

Emerging conformational analysis protocols from the RTCONF-16K reaction thermochemistry conformational benchmark set

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Abstract

Here, we provide a new, reactive conformational analysis benchmark set (RTCONF-16K) based on state-of-the-art and cost-efficient methods to assess different protocols. Our comprehensive reference calculations were used to underpin the accuracy of the CENSO (JPCA, 2021, 4039) procedure and to provide alternative recipes with different cost-accuracy compromises. Our general-purpose and economical protocols (CENSO-light and zero, respectively), were found to be 10-30 times faster than the original algorithm while adding only 0.4-0.7 kcal/mol absolute error to the relative free energy estimates.

1 Introduction

Achieving high-quality results in computational chemistry relies significantly on systematic improbability. The level of electron correlation and basis set can be, in principle, converged systematically following Pople’s diagram.¹ Even the accuracy of the popular and cost-efficient Density Functional Theory (DFT) methods can be improved using the concept of Jacob’s Ladder^{2–4} and extensive benchmark studies,^{5–14} albeit the systematic approach is replaced to some extent with empiricism. Additionally, the terms beyond the non-relativistic treatment can be systematically addressed by opening an additional dimension of complexity (Csaszar’s cube).¹⁵ Consequently, as of today, accurate electronic structure calculations are possible at the (local) CCSD(T)/CBS level for molecules with over a hundred atoms,^{16,17} which can be augmented with cost-efficient thermal contributions via the rigid-rotor harmonic oscillator approximation.^{18–20} To reach chemical accuracy for free energy estimates,²¹ this correction can also be systematically improved by the vibrational perturbation theory.²²

However, if the thermochemistry of large flexible molecules is considered, free-energy differences between individual configurations cannot explain finite-temperature experiments. Instead, the relative stability of the two *corresponding conformational ensembles* will be relevant.^{23–25} With the advent of low scaling and economical semiempirical methods,^{26–29} this principle is gaining popularity and entering the mainstream of static quantum chemistry.^{25,30,31}

Although the conformational problem may appear more approachable than electronic structure calculations, it presents comparable challenges, as pointed out by Grimme et al.²⁴ Unlike quantum-chemistry methods, however, conformational sampling has no golden standard, results are difficult to systematically improve, its computational cost scales immensely with the increasing number of rotatable bonds,³² and is often not predictable. Accordingly, many different approaches exist for generating conformers and corresponding energetic ranking, both essential for uncovering the low-energy conformer space. Protocols can

be categorized based on their method of conformer generation, which can be done either in a stochastic or systematic manner.^{33,34} Stochastic approaches include, for example, molecular dynamics-based,^{35–38} Monte Carlo,^{39–41} distance geometry,^{42–44} and genetic algorithm^{45–47} methods. However, these methods generally suffer from a nonpredictable sampling time and the bias of initial geometry.³⁴ Alternatively, conformers can be generated systematically by varying the torsional angles, but this becomes very soon unfeasible due to the exponential scaling of the problem. More advanced systematic tools restrain the conformer space by applying cheminformatic rules based on knowledge databases (usually derived from solid-state structure databases) to ensure efficiency.^{48–50} However, these rule-based approaches easily fail in the case of unknown systems.³⁴ Regardless of the method chosen for conformer sampling, employing force-field methods for geometry optimization and energetic ranking of conformers (e.g. AMBER,⁵¹ UFF,⁵² MMFF⁵³) result in significant errors,^{54,55} also they do not apply to transition metal complexes due to the lack of parametrization.⁵⁶ One usual approach is to refine energies obtained from low-level MM/QM calculations on the lowest energy conformer.^{57,58} This can be improved by selecting a larger set of low-energy conformers to refine. Multilevel workflows have been developed for this purpose, leveraging a funnel-like strategy that utilizes a series of methods, each progressively more accurate to predict chemical properties such as pK_a values.^{59–61} One outstanding example of these approaches, the CRENSO protocol enables efficient, general metadynamics-based conformational sampling using CREST,^{62,63} and further refinement of the ensemble starting from the semiempirical GFN2-xTB level to more accurate DFT functionals in CENSO.^{24,64} This has proven to be a robust tool for the prediction of dynamic molecular properties in solution, such as NMR shift,^{65,66} optical rotation,⁶⁷ and conformational entropy^{68,69} for large flexible molecules.

The accuracy of applied quantum mechanics (QM) methods is a pivotal factor in determining the overall performance of a multilevel protocol. Recent years have seen efforts to assess the performance of many Density Functional Theory (DFT) functionals through benchmark calculations, particularly with regard to relative conformer energies^{5,10,24,56} and

conformational entropy of individual molecules.^{68,70–73} Additionally, some studies have applied conformational analysis to investigate specific chemical reactions, highlighting the significance of including conformational entropy to predict reaction-free energies.^{68,74,75}

However, despite the above-mentioned advancements, there is no publicly available dataset or systematic study to evaluate the precision of different protocols for predicting reaction-free energies, including conformational flexibility. Although different CREST-based methods are emerging for mechanistic investigations of complex organocatalytic reactions,^{30,76–79} they face key challenges: they are either expensive or contain simplifications of the protocol, that may introduce unknown and uncontrolled errors, while the computational savings from such simplifications are unexplored.

Given the instrumental nature of this problem and potentially achievable savings in computational power, we have assembled a versatile reactive conformational thermochemistry benchmark set based on challenging chemical reactions of flexible molecules, where conformational space might significantly change throughout the transformation (e.g., due to ring-closures). These reactions have been supplemented with organic (ISOL24)¹⁴ and organometallic (MOBH36)¹² reactions to yield our final collection (here termed RTCONF-16K), consisting of 55 diverse chemical reactions with over 16 000 DFT optimized conformers in total (see Supp. for more details and Figure 4 for representative examples). Using this data, we are putting forward new variants of the CENSO protocol that provide large computational savings with moderate loss in accuracy.

2 Methodology

To calculate reaction-free energies between two ensembles, we introduce the Gibbs-free energy of a conformational ensemble:^{24,68,70,74,80,81}

$$G_{\text{ens}} = \overline{G} - TS'_{\text{conf}}, \quad (1)$$

where \overline{G} denotes the average free energy of individual conformers, T is the thermodynamic temperature, and S'_{conf} is the conformational entropy. This expression can be transformed via a short derivation (see Appendix) to a sum of the free energy of a representative (typically the lowest energy) structure (G^0) and an additive term that describes the entropic stabilization due to the population of multiple conformers

$$G_{\text{ens}} = G^0 + G_{\text{conf}}^{\text{rel}} \quad (2)$$

The latter can be expressed as $G_{\text{conf}}^{\text{rel}} = -RT \ln Z^{\text{rel}}$, where Z^{rel} is the partition function defined with the relative free energies of the conformers with respect to the representative configuration. Therefore, to assess the performance of a given conformational free energy estimation protocol, the importance and accuracy of these two terms have to be estimated.

To generate conformational ensembles for each state, we have used the CREST²⁴ program with GFN2-xTB in the iMTD-sMTD workflow, applying a 6.0 kcal/mol energy window.⁶² The sorting and optimization of the ensemble have been carried out using CENSO²⁴ together with Orca⁸² on different levels of theory (GGA and RSH) according to Jacob’s ladder of DFT (see Table 1, for more details, see the Supplementary Information). For all conformers, thermal contributions have been accounted for on the xTB//xTB level, as it was shown to predict changes in thermostatical correction with good accuracy.¹⁹ Given the fact that solvation of conformational ensembles was found to be crucial for the accurate description of flexible molecules,⁶⁹ we applied solvent models for calculations at all levels using DCM as a solvent.

Table 1: Applied electronic structure methods and abbreviations

level of theory	chosen methodology	role
xTB	GFN2-xTB, ²⁶ ALPB(DCM) ⁸³	conformational search
GGA	B97-3c, ^{27,84} CPCM(DCM) ⁸⁵	higher level SP and OPT
RSH	ω B97M-V ⁸⁶ /def2-TZVPP, ⁸⁷ CPCM(DCM) ⁸⁵	final SP

As the generation of an exact conformational ensemble is unfeasible, we accept the fol-

lowing protocol as the ground truth for our studies (here termed CENSO-brute-force). In this protocol, all conformers resulting from the CREST calculations have been optimized on the GGA level, and single-point energies were calculated on the RSH level for all conformers. This will be later referred to as the reference (see Table 2). In the method termed CENSO-zero, the lowest energy conformer according to the xTB sorted and xTB-optimized ensemble was selected and refined on the RSH//GGA level. In the CENSO-light protocol, the lowest-energy conformer was determined using GGA ranking in the xTB optimized ensemble.

Table 2: Applied conformational protocols. *Calculated on a narrowed ensemble **reference method

label	ensemble optimization	ensemble ranking	refinement
CENSO-zero	xTB	xTB	RSH//GGA
CENSO-light	xTB	GGA	RSH//GGA
CENSO-default	GGA*	RSH*	RSH//GGA
CENSO-brute-force**	GGA	RSH	RSH//GGA

In the method termed CENSO-default, we applied the default energy thresholds of this algorithm. The CENSO funnel-like sorting algorithm (see Figure 1) takes the xTB-optimized ensemble and performs a GGA//xTB level sorting to select conformers within a 4.0 kcal/mol threshold. Next, sequential ensemble optimization is performed, and optimized conformers are filtered based on their GGA//GGA level energies (part2, threshold=2.5 kcal/mol). Finally, the conformer energies within a 99% Boltzmann population sum are refined using RSH single-point calculations on the part2 ensemble (part3).

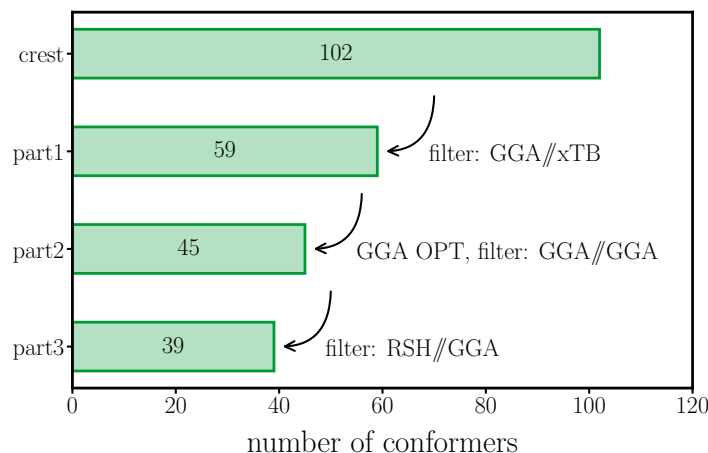


Figure 1: The sequence of different stages in the CENSO-default protocol and the corresponding number of conformers for reaction r34 (reactant and product conformers summed)

3 Results and Discussion

At the beginning of our study, we aimed to stress the importance of incorporating conformational analysis into static reaction modeling. To demonstrate this, we evaluated the errors that may arise from ignoring conformational sampling. We did this by calculating the reaction-free energies for the original geometries of the ISOL24 and MOBH35 benchmark sets (which were re-optimized using B97-3c), and then comparing these results to the reference lowest energy conformers. We also took into account the conformational entropy correction. The resulting errors are quite significant on average (MAE=2.6, RMSE=5.1 kcal/mol), and the maximum error is even more alarming (reaction r39, 20.5 kcal/mol). This is comparable to the additional error of using GGA functionals instead of RSH functionals when compared to local coupled cluster methods.¹² The large errors suggest that chemical reaction benchmark sets with flexible molecules do not represent the low-energy conformer space. In some cases, the initial geometry bias contributes to unacceptable errors (3 reactions that have an absolute error larger than 10 kcal/mol). The corresponding geometrical difference is also illustrated in Figure 2 for the highest error reaction r39, where a ruthenium complex shows

significant conformational change after conformational analysis has been performed both in the reactant and product states (for more details, see SI). This eye-opening finding suggests that comparisons of new methods with these computational benchmark sets implicitly measure performance on conformational and chemical dimensions in an entangled manner.

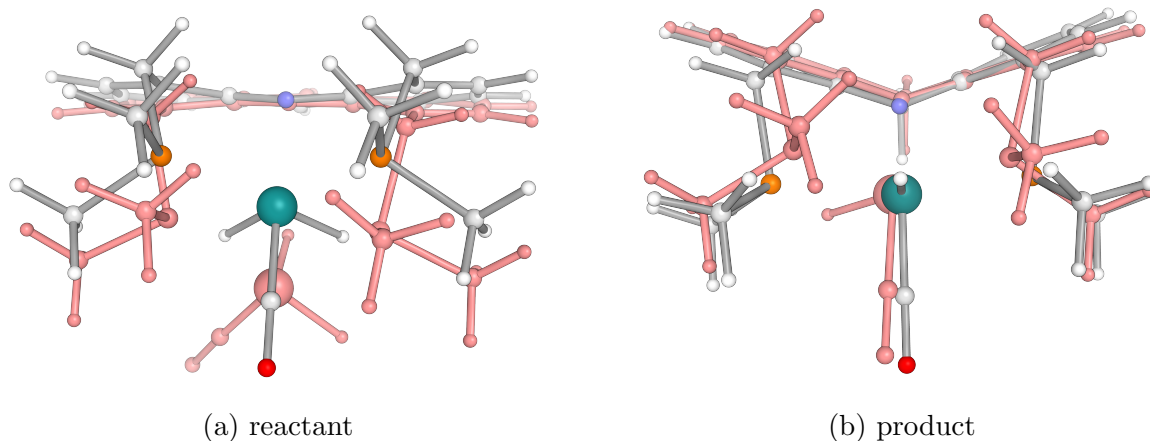


Figure 2: The lowest energy conformers of reactant and product states in r39, overlaid with the original structures (red). Atoms are shown in the respective coloring: teal-ruthenium, orange-phosphorus, red-oxygen, slate-blue-nitrogen, grey-carbon, and white-hydrogen.

Therefore, conformational analysis is essential when describing chemical reactions to accurately describe reaction-free energies and conformer geometries. However, the cost of conformational analysis might exceed the cost of demanding local-correlation single-point energy calculations. Therefore, one needs a recipe for efficient management of computational resources. To provide a cost-efficient approach, we have evaluated different protocols for the energetic sorting of the conformers. Additionally, we have also considered refining the lowest-energy conformer for each method.

Compared to the results when conformational analysis was omitted, even rudimentary energetic sorting of the conformers using semi-empirical xTB, we observed a significant improvement if the final refinement of the lowest energy conformer was done on the RSH//GGA level (CENSO-zero, MAE=0.9, MAX=10.5 kcal/mol). Further improvement is possible if the xTB-based conformer ensemble is sorted by GGA single-point energies (CENSO-light, MAE=0.6 kcal/mol, MAX=6.0 kcal/mol). Applying a whole ensemble optimization on the

GGA level, only a small improvement can be achieved compared to the immense cost of the calculation (see Figure 3). Finally, we have assessed the accuracy of a default funnel-like CENSO protocol. It resulted in a MAE of only 0.2 kcal/mol, while reducing the overall cost by half compared to the reference method, allowing impressive cost-efficiency (see Figure 3).

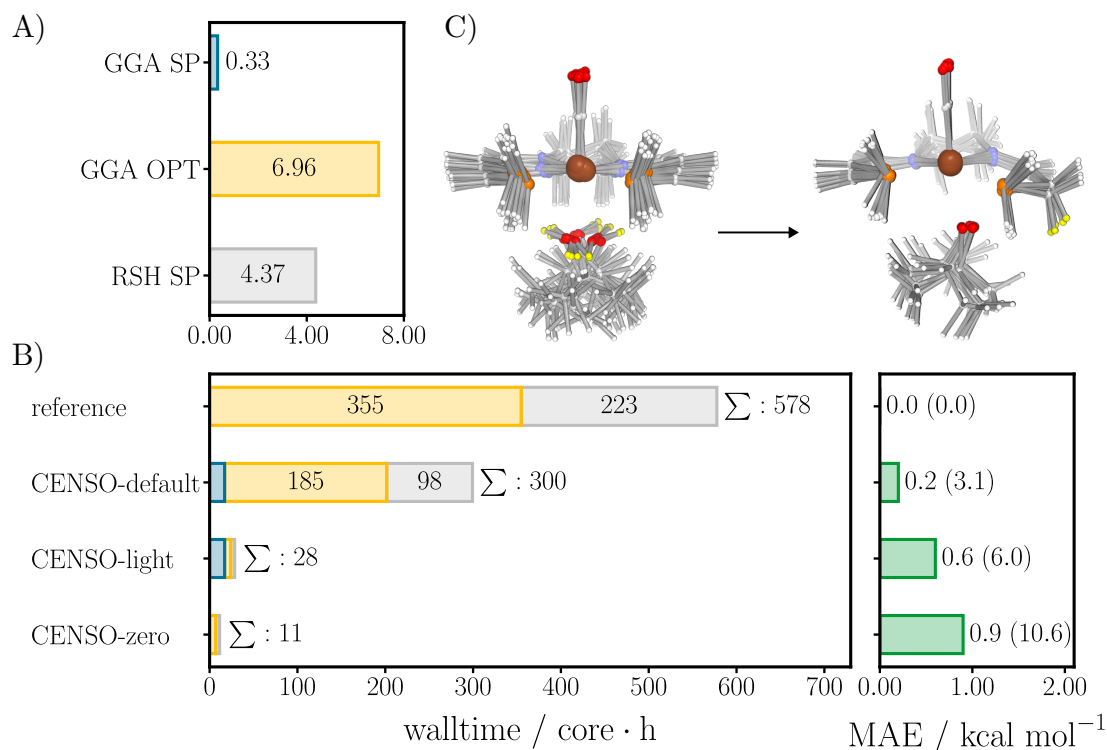


Figure 3: A) Respective timings of a GGA single-point (blue), GGA optimization (yellow), and RSH single-point calculations (gray) per conformer during a CENSO run in reaction r34 B) Timings of different conformer sorting approaches for reaction r34 (102 conformers in total) indicating the various parts of the calculations with the same colors as in panel A. The computational cost of CREST calculations (4.4 core·h) is committed for clarity. C) 3D structures of the reactant and product states of reaction r34 showing every 4th conformer. Hydrogens that are replaced throughout the reaction are highlighted in yellow. Atoms are shown in the respective coloring: brown-iron, orange-phosphorus, red-oxygen, slate-nitrogen, gray-carbon, and white-hydrogen.

In spite of computational gain through the efficient CENSO algorithm, the conformational analysis's relative cost is still ca. 25 times higher than the optimization and single-point energy calculation of the lowest-energy conformers. Compared to this, the method using GGA//XTB energetic sorting with RSH//GGA refinement on the lowest conformer (CENSO-

light) shows a very favorable cost-accuracy method that provides results with moderate to negligible errors. This method avoids the DFT optimization of the whole (or restricted) ensemble and requires more accurate single-point calculation only for the lowest energy conformer, which makes it a magnitude faster than CENSO-default (see Figure 3) at the cost of 0.4 kcal/mol additional error in MAE (0.6 kcal/mol), and a 2.9 kcal/mol increase in MAX (6.0 kcal/mol). With our present setup, this protocol is only three times more expensive, than omitting conformational analysis. Considering additional error terms in the applied methods (RSH DFT, solvent model, and thermostistical contributions), CENSO-light can include the conformer ensemble treatment with sufficient accuracy. Alternatively, the CENSO-zero method, which utilizes the xTB//xTB sorting approach, demonstrates a highly appealing cost-accuracy balance. In this case, the computational overhead beyond a standard DFT protocol (geometry optimization and accurate single-point energy evaluation) is minor as it is practically just an additional CREST calculation (4.4 core-h for reaction r34). It is worth mentioning that even this overhead can be sped up by a factor of 5-6 using GPU acceleration.⁸⁸ Although this protocol is characterized by larger errors than CENSO-light (MAE=0.9 kcal/mol), its low computational complexity makes it a viable option for quick exploration. Therefore, the additional computational demand of the CENSO-default can only be justified if final single-point energies are calculated using high-precision (e.g., wave-function) methods. For example, in the study of a multistep reaction mechanism, the cost-efficient CENSO-zero/light can be applied to each state to locate rate-determining states,⁸⁹ and then, a more demanding CENSO protocol might be applied to refine those states further. Additionally, by avoiding DFT-level ensemble optimization, it could also enable the conformer search for transition states in a straightforward way, which is currently very tedious due to the TS optimization of the ensemble.^{30,76,77} Evaluation of our protocols on TS structures is underway in our laboratory.

Finally, we aimed to examine the role of $\Delta_r G_{\text{conf}}^{\text{rel}}$ term individually in chemical reactions, as there has been no such systematic study to date. Our brute-force reference calculations

generally revealed that this term cancels out in most reactions, giving only a 0.8 kcal/mol average absolute value. However, there are significant exceptions, chemically speaking due to ring-transformation or other factors resulting in large changes of conformation degrees of freedom. In particular, in our examples, the ring-closure reactions have shown a positive $\Delta_r G_{\text{conf}}^{\text{rel}}$ between 0-2 kcal/mol (see Figure 4), and somewhat larger values in the double-ring closure of r03 and r06 (1.5 and 1.9 kcal/mol, respectively). Interestingly, for macrocyclic-ring closure of r02 we have obtained a lower $\Delta_r G_{\text{conf}}^{\text{rel}}$ value (0.5 kcal/mol). These results can be understood based on the change in the degree of freedom (DOF) in the rings.⁶⁸

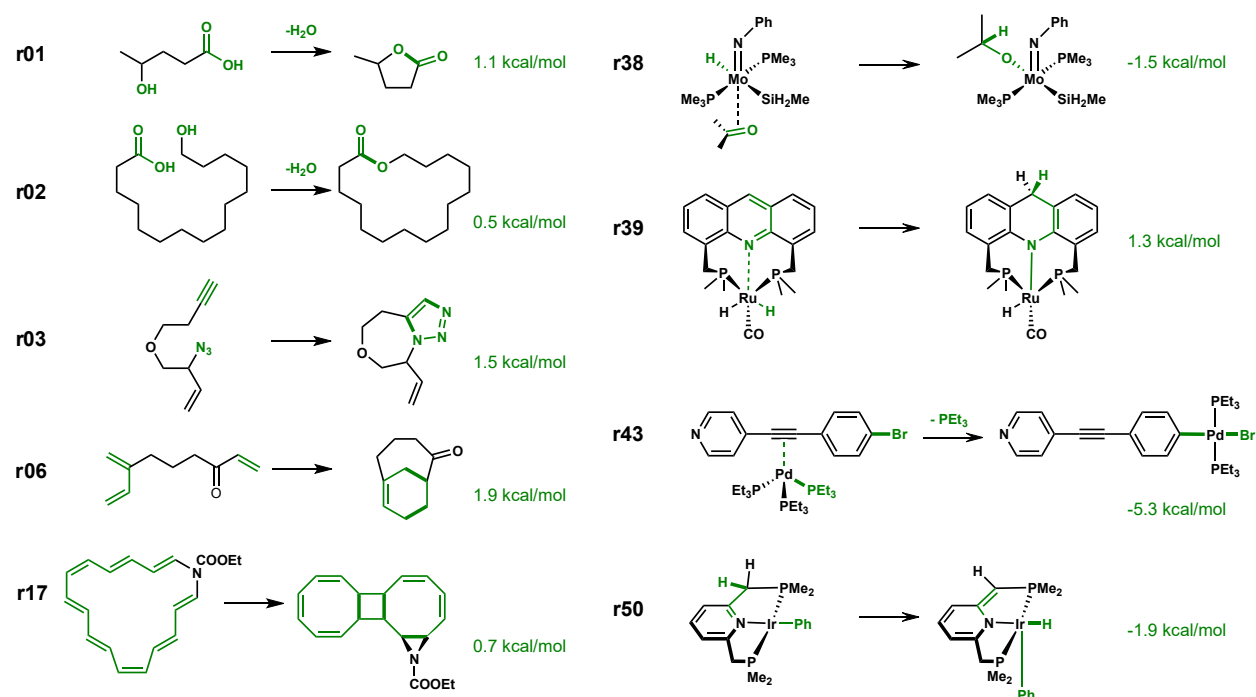


Figure 4: Selected reactions and the corresponding changes of the relative conformational free energies ($\Delta_r G_{\text{conf}}^{\text{rel}}$)

Remarkably, reactions involving the dissociation of a PEt_3 molecule show the largest magnitude of $\Delta_r G_{\text{conf}}^{\text{rel}}$ (r43, -5.3 kcal/mol error and r44, -6.2 kcal/mol error), which can be explained in two terms: First, the large increase in the DOF in PEt_3 after dissociation. Second, the decrease in coordination number and the relief in steric congestion around palladium.

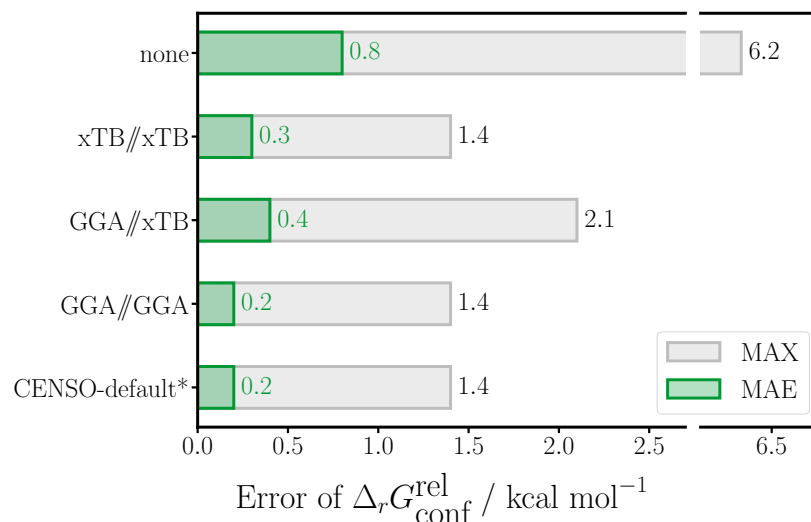


Figure 5: MAE and MAX errors of $\Delta_r G_{\text{conf}}^{\text{rel}}$ using different levels of energetic sorting *calculated based on the RSH//GGA level on the reduced ensemble of CENSO

Given that $\Delta_r G_{\text{conf}}^{\text{rel}}$ is a relatively small contribution, one might consider omitting its calculation. Although this approach comes with a moderate 0.8 kcal/mol MAE, the MAX errors are more significant (6.2 kcal/mol). Fortunately, evaluating this term on the cost-efficient xTB//xTB level (as in CENSO-zero), $\Delta_r G_{\text{conf}}^{\text{rel}}$ can be calculated accurately (MAE=0.3 kcal/mol) and importantly, it also shows good performance for outlier reactions, which is indicated by a favorable MAX error (1.4 kcal/mol). With increasing the applied level of theory, there is no significant improvement. Therefore, it can be concluded that calculating $\Delta_r G_{\text{conf}}^{\text{rel}}$ is necessary to achieve chemical accuracy.

4 Conclusions

In a systematic study, we generated a conformational database that features cost-efficient but reasonably accurate energies for over 16 000 conformers in total for 55 versatile reactions. Based on these well-converged conformational analyses, we have examined the role of different protocols in estimating chemical reaction-free energies. Our analysis has shown that the magnitude of $\Delta_r G_{\text{conf}}^{\text{rel}}$ is not significant on average, and a calculation based on xTB already

provides an accurate estimation (MAE=0.3 kcal/mol).

Furthermore, the most instrumental part of the conformational analysis was identifying a representative low-energy conformer through a cost-effective approach. It has been revealed that GGA level optimization of exclusively the lowest-energy conformer provides a good estimate of the geometric relaxation energy for the whole ensemble. Accordingly, we suggest the CENSO-zero protocol (MAE=0.9 kcal/mol, 30-40x speed-up compared to CENSO-default) if quick estimates are required (especially if GPU acceleration is available). The CENSO-light protocol is recommended for general-purpose conformational analysis, as it can achieve more accurate results (MAE=0.6 kcal/mol) while it keeps the computational overhead minimal (10x speed-up compared to CENSO-default). The most sophisticated CENSO-default approach (MAE=0.2 kcal/mol) becomes critical only when the final electronic energies are calculated using high-precision electron-correlation methods.

Finally, the necessity of conformational analysis for reactions involving flexible molecules has been confirmed. Our study has shown that some flexible-molecule benchmark sets do not represent the low-energy conformer space showing significant errors (MAE=2.6 kcal/mol, MAX=20.5 kcal/mol), comparable to substituting modern range-separated hybrid (RSH) functionals with inferior GGAs. Based on our study, these protocols are a must-have tool for a computational chemist and should be just as routinely applied as RSH functionals.

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6 Appendix

Here we describe the derivation for the free energy of a conformational ensemble. First, we introduce the partition function $Z = \sum_{j=1}^{n_{\text{rot}}} e^{-\frac{G_j}{RT}}$, and the population of rotamers in the ensemble p_j :

$$p_j = \frac{e^{-\frac{G_j}{RT}}}{\sum_{j=1}^{n_{\text{rot}}} e^{-\frac{G_j}{RT}}} \quad (3)$$

Where G_j is the molar free energy of rotamer j . Note that the summation over rotamers might be converted to a conformer-based one, as shown by Pracht and Grimme.⁶⁸ Therefore, we decompose the sum over rotamers to sums over subsets rotamers corresponding to a single conformer

$$\sum_{j=1}^{n_{\text{rot}}} e^{-\beta G_j} = \sum_{j=1}^{g_1} e^{-\beta G_j} + \sum_{j=g_1+1}^{g_1+g_2} e^{-\beta G_j} + \dots + \sum_{\sum_1^{i-1} g_i+1}^{n_{\text{rot}}} e^{-\beta G_j}, \quad (4)$$

where the number of rotamers that belong to the conformer i is labeled with g_i . Using that the energies of rotamers corresponding to one conformer are the same due to permutational symmetry, the partition sum simplifies to a sum over n_{conf} conformers:

$$\sum_{j=1}^{n_{\text{rot}}} e^{-\beta G_j} = \sum_{i=1}^{n_{\text{conf}}} g_i e^{-\beta G_i}. \quad (5)$$

Accordingly, the difference between rotamer and conformer populations must be considered. To this end, the conformational entropy can be written according to the Gibbs-Shannon equation. As all states have to be included, this must be done using the populations of individual rotamers (p_j) in a sum over all rotamers:

$$S'_{\text{conf}} = -R \sum_{j=1}^{n_{\text{rot}}} p_j \ln p_j = -R \sum_{j=1}^{n_{\text{rot}}} p_j \ln \left(\frac{e^{-\frac{G_j}{RT}}}{Z} \right) \quad (6)$$

$$= -R \sum_{j=1}^{n_{\text{rot}}} p_j \left(\ln \left(e^{-\frac{G_j}{RT}} \right) - \ln Z \right) \quad (7)$$

$$= R \sum_{j=1}^{n_{\text{rot}}} p_j \frac{G_j}{RT} + R \left(\sum_{j=1}^{n_{\text{rot}}} p_j \right) \ln Z = \frac{1}{T} \sum_{j=1}^{n_{\text{rot}}} p_j G_j + R \ln Z \quad (8)$$

Using the definition of average molar free energy: $\bar{G} = \sum_{j=1}^{n_{\text{rot}}} p_j G_j$.

$$S'_{\text{conf}} = \frac{\bar{G}}{T} + R \ln Z \quad (9)$$

Now substituting into the Gibbs free energy of the ensemble, G_{ens} :

$$G_{\text{ens}} = \bar{G} - T S'_{\text{conf}} = \bar{G} - T \left(\frac{\bar{G}}{T} + R \ln Z \right) = -RT \ln Z \quad (10)$$

From a numerical point of view, we factor out the free energy of a representative conformer G^0 (conveniently, the lowest energy one), and use only relative conformer free energies ΔG_j in the exponent, and name the resulting ΔG_j -based partition function Z^{rel} .

$$Z = \sum_{j=1}^{n_{\text{rot}}} e^{-\frac{G_j}{RT}} = \sum_{j=1}^{n_{\text{rot}}} e^{-\frac{\Delta G_j + G^0}{RT}} = \left(\sum_{j=1}^{n_{\text{rot}}} e^{-\frac{\Delta G_j}{RT}} \right) \cdot e^{\frac{G^0}{RT}} = Z^{\text{rel}} \cdot e^{\frac{G^0}{RT}} \quad (11)$$

Substituting this into G_{ens} , we get

$$G_{\text{ens}} = -RT \ln Z = G^0 - RT \ln Z^{\text{rel}} = G^0 + G_{\text{conf}}^{\text{rel}} \quad (12)$$

Alternatively, one might approximate the partition function using energies instead of free energies, and use thermic correction only on the representative conformer.

$$\sum_{j=1}^{n_{\text{rot}}} e^{-\frac{\Delta G_j}{RT}} \approx \sum_{j=1}^{n_{\text{rot}}} e^{-\frac{\Delta E_j}{RT}} \quad (13)$$

This might save a considerable computational time depending on the applied level of theory. However, it causes a comparable error (MAE=0.4 kcal/mol, MAX=1.5 kcal/mol) to

the value of $\Delta_r G_{\text{conf}}^{\text{rel}}$ (average absolute value of 0.8 kcal/mol, See Supporting Information for more details). To address this problem, we added ($G - E$) corrections on the xTB level for all conformers.²⁰

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