the self-term ratio $(E_{\text{self}}^{\text{Tot}}/E)_{\text{LoT}}$ in the series

$$\frac{(E_{\text{self}}^{\text{Tot}})_{\text{LoT}}}{E_{\text{LoT}}} = \frac{(E_{\text{self}}^{\text{Tot}})_{\text{CCSD}} + \Delta_{\text{self}}^{\text{Tot}}}{E_{\text{CCSD}} + \Delta E} \approx \frac{(E_{\text{self}}^{\text{Tot}})_{\text{CCSD}}}{E_{\text{CCSD}}} + \frac{\Delta_{\text{self}}^{\text{Tot}}}{E_{\text{CCSD}}} + \frac{\Delta E}{E_{\text{CCSD}}} \approx \frac{(E_{\text{self}}^{\text{Tot}})_{\text{CCSD}}}{E_{\text{CCSD}}} \quad (18)$$

shows that the fractional contribution of the total self-molecular energy to E should not depend on the LoT or approximation used (the same applies to interaction energies). Hence, we have computed the $R_{\text{self}}^{\text{Tot}} = (E_{\text{self}}^{\text{Tot}}/E)_{\text{CCSD/BBC1}}$ and $R_{\text{int}}^{\text{Tot}} = (E_{\text{int}}^{\text{Tot}}/E)_{\text{CCSD/BBC1}}$ ratios and used them to compute the expected relevant energy contributions for each LoT/LoA combination, $(\text{Expect } E_{\text{self}}^{\text{Tot}})_{\text{LoT}} = R_{\text{self}}^{\text{Tot}} \times E_{\text{LoT}}$ and $(\text{Expect } E_{\text{int}}^{\text{Tot}})_{\text{LoT}} = R_{\text{int}}^{\text{Tot}} \times E_{\text{LoT}}$. In sections that follow we will explore the origin of the departure from the CCSD/BBC1 values computed for the above energy terms as a difference between the computed and expected values (e.g., as $(\Delta_{\text{self}}^{\text{Tot}})_{\text{LoT/LoA}} = (\text{Comput } E_{\text{self}}^{\text{Tot}})_{\text{LoT/LoA}} - (\text{Expect } E_{\text{self}}^{\text{Tot}})_{\text{LoT}}$ for self-molecular energy; note that $\Delta_{\text{self}}^{\text{Tot}}$ is our best approximation of the exact error, $err_{\text{self}}^{\text{Tot}}$ (Eq. 16). Of course, it is obviously true that within CCSD data the simple expressions, i.e., $(\text{Expect } E_{\text{self}}^{\text{Tot}})_{\text{CCSD}} = (\text{Comput } E_{\text{self}}^{\text{Tot}})_{\text{CCSD}}$ for each approximation and $(\Delta_{\text{self}}^{\text{Tot}})_{\text{CCSD/LoA}} = (\text{Comput } E_{\text{self}}^{\text{Tot}})_{\text{CCSD/LoA}} - (\text{Comput } E_{\text{self}}^{\text{Tot}})_{\text{CCSD/BBC1}}$, for example, could be used for estimating the errors without any energy scaling procedure. Moreover, all expected values, $(\text{Expect } E_{\text{self}}^{\text{Tot}})_{\text{LoT}}$ and $(\text{Expect } E_{\text{int}}^{\text{Tot}})_{\text{LoT}}$, will be the same for all approximations at a specific level of theory.

Data obtained for all conformers are included in Table 2; its analysis leads to several important observations and let us start with the BBC1 approximation first:

- a) In each case $\Delta_{\text{self}}^{\text{Tot}} < 0$; hence, all computed self-molecular energies for three conformers are overestimated (i.e., more negative quantities) relative to what is predicted from the CCSD/BBC1 level, on average by -10 ± 1 and -16 ± 1 kcal/mol at CCSD(T) and MP2, respectively.
- b) Considering the total interaction energies $E_{\text{int}}^{\text{Tot}}$, they were underestimated by 23 ± 1 kcal/mol at CCSD(T). However, the MP2 values nearly reproduced the expected ones, as they were overestimated only by -3 ± 1 kcal/mol.

Table 2. Estimated errors, $\Delta_{\text{self}}^{\text{Tot}}$ and $\Delta_{\text{int}}^{\text{Tot}}$, in the total self-molecular and total interaction energies, respectively, in three conformers of glycol at specified level of theory and approximation.^a

<i>E</i> -term	CCSD			CCSD(T)			MP2		
	LEC / lowest energy conformer								
	Expect $E_{\text{self}}^{\text{Tot}} = -226.5280$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1849$			Expect $E_{\text{self}}^{\text{Tot}} = -226.5504$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1852$			Expect $E_{\text{self}}^{\text{Tot}} = -226.4930$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1844$		
	BBC1	BBC2	Müller	BBC1	BBC2	Müller	BBC1	BBC2	Müller
Comput $E_{\text{self}}^{\text{Tot}}$	ref	-226.4160	-226.8138	-226.5648	-226.4410	-226.8792	-226.5162	-226.4138	-226.7698
$\Delta_{\text{self}}^{\text{Tot}}$	–	70.3	-179.3	-9.0	68.6	-206.3	-14.5	49.7	-173.7
Comput $E_{\text{int}}^{\text{Tot}}$	ref	-3.1865	-3.1690	-3.1497	-3.1518	-3.1322	-3.1878	-3.1906	-3.1730
$\Delta_{\text{int}}^{\text{Tot}}$	–	-1.1	9.9	22.3	20.9	33.2	-2.2	-3.9	7.1
$\Delta_{\text{self}}^{\text{Tot}} + \Delta_{\text{int}}^{\text{Tot}}$	–	69.2	-169.4	13.2	89.6	-173.1	-16.7	45.8	-166.6
Ecl / eclipsed conformer									
<i>E</i> -term	Expect $E_{\text{self}}^{\text{Tot}} = -226.5276$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1605$			Expect $E_{\text{self}}^{\text{Tot}} = / -226.5500$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1608$			Expect $E_{\text{self}}^{\text{Tot}} = -226.4920$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1600$		
		BBC1	BBC2	Müller	BBC1	BBC2	Müller	BBC1	BBC2
Comput $E_{\text{self}}^{\text{Tot}}$	ref value	-226.4152	-226.8213	-226.5656	-226.4410	-226.8867	-226.5167	-226.4114	-226.7762
$\Delta_{\text{self}}^{\text{Tot}}$	–	70.5	-184.3	-9.8	68.4	-211.3	-15.5	50.6	-178.3
Comput $E_{\text{int}}^{\text{Tot}}$	ref value	-3.1621	-3.1462	-3.1226	-3.1246	-3.1074	-3.1631	-3.1661	-3.1491
$\Delta_{\text{int}}^{\text{Tot}}$	–	-1.0	9.0	24.0	22.7	33.6	-1.9	-3.8	6.8
$\Delta_{\text{self}}^{\text{Tot}} + \Delta_{\text{int}}^{\text{Tot}}$	–	69.5	-175.3	14.2	91.1	-177.7	-17.4	46.8	-171.5
Lin / linear conformer									
<i>E</i> -term	Expect $E_{\text{self}}^{\text{Tot}} = -226.5322$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1665$			Expect $E_{\text{self}}^{\text{Tot}} = -226.5544$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1668$			Expect $E_{\text{self}}^{\text{Tot}} = -226.4969$; Expect $E_{\text{int}}^{\text{Tot}} = -3.1660$		
		BBC1	BBC2	Müller	BBC1	BBC2	Müller	BBC1	BBC2
Comput $E_{\text{self}}^{\text{Tot}}$	ref value	-226.4181	-226.8240	-226.5710	-226.4448	-226.8895	-226.5238	-226.4188	-226.7811
$\Delta_{\text{self}}^{\text{Tot}}$	–	71.6	-183.1	-10.5	68.7	-210.3	-16.9	49.0	-178.4
Comput $E_{\text{int}}^{\text{Tot}}$	ref value	-3.1665	-3.1549	-3.1289	-3.1291	-3.1167	-3.1722	-3.1737	-3.1606
$\Delta_{\text{int}}^{\text{Tot}}$	–	0.0	7.3	23.7	23.6	31.4	-4.0	-4.8	3.3
$\Delta_{\text{self}}^{\text{Tot}} + \Delta_{\text{int}}^{\text{Tot}}$	–	71.6	-175.8	13.3	92.3	-178.9	-20.9	44.2	-175.0

[a] The expected and computed values ($\text{Expect } E_{\text{self}}^{\text{Tot}}$, $\text{Expect } E_{\text{int}}^{\text{Tot}}$, $\text{Comput } E_{\text{self}}^{\text{Tot}}$, $\text{Comput } E_{\text{int}}^{\text{Tot}}$) are in au; errors ($\Delta_{\text{self}}^{\text{Tot}}$, $\Delta_{\text{int}}^{\text{Tot}}$) are in kcal/mol. ref value = reference value.

- c) The estimated errors, $\Delta_{\text{self}}^{\text{Tot}}$ and $\Delta_{\text{int}}^{\text{Tot}}$, in absolute term, differ significantly at each LoT. Hence, $\Delta_{\text{self}}^{\text{Tot}} + \Delta_{\text{int}}^{\text{Tot}} \neq 0$ and we note that at MP2 both values, $E_{\text{self}}^{\text{Tot}}$ and $E_{\text{int}}^{\text{Tot}}$ are consistently slightly overestimated.
- d) In general, the errors computed for all conformers at each LoT, but only for BBC1, can be seen as tolerable (if not ‘negligible’) when one considers how small %-fraction of the total E they constitute. To support this, on average the $\Delta_{\text{self}}^{\text{Tot}}/\Delta_{\text{int}}^{\text{Tot}}$ values were found to be $-16/-3$ kcal/mol at MP2 which constitutes about 0.011/0.002% of the total averaged molecular energy of glycol conformers.

Our focus is now on the BBC2 and Müller approximations. Regardless of the level of theory, self-molecular energies:

- a) Are (i) significantly underestimated by BBC2, with the average error $(\Delta_{\text{self}}^{\text{Tot}})_{\text{BBC2}}$ of +63 kcal/mol and (ii) largely overestimated in the case of the Müller approximation, with the average $(\Delta_{\text{self}}^{\text{Tot}})_{\text{Müller}} = -189$ kcal/mol - see Figure S3 in the ESI for pictorial presentation.
- b) Errors generated by the Müller approximation are an order of magnitude larger when compared with those obtained at BBC1 and the following trend, $|\Delta_{\text{self}}^{\text{Tot}}|_{\text{BBC1}} < |\Delta_{\text{self}}^{\text{Tot}}|_{\text{BBC2}} < |\Delta_{\text{self}}^{\text{Tot}}|_{\text{Müller}}$, was found. This is illustrated for **LEC** in Figure 3 where errors are shown as $-\Delta_{\text{self}}^{\text{Tot}}$ to illustrate them in more intuitive fashion (e.g., a positive value means that the self-molecular energy was overestimated). Similar pictures were obtained for the remaining conformers – see Figure S4 in the ESI.

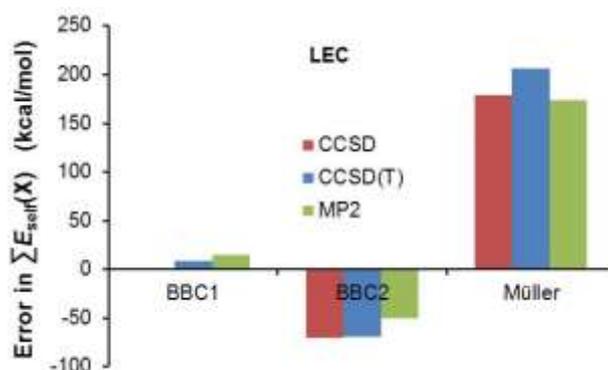


Figure 3. Estimated errors (as $-\Delta_{\text{self}}^{\text{Tot}}$ values in Table 2) in the computed total self-molecular energy of the **LEC** of glycol at the indicated LoT/LoA combination.

Focusing on the computed total interaction energies, we found that:

- With one exception for CCSD(T)/BBC1, errors in the $E_{\text{int}}^{\text{Comput}} E_{\text{int}}^{\text{Tot}}$ values are consistently and often more than an order of magnitude smaller when compared with the relevant errors in self-molecular energies.
- BBC2 generated slightly overestimated values, by -1 ± 1 and -4 ± 1 kcal/mol at CCSD and MP2, respectively. Opposite trend was found at the CCSD(T) level as for the three conformers of glycol they were underestimated, on average, by 22 ± 1 kcal/mol.
- They were consistently underestimated when Müller approximation was used, on average for three conformers by 9 ± 1 (CCSD), 33 ± 1 (CCSD(T) and 6 ± 2 (MP2) kcal/mol.

It is important to note that errors in the $E_{\text{int}}^{\text{Comput}} E_{\text{int}}^{\text{Tot}}$ values are consistently largest at the CCSD(T) level whereas errors at CCSD and MP2 can be seen as comparable and indeed negligible. From that it follows that acceptable description of interatomic interactions can be obtained at MP2/BBC1. Hence, when the associated cost of optimization and IQA computation is considered, there appears to be no significant weighted (against the cost) advantage of using IQA on CCSD-generated wavefunction and particularly so in the case of CCSD(T).

4.3. Relative to CCSD/BBC1, errors in computed individual self-atomic energies.

To gain deeper insight on significance of the errors in the total self-molecular energy it was of paramount importance to learn about errors in individual atoms' self-energies. To achieve that we made use of the same approach as used in computing $\Delta_{\text{self}}^{\text{Tot}}$ errors; hence, the $E_{\text{self}}^{\text{X}}$ values obtained at CCSD/BBC1 were used as reference in predicting the expected self-atomic energy for each atom in the conformers. The computed errors, $(\Delta_{\text{self}}^{\text{X}})_{\text{LoT/LoA}}$, for the LEC are shown in Figure 4, where results from BBC1 and Müller approximations are depicted; relevant data for

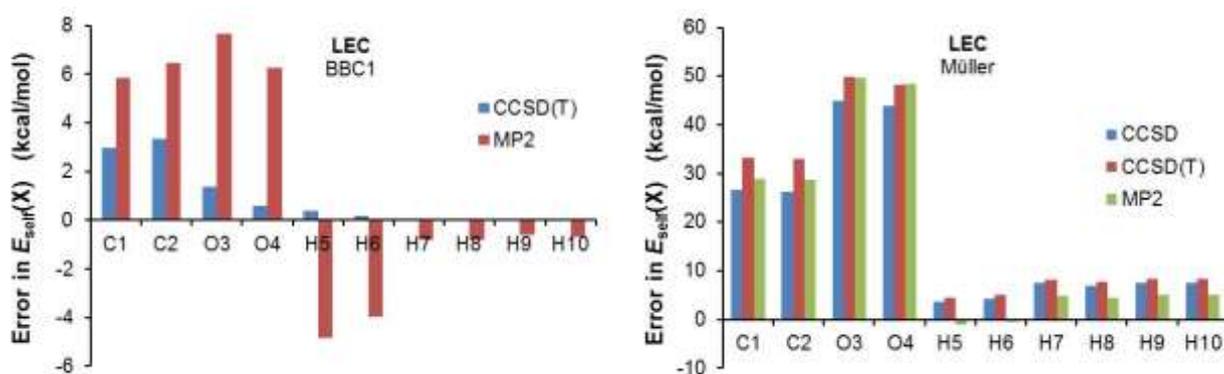


Figure 4. Relative to CCSD/BBC1 data, errors in computed self-atomic energies of the LEC of glycol at the indicated LoT/approximation combination.

BBC2 are shown in Figure S5 in the ESI and a full set of data for **Ecl** and **Lin** is shown in Figures S6-S7 in the ESI.

Firstly, it is important to note that the distribution of $\Delta_{\text{self}}^{\text{X}}$ errors and their values are nearly the same for all conformers for each LoT/LoA combination. Moreover, the smallest/largest errors were consistently obtained from BBC1/Müller approximation.

Focusing on the Müller approximation, the $\Delta_{\text{self}}^{\text{O}} > \Delta_{\text{self}}^{\text{C}} > \Delta_{\text{self}}^{\text{H}}$ trend is observed at each LoT tested. This is an informative finding as it clearly confirms that the main origin of errors for this approximation is rooted in the improper evaluation of the V_{ce}^{X} term and thus the increase in errors is linked with a larger number of electrons populating an atomic basin. Hence, the largest deviations are expected for heavier atoms for which we have larger $E_{\text{self}}^{\text{X}}$. However, the computed $\Delta_{\text{self}}^{\text{X}}$ errors are not proportional to the $E_{\text{self}}^{\text{X}}$ values (see Figure 4) where $\Delta_{\text{self}}^{\text{H}}$ are disproportionally larger when compared with the $\Delta_{\text{self}}^{\text{O}}$ and $\Delta_{\text{self}}^{\text{C}}$ values. Interestingly, in the case of BBC1 and BBC2 approximations, quite random variation in the $\Delta_{\text{self}}^{\text{X}}$ errors is observed that does not correlate with self-atomic energies at all – Figures S6-S7 in the ESI.

In general, (i) quite reasonable $E_{\text{self}}^{\text{X}}$ values were obtained at CCSD(T)/BBC1 and MP2/BBC1 with the former showing significantly smaller errors, (ii) several times largest errors are observed for BBC2 and (iii) up to an order of magnitude larger errors in $E_{\text{self}}^{\text{X}}$ can be expected when Müller approximation is used. It is surprising that, even for methylene hydrogens (H7-H10), the $\Delta_{\text{self}}^{\text{H}}$ errors from Müller approximation are extremely large as they amount up to about of 10 kcal/mol (the $E_{\text{self}}^{\text{H}}$ values were overestimated).

4.4. Relative to CCSD/BBC1, errors in computed diatomic interaction energies.

We followed the same approach as applied for computing errors in individual atoms' self-energies. Data obtained, $\Delta_{\text{int}}^{\text{X,Y}}$, for the **LEC** at MP2/BBC1 is shown in Figure 5 (a full set of data obtained for each conformer at all LoT/LoA combinations is shown in Figures S8-S16 in the ESI).

Largest errors are generally observed for the interactions involving heavier atoms, e.g., $E_{\text{int}}^{\text{C1,C2}}$ of -91.2 kcal/mol in **LEC** was overestimated, hence more attractive, by $-7.1/-1.6$ kcal/mol or $E_{\text{int}}^{\text{C1,O4}}$ of -363.1 kcal/mol was underestimated, hence less attractive, by $+7.3/+7.8$ kcal/mol at

MP2/CCSD(T), all values from BBC1. Surprisingly, the errors are not dramatically different when Müller approximation was used; for the $E_{\text{int}}^{\text{C1,C2}}$ and $E_{\text{int}}^{\text{C1,O4}}$ interaction energies in the **LEC** we obtained for the MP2/Müller combination errors of -6.7 and $+7.3$ kcal/mol, respectively.

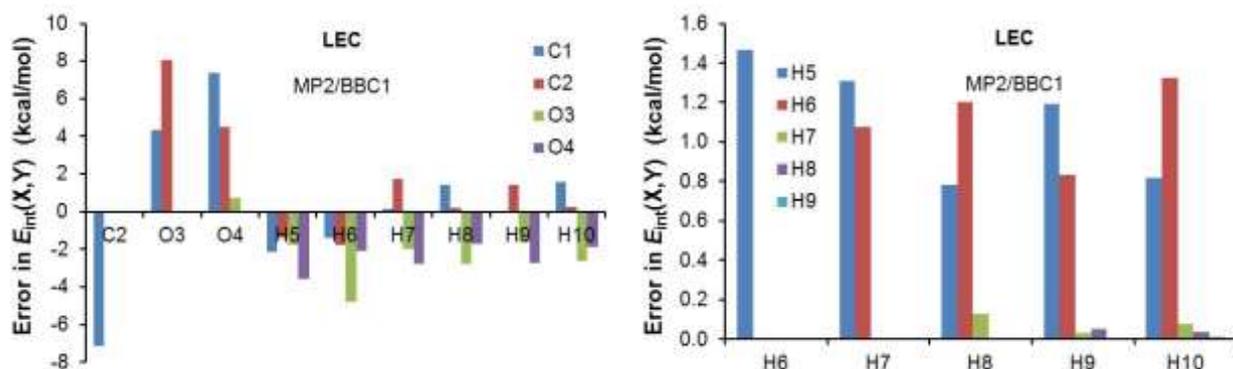


Figure 5. Relative to CCSD/BBC1, errors in the computed diatomic interactions in the **LEC** of glycol at MP2 using the BBC1 approximation.

Focusing on the $\text{H6}\cdots\text{O4}$ intramolecular interaction of interest in the **LEC** ($E_{\text{int}}^{\text{H6,O4}} = -90.9$ kcal/mol) we found the $\Delta_{\text{int}}^{\text{H6,O4}}$ error to be $+1.3/+1.7$ kcal/mol at CCSD(T) or $-2.1/-1.4$ kcal/mol at MP2 using BBC1/Müller approximation. In the case of the steric $\text{O3}\cdots\text{O4}$ clash in the **Ecl** conformer ($E_{\text{int}}^{\text{O3,O4}} = +121.2$ kcal/mol) the $\Delta_{\text{int}}^{\text{O3,O4}}$ error was found to be $+0.4/+6.9$ kcal/mol at MP2 using BBC1/Müller approximation.

The performed analysis of errors clearly shows that largest deviations are expected for covalently bonded atoms. However, for more classically (electrostatically) interacting atomic pairs, such as $\text{H6}\cdots\text{O4}$ or $\text{O3}\cdots\text{O4}$, the errors are substantially smaller. This could be explained by distorted description (by means of approximated 2EDM) of proper exchange and correlation terms, which play dominant role in covalent bonding. In the case of electrostatic interactions, only electron densities are responsible for evaluation of the $V_{\text{en}}^{\text{X1,X2}}$ term and Coulomb interatomic integral $J_{\text{ec}}^{\text{X1,X2}}$, thus giving comparable results for all approximations.

Finally, if the weak diatomic interactions are of primary interest then one must be cautious because, relative to the CCSD/BBC1 data, the change in the sign, hence the change in the nature of an interaction, might take place. Surprisingly, this was found almost entirely in the case of the BBC2 approximation, e.g., $E_{\text{int}}^{\text{O3,H7}} = +1.5$ kcal/mol at CCSD/BBC1 was found to be -0.2 kcal/mol at MP2/BBC2.

4.5. FAMSEC-based analysis of selected molecular fragments

Linear→**LEC structural change.** The main contact of interest is H6--O4 in the **LEC** (Figure 1) with $d(\text{O4,H6}) = 2.376 \text{ \AA} < (\text{sum of van der Waals radii})$. Note that QTAIM-defined an Atomic Interaction Line (AIL), commonly interpreted as a Bond Path (BP),⁷ is not present. Hence, not only it is impossible to interpret this interaction using topological properties at a bond critical point (as it is not present) but also this interaction would not be seen as an intramolecular H-bond as it does not meet the topological criteria.³⁰ There are two commonly used representations of intramolecular H-bonds. According to the IUPAC recommendation,³¹ H-bonds should be represented as X–H··Y–Z, where X–H and Y–Z represent the hydrogen bond donor and a molecular fragment acting as the acceptor, respectively, where Y is bonded to Z. A classical intramolecular H-bond has been also interpreted using the X–H··Y notation when H is bonded to electronegative atom O, N or F.³² In order to fully explore the nature of this intramolecular contact from the FAMSEC perspective, we decided to investigate three possible options, namely the diatomic interaction itself (H6··O4), three-atom representation (O3–H6··O4) and the IUPAC recommended one (O3–H6··O4–C1). There are two major aims, namely (i) to characterise these three molecular fragments at the CCSD/BBC1 and (ii) find out how different interpretation would result at CCSD(T) and MP2 using different approximations. To this effect we will monitor five descriptors, namely $\Delta E_{\text{self}}^{\mathcal{F}}$, $\Delta E_{\text{int}}^{\mathcal{F}}$, $E_{\text{attr-loc}}^{\mathcal{F}}$, $\Delta E_{\text{int}}^{\mathcal{F}f}$, and $E_{\text{attr-mol}}^{\mathcal{F}}$ (see Eqs. 11-12) that, for simplicity reason, will be shown in following Figures and Tables as (1), (2), (3), (4), and (5), respectively.

Description of the H6--O4 contact. Variation with the level of theory at the BBC1 approximation of the five FAMSEC descriptors for $\mathcal{F} = \{\text{O4,H6}\}$ is shown in Figure S17 in the ESI and a full set of data is included in Table 3. Focusing on data obtained at CCSD/BBC1 we note that:

- Self-energy, (1) in Table 3, has slightly increased, by 4.5 kcal/mol. This is typical, although not exclusive, IQA signature of atoms directly involved in the stabilizing interaction when a classical H-bond is formed.³³
- The intrafragment interaction energy, (2) in Table 3, which in this case describes a diatomic interaction energy, has changed in a stabilizing manner by a large value of –40.5 kcal/mol, from –50.4 in the **Lin** conformer to –90.9 kcal/mol in the **LEC**.
- \mathcal{F} became highly stabilized in the **LEC**, by –36.0 kcal/mol, (3) in Table 3.

- d) Interactions between atoms of \mathcal{G} and all remaining atoms of glycol, (4) in Table 3, changed in highly unfavourable manner, by +56.1 kcal/mol.
- e) The last descriptor, $E_{\text{attr-mol}}^{\mathcal{G}}$, clearly demonstrates that this fragment has increased the molecular energy of the **LEC** by +20.1 kcal/mol, (5) in Table 3.

Table 3. FAMSEC-based description of the {O4--H6} and {O3-H6--O4-C1} molecular fragments in the **LEC** conformer showing $\Delta E_{\text{self}}^{\mathcal{G}}$ as (1), $\Delta E_{\text{int}}^{\mathcal{G}}$ as (2), $E_{\text{attr-loc}}^{\mathcal{G}}$ as (3), $\Delta E_{\text{int}}^{\mathcal{G}/f}$ as (4), and $E_{\text{attr-mol}}^{\mathcal{G}}$ as (5). These indices were computed on the **Lin**→**LEC** structural change at the CCSD, CCSD(T) and MP2 levels of theory using the BBC1, BBC2 and Müller approximations. All values are in kcal/mol.

Level of theory	{O4...H6}					{O3-H6...O4-C1}				
	(1)	(2)	(3)	(4)	(5)	(1)	(2)	(3)	(4)	(5)
BBC1										
CCSD	4.5	-40.5	-36.0	56.1	20.1	1.1	2.7	3.8	-23.1	-19.3
CCSD(T)	5.1	-39.9	-34.8	54.5	19.7	2.2	2.9	5.1	-24.4	-19.3
MP2	5.8	-41.5	-35.8	58.5	22.8	2.9	1.7	4.6	-20.2	-15.5
Avr:	5.1	-40.6	-35.5	56.4	20.8	2.1	2.4	4.5	-22.5	-18.0
Std.Dev.	0.6	0.8	0.7	2.0	1.7	0.9	0.7	0.6	2.2	2.2
BBC2										
CCSD	3.9	-40.6	-36.7	55.2	18.5	0.2	2.2	2.4	-24.1	-21.7
CCSD(T)	4.4	-39.9	-35.5	53.5	18.0	1.2	2.3	3.4	-25.3	-21.9
MP2	5.5	-41.6	-36.1	57.5	21.4	1.6	0.9	2.5	-20.1	-17.6
Avr:	4.6	-40.7	-36.1	55.4	19.3	1.0	1.8	2.8	-23.2	-20.4
Std.Dev.	0.8	0.8	0.6	2.0	1.9	0.7	0.8	0.6	2.7	2.4
Müller										
CCSD	6.1	-40.4	-34.3	58.2	23.9	3.3	3.9	7.2	-21.4	-14.2
CCSD(T)	6.5	-40.0	-33.5	57.7	24.2	3.6	4.2	7.9	-22.1	-14.2
MP2	6.5	-41.3	-34.8	60.3	25.5	4.2	3.7	7.9	-20.5	-12.6
Avr:	6.4	-40.6	-34.2	58.7	24.5	3.7	3.9	7.7	-21.3	-13.7
Std.Dev.	0.2	0.7	0.6	1.4	0.9	0.5	0.3	0.4	0.8	0.9

Looking at the CCSD(T) and MP2 data in Table 3, when BBC1 approximation was used, it is clear that, relative to the CCSD/BBC1 data, negligible differences in all five FAMSEC descriptors are observed. Hence, not only qualitative but also quantitative interpretation obtained at CCSD(T) and MP2 levels is fully comparable with that obtained at CCSD.

It was then of great interest and importance to find out how the above interpretation would change with the use of the BBC2 and Müller approximations. Data in Table 3 reveals that, regardless of the LoT/LoA combination used, we would arrive at exactly the same description as

obtained at the best performing CCSD/BBC1. For instance, the {H6...O4} fragment (i) has been stabilized, on average, by $E_{\text{attr-loc}}^{\mathcal{F}} = -35.5 \pm 0.7$ kcal/mol using BBC1 and very much comparable values were obtained for the BBC2 and Müller approximations, -36.1 ± 0.6 and -34.2 ± 0.6 kcal/mol, respectively, (ii) destabilized the **LEC**, on average by $E_{\text{attr-mol}}^{\mathcal{F}}$ of 20.8 ± 1.7 , 19.3 ± 1.9 and 24.5 ± 0.9 kcal/mol for the BBC1, BBC2 and Müller approximation, respectively. The origin of this ‘excellent’ set of data, which appears to be insensitive toward either the LoT or LoA will be explored in the dedicated section.

Description of the O3–H6...O4 interaction. We will briefly explore the interaction between H6 and O4 using the $\mathcal{F} = \{\text{O3}, \text{O4}, \text{H6}\}$ fragment. Figure 6 shows that, relative to the 2-atom fragment (Table 3), two major changes took place and, importantly, they agree with chemists’ general knowledge and intuition; this 3-atom fragment:

- Experienced more attractive molecular environment when in the **LEC** as exemplified by more attractive interfragment interactions, $\Delta E_{\text{int}}^{\mathcal{F}, \mathcal{F}'} < 0$, and
- Has stabilised **LEC**, relative to the **Lin** conformer, as recovered from $E_{\text{attr-mol}}^{\mathcal{F}} = -9.5$ kcal/mol at CCSD/BBC1.

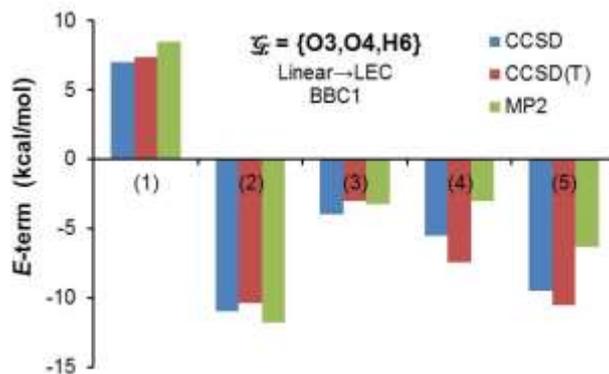


Figure 6. Energy terms $\Delta E_{\text{self}}^{\mathcal{F}}$ as (1), $\Delta E_{\text{int}}^{\mathcal{F}}$ as (2), $E_{\text{attr-loc}}^{\mathcal{F}}$ as (3), $\Delta E_{\text{int}}^{\mathcal{F}, \mathcal{F}'}$ as (4) and $E_{\text{attr-mol}}^{\mathcal{F}}$ as (5) computed for the $\mathcal{F} = \{\text{O3}, \text{O4}, \text{H6}\}$ fragment at the indicated level of theory using the BBC1 approximation for the **Lin** \rightarrow **LEC** structural change of glycol.

Exactly the same qualitative description one would also obtain from any combination of LoT/LoA – see Table S1 in the ESI. However, the quality of approximation starts to play a role in this case as, relative to CCSD/BBC1, quite different values were obtained and particularly so in the case of Müller approximation. As an example, the {O3–H6...O4} fragment was stabilized by, on average for three LoTs tested, -3.4 ± 0.5 kcal/mol using BBC1 but hardly so using Müller

approximation that predicted $E_{\text{attr-loc}}^{\mathcal{F}}$ to be -1.1 ± 0.3 kcal/mol. Moreover, this fragment added to stability of the **LEC** -8.8 ± 2.2 kcal/mol (BBC1) but the $E_{\text{attr-mol}}^{\mathcal{F}}$ term computed using Müller approximation was only -3.1 ± 0.7 kcal/mol.

Description of the O3–H6...O4–C1 interaction. A full set of data obtained for all LoT/LoA combinations is included in Table 3 (see also Figure S18 in the ESI for pictorial representation). Comparison of descriptors obtained for the 2-, 3- and 4-atom fragments, where directly interacting atoms are included, clearly shows that the size of a fragment might have a significant impact on interpretation. Not only the values but also the sign (hence the nature, stabilizing or otherwise) can change. For instance, signs of four descriptors computed for the {O3–H6...O4–C1} fragment changed relative to data obtained for the {H6...O4} fragment. Possibly counter-intuitively, the {O3–H6...O4–C1} fragment became destabilized in the **LEC** ($E_{\text{attr-loc}}^{\mathcal{F}} > 0$) on the intramolecular H-bonding. However, the 4-atom representation of the intramolecular H-bonding produced more significant contribution toward stability of the **LEC** with $E_{\text{attr-mol}}^{\mathcal{F}} = -18.0 \pm 2.2$ kcal/mol, over twice as much as found from the X–H...Y representation (data for the BBC1 approximation).

To conclude, it is important to stress that the FAMSEC-based general physical description of this bonding interaction is not influenced by the selection of either the LoT or approximation. Two general notions were fully recovered:

1. A fragment made of two atoms involved in highly attractive interaction becomes locally stabilised. To this effect, averaged over all LoTs value of $E_{\text{attr-loc}}^{\mathcal{F}}$ for the {O4...H6} fragment in **LEC** was found to be -35.5 , -36.1 and -34.2 kcal/mol from BBC1, BBC2 and Müller approximation, respectively (Table 3). Even by combining data for all LoT/LoA combinations we obtained very consistent picture with rather insignificant variation in the $E_{\text{attr-loc}}^{\text{O4,H6}}$ term, -35.3 ± 1.0 kcal/mol; similar applies to the two components of $E_{\text{attr-loc}}^{\text{O4,H6}}$, namely $\Delta E_{\text{self}}^{\text{O4,H6}}$ and $\Delta E_{\text{int}}^{\text{O4,H6}}$, for which we obtained $+5.4 \pm 0.9$ and -40.6 ± 0.7 kcal/mol, respectively.
2. The intramolecular H-bond (using either 3- or 4-atom representation) is stabilizing the molecule. For instance, we found that the averaged over all LoTs and approximations $E_{\text{attr-mol}}^{\mathcal{F}}$ term of -17.4 ± 3.4 kcal/mol (computed for the {X–H...Y–Z} fragment) can be used to explain why the **LEC** is more stable than the **Lin** conformer. Moreover, the origin of $E_{\text{attr-mol}}^{\mathcal{F}} < 0$ was

consistently attributed to more favourable molecular environment in the **LEC** as, on average for all LoT/LoA combinations, we obtained $\Delta E_{\text{int}}^{\mathcal{F},\mathcal{H}}$ of -22.3 ± 2.0 kcal/mol.

Linear→**Eclipsed structural change**. The steric clash between O-atoms in the **Ecl** conformer, the {O3,O4} fragment, is an obvious selection for FAMSEC-based investigation. Moreover, we have also decided to investigate {O3,O4,H5,H6} because (i) it is made of two chemically meaningful O–H functional groups, (ii) analysis of data obtained for the **Lin**→**LEC** structural change strongly suggests that better (or more reliable) results are obtained for 3- or 4-atom fragments, and (iii) this affords us an additional fragment to analyse the influence of approximation on the reliability and consistency of FAMSEC-based interpretation. A full set of descriptors obtained for the two fragments is presented in Table 4 and, for illustration purposes, pictorial representation of data obtained is shown in Figures S19–S20 in the ESI.

Table 4. FAMSEC-based description of the {O3--O4} and {H5–O4--O3–H6} molecular fragments in the **Ecl** conformer showing $\Delta E_{\text{self}}^{\mathcal{F}}$ as (1), $\Delta E_{\text{int}}^{\mathcal{F}}$ as (2), $E_{\text{attr-loc}}^{\mathcal{F}}$ as (3), $\Delta E_{\text{int}}^{\mathcal{F},\mathcal{H}}$ as (4), and $E_{\text{attr-mol}}^{\mathcal{F}}$ as (5). These indices were computed on the **Lin**→**Ecl** structural change at the CCSD, CCSD(T) and MP2 levels of theory using the BBC1, BBC2 and Müller approximations. All values are in kcal/mol.

Level of theory	{O3- -O4}					{H5–O4- -O3–H6}				
	(1)	(2)	(3)	(4)	(5)	(1)	(2)	(3)	(4)	(5)
	BBC1									
CCSD	-1.7	18.0	16.3	-6.3	10.0	-4.9	11.8	6.9	4.6	11.5
CCSD(T)	-1.2	17.4	16.2	-5.9	10.2	-4.3	11.3	7.1	4.7	11.8
MP2	-0.9	18.0	17.1	-6.5	10.6	-4.0	11.6	7.6	5.0	12.7
Avr:	-1.3	17.8	16.5	-6.3	10.3	-4.4	11.6	7.2	4.8	12.0
Std.Dev.	0.4	0.4	0.5	0.3	0.3	0.5	0.3	0.4	0.2	0.6
	BBC2									
CCSD	-2.4	16.6	14.1	-5.2	8.9	-5.6	10.3	4.6	5.8	10.4
CCSD(T)	-1.9	15.8	13.9	-4.9	9.1	-4.9	9.7	4.8	5.9	10.6
MP2	-0.9	17.0	16.1	-6.4	9.8	-3.9	10.4	6.6	5.3	11.8
Avr:	-1.7	16.5	14.7	-5.5	9.2	-4.8	10.1	5.3	5.6	11.0
Std.Dev.	0.8	0.6	1.2	0.8	0.5	0.9	0.4	1.1	0.3	0.8
	Müller									
CCSD	-1.3	19.7	18.4	-6.3	12.0	-4.8	13.5	8.7	4.6	13.4
CCSD(T)	-0.9	19.1	18.2	-5.8	12.4	-4.3	13.0	8.7	5.1	13.8
MP2	-0.7	19.5	18.8	-6.6	12.3	-4.1	13.0	8.9	5.3	14.2
Avr:	-1.0	19.4	18.5	-6.2	12.2	-4.4	13.2	8.8	5.0	13.8
Std.Dev.	0.3	0.3	0.3	0.4	0.2	0.4	0.3	0.1	0.3	0.4

Analysis of the data (Tables 4) confirms again that any combination of LoT/LoA can be used to obtain physically sound interpretation. We will briefly discuss data for the $\mathcal{F} = \{\text{H5-O4--O3-H6}\}$ molecular fragment containing clashing O-atoms as it generated more consistent and convincing picture (see Figure S20 in the ESI) illustrating an impact of the steric clash on molecular stability.

Let us firstly note that the self-energy of the fragment decreased, on average over all LoT and approximations, by -4.5 ± 0.6 kcal/mol, (1) in Table 4, which is an opposite trend to that observed for a bonding interaction. All the remaining descriptors, (2) to (5) in Table 4, are positive and this resulted in perfectly consistent interpretation. Looking at the averaged for all LoT values obtained for the BBC1 approximation we conclude that this fragment: (i) experienced less attractive intrafragment interaction energies, $+11.6 \pm 0.3$ kcal/mol, due to more repulsive, by $+17.8 \pm 0.4$ kcal/mol, interaction between clashing O-atoms; (ii) became destabilized in the **Ecl** conformer; hence, relative to the **Lin** conformer, became strained, $E_{\text{attr-loc}}^{\mathcal{F}} = +7.2 \pm 0.4$ kcal/mol; (iii) has less favourable molecular environment in the **Ecl** conformer as interfragment interaction energies became less attractive, $\Delta E_{\text{int}}^{\mathcal{F}f} = +4.8 \pm 0.2$ kcal/mol; and finally (iv) has destabilized **Ecl** conformer, $E_{\text{attr-mol}}^{\mathcal{F}} = +12.0 \pm 0.6$ kcal/mol, which agrees with commonly accepted notion.

It is important to note that all averaged descriptors at the BBC1 approximation are characterised by a small standard deviation (much below 1 kcal/mol). From this follows that there is no obvious gain in using so expensive CCSD and CCSD(T) levels as MP2 has generated the same quality description of this fragment role in relative stability of glycol conformers. As a matter of fact, physically sound picture emerged at all approximations with very much comparable quantitative interpretation. This is clearly supported by averaged over all LoT/LoA combinations values of -4.5 ± 0.6 , $+11.6 \pm 1.3$, 7.1 ± 1.6 , 5.1 ± 0.5 , and 12.2 ± 1.3 kcal/mol that were obtained for the $\Delta E_{\text{self}}^{\mathcal{F}}$, $\Delta E_{\text{int}}^{\mathcal{F}}$, $E_{\text{attr-loc}}^{\mathcal{F}}$, $\Delta E_{\text{int}}^{\mathcal{F}f}$, and $E_{\text{attr-mol}}^{\mathcal{F}}$ energy terms, respectively.

The origin of FAMSEC data ‘insensitivity’ toward the LoT and LoA. Data in Table 1 illustrates large errors in IQA-computed molecular energy. The main origin of $\Delta E_{\text{IQA,E}} \neq 0$ is indicated in Table 2; it shows that errors in the total self-molecular energy can reach a staggering value of -180 kcal/mol by use of Müller approximation, even at the CCSD level for a 10-atom molecule. Unfortunately, errors in individual self-atomic energies are not distributed evenly and Figure 4 revealed that they can reach a value of up to 50 kcal/mol when Müller approximation is

used. Moreover, errors in individual diatomic interaction energies can be in the range of ± 8 kcal/mol, regardless of the LoT (Figures S8-S16 in the ESI).

Then, how is that possible that (i) the FAMSEC data provided a valid and physically sound description of any molecular fragment discussed above and (ii) FAMSEC-defined descriptors did not differ dramatically among all LoT/LoA combinations. The answer is surprisingly simple when one realizes that FAMSEC is a relative approach where data obtained for fragments of interest are compared with the data obtained for the same fragments in the *ref*-state of the molecule. This means that for both molecules (*fin*-state and *ref*-state):

- a) Atomic composition of selected fragments and their size are exactly the same.
- b) Errors in computed either self-atomic or diatomic interaction energies are comparable for the same atoms in the two states of a molecule.
- c) Parameters selected for computing IQA-defined energy terms are the same throughout; hence, relevant numerical errors should (to a large degree) cancel out in computing changes taking place on *ref*-state \rightarrow *fin*-state structural change of a molecule.
- d) As this study shows, each approximation (or functional used to approximate 2EDM) is introducing a specific but extremely consistent errors in both, *ref*- and *fin*-state of a molecule; these errors largely (nearly entirely) cancel out in the FAMSEC analysis.

To illustrate the above points, let us analyse selected properties computed for the **Lin** \rightarrow **LEC** conformational change at most affordable, when the associated cost of computations on real-life molecules goes, MP2 level using the worst performing Müller approximation. Figure S21 in the ESI shows relatively small, just few kcal/mol, variations in self-atomic energies even though errors in the individual self-atomic energies were between +30 (for C-atoms) and + 50 (for O-atoms) kcal/mol for all conformers. Due to error cancellation, however, the computed ($\Delta E_{\text{self}}^{\text{X}}$)_{MP2/Müller} values reproduced those from CCSD/BBC1 to a small fraction of kcal/mol – see Figure S22 in the ESI. Furthermore, (i) changes in diatomic interactions of up to ± 35 kcal/mol were computed at our reference CCSD/BBC1 level (Figure S23 in the ESI) and (ii) errors in computed individual interaction energies in each conformer were up to ± 8 kcal/mol at MP2 for all approximations. However, as shown in Figure S24 in the ESI, the trends in the $\Delta E_{\text{int}}^{\text{X,Y}}$ values obtained at CCSD/BBC1 were reproduced well at the MP2/Müller level, to within ± 1 kcal/mol. Clearly, the MP2/Müller level generated at least tolerable, if not negligible, departures from the CCSD/BBC1 computed $\Delta E_{\text{self}}^{\text{X}}$ and $\Delta E_{\text{int}}^{\text{X,Y}}$ values even though, on average for all conformers of

glycol, $\Delta E_{\text{IQA,E}}$ of -167.1 ± 1.0 kcal/mol was obtained that nearly perfectly mimics the value of the $\Delta V_{\text{ec}}^{\text{Tot}}$ term, -167.3 ± 1.1 kcal/mol.

All the above leads us to the following conclusions and recommendations applicable to solely comparative studies, such as the FAMSEC method. To monitor and explain changes in, e.g., intra- and intermolecular bonded and non-bonded interactions, qualitatively and quantitatively with accuracy comparable to that of CCSD/BBC1 level, it should be sufficient to perform IQA calculations using much cheaper MP2/BBC1, or even MP2/Müller combination that is already implemented in AIMAll. Moreover, this is not the departure of $\Delta E_{\text{IQA,E}}$ from zero to be concerned the most, but rather the difference between $E(\text{IQA})$ computed for the *fin*-state and *ref*-state of the molecular system – this is clearly demonstrated in the ESI, Section ‘Importance of $\Delta E(\text{IQA}) \approx 0$ in the FAMSEC analysis’. Hence, we propose here a simple criterion to assess quality of the IQA data when employed in the *comparative analysis*, namely $\Delta E(\text{IQA}) \approx \Delta E$, where both terms are computed as (value in the *fin*-state) minus (value in the *ref*-state).

One must realize that, unfortunately, using the MP2/Müller combination does not allow one to gain a trustworthy insight on two-body properties in either *fin*- or *ref*-state of a molecule under investigation. This is because the errors in computed energy terms are unknown and might be large. Clearly, to learn about fundamental properties of a molecule one must use the BBC1 approximation and with an increase in the level of theory more accurate IQA data can be obtained.

5. CONCLUSIONS

The use of an exact form of 2EDM in IQA analysis implies unpractical (or unaffordable) computational cost when real-life molecules are concerned. This is the reason why IQA is hardly used. In order to overcome the need of the exact 2EDM, numerous approximations were proposed but there is very little known about these approximations influence on the quality and reliability of the IQA data. In this study we decided to investigate three, BBC1, BBC2 and Müller, approximations using, as a case study, three conformers of glycol (10-atom molecule). Our motivation steams from the fact that only the Müller approximation is implemented in most frequently used AIMAll software, which is dedicated to topological analyses but many approximations to exact 2PDM, among them BBC1 and BBC2 functionals, are implemented in TWOe software. For each level of theory and approximation (LoT/LoA) combination, the quality of (i) fundamental IQA-computed properties and (ii) their changes caused by a structural

transformation from the linear to either lowest energy (**Lin** → **LEC**) or eclipsed conformer (**Lin** → **Ecl**) was assessed using the CCSD/BBC1 data as a reference.

The electronic energy of glycol was recovered to 0.01% at MP2/BBC1 (E was overestimated by about -14 kcal/mol). An order of magnitude larger errors were generated at the Müller approximation with $\Delta E_{\text{IQA},E} = E(\text{IQA}) - E$ of about -170 kcal/mol for all LoTs. In search for the origin of $\Delta E_{\text{IQA},E} \neq 0$ we have established that the main contribution comes from the $\Delta V_{\text{ee}}^{\text{Tot}} = V_{\text{ee}}^{\text{IQA,Tot}} - V_{\text{ee}}^{\text{Exact,Tot}}$ term (it accounts for all one- and two-centre electron-electron interaction energy components). This resulted in the errors of up to $+50$ kcal/mol and ± 10 kcal/mol computed at all LoTs for self-atomic and diatomic interaction energies, respectively, when the Müller approximation was used. Hence, to gain a reasonable insight on significance of individual IQA-defined energy terms, the BBC1 rather than commonly used Müller approximation should be used in the IQA calculations.

To examine accuracy in FAMSEC-defined descriptors we have investigated the O4--H6 and O3--O4 contacts in the **LEC** and **Ecl** conformers, respectively. Data obtained from CCSD/BBC1 level were reproduced qualitatively (exactly) and quantitatively (well) at all LoT/LoA combinations. Hence the physical picture obtained at the CCSD/BBC1 level was fully recovered and relative stability of conformers explained correctly. To this effect, the averaged over all LoTs stabilizing energy contributions made by the {O3–H6...O4–C1} fragment in the **LEC** was found to be -18.0 ± 2.2 , -20.4 ± 2.4 and -13.7 ± 0.9 kcal/mol for, respectively, BBC1, BBC2 and Müller approximation; this is in fully agree with chemists intuition and general knowledge when stabilizing contribution of intramolecular H-bonding is considered. Focusing on the {H5–O4--O3–H6} fragment containing a steric O--O clash in the **Ecl** conformer, we found that (i) its self-energy decreased, on average over all LoT and approximations by -4.5 ± 0.6 kcal/mol, which is an opposite trend to that observed for a bonding interaction and (ii) it has destabilized this conformer (by $+12.0 \pm 0.6$ (LoT/BBC1) and $+13.8 \pm 0.4$ (LoT/Müller) kcal/mol), which is in perfect agreement with a commonly accepted notion.

We have established that the FAMSEC-defined descriptors do not differ ‘dramatically’ among all LoT/LoA combinations because: (i) atomic composition of selected fragments and their sizes are exactly the same; (ii) errors in computed either self-atomic or diatomic interaction energies are comparable for the same atoms in the two states of a molecule; (iii) parameters selected for computing IQA-defined energy terms are the same for all conformers; hence, consistent in value numerical errors are generated; (iv) each approximation generates consistent errors in the *ref-*

and *fin*-state of a molecule. As a result, all these errors nearly entirely cancel out when changes in the IQA-defined energy terms are computed on the *ref*-state \rightarrow *fin*-state structural transformation of a molecule. Because of that, the FAMSEC-based interpretations (qualitative and quantitative) at all LoT/LoA combinations appeared to be highly comparable even though, in most instances, molecular energy was not reproduced well by IQA terms.

We have shown that reliability of the comparative analyses, such as FAMSEC, can be estimated by comparing $\Delta E(\text{IQA}) = E(\text{IQA})_{\text{fin-state}} - E(\text{IQA})_{\text{ref-state}}$ against $\Delta E = E_{\text{fin-state}} - E_{\text{ref-state}}$. Hence, a new criterion is proposed here, namely $\Delta E(\text{IQA}) \approx \Delta E$. Our results strongly suggest that the closer $\Delta E(\text{IQA})$ approaches ΔE the closer FAMSEC data obtained at any LoT/LoA combination approach the values obtained at CCSD/BBC1 level. Finally, we (i) recommend MP2/BBC1 combination because it is most affordable (computationally) and reproduced the CCSD/BBC1 FAMSEC data very well and (ii) showed that the Müller approximation implemented in AIMAll has generated reasonable FAMSEC-defined descriptors.

Acknowledgments

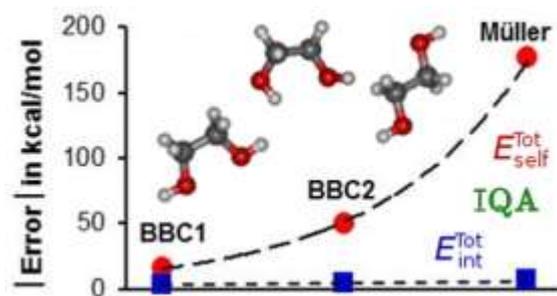
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The BBC1 approximation is recommended for the IQA calculations; MP2/BBC1 and CCSD/BBC1 produced highly comparable FAMSEC-based interpretations of intramolecular interactions.