Comparing Heat of Reaction data produced from TAFFI Component Increment Theory (TCIT) and Chemical Thermodynamic and Energy Release (CHETAH) for assorted reactions

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December 8th, 2023

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Introduction

In the pharmaceutical industry, it is important to know the heat of reaction for a variety of compounds. Understanding the heat of reaction can help with process optimization involving drug synthesis, scale-up and manufacturing, and quality control. Additionally, heat of reaction values is crucial for assessing the safety of a chemical process. Reactions that are highly exothermic are hazardous as they will release a large amount of heat that needs to be dispersed safely.

When new compounds are being developed regularly, there is not always previous data that can be used to estimate the heat of reaction. To avoid having to run a multitude of small-scale tests to determine experimental values, computational tools can be used to predict the overall heat of reaction and the heat of formation for individual components. The current commercially available prediction tool is the software CHETAH (Chemical Thermodynamic and Energy Release) that has been around since 1974. However, CHETAH can't handle a variety of compounds, including some ring structures, charged molecules, radicals, and more. TCIT (TAFFI Component Increment Theory) is being designed by Professor Savoie's team at Purdue University. While TCIT is still in development, the goal is to have it correct some of the deficiencies of CHETAH leading to more accurate predictions. The results from TCIT and CHETAH are being compared with experimental data to give an increased understanding of the accuracy of each program, and highlight what compounds, functional groups, or elements, aren't covered by the program.

Objective

The overall goal of this project is predicting the heat of reaction values for reactions and compounds provided from representatives of pharmaceutical companies. These predictions generated TCIT and CHETAH can then be compared to experimental values found in the literature or given by the representatives. The compounds investigated included the decomposition reactions of Di-tert Butyl Peroxide, T-butyl Hydrogen Peroxide, hydrogen peroxide, and hydrazine as well as the analysis of sulfur containing reactions from the previously published paper by Weisenburg et al., 2007. A secondary focus included the use of the software YARP (Yet Another Reaction Program), developed by Professor Savoie's team along TCIT, which predicts decomposition products and the activation energy required for those reactions.

Methods

CHETAH and Benson Group Increment Theory

Chemical Thermodynamic and Energy Release (CHETAH) is a commercially available program from ASTM International that utilizes Benson Group Increment Theory (BGIT) to calculate and heat of formation for a compound. Benson Group Theory relies on the known heats for formation for smaller compounds to estimate the heat of formation for the larger compound. The theory assumes that the smaller groups are very localized and do not experience any interaction effects from neighboring groups and the small groups are typically generated as the atom of interest and the atoms connected to it. The heat of formation for the smaller compounds is summed to provide an overall heat of formation for the compound of interest. In addition to running individual heat of formation calculations for compounds, CHETAH can run a whole reaction at once and provide the heat of reaction.

TCIT

TAFFI (Topology automated force-field interactions) Component Increment Theory (TCIT) is based on component theory. This differs from group theory in how the atoms are analyzed and building blocks are generated. In component theory, atoms are analyzed two positions away from the atom of interest, resulting in a greater accuracy than from BGIT where atoms are only analyzed one position away. Every molecule analyzed is broken down into components, as shown in figure 1.

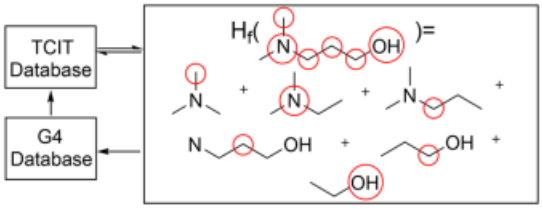


Figure 1: Example of a G4 breakdown as utilized in TCIT.

These smaller segments have their heat of formation calculated though the Gaussian-4 (G4) database which is a composite quantum chemistry computational model. One of the advantages of TCIT compared to CHETAH is that TCIT will automatically include ring corrections. TCIT currently has a full working program for all molecules containing only hydrogen, carbon, oxygen, and nitrogen, though it can handle some molecules containing other elements. TCIT is currently being expanded to have a full database for additional elements like Sulfur, Chlorine, and Bromine.

ΔH_{rxn} Calculation method

CHETAH and TCIT both calculate the heat of reaction by the equation below, which relates the heats of formation for each compound in a reaction:

$$\Delta H_{rxn} = \sum mH_{f,products} - \sum nH_{f,reactants} \quad (1)$$

The coefficients m and n represent the coefficients in the stoichiometric equation relating the compounds A and B as shown below:

$$nA \rightarrow mB \quad (2)$$

YARP

Yet Another Reactor Program (YARP) is currently in development at Purdue University. The goal of the program is to take a compound and predict the decomposition products, as well as the activation energy needed to achieve that product. YARP automatically filters some unrealistic decomposition products if their Lewis structures are unreasonable. YARP performs only what could be considered the first step in a decomposition reaction, and so in order to get the true final decomposition products, it may be necessary to take the first round of results and run them through the program again.

Results

All decomposition and sulfur containing reactions were run at 298 K, with all reactants and products in a neat gaseous state to ensure accurate comparison between experimental values and TCIT and CHETAH calculations. The results for the decomposition reactions run this semester can be seen below in table 1. The table contains the compound decomposed, the potential reaction pathway, the experimental data, TCIT and CHETAH computed values, and the percent error for the CHETAH and TCIT values as compared to the experimental values. The percent error is calculated using the equation below:

$$\%\ error = \frac{Experimental\ value - Calculated\ value}{Experimental\ value}\ x\ 100 \quad (3)$$

Experimental values for these reactions were provided from the pharmaceutical representatives, online databases, or from literature. Experimental data for the di-tert-butyl peroxide decompositions was from the Iizuka Paper titled: “Comprehensive kinetic model for adiabatic decomposition of di-*tert*-butyl peroxide using batchcad.” For the decomposition reactions, few substitutions were needed in the CHETAH program, as the only compounds

present in most of the compounds are the base elements hydrogen, carbon, oxygen, and nitrogen.

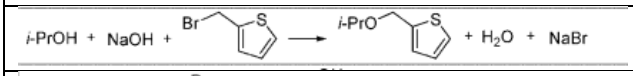
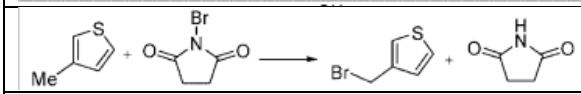
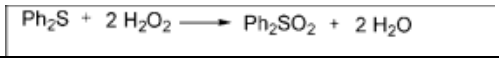
Table 1: Decomposition reactions

Compound	Predicted decomposition products	Experimental Heat of Reaction (kJ/mol)	CHETAH Heat of Reaction (kJ/mol)	TCIT Heat of Reaction (kJ/mol)	CHETAH percent error (%)	TC IT percent error (%)
di-Tert butyl peroxide	4DTBP -> 4acetone + t-butanol + 2IBO + MEK + C2H4 + 2CH4	-124.83	-177.34	-151.411	42.07	21.29
	DTBP + 2toluene -> acetone + t-butanol + diphenyl ethane + methane	-170.707	-179.326	-222.003	5.05	30.05
	DTBP + benzene -> acetone + t-butanol + toluene	-179.619	-231.710	-222.913	29.00	24.10
T-butyl hydrogen peroxide	TBHP -> acetone + methanol	-209	-191.920	-179.816	8.17	13.96
	TBHP -> isobutylene oxide + water	-209	-245.684	-164.972	17.55	21.07
	THBP -> ½ acetone + ½ methanol + ½ isobutylene oxide + ½ water	-209	-218.802	-172.394	4.69	17.51
Hydrogen Peroxide	2H2O2 -> 2H2O + O2	-94.6	-105.688	107.53	11.72	13.67
Hydrazine	N2H4 -> 1/3N2 + 4/3NH3	-176	-156.55	-157.46	11.05	10.53

The results from the decomposition reactions were overall acceptable, and many had an error below 20% both TCIT and CHETAH with a few exceptions. This is very promising when looking at TCIT's developing capabilities.

Table 2 contains the TCIT and CHETAH results for some of the sulfur containing reactions found in the Pfizer paper. Not all the sulfur containing reactions were able to be run, as they either contained ionic bonds or elements that TCIT and CHETAH can't handle. Any simple ionic compound, like sodium hydroxide, was unable to be run in TCIT, and the heat of formation used in the overall calculations is from the National Institute of Standards and Technology (NIST) databases. For the second reaction in this table, CHETAH was unable to make appropriate substitutions to run the reactions, and so there is no data to compare to the experimental value. This inability from CHETAH is contradicted by the TCIT's ability to generate a prediction, even if it is not the most accurate. As you can see, the results from the sulfur reactions varied more than the decomposition reactions.

Table 2: Sulfur Containing reactions results

Reaction	Experimental Heat of Reaction (kJ/mol)	CHETAH Heat of Reaction (kJ/mol)	TCIT Heat of Reaction (kJ/mol)	CHETAH percent error (%)	TC IT percent error (%)
	-88.0	97.445	-61.891	210.73	29.67
	-122.2	n/a	-37.318	n/a	69.46
	-565.547	-584.547	-481.855	3.36	14.80

Conclusion and Future Work

Many of the decomposition reactions being analyzed this semester showed similar results for TCIT and CHETAH, with the percent error margin being in the acceptable range of less than 20%. This indicated that for compounds composed of simply the base elements hydrogen, carbon, oxygen, and nitrogen, both programs can produce reliable results. These accurately predicted heat of reactions ensure that the pharmaceutical industries can adequately prepare for the reactions and prevent any potential hazards.

More work needs to be done for the sulfur containing reactions. It is possible that the higher error percentages are due to the presence of ionic compounds and other halogens like bromide. So, in addition to continuing work on the sulfur reactions provided from the Weisenburg et al., 2007 paper, it could be beneficial to compare simpler sulfur containing reactions to isolate the effect the sulfur atom has on TCIT and CHETAH predictions. The pharmaceutical representatives have expressed interest in some persulfate reactions, and once the issues with running them in TCIT are resolved, they could be a good benchmark as the only elements in those reactions are hydrogen, oxygen, and sulfur.

The pharmaceutical representatives have also indicated an interest in azide-containing compounds, and the abilities of the program YARP. They have provided some azide compounds for our use, but TCIT has no model compounds for the azide compounds. Once those are added by Professor Savoie's team, we should be able to start comparing the results of the TCIT and CHETAH for those compounds. Regarding YARP, there are several compounds that should be explored, including di-tert butyl peroxide and tert-butyl hydrogen peroxide that were run this semester and are in table 1, to see if the predicted compounds match what YARP predicts.

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