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Evaluation and Prediction of Thermal Hazards in 5-Membered Aromatic Heterocycles

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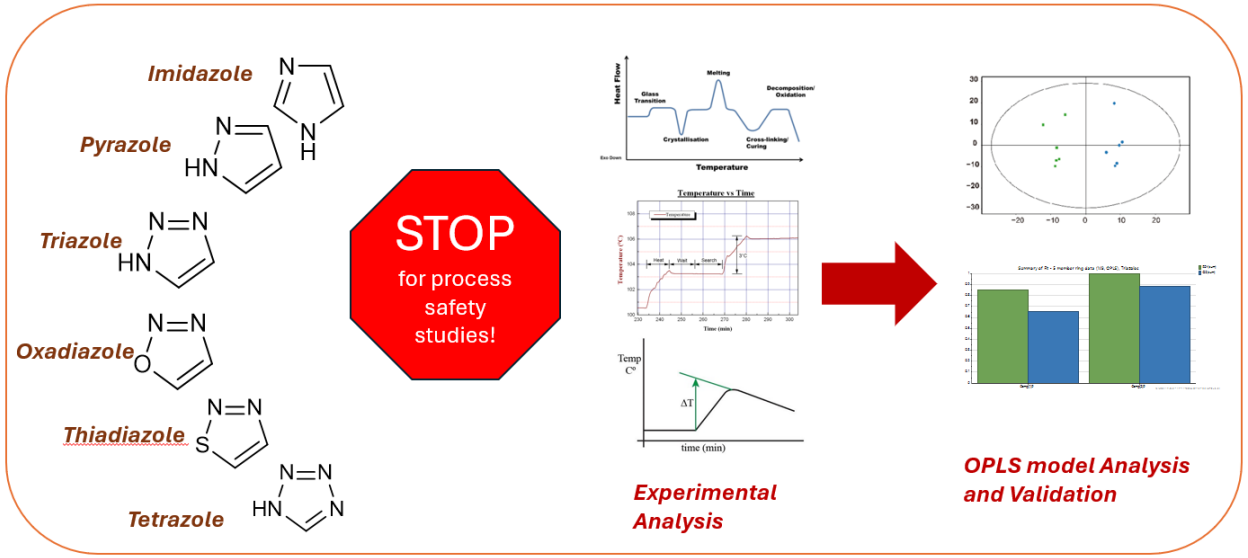
Agenda



Introduction

Motivation for work

Experimental data and interpretation.

Multivariate model

OPLS model work flow

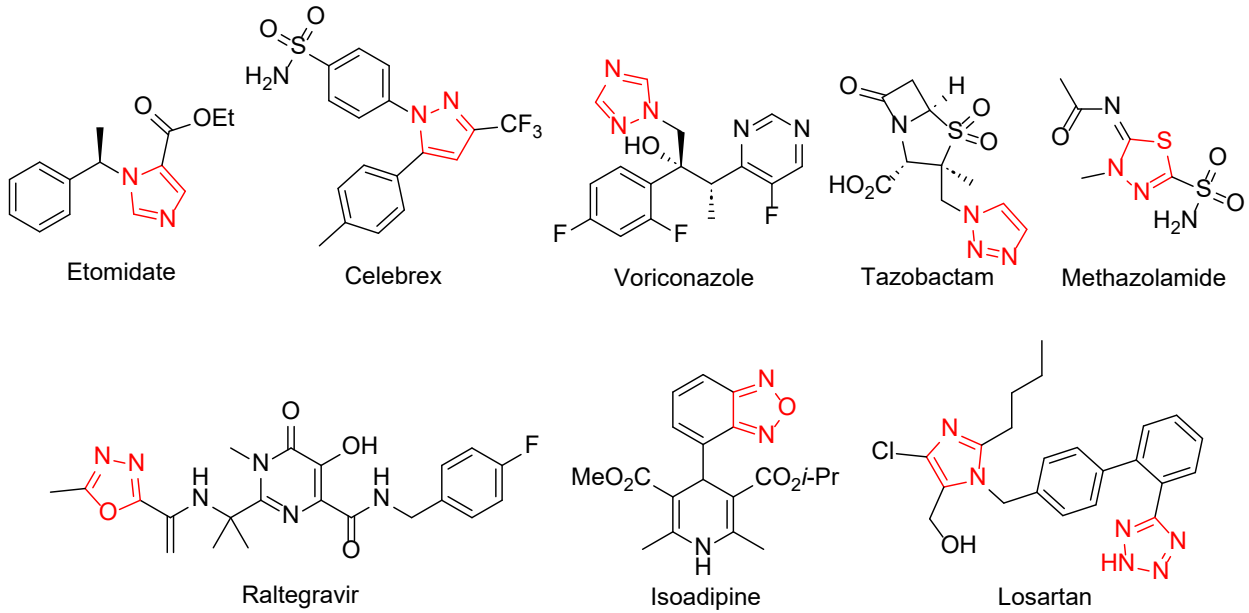
Interpretation of model data.

Summary

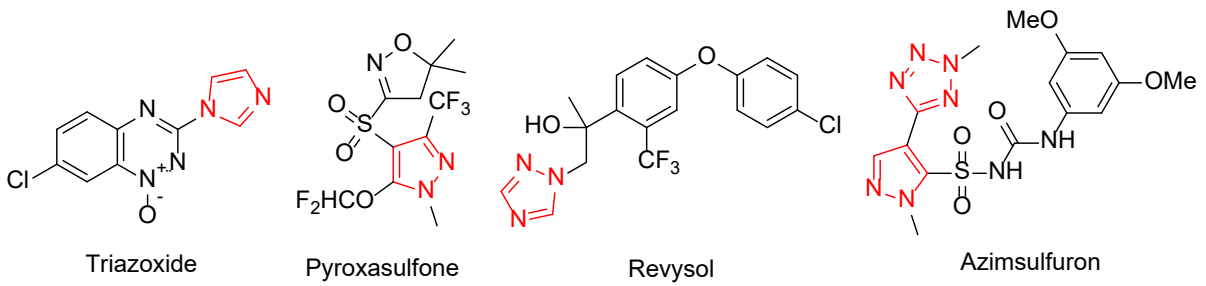
Introduction

- **5-member ring molecules:** Common in pharmaceuticals and agrochemicals.
- **Commercialized**: Many active ingredients contain these moieties.
- **High-Energy Groups**: Often decompose at low temperatures, releasing higher amount of heat.
- **Explosive Potential**: Some derivatives are studied for explosives. (triazole and oxadiazole)
- **Thermal Impact**: Functional groups affect decomposition behavior.

Pharmaceutical APIs:



Agrochemical AIs:



Motivation for work

1. Safety Data: DSC data on T_{onset} and ΔH are crucial for defining safe operating limits to handle chemicals safely.

2. Data Availability: Safety data for 5-membered aromatic heterocycles with heteroatoms is not systematically available at early stages.

3. Misinformation Risks:

1. Example; Synthesis of 1,1′-Azobis-1,2,3-triazole.[1]
2. There is need to predict T_{onset} and ΔH without experiments.

4. OPLS Model: Utilized to correlate structural features with thermal properties using experimental DSC data.

5. Systematic Approach: Ensures accurate correlation and prediction of thermal properties.

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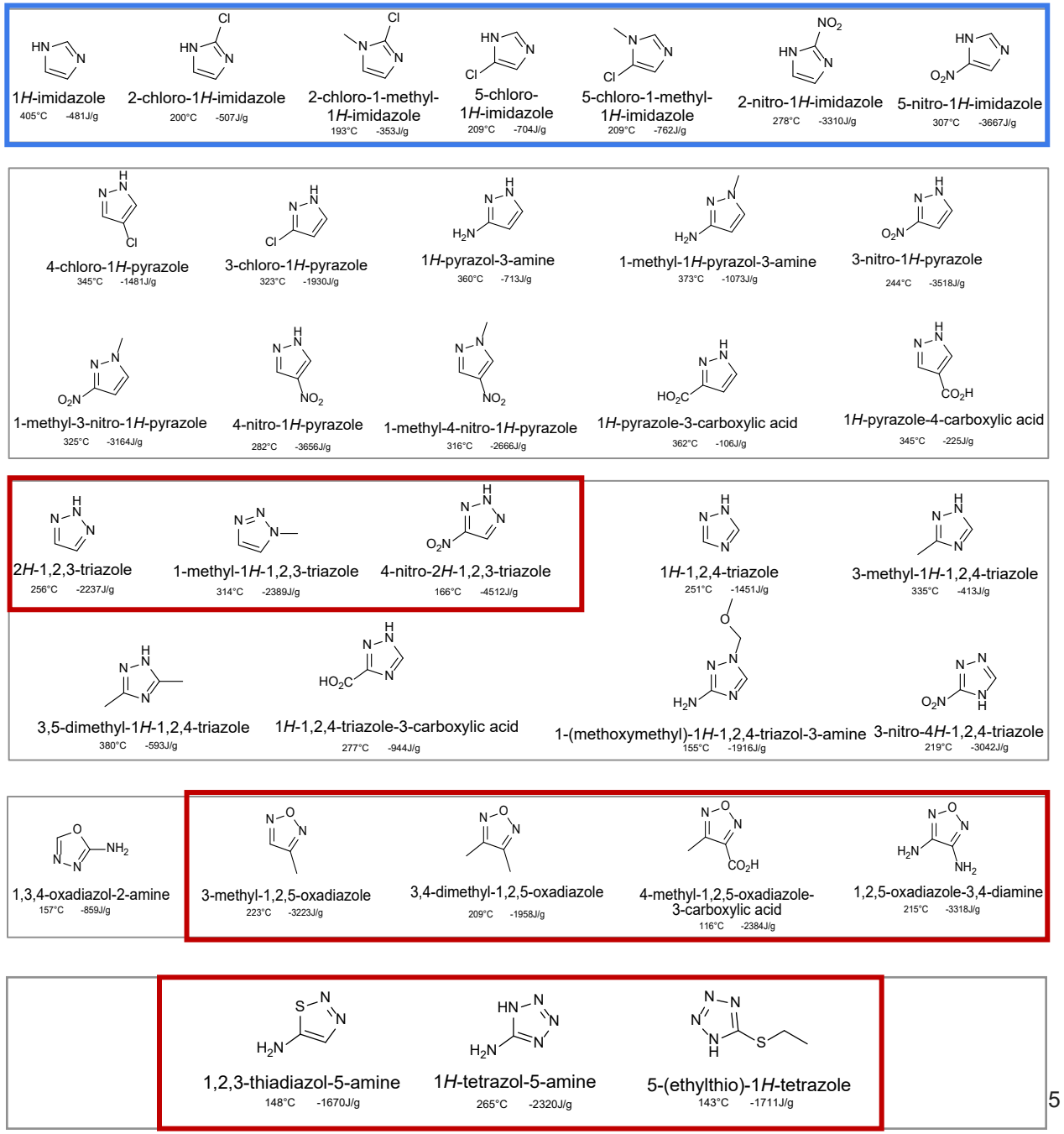
1. https://doi.org/10.1021/acs.oprd.4c00404

Experimental data and interpretation

- **Thermal hazard data:** imidazole, pyrazoles, triazoles, oxadiazoles, thiadiazoles, and tetrazoles.
  - Tonset, peak temperature, and ΔH are experimentally investigated.
- The UN Test Manual classifies contiguous nitrogen atoms and nitro (**NO2**) groups as high-energy functional groups.
- Substrates with **three or four contiguous heteroatoms** (e.g., 1,2,3-triazoles, 1,2,5-oxadiazoles, 1,2,3-thiadiazole, and tetrazoles) exhibited higher ΔH than those with only two contiguous heteroatoms (e.g., 1,2,4-triazoles, 1,3,4-oxadiazole, pyrazoles).
- **Imidazoles** showed lower ΔH compared to other rings, as they do not contain contiguous nitrogen atoms in the ring.



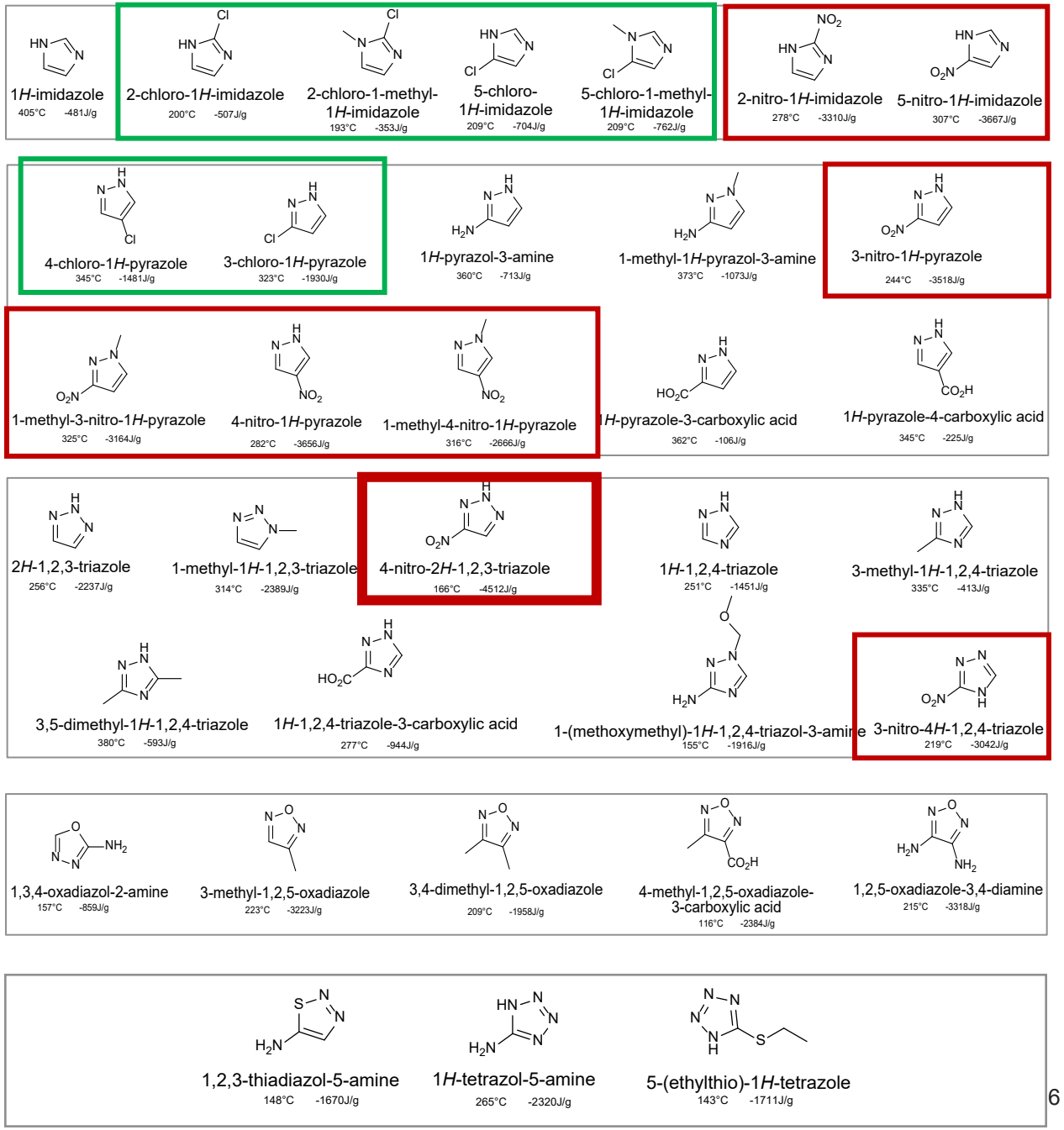
Experimental data and interpretation

- Adding a **high-energy NO_2 group** significantly increased the ΔH to -3000 J/g or more in several compounds.

- 4-nitro-2H-1,2,3-triazol exhibited the highest ΔH of >-4500 J/g.

- Other functional groups such as methyl (**CH_3**), chloro (**Cl**), and amino (**NH_2**) did not significantly influence the thermal behaviors compared to the **NO_2** group.

- The presence of **Cl** on the ring consistently lowered the onset temperatures while increasing the ΔH in several compounds, **despite Cl not being classified as a high-energy** functional group.



Experimental data and interpretation

Heterocycles with a single $\mathbf{NH_2}$ substituent

1H-tetrazol-5-amine: -2320 J/g.

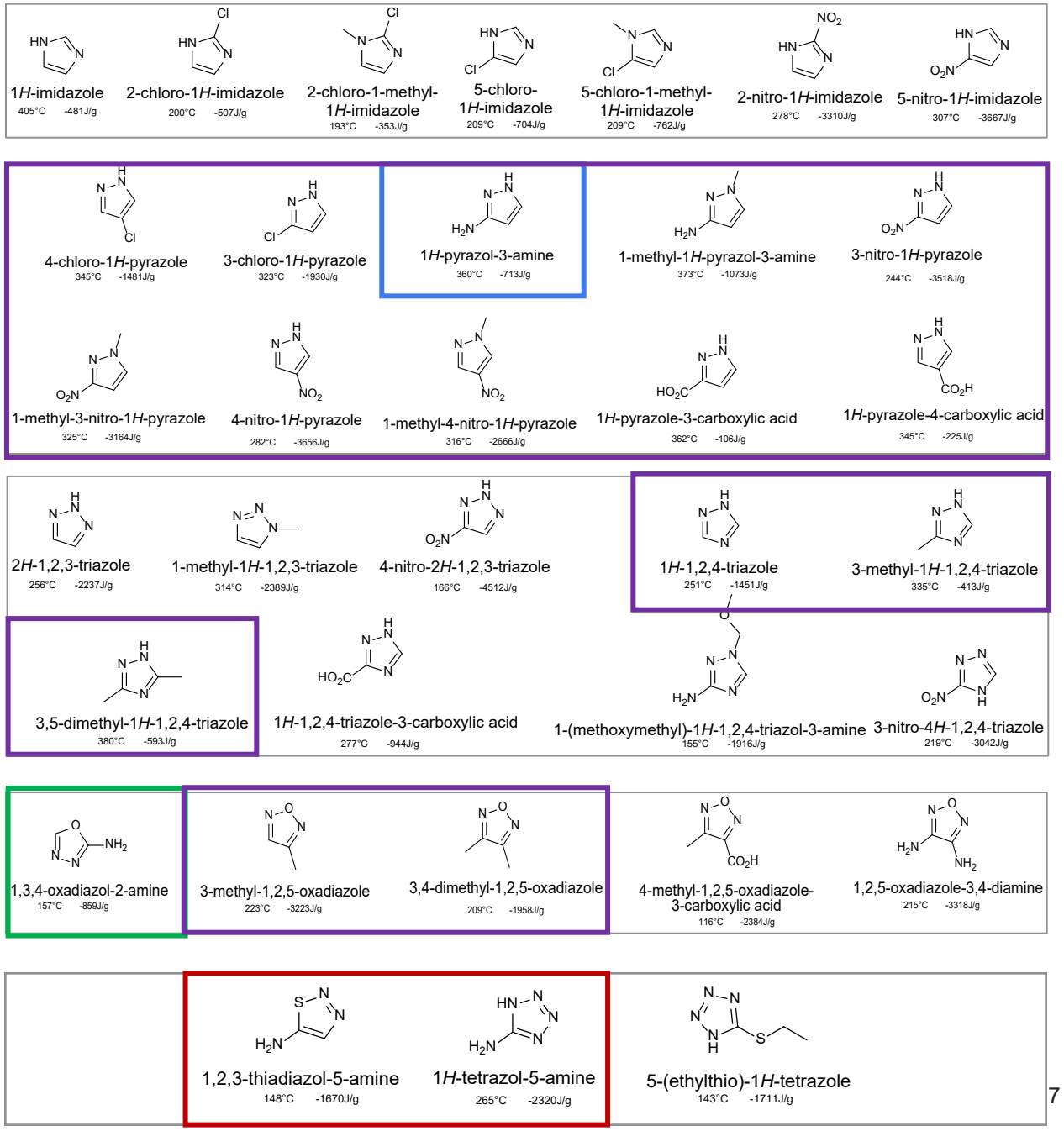
1,2,3-thiadiazol-5-amine: -1670 J/g.

1,3,4-Oxadiazol-2-amine: -859 J/g.

1H-pyrazol-3-amine: -713 J/g.

Trend Explanation: Adjacent nitrogen and sulfur atoms enhance energetic properties.

The CH_3 group increases T_{onset} and decreases the ΔH.

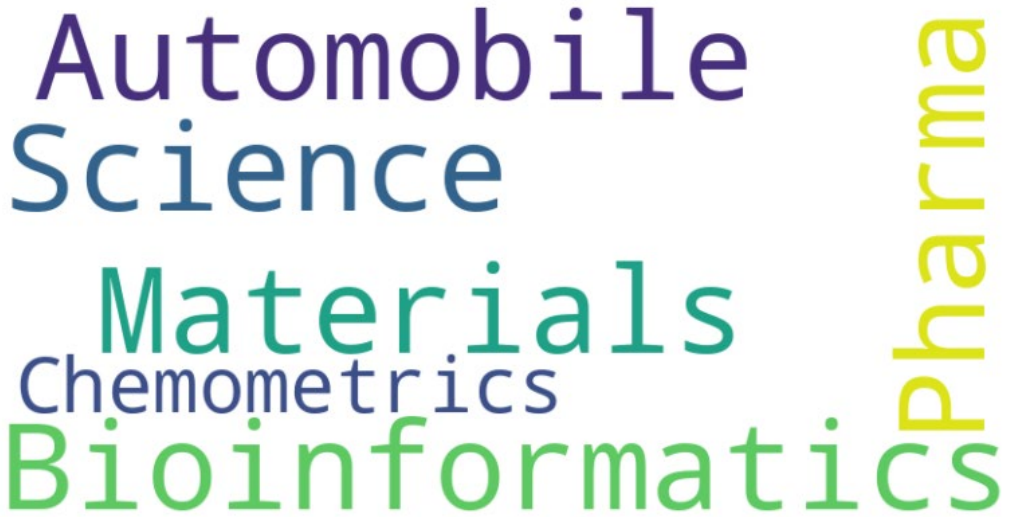


Multivariate modelling

- Orthogonal Projection to Latent Structure (OPLS) is a multivariate statistical method is an extension of Partial Least Squares (PLS) regression
- OPLS separates predictive variation from orthogonal (non-predictive) variation, improving model interpretation
- Its power can be used for correlating and predicting thermal hazard properties like Tonset and ΔH.
- Applications: OPLS is widely adopted in chemometrics, bioinformatics, and materials science.

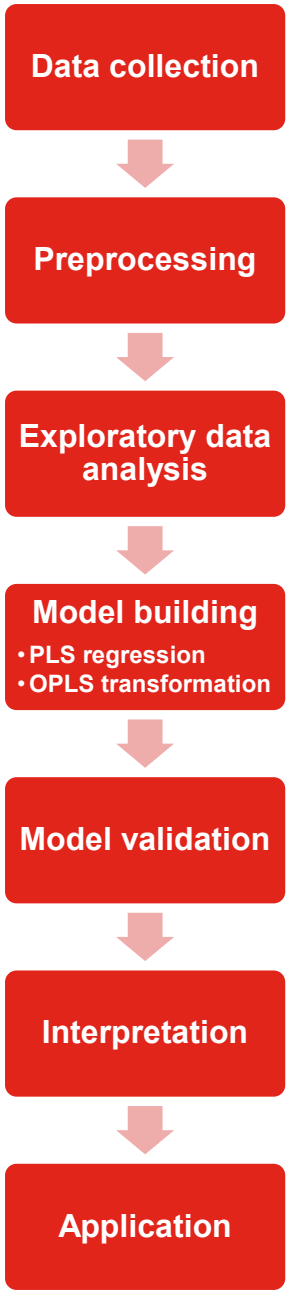
Literature on safety related work:

- Zohari et al.: QSPR model to predict Tonset and ΔH of organic peroxides,
- Barnes et al.: machine learning to predict thermal decomposition temperatures of energetic materials,.
- Zhang et al.: non-linear QSPR model for predicting thermal decomposition temperature of nitrogen-rich energetic ionic salts.
- Margelefsky et al.: shock sensitivity prediction using DSC data and molecular structure, refining Yoshida correlation with machine learning techniques for higher accuracy.

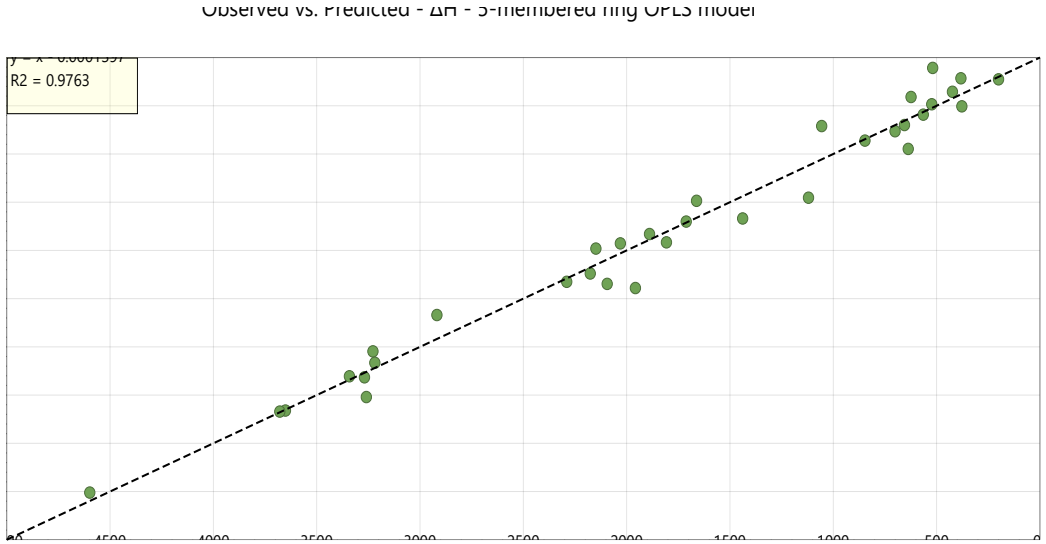


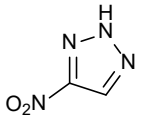
OPLS model work flow

- **Thermal Data** on 32 five member ring molecules were gathers.
- **Scaling**: Descriptors scaled to unit variance before model development.
- **Molecular Descriptors**: Various descriptors used, including the number of carbon atoms and NO2 functional groups.
- **Total Descriptors**: 44 descriptors (X variables), some categorical; 2 Y variables (Tonset and ΔH).
- **Selection Criteria**:
  - Based on prior knowledge of influence on thermal properties (e.g., explosophores, nitro group).
  - Initially developed with all descriptors, refined using correlation matrix and VIP plot.
- **Validation Sets**: Different sets used for forecasting Tonset and predicting ΔH.
- **Interpretation**: LED and oxygen balance correlated with ΔH; type of atom and its position correlated with Tonset.



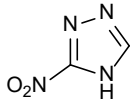
Interpretation of model for ΔH





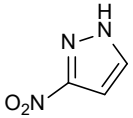
4-nitro-2*H*-1,2,3-triazole

166°C -4512J/g



3-nitro-4*H*-1,2,4-triazole

219°C -3042J/g



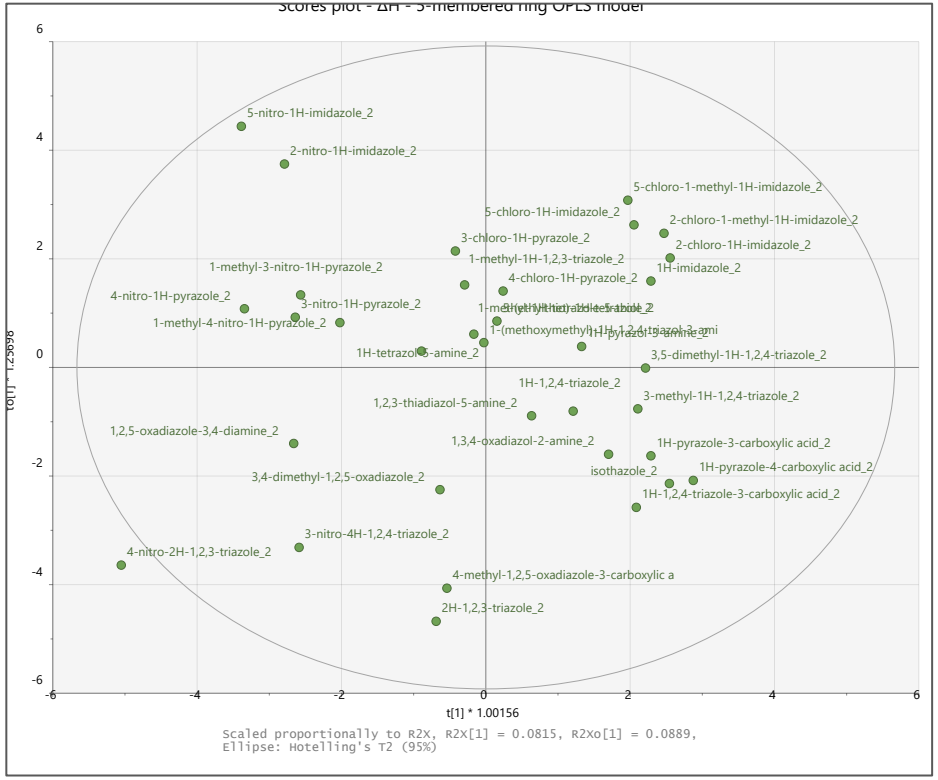
3-nitro-1*H*-pyrazole

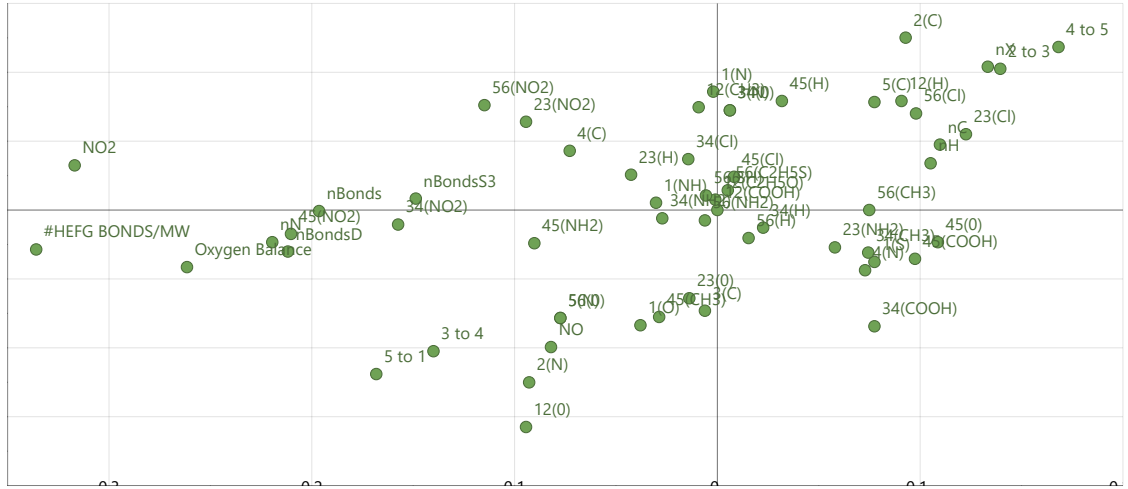
244°C -3518J/g

- Strong correlation with R^2 value of **0.97.**
- Error Metrics: RMSEE = 204, RMSEcv = 654.
- **High Correlation Variables**:
  - Lilly energy density (LED) (80%)
  - Number of NO2 groups (75%)
  - Oxygen balance (64%)
  - Number of nitrogen atoms (54%)
- **Explosophores**: Presence increases heat released during decomposition.
  - 4-Nitro-2H-1,2,3-triazole has highest ΔH with five explosophores.
  - Other high-energy compounds (e.g., 3-9, 2-6) have four explosophores.
- Other **Correlated Variables**:
  - Number of double bonds (49.2%)
  - NO2 group at 4th position in 5-membered ring (47%)
  - Number of bonds excluding hydrogen (46%)
- Reduced ΔH due to presence of halides, carbon, hydrogen, chlorine at 2nd position, and carboxylic acid at 4th position.

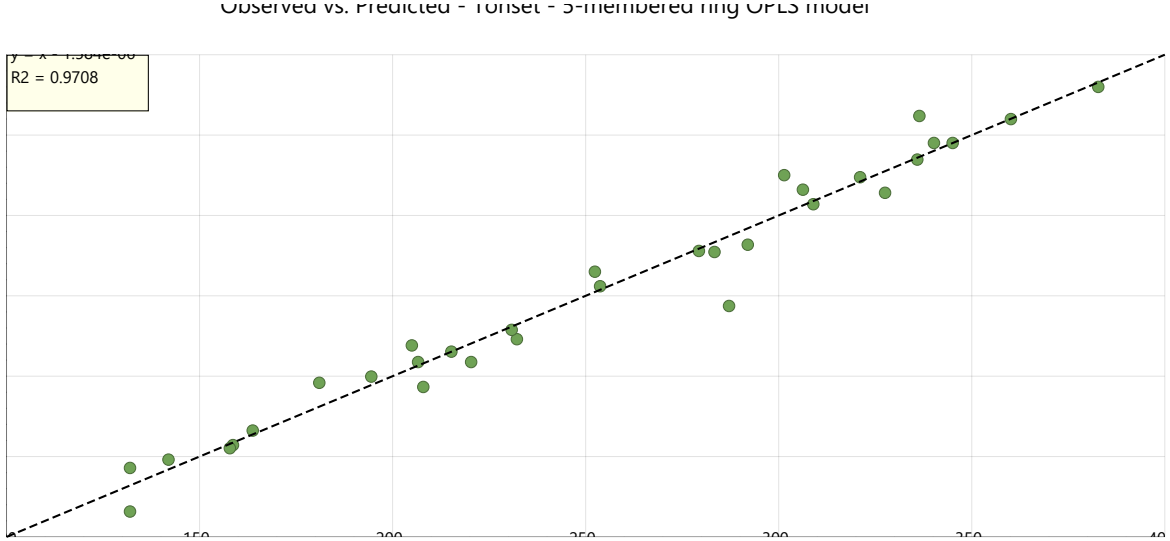
Interpretation of model for ΔH

- **Scores Plot:**
  - Molecules with Cl cluster in the upper right quadrant.
  - Molecules with COOH group in the lower right quadrant.
  - High-energy molecules on the left-hand side.
  - Lower energy molecules on the right-hand side.
- **Loading Plot:**
  - Variables on the left side contribute more to ΔH.
  - Increase in these variables results in higher ΔH.
  - Variables on the right side contribute less to ΔH.
  - Molecules with more of these variables result in lower energy.

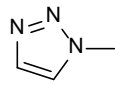




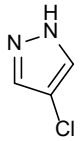
Interpretation of model for T_{onset}



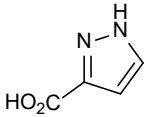
- Strong correlation with R^2 value of **0.97.**
- Error Metrics: RMSEE = 14, RMSEcv = 52.
- Influential Variables:
  - Positive Impact: Nitrogen at the first position and hydrogen attached to the first atom in a 5-member ring increase T_{onset}.
  - Negative Impact: Sulphur or oxygen at the first position of a 5-member ring decrease T_{onset}.
- Examples:
  - Higher T_{onset}: Compounds 3-2, 2-1, and 2-9 (due to nitrogen at the first position).
  - Lower T_{onset}: Compounds 3-8, 4-4, and 5-1 (due to sulphur or oxygen at the first position).



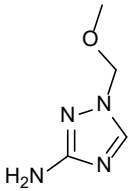
1-methyl-1*H*-1,2,3-triazole
314°C -2389J/g



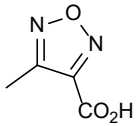
4-chloro-1*H*-pyrazole
345°C -1481J/g



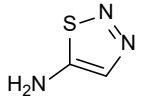
1*H*-pyrazole-3-carboxylic acid
362°C -106J/g



1-(methoxymethyl)-1*H*-1,2,4-triazol-3-amine
155°C -1916J/g



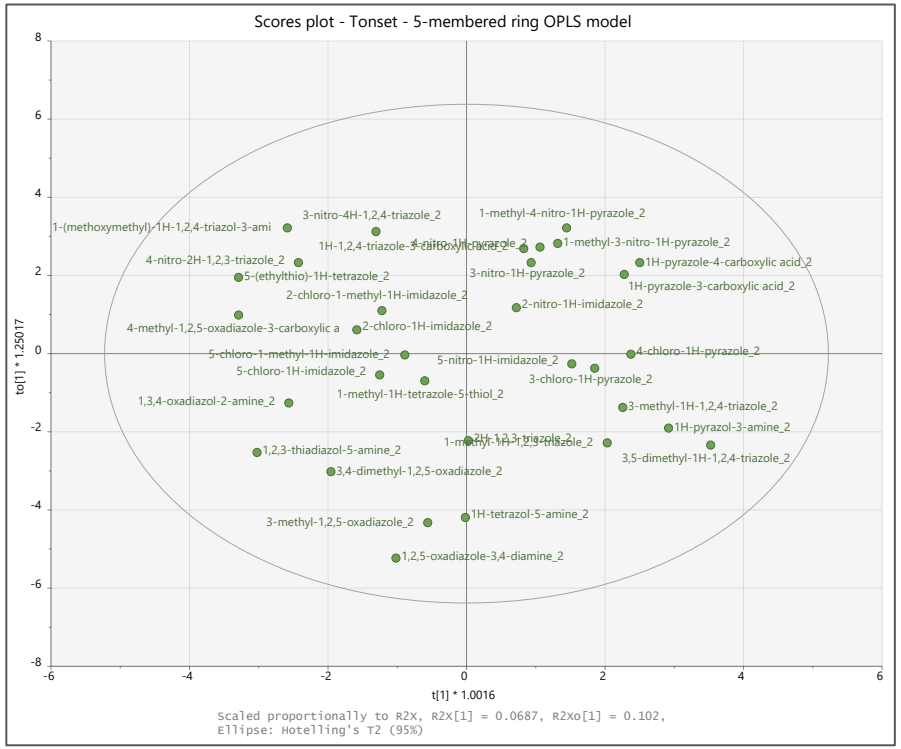
4-methyl-1,2,5-oxadiazole-3-carboxylic acid
116°C -2384J/g

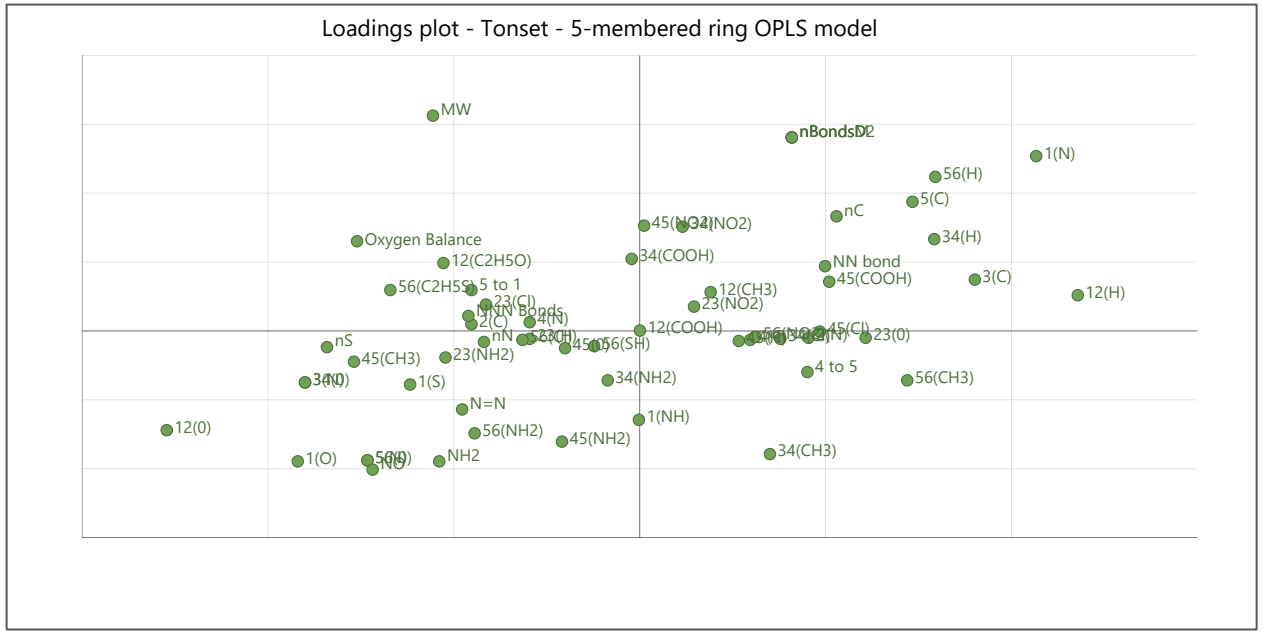


1,2,3-thiadiazol-5-amine
148°C -1670J/g

Interpretation of model for T_{onset}

- **Scores Plot**: Molecules on the right side exhibit higher T_{onset}; those on the left side exhibit lower T_{onset}.
- **Tonset Trend**: Tonset increases from left to right in the scores plot.
- **Loading Plot**: Variables on the right side contribute more significantly to T_{onset}.





Summary

- Evaluated thermal hazards of 5-membered aromatic heterocycles with at least two heteroatoms experimentally.
- **Compounds Analyzed**: Includes triazoles, oxadiazoles, thiadiazoles, and tetrazoles.
- Several functional groups like, NO_2, CH_3, NH_2 and halides **influence thermal decomposition.**
- **OPLS Model**: Developed to predict thermal properties accurately based on compound structures.
- **Functional Groups Impact**: Introduction of high-energy nitro (NO_2) groups increases decomposition severity by lowering onset temperature and increasing heat release.
- **Model Effectiveness**: OPLS model is effective for predicting thermal hazards, especially when experimental samples are unavailable.

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Thank you

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