Heat of Reaction Comparison between Chemical Thermodynamic and Energy Release (CHETAH) and TAFFI Component Increment Theory (TCIT) for Aryl Nitro Compounds

Madeline Mills[a], Roy Flanagan[b], Derek Brown[c], Jeff Sperry[d], Han Xia[e], Ray Mentzer[a]

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[a]*Davidson School of Chemical Engineering, Purdue University, West Lafayette, IN*

[b]*GlaxoSmithKline, 5 Moore Dr, Research Triangle, NC 27709*

[c]*Amgen Inc., 1 Amgen Center Dr, Thousand Oaks, CA 91320*

[d] *Vertex Pharmaceuticals, 50 Northern Ave, Boston, MA 02210*

[e]*Eli Lilly and Company, 893 Delaware St, Indianapolis, IN 46225*

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Introduction

In the process of developing pharmaceutical products, many energetic, or explosive, materials and intermediates are used. Some examples of compounds that tend to be considered energetic materials include compounds that contain a nitro group, such as TNT. It is crucial to know the temperatures these compounds will naturally degrade at, the heat of reaction, and the products that will form upon thermal degradation. The current industry-wide practice is to perform Differential Scanning Calorimetry (DSC) on an individual basis. However, this process is time intensive and costly as it consumes each compound tested. Additionally, sometimes the temperatures at which this calorimetric test is run does not comprise of the full thermal decomposition, and the products following degradation are unknown. To determine the thermal degradation heat of reaction and the decomposition products of these compounds, two predictive methods were investigated and were compared to the experimental DSC results. The two software methods used were CHETAH (Chemical Thermodynamic and Energy Release) and TCIT (TAFFI Component Increment Theory). Previous work conducted that compared CHETAH and TCIT included the prediction of the heats of reaction for pyrazoles and additional reactions such as halogenation and Suzuki couplings (Young et al., 2022) . This paper seeks to expand upon the reactions that have predicted heats of reaction using these programs.

Objective

The overall goal of this on-going project is to predict the heats of decomposition for various pharmaceutical compounds through the comparison of two computer programs, CHETAH and TCIT. Specifically, the compounds investigated were aryl compounds primarily containing a nitro group, along with additional substitutions. While the heats of reaction were accurately predicted for these compounds using both programs, a secondary goal of predicting the decomposition products was also accomplished.

Methods

CHETAH and Benson Group Increment Theory

Two programs were utilized to calculate the heats of reaction of the aryl nitro and pyrazole compounds. The first program, Chemical Thermodynamic and Energy Release, or CHETAH, is a commercially available program and is the most widely used in industry. CHETAH utilizes Benson Group Increment Theory (BGIT) to calculate the heat of formation (Hf) of a compound. Benson Group Increment Theory relies on the known heats of formation of smaller compounds. The theory assumes that the individual groups are relatively localized, and they do not experience significant interactions from neighboring groups. In order to determine the heat of formation of a compound, one simply must sum the number of groups in a compound. An example from Moiseeva et al. is shown in Figure One below.

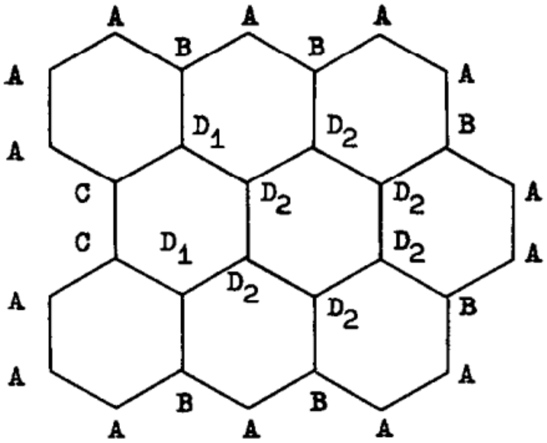


Figure 1: *Image from Moiseeva et al. displaying the different carbon environments in a Benson Group Increment Theory calculation*

In the above image, each letter represents a different type of carbon. For example, the D carbons are bonded to three other carbons, whereas the A carbons are bonded to two other carbons. According to BGIT, it does not matter whether an “A” carbon is bonded to other “A” carbons or a “B” carbon; the contribution from all “A” carbons is the same. Conversely, for the theory utilized by the second program, TCIT, the “A” carbon would have a different value if it were bonded to a “B” or “C” carbon.

TCIT and Component Increment Theory

While Benson Group theory has been the standard for several decades, recent advances have led to the conclusion that it is necessary to account for neighboring atoms in heats of formation calculations. According to (Zhao & Savoie, 2020) it is possible to take atomic interactions into account when utilizing TAFFI component increment theory, where TAFFI refers to topology-automated force field interactions. The method accounts for nearby atoms up to two carbons away, as illustrated in part d of Figure Two below.

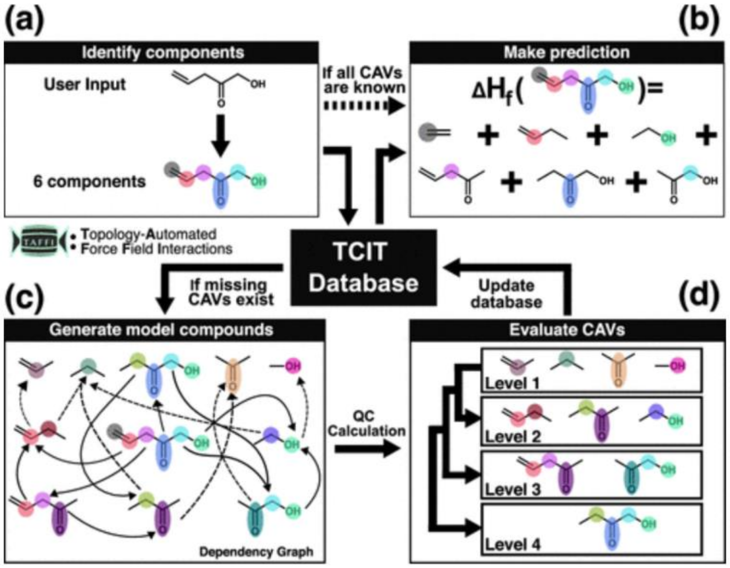


***Figure 2**: Graphical diagram from Zhao & Savoie demonstrating the inner calculations within the TCIT program.*

Level one consists of the base units, followed by the addition of more adjacent carbons in the following levels. These interactions are used to calculate component additive values (CAVs), which are then used to determine the compound heat of formation. TCIT is a publicly available software for use with Linux.

Calculation Procedure

After obtaining the heats of formation for each compound and its products, the overall heat of reaction was calculated according to Equation One below:

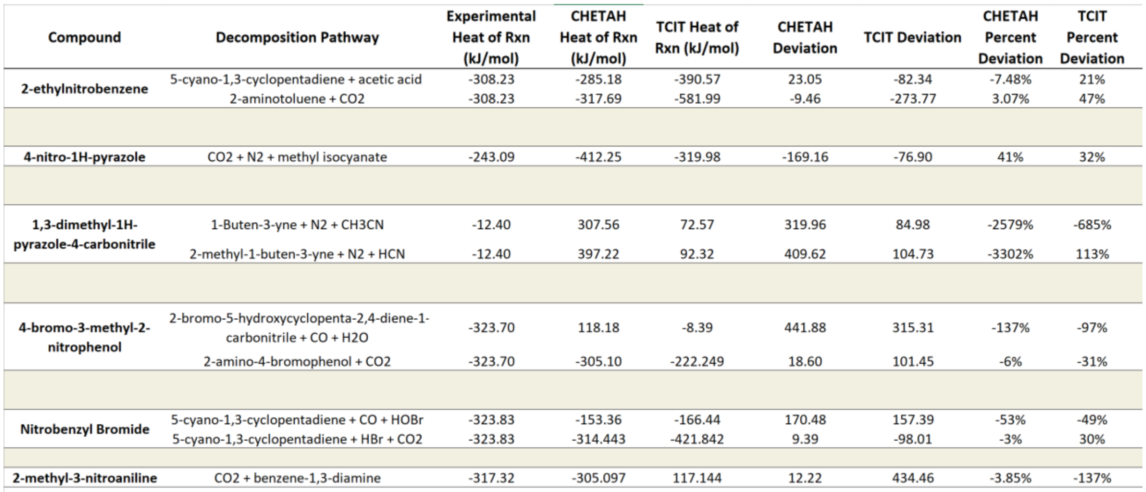
$$\Delta H_{rxn} = \sum mH_{f,products} - \sum nH_{f,reactants} \quad (1)$$

Where m and n are coefficients to reactants A and products B in the balanced stoichiometric reaction equation:

$$mA \xrightarrow{yields} nB \qquad (2)$$

Results

The overall results can be seen in Table One below. Table One features the compound name, decomposition pathways predicted, and comparisons between the experimental heat of reaction from a DSC curve along with the predicted heats of reaction from both the CHETAH and TCIT program. The final two columns of the table consist of the percent deviation between the CHETAH results and experimental results and the TCIT and experimental results, respectively.



Compound	Decomposition Pathway	Experimental Heat of Rxn (kJ/mol)	CHETAH Heat of Rxn (kJ/mol)	TCIT Heat of Rxn (kJ/mol)	CHETAH Deviation	TCIT Deviation	CHETAH Percent Deviation	TCIT Percent Deviation
2-ethylnitrobenzene	5-cyano-1,3-cyclopentadiene + acetic acid	-308.23	-285.18	-390.57	23.05	-82.34	-7.48%	21%
	2-aminotoluene + CO2	-308.23	-317.69	-581.99	-9.46	-273.77	3.07%	47%
4-nitro-1H-pyrazole	CO2 + N2 + methyl isocyanate	-243.09	-412.25	-319.98	-169.16	-76.90	41%	32%
1,3-dimethyl-1H-pyrazole-4-carbonitrile	1-Buten-3-yne + N2 + CH3CN	-12.40	307.56	72.57	319.96	84.98	-2579%	-685%
	2-methyl-1-buten-3-yne + N2 + HCN	-12.40	397.22	92.32	409.62	104.73	-3302%	113%
4-bromo-3-methyl-2-nitrophenol	2-bromo-5-hydroxycyclopenta-2,4-diene-1-carbonitrile + CO + H2O	-323.70	118.18	-8.39	441.88	315.31	-137%	-97%
	2-amino-4-bromophenol + CO2	-323.70	-305.10	-222.249	18.60	101.45	-6%	-31%
Nitrobenzyl Bromide	5-cyano-1,3-cyclopentadiene + CO + HOBr	-323.83	-153.36	-166.44	170.48	157.39	-53%	-49%
	5-cyano-1,3-cyclopentadiene + HBr + CO2	-323.83	-314.443	-421.842	9.39	-98.01	-3%	30%
2-methyl-3-nitroaniline	CO2 + benzene-1,3-diamine	-317.32	-305.097	117.144	12.22	434.46	-3.85%	-137%

Table 1: *A summary table of aryl nitro and pyrazole compounds that have heat of reaction predictions from CHETAH and TCIT*

The percent deviation utilized was found according to the following equation:

$$percent\ deviation = \frac{\frac{CHETAH}{TCIT}value - DSC\ experimental\ value}{DSC\ experimental\ value} \qquad (3)$$

Where the experimental results refer to the measurements from TCIT and CHETAH, and the theoretical results are the results from the differential scanning calorimeter. The results from the calorimeter are assumed to be the accurate and standard measurements that the results from the programs are compared to. Previous literature trends maintain that CHETAH is less accurate than TCIT due to CHETAH often needing substitutions for compounds in the heat of formation calculation. However, if CHETAH did not provide a substitution, a literature value from NIST was utilized. The use of literature values, coupled with the current difficulties that TCIT encounters with nitro-containing compounds, could be the cause for the deviation from the literature trend.

The primary focus on the class of compounds studied in Table One was on aryl compounds containing a nitro group that was ortho (or adjacent to) an alkyl sidechain. The general structure of these compounds can be seen in Figure Three below.

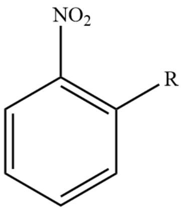


Figure 3: *Drawing of a general aryl nitro compound, with the nitro group ortho to the alkyl group*

Table Two below contains drawings of the mechanistic pathways for several of these molecules. By examining percent deviation associated with each pathway, it is evident that the mechanisms that contain carbon dioxide as a product generally have predicted heats of reaction with less percent deviation from the accepted value. This observation leads to determining a general mechanism for most aryl compounds with adjacent nitro and alkyl chains, in which the nitrogen oxidizes the alkyl group to produce carbon dioxide. The general proposed mechanism typically produces an amino aryl compound, along with carbon dioxide and other products based off the substituents present.

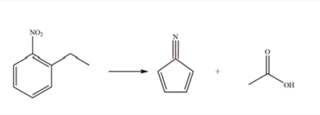
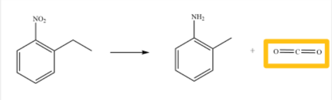
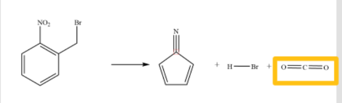
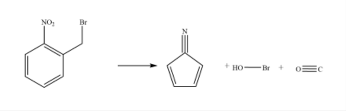
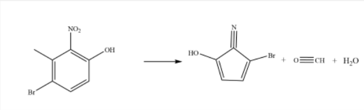
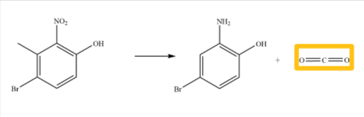
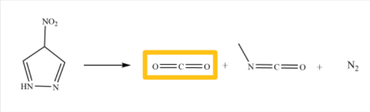
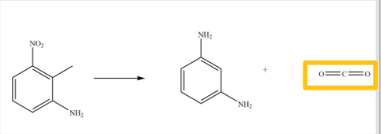
Compound	Mechanism Drawing	CHETAH Percent Deviation	TCIT Percent Deviation
2-ethylnitrobenzene		-7.48%	21%
		3.07%	47%
2-nitrobenzyl bromide		-2.90%	30%
		-63%	60%
4-bromo-3-methyl-2-nitrophenol		-137%	97%
		-6%	-31%
4-nitro-1H-pyrazole		41%	32%
2-methyl-3-nitroaniline		-3.85%	-137%

***Table 2**: A table containing drawing of each mechanism for a variety of aryl compounds, along with the associated percent deviation of each program's results from the DSC value*

However, as seen in Table One, four of the five compounds with expected mechanisms had at least one pathway that had error less than 42% for both calculations, except for 1,3-dimethyl-1H-pyrazole-4-carbonitrile. The hypothesis for this lack of accuracy for the pyrazole is because the full decomposition is not captured in the DSC curve. The curve begins to trend upwards on the far-right x-axis, around 350 degrees Celsius. Because the calorimetric test cannot be run at temperatures higher than 350 degrees, it is difficult to accurately predict the decomposition products when the decomposition is just beginning at temperatures around 350-400 degrees Celsius.

Conclusions and Future Work

The determination of a general mechanism and comparison of results from TCIT and CHETAH for *o*-nitro aryl compounds is significant. From a safety standpoint, it is possible to predict the heat of reaction and the products for this class of compounds prior to beginning a pharmaceutical process containing aryl nitro intermediates. The results of five of the six compounds from Table One have been deemed accurate as the error is less than approximately 40% for each predicted heat of reaction.

With regards to future work, more aryl nitro compounds will be investigated. These compounds contain substituents that are either meta or para to the nitro group. The full list of compounds is shown in Table 3 below. The boxes containing a green background represent compounds that have DSC data, CHETAH heat of formation calculations, and TCIT heat of formation calculations, but there is no proposed mechanism for the green compounds. The yellow compounds require both a proposed mechanism and heat of formation predictions using both programs. The addition of accurately predicted heats of reaction for these compounds, along with mechanistic pathways, will ensure that the pharmaceutical industry will have data before an experiment or formulation begins, allowing the process to be safer.

4-((4-nitrophenyl)sulfonyl)morphine	2-chloro-6-methoxy-3-nitropyridine	2-nitrobenzenesulfonic acid
4-nitrobenzyl alcohol	4-bromo-3-methyl-2-nitrophenol	2-bromo-3-nitrotoluene
4-nitrotoluene	3-nitrosalicylaldehyde	2-methyl-6-nitroaniline
5-bromo-2-nitroanisole	2-nitrobenzenesulfonyl chloride	

Table 3: *A table of the compounds that will be considered in the future. All compounds have DSC data, green compounds have calculated heats of formation but no predicted mechanism, and yellow compounds require both heats of formation and mechanisms.*

References

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