

# A Systematic Method to Estimate and Validate Enthalpies of Formation Using Error-Cancelling Balanced Reactions

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## Abstract

This paper presents an automated framework that uses overlapping subsets of reference data to systematically derive an informed estimate of the standard enthalpy of formation of chemical species and assess the consistency of the reference data. The theory of error-cancelling balanced reactions (EBRs) is used to calculate estimates of the standard enthalpy of formation. Individual EBRs are identified using linear programming. The first part of the framework recursively identifies multiple EBRs for specified target species. A distribution of estimates can then be determined for each species from which an informed estimate of the enthalpy is derived. The second part of the framework iteratively isolates inconsistent reference data and improves the prediction accuracy by excluding such data. The application of the framework is demonstrated for test cases from organic and inorganic chemistry, including transition metal complexes. Its application to a set of 920 carbon, hydrogen and oxygen containing species resulted in a rapid decrease of the mean absolute error for estimates of the enthalpy of formation of each species due to the identification and exclusion of inconsistent reference data. Its application to titanium-containing species identified that the available reference values of  $\text{TiOCl}$  and  $\text{TiO}(\text{OH})_2$  are inconsistent and need

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further attention. Revised values are calculated for both species. A comparison with popular high-level quantum chemistry methods shows that the framework is able to use affordable density functional theory (DFT) calculations to deliver highly accurate estimates of the standard enthalpy of formation, comparable to high-level quantum chemistry methods for both hydrocarbons and transition metal complexes.

*Keywords:* enthalpy of formation, heat of formation, error-cancelling balanced reactions, validation, thermochemical data, big data, algorithm, methodology, data consistency

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## 1. Introduction

The development of automated procedures, for analysing chemical species and mechanisms [1, 2, 3, 4, 5, 6], facilitate the investigation of progressively complex reaction systems. The availability of large sets of consistent chemical data is of key importance. Many data sets used by such tools are collated literature data [7, 8] that are held in repositories [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19] and are used for benchmarking computational methods [20, 21, 22, 23, 24, 25]. Alongside these opportunities there remain challenges. One question is concerned with the consistency of chemical data [see for example 26, 27, 28, 29, 30, 31]. Using accurate single-point level calculations to validate one species at a time is computationally demanding and quickly becomes intractable for large systems. This paper therefore presents a solution to this problem and provides a framework to systematically evaluate the consistency of thermochemical data for chemical species.

Consistent and accurate thermochemical data, such as species enthalpies, heat capacities, and Gibbs free energies, are an essential part of any detailed chemical model. The Active Thermochemical Tables (ATcT) [12, 32, 13, 33] for example define a network of known thermochemical data, which relies on multiple reported experimental measurements and accurate theoretical high-level estimates for each species. A final set of reference values is proposed by

processing the thermochemical network in a self-consistent fashion, until internal consistency is achieved. The uncertainties of the reference values are used to weight the contribution of each reference value within the thermochemical network. The systematic combination of multiple reference values allows for accurate and internally consistent estimates of thermochemical data.

The standard enthalpy of formation is a fundamental parameter required to calculate accurate values of the enthalpy and Gibbs free energy changes of the reactions in a chemical model. Inconsistencies in the standard enthalpy of formation could lead to significant errors affecting the accuracy, predictive performance and quality of any model using such data.

In the past, different methods have been introduced to estimate the enthalpies of formation. The simplest are *additive or group contribution methods* [34, 35, 36, 37]. They rely on the regularity of molecular and structural groups. They are computationally cheap and predictive in nature. To achieve qualitatively accurate results, their application is limited to well studied systems with precisely and accurately defined functional groups [38, 39]. Among others these include the Benson Group additivity method [34, 35]. *Molecular mechanics methods* are computationally less demanding than other methods but are not universally applicable because they rely on empirical parameters and correction terms [39]. Electronic structure calculations at a high level of theory are used by *quantum chemistry methods* to estimate the enthalpies of formation. This type of single-point calculation is computationally demanding. The errors scale with the size of the molecule [40, 41], and the calculations become intractable for large molecules [42, 43]. In addition, care must be taken to choose the right level of theory [44, 45, 42] and various correction terms needed to achieve consistent and accurate estimates. HEAT [46, 47, 48] is an example of a purely theoretical method, which considers various correction terms, used to estimate highly accurate standard enthalpies of formation for very small molecules.

Fortunately, the errors incurred in electronic structure calculations are systematic. Different methods have been developed to reduce and cancel the impact of these errors on estimates of the enthalpy of formation. Among these are the

bond additivity correction (BAC) [49, 50, 51, 52] and the atom additivity correction (AAC) [53, 38]. Both rely on predefined parameters associated with the level of theory used in the calculation.

Error-cancelling balanced reactions (EBRs) exploit structural and electronic similarities between the species in a reaction to reduce the impact of the inherited systematic errors. The standard enthalpy of formation from an EBR is calculated based on the application of Hess’s Law to the reaction. This method has been applied to a variety of different systems [see for example 54, 55, 56, 57, 58, 5]. The absence of any empirical parameters makes this method suitable for automation. The total electronic energies for all species in the reaction and the enthalpies of formation need to be known (experimentally or theoretically) for all except one species, for which the unknown enthalpy of formation can be estimated. This is achieved by re-organising the equation defining Hess’s Law

$$\Delta_r H_{298.15\text{ K}}^\circ = \sum_{s \in S^P} \nu(s) \Delta_f H_{298.15\text{ K}}^\circ(s) - \sum_{s \in S^R} \nu(s) \Delta_f H_{298.15\text{ K}}^\circ(s), \quad (1)$$

to solve for the unknown enthalpy of formation

$$\begin{aligned} \nu(s_T) \Delta_f H_{298.15\text{ K}}^\circ(s_T) &= \sum_{s \in S^P} \nu(s) \Delta_f H_{298.15\text{ K}}^\circ(s) \\ &\quad - \sum_{s \in S^R \setminus \{s_T\}} \nu(s) \Delta_f H_{298.15\text{ K}}^\circ(s) - \Delta_r H_{298.15\text{ K}}^\circ, \end{aligned} \quad (2)$$

where  $\nu(s)$  is the stoichiometric coefficient and  $\Delta_f H_{298.15\text{ K}}^\circ(s)$  is the standard enthalpy of formation of species  $s$ ,  $S^P$  and  $S^R$  are the set of products and reactants in the reaction and  $\Delta_r H_{298.15\text{ K}}^\circ$  is the reaction enthalpy. The standard enthalpies of formation on the right-hand side of Equation (2) are known. The standard enthalpy of formation of the target species  $s_T$  on the left-hand side of Equation (2) is to be calculated. The method requires the identification of suitable EBRs fulfilling a set of constraints defined by the type of EBR.

Since the introduction of EBRs by Pople and co-workers [59, 60], several types of EBRs have been proposed [59, 60, 61, 62, 63, 64, 65, 57, 66]. For example, isogyric, isodesmic, hypohomodesmotic, homodesmotic and hyperhomod-

esmotric reactions. The use of EBRs has been shown to enable the calculation of accurate estimates of the enthalpy of formation on the back of affordable electronic structure calculations. Generally, the more structural and electronic similarity that is preserved by the reaction, the more accurate the resulting estimate of the enthalpy of formation.

In our previous work [67] a high-level description was presented of an abstract and systematic framework to validate thermochemical data for chemical species and recommend what future experiments or calculations would be required to improve the data. The purpose of the current work is to give a detailed description of the algorithms used by the framework to identify error-cancelling balanced reactions (EBRs) and to calculate informed estimates of the standard enthalpies of formation. The framework facilitates the assessment of the consistency of chemical data, in this case for the standard enthalpy of formation. This is achieved by iteratively isolating potentially inconsistent reference data. By excluding such data, an improved prediction accuracy is achieved. The performance of the framework is demonstrated using four different reaction classes and test cases from organic and inorganic chemistry, including transition metal complexes. The required ground state energies and vibrational frequencies of reference species were calculated using affordable DFT. Calculated estimates of the standard enthalpy of formation for hydrocarbons and titanium-containing species are compared against calculated values using popular high-level quantum chemistry methods.

## 2. Methodology

This section presents a detailed description of the algorithms used to identify a set of EBRs, calculate informed estimates of the standard enthalpy of formation for a species and assess the consistency of the required reference data. The algorithms are implemented as part of an automated and systematic framework to estimate the standard enthalpy of formation for a set of target species. A set of reference species, each consisting of the total electronic energy, the molec-

ular connectivity, the spin multiplicity and a known enthalpy of formation, is required.

The definitions of the EBRs considered in this work are given in Section 2.1, followed by a description of the electronic structure calculations in Section 2.2. The reference data are described in Section 2.3, followed by a detailed algorithmic description of the framework in Section 2.4.

### 2.1. Types of error-cancelling balanced reactions

Many different reaction classes of EBRs have been proposed [59, 60, 61, 62, 63, 64, 65, 57, 66]. The following types of EBRs are used in this work.

*Isogyric reactions (reaction class RC1)* are the least restrictive and only conserve the number of spin pairs on either side of the reaction. An example for an isogyric reaction is given in Figure 1.

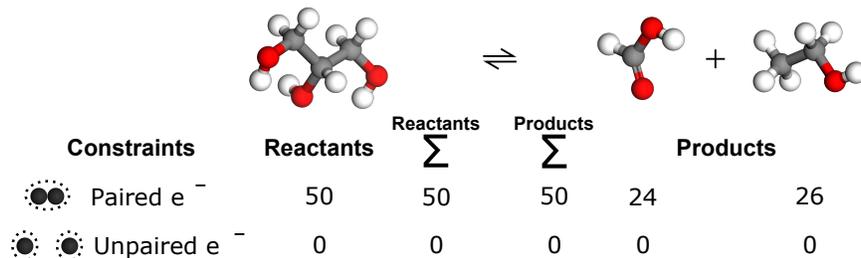


Figure 1: Example reaction for reaction class RC1 (isogyric reactions). The number of spin pairs is conserved on either side of the reaction.

*Isodesmic reactions (reaction class RC2)* conserve the number of each type of bond on either side of the reaction. No constraint is placed on the chemical environment near each bond. An example for an isodesmic reaction is given in Figure 2.

*Reaction class RC3* extends the concept of isodesmic reactions. The identity and the total number of additional atoms bonded to the atom on either side of the bond is conserved in addition to the number of each type of bond on either side of the reaction. Figure 3 presents an example of such a reaction.

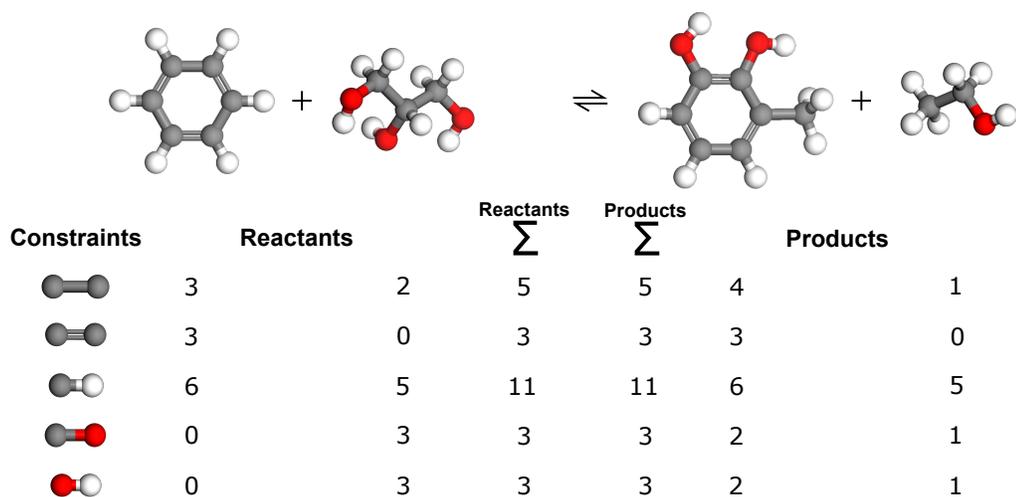


Figure 2: Example reaction for reaction class RC2 (isodesmic reactions). The number of each type of bond is conserved on either side of the reaction.

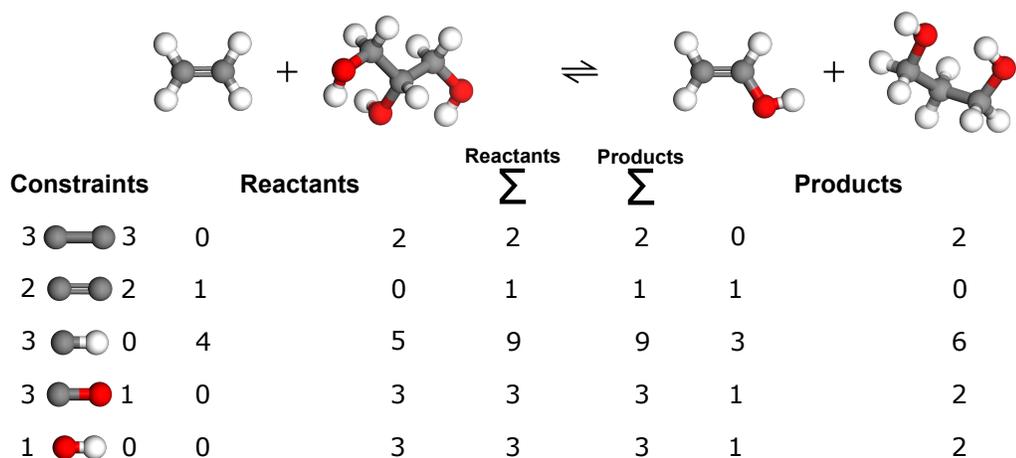


Figure 3: Example reaction for reaction class RC3. The number of each type of bond including the identity and the total number of additional atoms bonded to the atom on either side of the bond is conserved. The numbers next to the atoms in each bond show their total number of additional atoms bonded to the atom.

*Reaction class RC4* extends the concept of RC3. The bond type and identity of each neighbouring atom, including the total number of additional atoms bonded to the neighbouring atoms, is conserved in addition to the constraints

imposed by RC3. Possible constraints for propylene glycol ( $C_3H_8O_2$ ) are presented in Figure 4 and an example reaction is given in Figure 5.

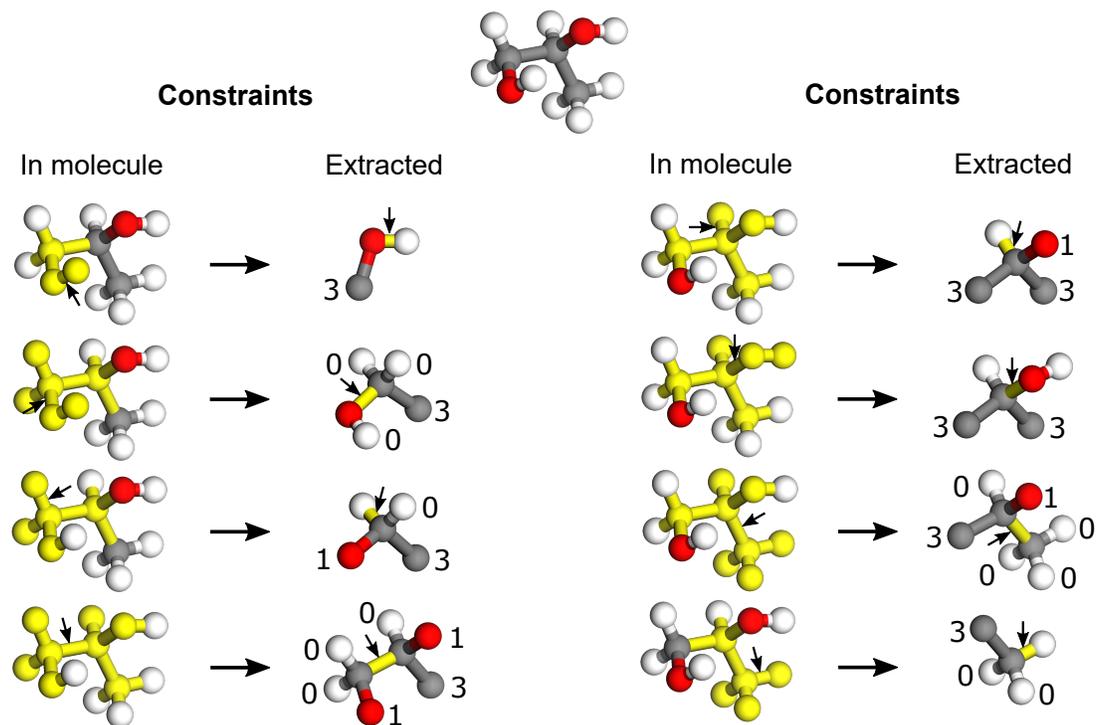


Figure 4: Conserved structural groups of propylene glycol ( $C_3H_8O_2$ ) using reaction class RC4. The labelled structural group is extracted and defines a constraint for the conserved bond. In each example, the conserved bond is labelled with a small arrow. The reaction class imposes that the number of each type of bond including the bond type, the identity of each neighbouring atom and the total number of additional atoms bonded to the neighbouring atoms is conserved. The numbers next to the atoms show their total number of additional atoms bonded to the atom.

In addition, all EBR classes conserve the atom-mass-balance of the reaction. The above reaction classes are presented in order of increasing restrictiveness. Isogyric reactions (RC1) are the least restrictive. Reaction class RC4 is the most restrictive.

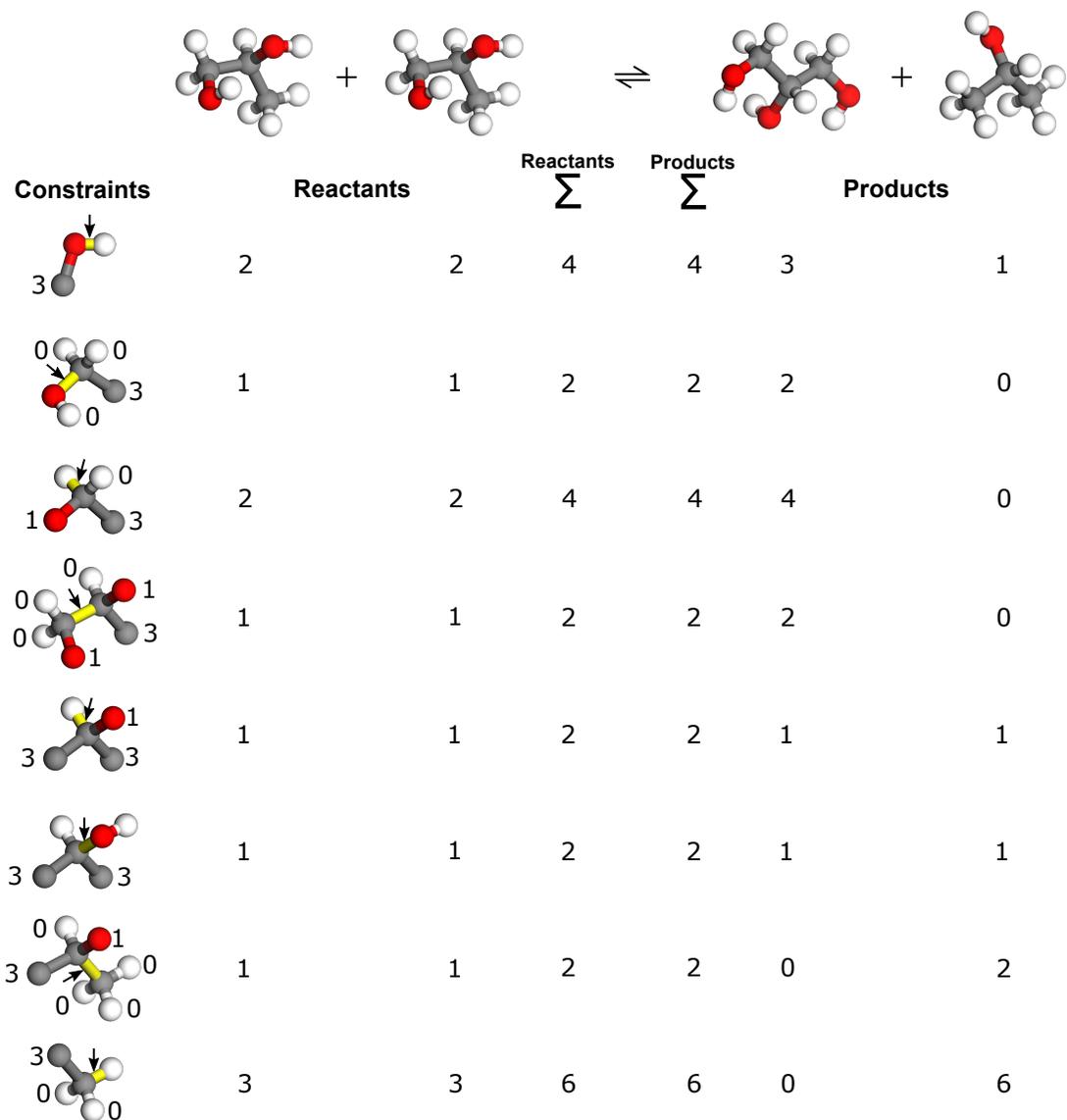


Figure 5: Example reaction for reaction class RC4. The number of each type of bond including the bond type and identity of each neighbouring atom and the total number of additional atoms bonded to these neighbouring atoms is conserved on either side of the reaction. The numbers next to the atoms define their total number of additional atoms bonded to the atom.

## 2.2. *Electronic structure calculations*

Ground state geometries and vibrational frequencies for all species used in this work were calculated using density functional theory (DFT) at the B97-1/6-311+G(d,p) level of theory, as per previous works [54, 56, 5, 67]. This functional has shown to be accurate [68, 69] and well suited for transition metal complexes [70, 71, 72]. For comparison purposes, ground state geometries and vibrational frequencies for all gas-phase species containing carbon, hydrogen and oxygen, were additionally calculated using the B3LYP/6-311+G(d,p) level of theory.

To compensate for overestimated vibrational frequencies, scaling factors were used for both functionals as proposed by Merrick et al. [73]. A simple rigid-rotor harmonic-oscillator approximation was assumed [74]. This presents the worst case scenario with respect to the accuracy of the total energy calculation and gives an idea about the predictive power of the method.

All electronic structure calculations were performed using the Gaussian09 software package [75], running on Intel Xeon CPU X5472@3GHz/8GB nodes with 8 cores per node.

## 2.3. *Reference data*

### 2.3.1. *Carbon-Hydrogen-Oxygen species*

Reference data for 920 gas-phase species containing carbon, hydrogen and oxygen with known enthalpies of formation were retrieved from the NIST Chemistry WebBook [8]. This set includes open- and closed-shell species. The largest species is composed of 32 carbon and 66 hydrogen atoms. For each species, the reported 3-dimensional geometry was taken from the NIST Chemistry WebBook [8] as an initial guess of the geometry for the electronic structure calculations. Uncertainties are not reported for all species taken from the NIST Chemistry WebBook, and are currently not considered by the method. A full list of the species is given in the Supplementary Material provided by Buerger et al. [67].

### 2.3.2. *Other species*

Reference data for other species, including titanium- and chlorine-containing species, were retrieved from various sources. The final set of reference values are presented in Table 1. The additional chlorine-containing species (listed under the heading *Other species* in Table 1) are required for the validation of the data for the chlorine-containing titanium species. The reference values for  $\text{TiOCl}$  and  $\text{TiO}(\text{OH})_2$  have been revised as part of this work and are discussed in Sections 3.2.3 and 3.2.4. Ground state geometries for each titania species were taken from previous works [54, 5].

Table 1: Reference data for standard enthalpies of formation for relevant species.

| species  | $\Delta_f H_{298.15 \text{ K}}^\circ$<br>[kcal mol <sup>-1</sup> ] | species                        | $\Delta_f H_{298.15 \text{ K}}^\circ$<br>[kcal mol <sup>-1</sup> ] |
|--|--|--------------------------------|--|
| <i>Ti-Cl species</i>                             |  | <i>Other species</i>           |  |
| TiCl <sub>4</sub>                                | -182.40 [9, 8]   | ClO                            | 24.29 [9, 8, 76, 77, 78]   |
| TiCl <sub>3</sub>                                | -121.50 [79]   | ClO <sub>2</sub>               | 23.42 [9, 8]   |
| TiCl <sub>2</sub>                                | -49.00 [79]  | ClO <sub>3</sub>               | 48.04 [80]   |
| TiCl   | 40.90 [79]   | ClO <sub>4</sub>               | 54.80 [81]   |
|  |  | OCIO                           | 22.6 [76, 82, 83, 9, 8]  |
| <i>Ti-O-Cl species</i>                           |  | Cl <sub>2</sub>                | 0.00 [9, 8]  |
| TiOCl <sub>2</sub>                               | -141.80 [84]   | ClOCl                          | 19.79 [78]   |
| TiOCl  | -68.42 <sup>a</sup>  | Cl <sub>2</sub> O              | 21.51 [9, 8]   |
|  |  | Cl <sub>2</sub> O <sub>2</sub> | 36.86 [85, 86, 9, 8]   |
| <i>Ti-O species</i>                              |  | Cl <sub>2</sub> O <sub>3</sub> | 32.74 [78]   |
| TiO <sub>2</sub>                                 | -73.00 [9, 8]  | Cl <sub>2</sub> O <sub>4</sub> | 44.48 [87]   |
| TiO  | 13.00 [9, 8]   | Cl <sub>2</sub> O <sub>5</sub> | 61.74 [87]   |
|  |  | Cl <sub>2</sub> O <sub>6</sub> | 66.56 [87]   |
| <i>Ti-O-H species</i>                            |  | Cl <sub>2</sub> O <sub>7</sub> | 76.79 [87]   |
| Ti(OH) <sub>4</sub>                              | -303.20 [84]   | ClOClO                         | 41.95 [85, 9, 8]   |
| TiO(OH) <sub>2</sub>                             | -200.65 <sup>a</sup>   | ClOCl                          | 31.79 [78]   |
|  |  | O <sub>2</sub>                 | 0.00 [9, 8]  |
| <i>Ti-O-C-H species</i>                          |  |                                |  |
| Ti(OC <sub>3</sub> H <sub>7</sub> ) <sub>4</sub> | -360.40 ± 2.20 [9, 8]  |                                |  |
| Ti(OC <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> | -324.60 ± 2.40 [9, 8]  |                                |  |
| <i>Other Ti species</i>                          |  |                                |  |
| TiH  | 116.4 ± 2.3 [88]   |                                |  |

<sup>a</sup> this work

## 2.4. Algorithms

### 2.4.1. Overview

Figure 6 gives an overview of the method used to calculate informed estimates of the enthalpy of formation from a set of reference data. A global cross-validation was used to assess the consistency of the reference data. Data which gave cause for concern were identified and excluded. Multiple EBRs were identified and used to construct a distribution of estimates for the enthalpy of formation of each target species. The resulting distributions were post-processed to derive an informed estimate for each target species.

The algorithm used to identify individual EBRs is introduced in Section 2.4.2. This is extended to identify multiple EBRs in Section 2.4.3. The global cross-validation is described in Section 2.4.4. A modified version of the cross-validation that can be applied to a predefined set of species is introduced in Section 2.4.5. Pseudocode listings for the algorithms are provided as Supplementary Material.

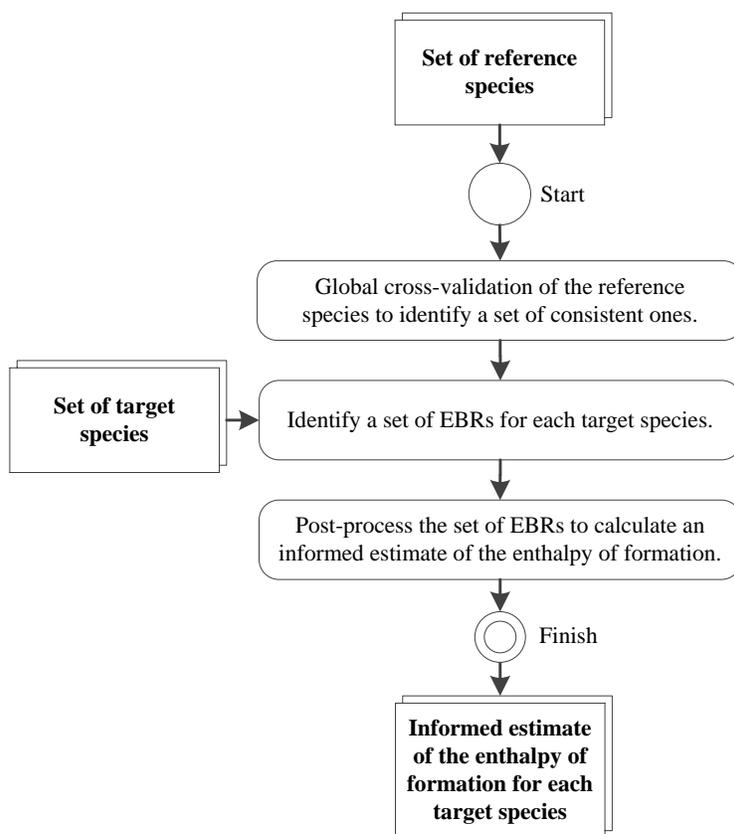


Figure 6: Overview of the method used to estimate the enthalpy of formation.

#### 2.4.2. Identification of an individual error-cancelling balanced reaction

*Linear programming.* Linear programming is a constrained optimisation technique [89, 90, 91]. It was used in this work to identify possible EBRs fulfilling the constraints defined by the chosen reaction class. Each EBR is defined by a combination of reactants and products. The species must be chosen so as to

conserve electronic and structural properties on either side of the reaction as required by the reaction class. This problem can be expressed in the form of an objective function which can be solved using linear programming.

*Problem.* The problem of identifying a possible EBR can be defined by applying the general linear objective function [89, 90, 91]. In this work it is defined by,

$$f(\nu) = \sum_{s \in S^{\text{ref}}} |\nu(s)| \sum_{c \in C} \eta(s, c), \quad (3)$$

where  $S^{\text{ref}}$  is the set of reference species,  $C$  is the set of constraints, defined by the selected reaction class,  $\nu$  is a vector of stoichiometric coefficients,  $\nu(s)$  is the stoichiometric coefficient of species  $s$  and  $\eta(s, c)$  is the coefficient for the constraint  $c$  in species  $s$ . The objective function  $f$  is minimised with respect to  $\nu$ , subject to the constraints

$$\sum_{s \in S^{\text{ref}}} \nu(s) \eta(s, c) = 0, \quad \forall c \in C, \quad (4)$$

such that the required quantities are conserved (see Section 2.1 for the definition of the reaction classes). The stoichiometric coefficients  $\nu$  are treated as real numbers. This increases the number of possible EBRs and reduces the computational complexity from that of solving an integer problem to that of solving a linear problem.

*Solver.* Many linear programming solvers [92, 93, 94, 95, 96] are available. The GNU Linear Programming Kit (GLPK) [92] and `lp_solve` [93] linear programming solver were used in preliminary tests. It was observed that `lp_solve` did not always manage to solve the defined problem. This issue was also encountered in the work of Gearhart et al. [97]. No issues were encountered with GLPK and it was therefore used for the remainder of this work.

### 2.4.3. Identification of multiple error-cancelling balanced reactions

Manual identification of EBRs can be time-consuming and error-prone. An automated procedure that can be applied systematically to identify multiple

EBRs offers many advantages, including the ability to calculate a distribution of values for the enthalpy of formation of any given species.

Figure 7 presents an overview of the algorithm used to identify multiple EBRs. Details about the algorithm are given below. In addition, a detailed description of the individual steps as well as two examples are provided as Supplementary Material.

*Input.* This algorithm requires: (i) A set of reference data. (ii) A list of the target species for which the standard enthalpy of formation should be estimated. (iii) A hierarchy of reaction classes which are ordered from most to least restrictive class. (iv) The minimum number of required EBRs ( $n$ ). (v) The maximum number of identification attempts. (vi) The maximum search depth.

*Output.* A set of identified EBRs for each target species. The EBRs may be subject to additional user defined constraints, for example to prevent a one-to-one mapping between a reactant and a product in cases where different values of the enthalpy of formation are available for a given species and are being evaluated to assess the consistency of the reference data.

*Initialisation.* The hierarchy of reaction classes is iteratively searched to find an initial EBR. The same reaction class is recommended to be used for the subsequent recursive identification of multiple EBRs.

*Identification of EBRs.* The set of species that are included in the reference set is systematically manipulated in order to identify multiple EBRs. The manipulation is implemented using a recursive algorithm.

The initial step after entering the recursion is to check whether the required number of EBRs have been found, or whether the maximum search depth or maximum number of search attempts have been reached. If so, the algorithm is completed. If not, the algorithm recursively excludes from the reference set each combination of species (ignoring the target species) that exist in the current set of identified EBRs. At each recursion, the algorithm attempts to identify an

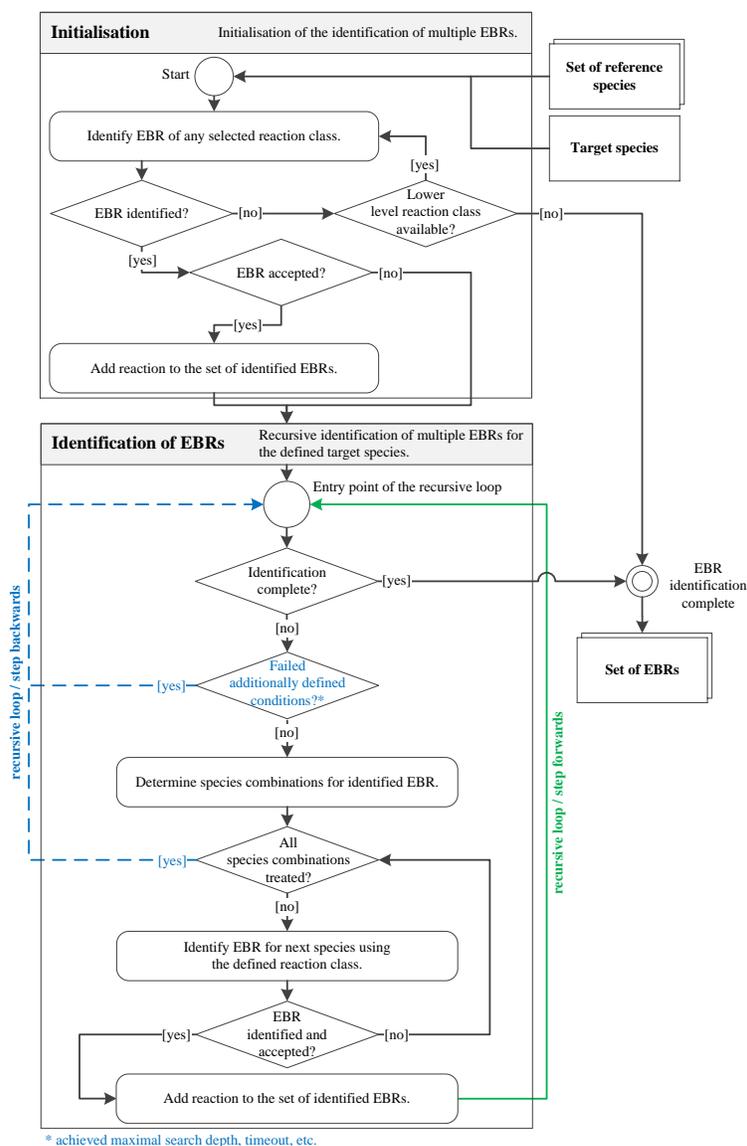


Figure 7: Recursive algorithm used to identify a set of error-cancelling balanced reactions (EBRs). The input includes a set of reference data and a list of the target species for which the enthalpy of formation is to be estimated. A set of EBRs, which can be used to estimate the standard enthalpy of formation of the target species, is recursively identified and returned. The forward step in the recursion is indicated by the green solid line and the backward steps by the blue dashed lines.

EBR. If a distinct EBR is found and it adheres to any additional user defined constraints, it is added to the set of identified EBRs.

The algorithm terminates when it reaches the required number of EBRs, or when all combinations of species that exist in the set of identified EBRs have been excluded and analysed, or when it reaches a maximum number of search attempts.

This type of recursive algorithm is commonly used for processing an abstract data type known as a tree. A well-known example from the chemical literature is the mechanism reduction algorithm introduced by Lu and Law [98] and its subsequent developments [99, 100, 101, 102].

#### *2.4.4. Global cross-validation*

It is important to allow for the possibility that some of the reference data are potentially inconsistent. Simply excluding data for which the absolute difference between the calculated enthalpy of formation and the reference value exceeds a predefined error threshold could lead to the exclusion of accurate and consistent data, while inaccurate and inconsistent data remain due to the dependence on the order of processing the reference data. A method is required to:

- Assess the consistency of the reference data independently of the order of processing the data.
- Choose the reference data for a species where multiple conflicting choices of data exist.

Evaluating every possible combination of data would identify potentially inconsistent species. However, this is intractable for large reference sets. An alternative cross-validation algorithm is proposed to solve this issue. Figure 9 gives a simplified illustration of the algorithm.

Cross-validation of data sets is widely used in the field of data mining and statistical analysis [103, 104, 105]. It assesses the fit of models by separating the given data into complementary test and training sets. The training set is

used to train the model which then attempts to predict results from the test set. The algorithm presented in this work has been developed based on this concept. It relates the resulting error from the cross-validation to each species in the reference data set. Based on the calculated error contributions, potentially inconsistent species are isolated and iteratively excluded from the reference set. The cross-validation is continued until defined convergence criteria are achieved or no further changes are observed.

Note that the algorithm does not identify the source of the inconsistency. For this reason it remains important to have additional data sources, experimentally or theoretically, and to check the quality of the considered data (*e.g.* calculated energy) fed to the method. For example, an error in the calculated energy of the target species always propagates to the estimate of the standard enthalpy of formation. A second potential source of error is where the connectivity contains some ambiguity, where the choice of connectivity would affect the set of possible EBRs. The propargyl radical is one such example. Figure 8 demonstrates this problem. It is possible to define the connectivity as having either a triple bond and a single bond between the carbon atoms (Figure 8a, used in this work) or double bonds between carbon atoms (Figure 8b). In this work, the connectivity was defined using OpenBabel [106] to post process the results of the electronic structure calculations. The cross-validation was used to identify species that caused inconsistencies.

*Overview.* The algorithm used for the global cross-validation can be organised into three distinct modules:

- The *data pre-processing* is concerned with an initial evaluation of the reference data. It calculates an initial error contribution for each species. This provides the basis for further analysis.
- Based on the species error contribution, the *initial data analysis* attempts to identify and exclude the species from which the errors originate.
- If the initial data analysis is inconclusive, an *extended data analysis* is

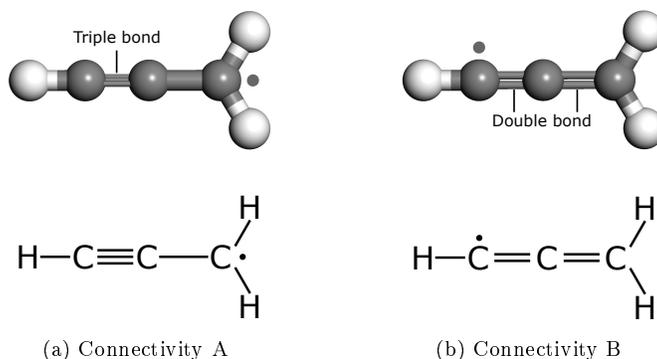


Figure 8: Two different possible connectivities of the propargyl radical. The molecules are presented as a 3-dimensional structure and as a sketch. The position of the sub-valent site is indicated with a dot.

conducted to investigate problematic species in more detail.

In the following, the modules of the algorithm are explained in more detail. Where required, the algorithms presented in Sections 2.4.2 and 2.4.3 are used to identify a set of EBRs and estimate the standard enthalpy of formation for a species. An algorithmic description of the individual steps is provided as Supplementary Material.

*Input.* This algorithm requires: (i) The full list of reference data to be evaluated. (ii) A hierarchy of reaction classes which are ordered from most to least restrictive class. (iii) The minimum number of required EBRs ( $n$ ). (iv) The maximum number of identification attempts. (v) The maximum search depth. (vi) The magnitude of maximal acceptable error for each species. (vii) An upper limit of the number of iterations. (viii) A choice of how to calculate the error due to each species.

*Output.* Two lists of reference data: (i) A list of reference data found to be consistent when used to estimate the enthalpies of formation. (ii) A list of potentially inconsistent reference data which were found to introduce inaccuracies when used to estimate enthalpies of formation.

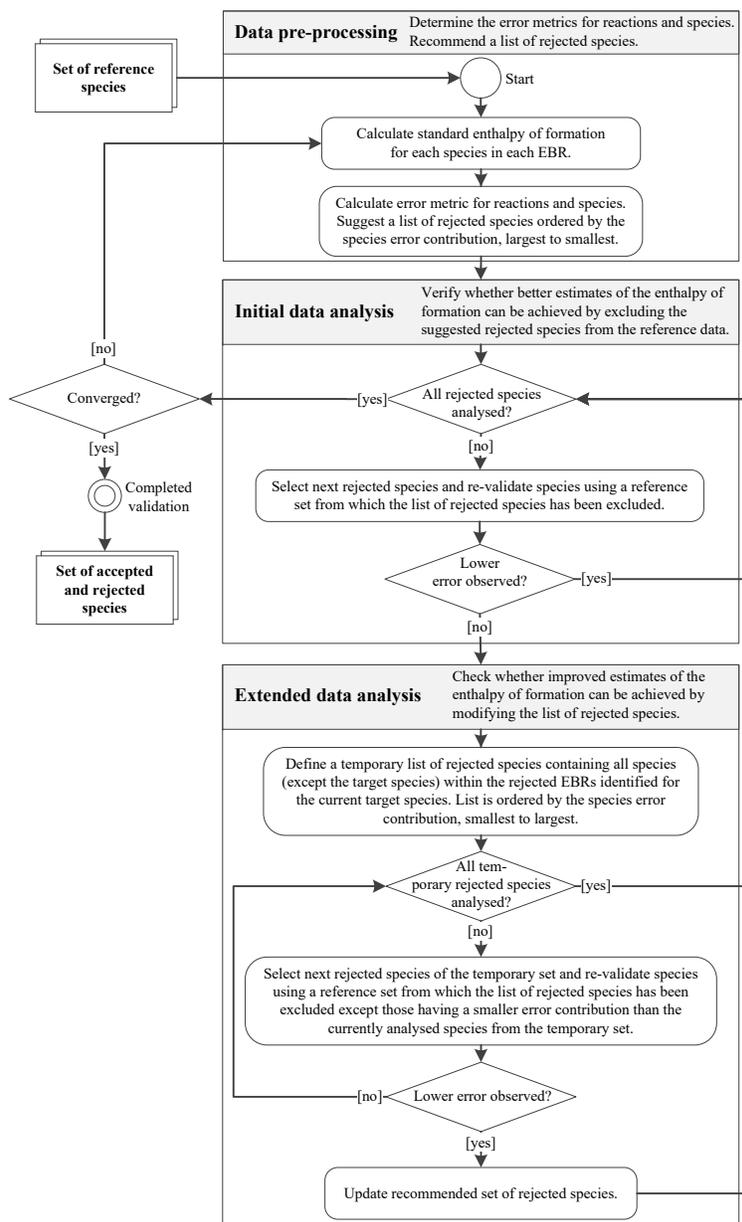


Figure 9: Global cross-validation algorithm. A set of reference data is needed as input. Data which are likely to introduce inaccuracies are isolated by analysing error-cancelling balanced reactions (EBRs). The output is a set of consistent (accepted) and a set of inconsistent (rejected) reference data.

*Data pre-processing.* The pre-processing is used to initially identify a set of EBRs to calculate the standard enthalpy of formation for each species in each EBR. Isolated species for which no EBRs are found are identified and excluded. The validation uses a pre-defined hierarchy of reaction classes. Results from the reaction class, highest in the hierarchy, leading to a successful termination are used and collected in a reaction set,  $R$ . The set of species participating in reaction  $r \in R$  is denoted by,

$$S^{\text{ref}}(r) := \{s \in S^{\text{ref}} | s \text{ is involved in } r\}, \quad (5)$$

where  $S^{\text{ref}}$  is the full reference set containing all species. An error metric for each combination of reaction  $r \in R$  and species  $s \in S^{\text{ref}}$  is calculated. The absolute difference between the reference value,  $\Delta_f^{\text{ref}} H_{298.15 \text{ K}}^{\circ}(s)$ , and the calculated enthalpy of formation,  $\Delta_f H_{298.15 \text{ K}}^{\circ}(r, s)$ , is calculated,

$$\varepsilon_r(r, s) = \begin{cases} |\Delta_f^{\text{ref}} H_{298.15 \text{ K}}^{\circ}(s) - \Delta_f H_{298.15 \text{ K}}^{\circ}(r, s)| & \text{if } s \in S^{\text{ref}}(r) \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

where reaction  $r$  is used to estimate the standard enthalpy of formation for species  $s$ .

A reaction  $r \in R$  is labelled to be accepted if  $\varepsilon_r(r, s)$  is smaller than a defined upper limit  $\varepsilon_r^{\text{max}}$  for all species  $s$ ,

$$\varepsilon_r(r, s) < \varepsilon_r^{\text{max}} \quad \forall s \in S^{\text{ref}}, \quad (7)$$

and otherwise rejected. The set of rejected reactions for a species  $s \in S^{\text{ref}}$ , for which the standard enthalpy of formation is to be determined, is defined by,

$$R^{\text{rej}}(s) := \{r \in R | \varepsilon_r(r, s) \geq \varepsilon_r^{\text{max}}\}. \quad (8)$$

The full set of all rejected reactions is then defined by,

$$R^{\text{rej}} := \bigcup_{s \in S^{\text{ref}}} R^{\text{rej}}(s), \quad (9)$$

and that of accepted reactions by,

$$R^{\text{acc}} := \{r \in R | \varepsilon_r(r, s) < \varepsilon_r^{\text{max}}\}, \quad \forall s \in S^{\text{ref}} \quad (10)$$

so that by definition the sets of accepted and rejected reactions are complements of each other within  $R$ , *i.e.*  $R^{\text{acc}} \cap R^{\text{rej}} = \emptyset$  and  $R^{\text{acc}} \cup R^{\text{rej}} = R$ .

The mean absolute error of a set of rejected reactions associated with a species  $s \in S^{\text{ref}}$  is defined by,

$$\bar{\varepsilon}_r(s) = \frac{\sum_{r \in R^{\text{rej}}(s)} \varepsilon_r(r, s)}{|R^{\text{rej}}(s)|}, \quad (11)$$

where the vertical bar notation denotes the number of elements within a set. Although not used here, the median absolute error could be employed. The contribution to  $\varepsilon_r$  can be calculated for each species  $s$  as a weighted contribution,

$$\varepsilon_s(r, s) = \frac{\nu(r, s) \varepsilon_r(r, s)}{\nu(r)} \quad \forall r \in R, s \in S^{\text{ref}}, \quad (12)$$

where  $\nu(r, s)$  are the weights of  $s$  in  $r$ . For example, the stoichiometry, number of atoms or the product of both. The sum of weights over  $S^{\text{ref}}(r)$  is defined by,

$$\nu(r) = \sum_{s \in S^{\text{ref}}(r)} \nu(r, s) \quad \forall r \in R. \quad (13)$$

The mean absolute error contribution for  $s$  is calculated from  $\varepsilon_s(r, s)$ ,

$$\bar{\varepsilon}_s(s) = \frac{\sum_{r \in R^{\text{rej}}(s)} \varepsilon_s(r, s)}{|R^{\text{rej}}(s)|} \quad \forall s \in S^{\text{ref}}. \quad (14)$$

Instead of the mean absolute error contribution for  $s$ , the median absolute error contribution could be used. In the remainder of the work, only results using Equation (14) are reported. The set of species assumed to be consistent is defined by,

$$S := \bigcup_{r \in R^{\text{acc}}} S^{\text{ref}}(r), \quad (15)$$

where all species appearing in identified reactions with an error lower than  $\varepsilon_r^{\text{max}}$  are assumed to be consistent.

The full set of rejected species is then defined by the set difference,

$$S^{\text{rej}} := S^{\text{ref}} \setminus S. \quad (16)$$

At this stage it is unclear which species are the cause of the error  $\varepsilon_r(r, s) \geq \varepsilon_r^{\text{max}}$  in the set of rejected reactions  $R^{\text{rej}}$ . It is assumed that the error could originate from any of the species.

*Initial data analysis.* The initial data analysis checks whether improved estimates of the enthalpy of formation can be achieved by re-analysing each species in  $S^{\text{rej}}$  using the current subset of accepted reference species  $S$ , initially defined by Equation (15). The species in  $S^{\text{rej}}$  are analysed in order, based on the size of the species error contribution, largest first.

A working set of rejected species  $\hat{S}^{\text{rej}}$  is defined. This is initially equal to the set of rejected species,

$$\hat{S}^{\text{rej}} \leftarrow S^{\text{rej}}. \quad (17)$$

The species with the largest error contribution  $\bar{\varepsilon}_s$ ,

$$s^{\text{max}} := \operatorname{argmax}_{y \in \hat{S}^{\text{rej}}} \bar{\varepsilon}_s(y), \quad (18)$$

is selected and excluded from  $\hat{S}^{\text{rej}}$ ,

$$\hat{S}^{\text{rej}} \leftarrow \hat{S}^{\text{rej}} \setminus \{s^{\text{max}}\}. \quad (19)$$

A new set of EBRs  $\hat{R}^{\text{new}}(s^{\text{max}})$  is determined for  $s^{\text{max}}$  using reference set  $S$ .  $\hat{R}^{\text{new}}(s^{\text{max}})$  is validated against the previous set of EBRs  $R(s^{\text{max}})$  for the same target species.

Two different validation methods are used: (i) The first validation method assumes that the alternative set of EBRs  $\hat{R}^{\text{new}}(s^{\text{max}})$  is an improvement over the previous set of EBRs  $R(s^{\text{max}})$  if the number of rejected reactions is smaller or, in cases with the same number of rejected reactions, the mean absolute error, as defined by Equation (11), is smaller than previously. (ii) The second validation method calculates and compares the mean absolute error, given by Equation (11), between the two sets.

In cases where the error is reduced,  $s^{\text{max}}$  is added to  $S$ . Otherwise, we enter the extended data analysis which attempts to modify the reference set  $S$  in order to reduce the error. After completion of the extended analysis the next iteration is performed.

Following a complete iteration through the set of rejected species, it is checked whether convergence has been achieved. The convergence criteria are

whether or not the sets of accepted and rejected species are unchanged compared to the previous iteration or whether a maximum number of iterations has been achieved. If this is the case, the final sets of accepted and rejected species are returned. Otherwise, the current set of accepted species defines the new set of reference species,  $S^{\text{ref}} \leftarrow S$ , and is re-analysed via another iteration of the cross-validation.

*Extended data analysis.* The purpose of the extended analysis is to improve the predictive performance for species  $s$ . This is accomplished by checking whether better results can be achieved by iteratively extending the set of accepted reference species  $S$  with species previously found to be present in rejected reactions identified for  $s$ .

The algorithm starts by identifying the set of species  $S^{\text{rej}}$  that were present in rejected reactions identified for  $s$ ,

$$S^{\text{rej}}(s) := \bigcup_{r \in R^{\text{rej}}(s)} S^{\text{ref}}(r). \quad (20)$$

The species under investigation  $s$  is excluded from this set,

$$\tilde{S}^{\text{rej}}(s) := S^{\text{rej}}(s) \setminus \{s\}. \quad (21)$$

The species in  $\tilde{S}^{\text{rej}}(s)$  with the smallest error contribution  $\bar{\varepsilon}_s(s)$ ,

$$s^{\text{min}}(s) := \underset{y \in \tilde{S}^{\text{rej}}(s)}{\text{argmin}} \bar{\varepsilon}_s(y), \quad (22)$$

is excluded from  $\tilde{S}^{\text{rej}}(s)$ ,

$$\tilde{S}^{\text{rej}}(s) \leftarrow \tilde{S}^{\text{rej}}(s) \setminus \{s^{\text{min}}(s)\}, \quad (23)$$

and is used to define the set of species that have smaller mean absolute error contributions. This set is defined as a subset of the full set of rejected species  $S^{\text{rej}}$ ,

$$\tilde{S}^{\text{err}}(s) := \{x \in S^{\text{rej}} \mid \bar{\varepsilon}_s(x) \leq \bar{\varepsilon}_s(s^{\text{min}}(s))\}. \quad (24)$$

If there is more than one species with the same species error contribution  $\bar{\varepsilon}_s(s)$ , a random selection is conducted.

Combining  $\tilde{S}^{\text{err}}(s)$  and  $S$ ,

$$S \leftarrow S \cup \tilde{S}^{\text{err}}(s), \quad (25)$$

results in an updated set of reference data. All species within  $\tilde{S}^{\text{err}}(s)$  have a lower mean absolute species error contribution than  $s^{\text{min}}(s)$  and it is assumed that by adding them to the reference set  $S$ , the resulting error for the identified alternative EBRs will be smaller than by adding species with larger mean absolute error contributions. The revised species set  $S$  is used to identify distinct EBRs and a new set of reactions  $\tilde{R}^{\text{new}}(s)$  for species  $s$ .

If the error, based on the selected validation method as discussed for the initial data analysis, is reduced by the use of  $\tilde{R}^{\text{new}}(s)$  instead of  $R(s)$ , the set of species required for the definition of the new reaction set,

$$S^{\text{new}}(s) := \bigcup_{r \in \tilde{R}^{\text{new}}(s)} S^{\text{ref}}(r). \quad (26)$$

is used to update the list of recommended rejected species,

$$S^{\text{rej}} \leftarrow S^{\text{rej}} \setminus S^{\text{new}}(s), \quad (27)$$

so that species required to achieve the improvement are excluded from the set of rejected species but the others remain in  $S^{\text{rej}}$ , even if they were temporarily in the reference set during the extended data analysis. Using the set of rejected species,  $S$  is then updated according to,

$$S \leftarrow S^{\text{ref}} \setminus S^{\text{rej}}. \quad (28)$$

If the error has increased or no results could be obtained, the species with the next larger  $\bar{\varepsilon}_s(s)$  in  $\tilde{S}^{\text{rej}}(s)$  is used. This is repeated until better results are achieved or all species in  $\tilde{S}^{\text{rej}}(s)$  have been treated.

#### 2.4.5. Modified global cross-validation

In some cases it is desired to only validate a subset of species rather than the full reference set. This is required for the validation of the titanium-containing species. The global cross-validation method described in the previous section

is modified by adding an additional input to specify a set of target species. Instead of validating every species within the reference set, only the specified target species are validated. The validation of all other species is skipped. It is assumed that they are consistent.

### 3. Results

The performance of the framework is demonstrated using different test cases. These include species from organic and inorganic chemistry, including transition metal complexes, and are organised as follows:

- The first test case consists of 920 species containing carbon, hydrogen and oxygen [67]. This is a large reference set and is used to demonstrate the functionality of the global cross-validation using a representative set of reference data that are widely available in the literature. Validation of these species is required to validate the titanium-containing species.
- The second test case consists of oxychloride species listed in Table 1. This demonstrates the application of the framework to a small reference set where there is considerable variation in the literature values of the reference data. Validation of these species data is essential to validate the titanium-chlorine-containing species.
- The final test case consists of titanium-containing species. The species are classified as Titanium-Oxygen-Chlorine (*i.e.* Ti-Cl, Ti-O-Cl and Ti-O species) and Titanium-Oxygen-Carbon-Hydrogen species (*i.e.* Ti-O, Ti-O-H, Ti-O-C-H and TiH species). The considered species are listed in Table 1. The estimation of standard enthalpies of formation for transition metal complexes is challenging [107, 108, 109, 71, 110] and several quantum chemistry methods have been validated for such transition metal complexes. These species were chosen to demonstrate the applicability of the framework to such systems.

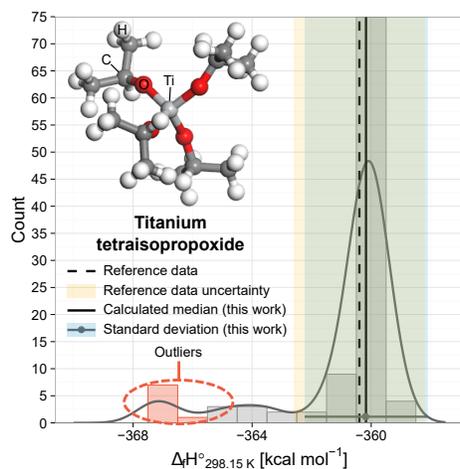
The following sections show that the framework delivers significant benefits that derive from the consideration of multiple EBRs, outlier detections, and the global cross-validation of the reference data. The framework is used to calculate and recommend new reference values of the standard enthalpy of formation for  $\text{TiOCl}$  and  $\text{TiO}(\text{OH})_2$ . These are important species in titanium-oxygen systems [54, 111, 5].

### 3.1. Benefits of multiple error-cancelling balanced reactions

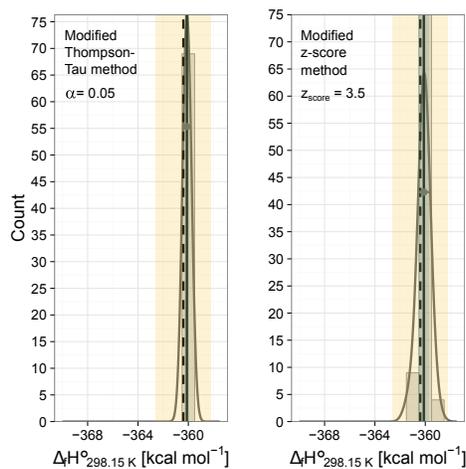
The use of multiple error-cancelling balanced reactions results in significant statistical benefits compared to using a single reaction. This includes a systematic and standardised way of analysing the results and the calculation of an informed estimate. The algorithms described in Section 2.4.2 and 2.4.3 were used for the identification of multiple reactions for a given target species.

Figure 10 presents example results for titanium tetraisopropoxide (TTIP,  $\text{Ti}(\text{OC}_3\text{H}_7)_4$ ) using reaction class RC2 (isodesmic reactions), calculated from multiple EBRs, each of which is used to calculate a single point value of the standard enthalpy of formation. The use of multiple EBRs therefore enables the construction of a histogram of calculated estimates of the standard enthalpy of formation.

The histogram derived from the full set of identified EBRs is shown in Figure 10a. The use of a central measure leads overall to a better estimate of the enthalpy of formation compared to an estimate that relies on a single reaction. The width of the distribution can be used to gain information about the statistical uncertainty of the calculation. In this work the empirical standard deviation, calculated from the distribution of estimates as determined from the set of EBRs, was used to define the statistical uncertainty. The distribution in Figure 10a results in an estimate of  $-360.18 \text{ kcal mol}^{-1}$  and a standard deviation of  $2.06 \text{ kcal mol}^{-1}$ , which compares well to a reference value of  $-360.40 \pm 2.15 \text{ kcal mol}^{-1}$  [8]. The difference is significantly less than  $3 \text{ kcal mol}^{-1}$ , which is the recommended value for the chemical accuracy of any transition metal complex proposed by DeYonker et al. [107, 108], and is within



(a) Full set of identified EBRs without the exclusion of outliers.



(b) Application of two common outlier detection methods: The modified Thompson-Tau method [112] and the modified z-score method [113].

Figure 10: Histogram of the estimated values of the standard enthalpy of formation for titanium tetraisopropoxide (TTIP,  $\text{Ti}(\text{OC}_3\text{H}_7)_4$ ). 106 distinct isodesmic reactions (RC2) were identified. The kernel density was estimated from post-processing the histogram. The reference value of  $-360.40 \pm 2.15 \text{ kcal mol}^{-1}$  (dashed line) for TTIP was taken from the NIST Chemistry WebBook [8]. Outliers giving particularly poor estimates are highlighted.

the reported statistical uncertainty of  $2.15 \text{ kcal mol}^{-1}$ .

The exclusion of outliers provides additional benefit. Figure 10b shows two post-processed distributions that were determined by automatically identifying and excluding outliers from the full distribution (Figure 10a). A modified Thompson-Tau method [112] with an  $\alpha$  value of 0.05 and a modified z-score method [113] with a  $z_{\text{score}}$  value of 3.5 were used. Important information about potentially inconsistent reference data is included in outliers. By systematically analysing this information, inconsistent data can be identified and excluded from the reference set. This information is exploited by the global cross-validation.

Similar results were observed for the test case consisting of species containing carbon, hydrogen and oxygen. This is discussed in detail elsewhere [67].

### *3.2. Identification of potentially inconsistent reference data*

#### *3.2.1. Carbon-Hydrogen-Oxygen-containing species*

Figure 11 (top panel) shows the decrease in the mean absolute error that was achieved by iteratively excluding inconsistent species from the set of carbon, hydrogen and oxygen containing species. The bottom panel shows the number of species which have been excluded for each iteration.

Different configurations of the parameters in the global cross-validation were evaluated. The first parameter was the rejection threshold  $\varepsilon_r^{\text{max}}$  as per Equation (7). It defines the magnitude of the maximum acceptable error for each species as defined by Equation (6). The second parameter defines the weighting of the species error contribution within a reaction as used in Equation (12). The weights in Equation (12) were defined as either the stoichiometry (S1), the number of atoms (S2) or the product of both (S3). The final parameter defines the validation method used to compare the two sets of EBRs. Method V1 assumed that the set with the smaller number of rejected reactions was the preferred set of EBRs. In cases with the same number of rejected reactions, the mean absolute error was used for comparison, as defined by Equation (11). Method V2 always used the mean absolute error.

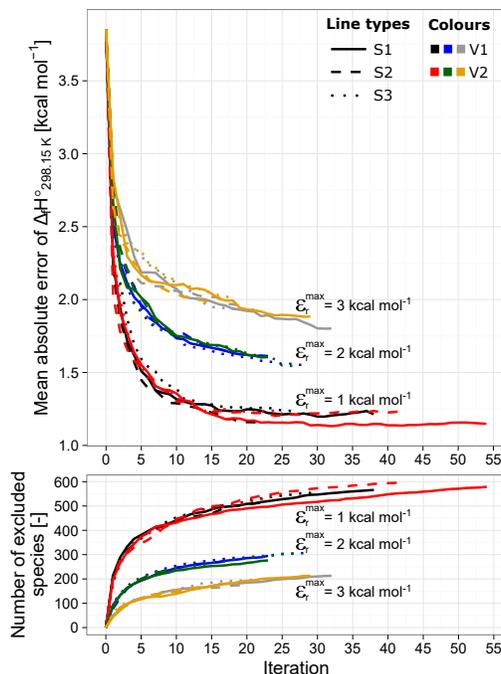


Figure 11: The mean absolute error (top panel) and the number of excluded species (bottom panel) for different configurations of the parameters in the global cross-validation. The rejection threshold parameter  $\epsilon_r^{\text{max}}$  defines the magnitude of the maximum acceptable error for each species. The weighting of the species error contribution within a reaction as used in Equation (12) is either calculated using the stoichiometry (S1), the number of atoms (S2) or the product of both (S3). Two different validation methods are used to compare sets of error-cancelling balanced reactions (EBRs). The first method (V1) recommends the set with the smaller number of rejected EBRs. In cases with the same number of rejected reactions, the mean absolute error contribution is used for comparison, as defined by Equation (11). The second method (V2) always uses the mean absolute error contribution.

A rapid asymptotic decrease in the observed mean absolute error was noticed for all parameter configurations. The results were grouped by the value of  $\epsilon_r^{\text{max}}$ . This implies that  $\epsilon_r^{\text{max}}$  was the most influential and sensitive parameter. The choice of how to weigh the species error contribution and the validation method had less impact. The lower the rejection threshold  $\epsilon_r^{\text{max}}$ , the more stringent and uncompromising the identification of consistent reference data.

A mean absolute error lower than  $\varepsilon_r^{\max}$  was observed for a threshold  $\varepsilon_r^{\max} \geq 2.0 \text{ kcal mol}^{-1}$ . On the other hand, for  $\varepsilon_r^{\max} \leq 1.0 \text{ kcal mol}^{-1}$  a mean absolute error just above  $1.0 \text{ kcal mol}^{-1}$  was observed. Reasons for this could include the loss of the statistical benefits from the selection of multiple EBRs due to the reduction in the size of the set of reference data, the choice of reaction class or the selected level of theory. In this work, errors in this range are to be expected from the use of the B97-1/6-311+G(d,p) level of theory. Below this point it is difficult to define whether the resulting discrepancies stem from the electronic structure calculations or inconsistencies in the reference data. Therefore, a trade-off must be made when choosing the level of theory, the configuration of the global cross-validation and the reaction class. Repeated analyses using the same configuration only showed small differences in the calculated mean absolute errors.

### 3.2.2. Oxychloride species

The reported literature values of the standard enthalpies of formation vary significantly for some of the oxychloride species. For example, differences of up to  $22.56 \text{ kcal mol}^{-1}$  can be observed between the reported literature values for  $\text{Cl}_2\text{O}_7$ . Choosing the wrong reference value inevitably leads to the propagation of the error to any estimates of the enthalpy of formation that use this data. The global cross-validation was used to find the most suitable set of reference data to estimate the standard enthalpies of formation for species with large uncertainties in the literature data.

The combination of a small reference set with the large uncertainties in the reference data impacted the performance of the global cross-validation algorithm. Therefore, configurations using  $\varepsilon_r^{\max} \geq 3.0 \text{ kcal mol}^{-1}$  were applied. Smaller values of  $\varepsilon_r^{\max}$  were found to be unsuitable due to the exclusion of too many species.

Multiple validation executions identified three potentially inconsistent reference species ( $\varepsilon_r^{\max} = 3.0 \text{ kcal mol}^{-1}$ ):  $\text{ClOCl}$ ,  $\text{ClOClO}$  and  $\text{Cl}_2\text{O}_7$ . Using the full reference set led to a mean absolute error of  $3.70 \text{ kcal mol}^{-1}$ . The effect

of excluding permutations of the above three potentially inconsistent reference species was evaluated. The largest improvement was achieved by excluding all three species from the reference set. However, the level of improvement was marginal. In some situations, the statistical benefit gained by considering more reference species outweighs the benefits of excluding species.

### 3.2.3. *Titanium-Oxygen-Chlorine species*

The number of titanium-oxygen-chlorine species for which reference data exist is very limited. As discussed in the previous section, the reference set for the oxychloride species is already small. This significantly affects the identification of multiple EBRs for the titanium-chlorides and titanium-oxychlorides, and consequently the accuracy of the estimated values of the standard enthalpy of formation. The modified global cross-validation (see Section 2.4.5) was applied to assess the quality of the reference data for  $\text{TiCl}_4$ ,  $\text{TiCl}_3$ ,  $\text{TiCl}_2$ ,  $\text{TiCl}$ ,  $\text{TiOCl}$ ,  $\text{TiOCl}_2$ ,  $\text{TiO}$  and  $\text{TiO}_2$  in addition to the oxychloride species.

The first execution of the global-cross validation was performed using a rejection threshold of  $3.0 \text{ kcal mol}^{-1}$ , which is the assumed chemical accuracy for transition metal complexes [107, 108]. It was found that the reported NIST Chemistry WebBook reference values of the standard enthalpy of formation of  $\text{TiOCl}$  (with a value of  $-58.38 \text{ kcal mol}^{-1}$ ) and  $\text{TiOCl}_2$  (with a value of  $-130.39 \text{ kcal mol}^{-1}$ ) were potentially inconsistent. When these values were replaced with reference values for  $\text{TiOCl}$  and  $\text{TiOCl}_2$  as estimated by West et al. [54] and for  $\text{TiOCl}_2$  by Wang et al. [84], the cross-validation found all the titanium-containing species to be consistent.

Upon decreasing the rejection threshold to  $2.0 \text{ kcal mol}^{-1}$ , the reference value for  $\text{TiOCl}$  was found to be potentially inconsistent. Excluding  $\text{TiOCl}$  and using the reference value for  $\text{TiOCl}_2$  reported by Wang et al. [84] (and recommended by the cross-validation) led to a mean absolute error of  $0.78 \text{ kcal mol}^{-1}$ . A new estimate of  $-68.42 \text{ kcal mol}^{-1}$  and a standard deviation of  $0.54 \text{ kcal mol}^{-1}$  (see Table 1) was calculated for  $\text{TiOCl}$  using reaction class RC2. This value differs significantly from that reported in the NIST Chemistry WebBook [8] and to a

lesser extent from the value reported by West et al. [54].

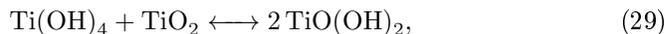
#### 3.2.4. Titanium-Oxygen-Carbon-Hydrogen species

The consistency of the following Ti–O–C–H species were validated using the modified global cross-validation:  $\text{Ti}(\text{OC}_3\text{H}_7)_4$ ,  $\text{Ti}(\text{OC}_2\text{H}_5)_4$ ,  $\text{Ti}(\text{OH})_4$ ,  $\text{TiO}(\text{OH})_2$ ,  $\text{TiO}$  and  $\text{TiO}_2$ .  $\text{TiH}$  was excluded from the analysis because of the absence of another species containing a Ti–H bond. The recommended chemical accuracy of transition metal complexes [107, 108] was used for the rejection threshold parameter ( $\epsilon_r^{\text{max}} = 3.0 \text{ kcal mol}^{-1}$ ). The reference set included the validated ( $\epsilon_r^{\text{max}} = 1.0 \text{ kcal mol}^{-1}$ ) set of carbon, hydrogen and oxygen containing species.

$\text{TiO}(\text{OH})_2$  and  $\text{TiO}_2$  were found to be potentially inconsistent. This result was unexpected for  $\text{TiO}_2$ . Manually inspecting the identified EBRs revealed that both species,  $\text{TiO}(\text{OH})_2$  and  $\text{TiO}_2$ , always appeared as a pair. As a result of the limited number of titanium-containing reference data, the algorithm was not able to clearly identify the species from which the error originated.

$\text{TiO}_2$  was validated in the previous section for the Ti–O–Cl test case. Therefore, a new reference set consisting of the oxychloride species, all titanium-containing species and the validated set of carbon, hydrogen and oxygen containing species ( $\epsilon_r^{\text{max}} = 1.0 \text{ kcal mol}^{-1}$ ) was defined. Using this set, a global cross-validation for the Ti–O–C–H species was performed which led to a slightly different conclusion. In this case only  $\text{TiO}(\text{OH})_2$  was identified to be potentially inconsistent. This was a consequence of the larger reference set which enabled the global cross-validation to identify the origin of the inconsistency. Excluding  $\text{TiO}(\text{OH})_2$  led to a mean absolute error of  $0.35 \text{ kcal mol}^{-1}$  for the Ti–O–C–H test case.

Based on the global cross-validation it was assumed that the reference values for  $\text{TiO}_2$  and  $\text{Ti}(\text{OH})_4$  are accurate. Using reaction,



gave an estimate of  $-200.65 \text{ kcal mol}^{-1}$ , which is within the uncertainty of

the previously reported reference value of  $-195.85 \pm 11.83$  kcal mol<sup>-1</sup> [114] for TiO(OH)<sub>2</sub>. The value of  $-200.65$  kcal mol<sup>-1</sup> and a standard deviation of  $3.18$  kcal mol<sup>-1</sup> is recommended and listed in Table 1.

A further global cross-validation using reaction class RC1 (isogyric reactions) allowed the calculation of the standard enthalpy of formation of TiH as  $110.81$  kcal mol<sup>-1</sup> and a standard deviation of  $9.42$  kcal mol<sup>-1</sup>. The error is significantly larger than for the estimates where it was possible to use RC2. This is not entirely unexpected due to the less restrictive reaction class. Similar errors were observed for the other titanium-containing species when using RC1 instead of RC2.

### 3.3. Effect of reaction classes and excluding inconsistent reference data

The availability of sufficient reference data affects whether or not it is possible to apply higher-level reaction classes, for example RC4 and the slightly less rigorous RC3. This is not an issue for the large set of species containing carbon, hydrogen and oxygen, but is a limitation for the other test cases. This section investigates the extent to which the choice of reaction class affects the results for the test case consisting of species containing carbon, hydrogen and oxygen.

Figure 12 shows the effect of the number of EBRs and the reaction class on the estimated enthalpies of formation using different sets of reference data. The lines represent the mean absolute error calculated over 50 independent executions. The shaded areas represent the corresponding standard deviations. The full reference set (RS1) contains all 920 species taken from the NIST Chemistry WebBook [8]. RS2 and RS3 are reduced versions of RS1, determined by applying the global cross-validation with a rejection threshold of  $\epsilon_r^{\max} = 1.0$  kcal mol<sup>-1</sup>. RS2 was a randomly selected reference set out of 50 independent executions of the global cross-validation on the full reference set of 920 species containing carbon, hydrogen and oxygen. RS3 has been created by combining all species found to be consistent at least once in any of these independent runs.

The mean absolute errors converged rapidly to an asymptotic value for each configuration. The results were shown to be repeatable between independent

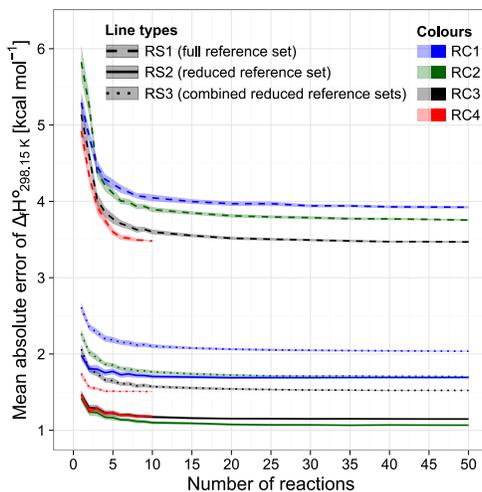


Figure 12: The mean absolute error in the estimated values of the standard enthalpies of formation for the carbon, hydrogen and oxygen containing test species set as a function of the number of considered error-cancelling balanced reactions (EBRs) for different reference sets and reaction classes. The lines represent the calculated mean absolute error and the shaded areas show the standard deviation over 50 independent runs. Reference set RS1 consists of the full set of 920 carbon, hydrogen and oxygen containing species retrieved from the NIST Chemistry WebBook [8], RS2 is a single randomly selected reference set out of 50 independent executions of the global cross-validation ( $\epsilon_r^{\max} = 1.0 \text{ kcal mol}^{-1}$ ) and RS3 is a combination of all identified consistent reference species over 50 independent global-cross validation runs using the same configuration.

runs, where the standard deviation decreased as the number of EBRs increased. However, considerable differences between the asymptotic errors were observed for the different reference sets. As expected, the lowest mean absolute errors were reported using the reduced reference set RS2. Although the mean absolute error using RS3 was significantly reduced compared to the full reference set RS1, the error was larger than for RS2. This is a consequence of not always identifying the same EBRs from the space of possible solutions during the global cross-validation. Therefore, potentially less consistent species are present in reference set RS3.

Generally, the mean absolute errors followed the rigorousness of the reaction

classes. The more rigorous the chosen reaction class, the more accurate the resulting estimate of the standard enthalpy of formation. Nevertheless, reaction class RC4 delivered poorer results than RC2 for reference set RS2. This can be attributed to a loss of the statistical benefit due to a reduction in the numbers of EBRs that could be found for the RC4 reaction class. However, the effect of the reduction in the number of EBRs that could be found for RC4 did not carry through to the statistical uncertainties represented by the standard deviation. The calculated statistical uncertainties were reduced by selecting a more rigorous reaction class.

Table 2 reports the mean standard deviations over all reference species when estimating the standard enthalpies of formation. Applying outlier detection methods, such as the modified Thompson-Tau [112] and modified z-score method [113] reduced the mean standard deviation. The most significant effect was observed for the full reference set RS1. This effect was reduced for the two validated reference sets (RS2 and RS3) due to the exclusion of inconsistent reference data.

Table 2: Effect of reference sets, reaction classes and outlier detection methods on the mean standard deviations calculated over all reference species.

| reaction type | mean standard deviation [kcal mol <sup>-1</sup> ] |      |      |   |                  |                  |                  |                  |                  |
|---------------|---|------|------|---|------------------|------------------|------------------|------------------|------------------|
|               | full reaction set                                 |      |      | revised reaction set excluding outliers |                  |                  |                  |                  |                  |
|               | RS1   | RS2  | RS3  | RS1 <sup>a</sup>                        | RS2 <sup>a</sup> | RS3 <sup>a</sup> | RS1 <sup>b</sup> | RS2 <sup>b</sup> | RS3 <sup>b</sup> |
| RC1           | 4.08  | 1.45 | 2.03 | 2.85                                    | 1.43             | 1.86             | 1.72             | 1.21             | 1.37             |
| RC2           | 5.21  | 1.22 | 1.79 | 2.69                                    | 1.20             | 1.69             | 1.43             | 1.03             | 1.16             |
| RC3           | 4.41  | 1.24 | 1.78 | 2.50                                    | 1.22             | 1.70             | 1.45             | 0.92             | 1.19             |
| RC4           | 2.98  | 1.14 | 1.33 | 1.78                                    | 1.06             | 1.11             | 1.66             | 0.88             | 1.08             |

<sup>a</sup> Modified z-score method with  $z_{\text{score}} = 3.50$

<sup>b</sup> Modified Thompson-Tau method with  $\alpha = 0.05$

For validation purposes, all calculations were additionally performed at the B3LYP/6-311+G(d,p) level of theory for species containing carbon, hydrogen and oxygen. Similar results were obtained, although the B97-1/6-311+G(d,p) level of theory led to slightly lower mean absolute errors. The other test cases

were only evaluated using reaction classes RC1 and RC2. In all cases, it was found that the reported mean absolute error using RC1 was significantly larger than using RC2.

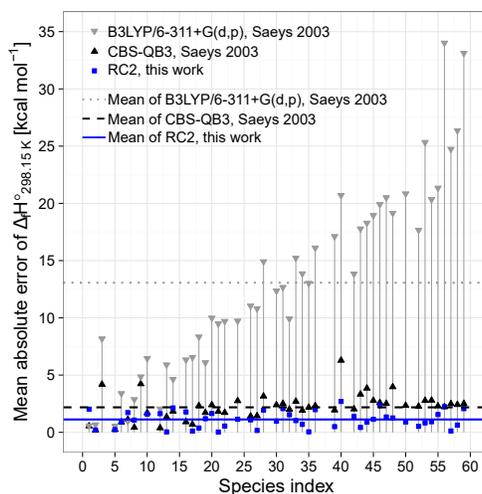
There is a trade-off between the reaction class, the number of EBRs, the choice of reference set and the expected accuracy of the resulting estimates. Given sufficiently accurate reference data, an increased number of EBRs and a more restrictive reaction class improves the accuracy of the estimate. However, the use of an overly restrictive reaction class can result in accurate estimates for individual samples at the expense of losing the statistical benefits of multiple EBRs, resulting in an overall loss of accuracy. Loose constraints, such as the conservation of spin states with isogyric reactions (RC1), result in poorer estimates even if a large number of EBRs and a validated reference set is considered. Isodesmic reactions (RC2) give a good compromise, providing that the reference set is sufficiently large.

### *3.4. Comparison to other methods*

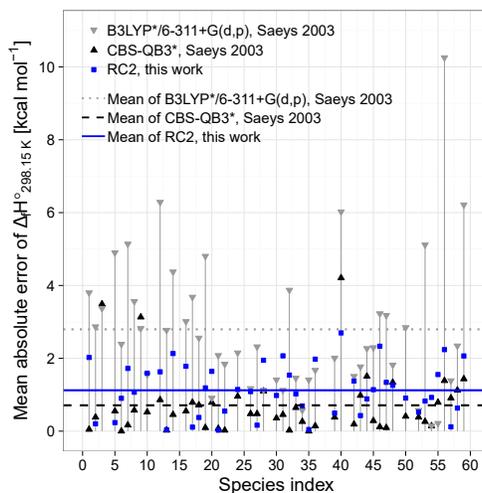
#### *3.4.1. Carbon-Hydrogen-Oxygen-containing species*

Figure 13 compares the calculated mean absolute errors for species overlapping between this work and that of Saeys et al. [53]. Although calculations were conducted using all four reaction classes in combination with reference set RS2, only results using reaction class RC2 are shown for ease of presentation. No additional outlier detection method was applied. For the purpose of comparison, the accuracy against popular quantum chemistry methods without (Figure 13a) and with additional AAC (Figure 13b) was assessed. The species in Figure 13 are ordered by size and agree with the order defined by Saeys et al. [53].

The most accurate estimates reported in Figure 13a were achieved by applying the method presented in this work and have a mean absolute error of 1.12 kcal mol<sup>-1</sup>. The use of CBS-QB3 led to a mean absolute error of 2.18 kcal mol<sup>-1</sup>, which is nearly twice the error obtained by using RC2 with RS2. The DFT method resulted in a significant mean absolute error of 13.07 kcal mol<sup>-1</sup>.



(a) No atom-additivity-correction



(b) With atom-additivity-correction

Figure 13: Comparison of calculated absolute errors against quantum chemistry methods with and without consideration of atom-additivity-correction (AAC). The data were reported by Saeys et al. [53].

A clear size dependence of the error was observed for DFT. A smaller size dependence was detected for the CBS-QB3 method. The errors calculated by the method in this work did not depend on the size of the molecule. It must be

noted that Redfern et al. [115] observed a dependence of the error on the size of the molecule using single isodesmic reactions (RC2) for *n*-alkane species. These calculations were repeated using the method presented in this work with RC2 and RS2 and did not show any dependence on size.

The errors using the quantum chemistry methods were significantly reduced by additionally considering AAC as shown in Figure 13b. The error dependence of the quantum chemistry methods on the size of the molecule was no longer observed. Despite significant improvement, using DFT with AAC still led to a mean absolute error of 2.80 kcal mol<sup>-1</sup>. CBS-QB3 with AAC led to a mean absolute error of 0.71 kcal mol<sup>-1</sup>. Even though the use of AAC significantly reduced the mean absolute errors, it is noted that AAC is not generally applicable to any system nor is it applicable for all levels of theory [53]. Replacing RC2 with more rigorous reaction classes reduced the error to 1.06 kcal mol<sup>-1</sup> for reaction class RC3 and to 0.70 kcal mol<sup>-1</sup> for reaction class RC4. Similar results were obtained using the B3LYP functional. The methodology presented in this work is capable of delivering estimates of the standard enthalpy of formation comparable in accuracy with computationally demanding quantum chemistry methods and without a dependence of the error on the size of the molecule.

#### 3.4.2. Titanium-containing species

The standard enthalpies of formation for various titanium-containing species considered in this work were also calculated by Wang et al. [84] using the computationally demanding coupled-cluster method with complete basis set extrapolation (CCSD(T)/CBS). This is currently considered the "*gold standard*" of quantum chemistry [40].

Table 3: Comparison of calculated standard enthalpies of formation for titanium-containing species using isodesmic reactions against selected reference values and CCSD(T)/CBS estimates as reported by Wang et al. [84].

| species             | this work <sup>a</sup><br>[kcal mol <sup>-1</sup> ] | CCSD(T)/CBS <sup>b</sup><br>[kcal mol <sup>-1</sup> ] | literature value <sup>c</sup><br>[kcal mol <sup>-1</sup> ] |
|---------------------|---|---|--|
| TiCl <sub>4</sub>   | -181.61(2.63)                                       | -181.5  | -182.4   |
| TiOCl <sub>2</sub>  | -141.26(0.65)                                       | -141.8  | -141.8 <sup>d</sup>  |
| TiO <sub>2</sub>    | -73.60(0.68)  | -67.8   | -73.0  |
| Ti(OH) <sub>4</sub> | -302.87(0.22)                                       | -303.2  | -303.2 <sup>d</sup>  |

<sup>a</sup> Calculated using isodesmic reactions using the reference values defined in Table 1 and the set of species containing carbon, hydrogen and oxygen [67]. The B97-1/6-311+G(d,p) level of theory was used. Calculated standard deviations are provided in parentheses.

<sup>b</sup> Calculated by Wang et al. [84].

<sup>c</sup> Reference values as selected in this work (Table 1).

<sup>d</sup> Reference value taken from Wang et al. [84].

Table 3 presents estimates of the standard enthalpy of formation for titanium-containing species calculated using the methodology presented in this work, compared to high-level quantum chemistry calculations at the CCSD(T)/CBS level of theory as reported by Wang et al. [84], and selected literature values as listed in Table 1. Excellent agreement was observed between our estimates and those obtained by CCSD(T)/CBS for TiCl<sub>4</sub>, TiOCl<sub>2</sub> and Ti(OH)<sub>4</sub>. There was excellent agreement with the literature value for TiO<sub>2</sub> but less so with the calculated value by Wang et al. [84]. The proposed method was able to predict highly accurate standard enthalpies of formation comparable to computationally demanding quantum chemistry methods.

#### 4. Conclusions

This paper presents an automated framework that uses overlapping subsets of reference data to systematically derive an informed estimate of the standard enthalpy of formation of a species using error-cancelling balanced reactions

(EBRs). A distribution of estimates is derived for each species using multiple EBRs from which an informed estimate can be determined. Overall, this is a more accurate estimate than can be obtained from a single reaction. A global cross-validation is used to assess the consistency of the reference data. The EBRs are used to calculate the error contribution from each species in the reference data set, enabling potentially inconsistent reference data to be isolated and excluded.

The functionalities of the framework were demonstrated using test cases from organic and inorganic chemistry, including transition metal complexes. The cases included 920 species containing carbon, hydrogen and oxygen retrieved from the NIST Chemistry WebBook [8], titanium-containing species and oxychloride species from various sources. Electronic structure calculations were performed using DFT at the B97-1/6-311+G(d,p) level of theory for all species considered in this work.

Constrained optimisation, in the form of linear programming, was used to identify individual EBRs. This was combined with a recursive algorithm to systematically identify multiple distinct EBRs. It was found that using multiple EBRs to calculate a distribution of the standard enthalpy of formation resulted in significantly better estimates than from a single reaction. An estimate of the expected statistical uncertainty resulting from the calculation could be derived from the width of the distribution of possible enthalpy values.

A global cross-validation was developed to assess the consistency of the reference data. Different parametrisations were evaluated. For all parameter configurations, the mean absolute error decreased asymptotically as a result of excluding potentially inconsistent reference species. The results of the cross-validation were found to be most sensitive to the rejection threshold parameter. Aspects such as the choice of the level of theory, the reaction class, the statistical benefit from the consideration of multiple EBRs and uncertainties in the reference data require consideration when choosing the rejection threshold. In general, the lower the rejection threshold, the smaller the expected mean absolute error and therefore the higher the accuracy.

Applying the global cross-validation to the test case with carbon, hydrogen and oxygen containing species showed that excluding potentially inconsistent species from the reference data set resulted in a significant reduction in the error in the estimated standard enthalpies of formation. A considerably reduced effect was observed for the smaller oxychloride reference set. In cases where the error reduction is significantly limited, a trade-off has to be made as to whether the statistical benefit from a larger reference set outweighs the exclusion of the potentially inconsistent species. As long as the given reference set is sufficiently large, using isodesmic reactions or an even more restrictive reaction class, should be considered for the global cross-validation. It is then further suggested to choose the same or a more restrictive reaction class for the estimation of the enthalpy of formation of the target species.

The choice of reaction class had an impact on the accuracy of the estimates for all of the reference sets investigated in the test case consisting of carbon, hydrogen and oxygen containing species. Generally, the more rigorous the reaction class, the more accurate the expected estimate. It is noted that there is a trade-off between the reaction class, the number of EBRs and the reference set. The statistical benefit of using multiple EBRs can outweigh the choice of a more rigorous reaction class. Overall, it was found that isogyric reactions should be avoided while isodesmic reactions offered a good compromise.

Applying outlier detection methods decreased the statistical uncertainty. The decrease was significantly larger in cases where the full reference set was used, compared to cases that used reduced sets of reference data that excluded potentially inconsistent species identified by the global cross-validation.

Comparison of the estimates of the enthalpy of formation obtained in this work for hydrocarbon species *versus* those calculated by Saeys et al. [53] showed that the framework is able to predict highly accurate standard enthalpies of formation, comparable to high-level quantum chemistry methods. This was further supported by the comparison of the estimates for the transition metal complexes to values obtained by the currently considered "*gold standard*" coupled-cluster calculation method with complete basis set extrapolation, for which excellent

agreement for  $\text{TiCl}_4$ ,  $\text{TiOCl}_2$  and  $\text{Ti(OH)}_4$  was achieved. The estimate for  $\text{TiO}_2$  was in excellent agreement with reported NIST-JANAF reference values [8, 9] but in slightly poorer agreement with the results from the coupled-cluster method.

Two potentially inconsistent transition metal complexes were found using the global cross-validation:  $\text{TiO(OH)}_2$  and  $\text{TiOCl}$ . Revised standard enthalpies of formation for both complexes were proposed. The reference data for all other considered transition metal complexes were found to be consistent.

The application to the titanium-containing species demonstrates that the framework is able to calculate accurate enthalpies of formation for systems where only a few reference values are available. This allows for a systematic and automated investigation of increasingly complex reaction systems. The global cross-validation is useful in identifying inconsistent reference data which can then be targeted to improve the quality of model.

It is intended to make this framework available as a web application. Users should be able to assess the consistency of their own data sets. Furthermore, it is envisaged that users are also able to use pre-validated data sets from linked databases and repositories to calculate informed estimates of the standard enthalpies of formation. A systematic consideration of reported uncertainties and error bars and an automated identification of the true source of the inconsistency would certainly be of great interest.

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