The use of Quantum Mechanical Calculations in Thermal Hazard Assessment

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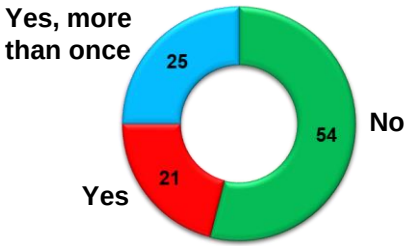
Importance of Safety Assessment

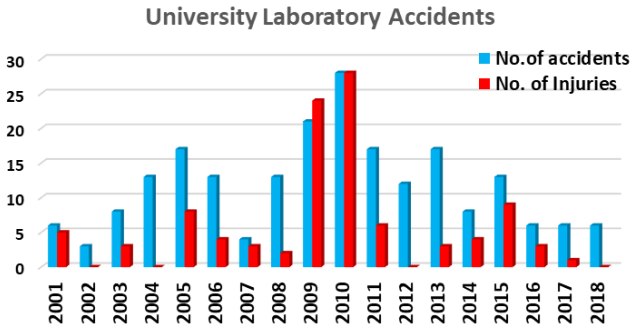
Do we need early phase safety assessment?

- Materials/reactions carried out at small scale
- A close comparison with university labs gives an idea why safety is important?

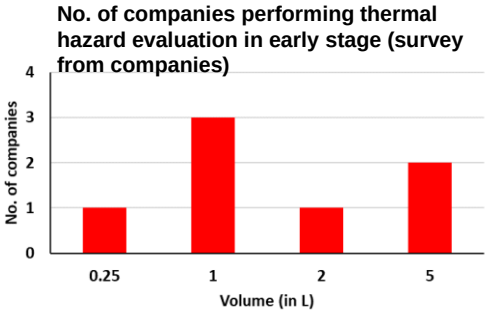
Have you ever sustained an injury of any kind in a laboratory setting while conducting research?



Nature 493**,** 2013, 9-10.



J. Loss Prev. Process Ind, 74 (2022) 104671.



Org. Process Res. Dev. 2020, 24, 2529

Safety incidents occur irrespective of scale, its all about “people”

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Early Phase Hazard Screening

Desk screening

- Literature search
- Oxygen Balance
- O.R.E.O.S.
- CHETAH
- Computational Modelling

Org. Process Res. Dev. 2021, 25, 2, 212

Experimental Techniques

- DSC
- C80
- ARC
- TSU
- Microcal

Org. Process Res. Dev. 2002, 6, 933

Measured decomposition onset temperature (ºC)

	DSC	C80	ARC	TSU1
Typical sample size	**10 mg**	**50m g**	**5 g**	**1-2 g**
4-nitrophenyl hydrazine	160	120	106	138
2,6-dichloro-4-nitroaniline	290	250	286	300
4-amino-1,2,4-triazole	260	200	190	240
5-nitro-1H-indazole	300	290	292	300
3-methyl-4-nitrophenol	247	188	181	240
di-tert-butyl peroxide	164	120	116	160

Org. Process Res. Dev. 2002, 6, 933

Limitations for Experiments in Early Phase

- Material availability
- Unknown hazards associated with new raw materials/Intermediates
- Onset temperature variation with respect to experimental technique
- Time factor
- Undesired reactions

We encourage a strong safety conscious work environment by the use of computational modelling for thermal hazards as a starting point

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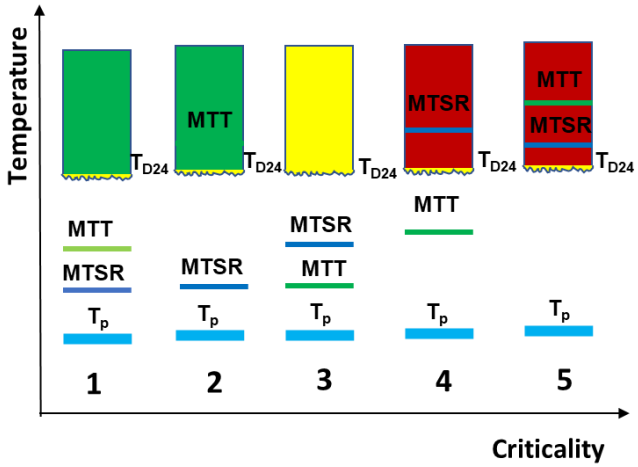
Chemical Reaction Safety

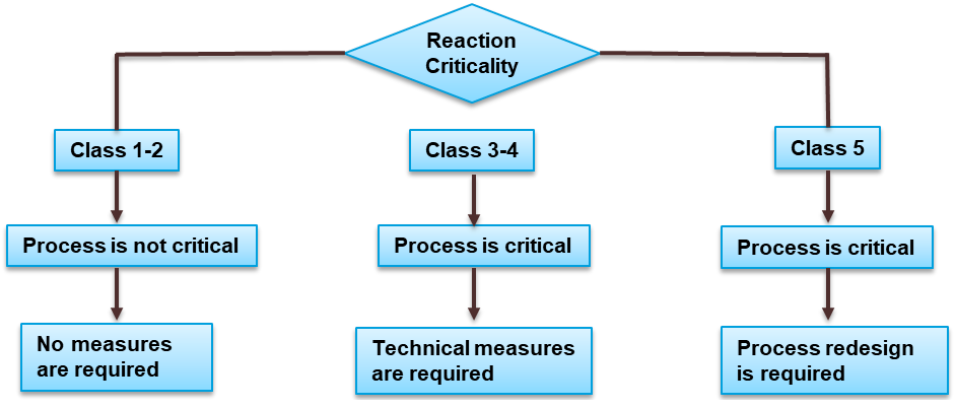
Stoessel's Criticality Class



$$\Delta T_{ad} = \frac{Q_r}{c_p' \times m} = \frac{CA_0 \times (-\Delta H_r)}{c_p' \times \rho}$$

$$T_{D24} = 0.7 \times T_{init} - 46$$

- T_p: Process temperature under desired conditions.
- ΔT_{ad}: Temperature increase due to cooling failure.
- MTSR: The highest temperature that can be reached in case of cooling failure;
- MTSR = $T_p + \Delta T_{ad}$.
- MTT: the highest temperature allowed by the system. If the reactor is operated at atmospheric pressure, MTT coincides with the boiling point of the solvent.
- T_{D24}: Temperature at which the time to maximum rate is 24 h.



Stoessel, F. Basel, CH, WILEY-VCH VerlagGmbH & Co. KGaA, 2008

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Heat of Reaction (ΔH_r) Predictions

Group Contribution Methods

Advantages

- Simple and easy to use
- Works well for hydrocarbons
- Less time-consuming

Limitations

- Isomerization effects
- Non-covalent interactions
- Salt formation predictions
- Solvation effects etc

Quantum Mechanical Methods

Advantages

- Electronic structure based calculation
- Stereoelectronic effects
- Accurate solvation modelling
- Non-covalent interactions

Limitations

- Time-consuming calculations
- Well defined structure is required

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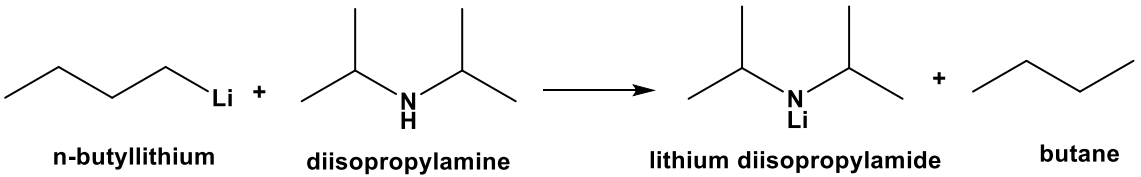
Importance of Explicit Solvation: LDA

Without explicit Solvation



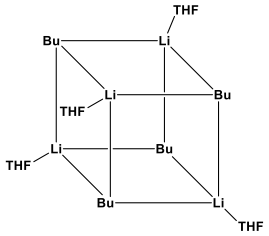
n-butyllithium + diisopropylamine → lithium diisopropylamide + butane

Predicted ΔH_r = -96.1 kJ/mol

Measured ΔH_r = -146.1 kJ/mol

Thermochim. Acta **1995,** *255*, 9

QM calculations predicted 34.2% error without consideration of explicit solvation



solution structure of n-BuLi in THF
Org. Lett. **2017,** *19*, 3966

Calculations underestimate heat of reaction if structural information is not correct

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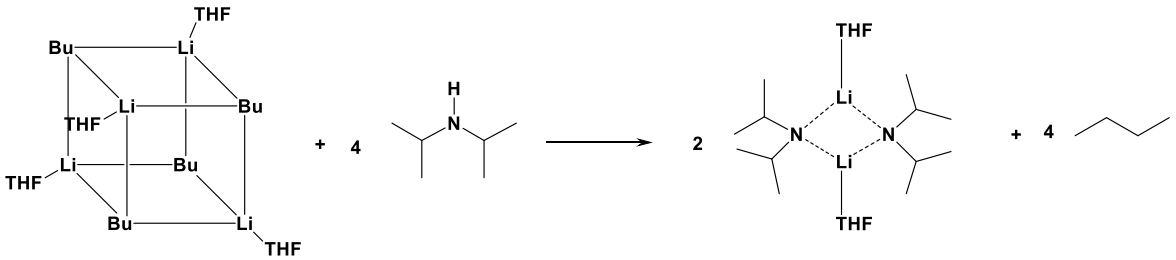
Importance of Explicit Solvation: LDA



Predicted ΔH_r = -149.2 kJ/mol

Measured ΔH_r = -146.1 kJ/mol

QM calculations predicted accurate ΔH_r with explicit solvation

Explicit solvation predicted ΔH_r accurately; So input structure is very important for calculations

J. Am. Chem. Soc. **2015,** *137*, 6292

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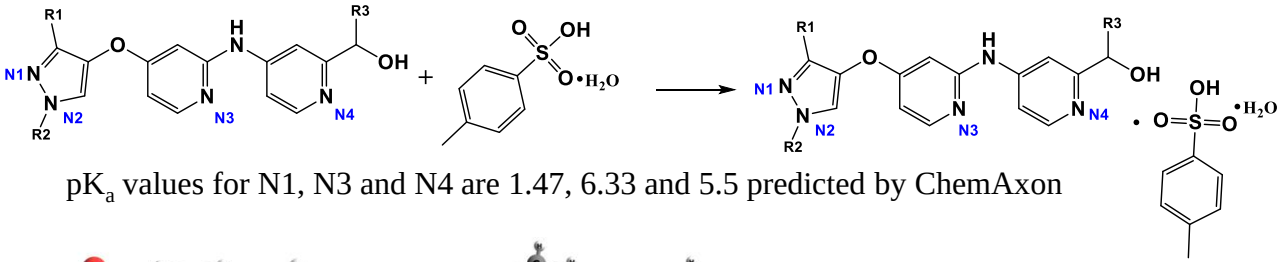
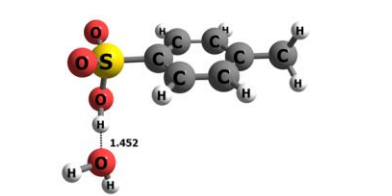
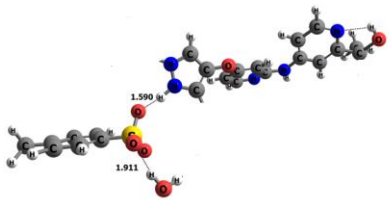
Predicting ΔH_r for a salt formation

Importance of water and site of salt formation

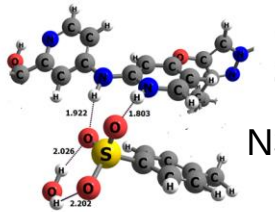


pK_a values for N1, N3 and N4 are 1.47, 6.33 and 5.5 predicted by ChemAxon

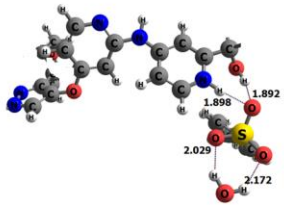




N1



N3



N4

Predicted ΔH_r with and without hydration

Protonation site	ΔH_r (TsOH)	ΔH_r (TsOH•H_2O)
N1	−70.9	−49.5
N3	−93.8	−67.9
N4	−96.2	−70.9

Measured ΔH_r -69.9 kJ/mol of TsOH•H_2O

Calculations overestimates ΔH_r if structural information is not correct

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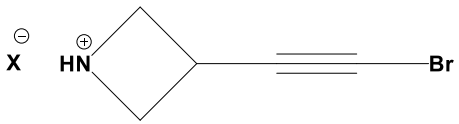
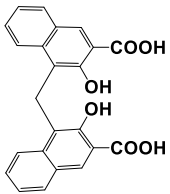
ΔH_r to predict thermal stability of salts

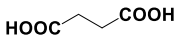
Azetidine Salts



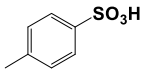
a H-Cl b H-OOCPh

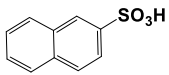


c d

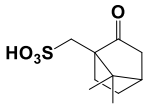


e HBF_4 f





g h

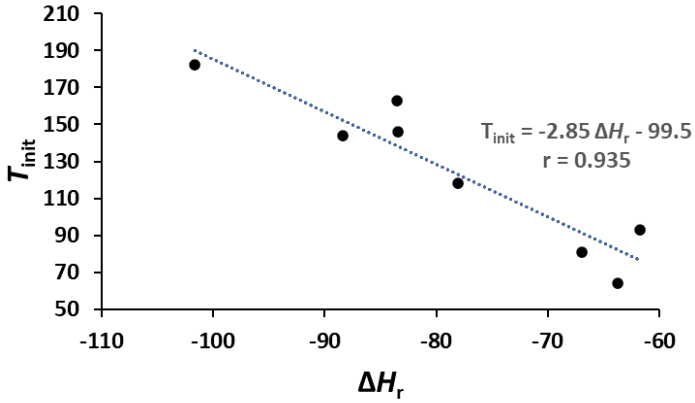


Org. Process Res. Dev. **2018,** *22*, 1409

Decomposition temperature T_{init}

Counterion	Measured T_{init} (°C)[a]	Predicted ΔH_r(kJ/mol)
a	93	−61.7
b	64	−63.7
c	118	−78.0
d	81	−66.9
e	163	−83.5
f	144	−88.4
g	146	−83.5
h	182	−101.7

Correlation between ΔH_r and T_{init}



ΔH_r can be used as a tool for high hazardous salt screening

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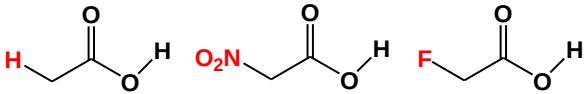
Molecular Electrostatic Potential (MESP) Topography

Substituent Effect

Hammett Equation, $\log (k_X) = \rho\sigma + \log (k_H)$

σ = Substituent constant
ρ = Reaction constant

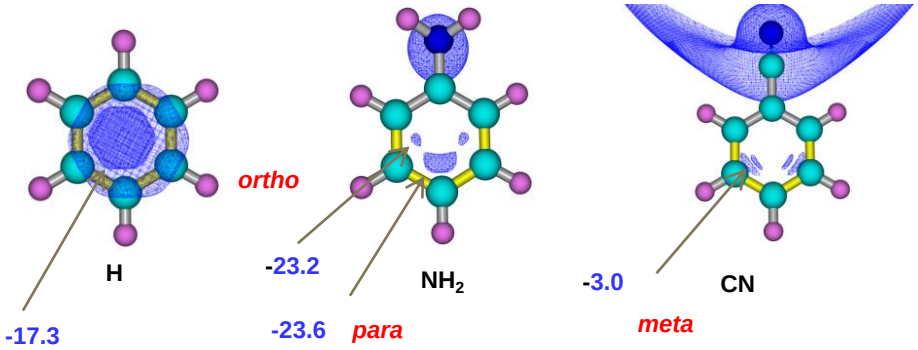


$pK_a = 4.76$ $pK_a = 1.68$ $pK_a = 2.66$

MESP topography

$$V(\mathbf{r}) = \sum_{A=1}^{N} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')d^3\mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|}$$

V_{min} = MESP minimum



substituent effect is reflected in V_{min} descriptor

Sayyed, F. B.; Suresh, C. H. *New. J. Chem.* 2009, *33*, 2465.
Sayyed, F. B.; Suresh, C. H. *Tetrahedron Lett.* 2009, *50*, 7351.

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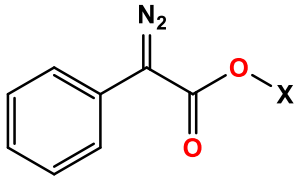
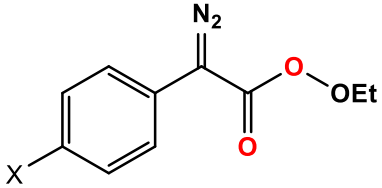
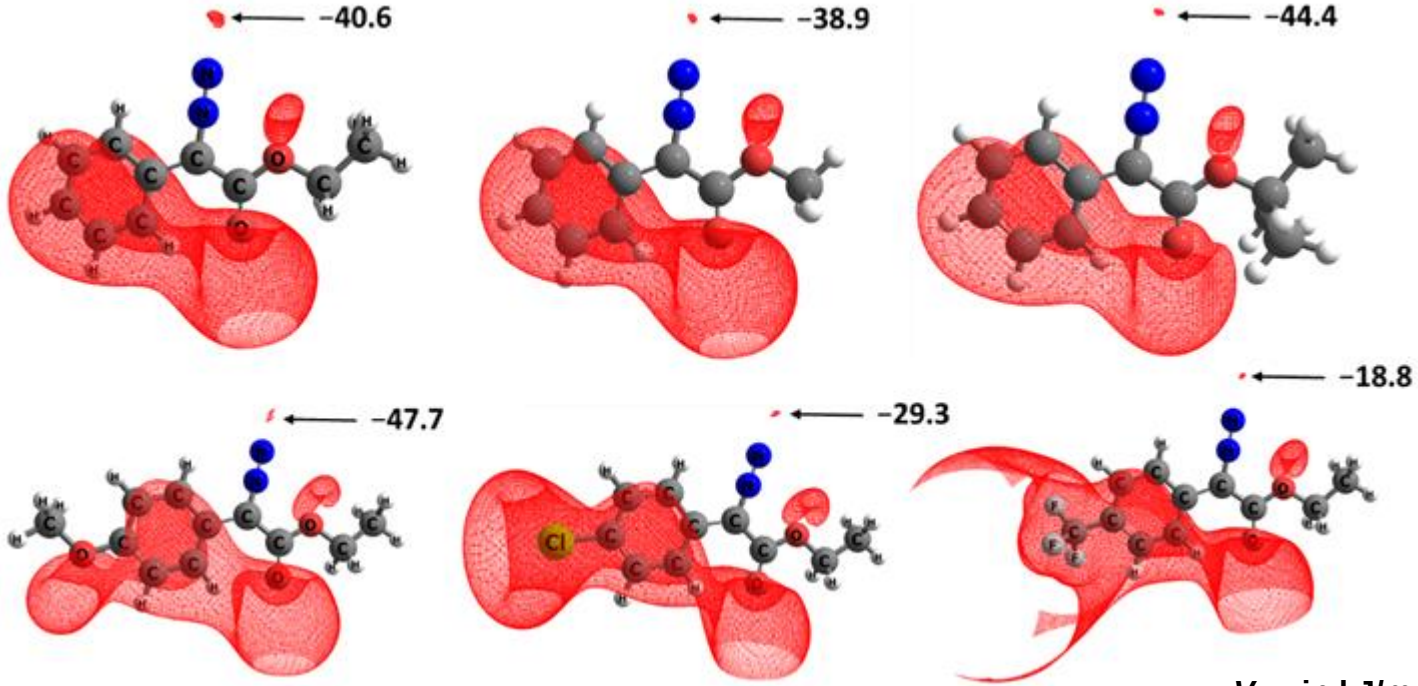
MESP topography of Diazo Compounds



X = Et, Me, tBu



X = OMe, Cl, CF_3



V_{min} in kJ/mol

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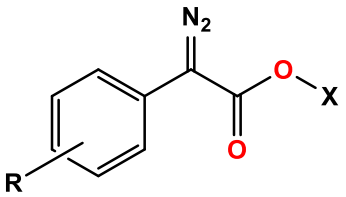
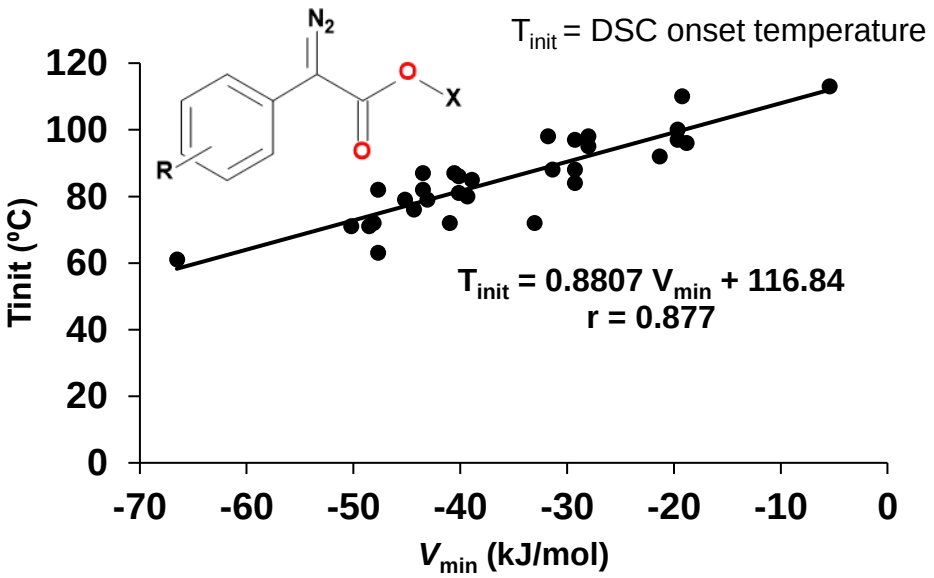
Correlation between T_{init} and V_{min}



X (R=H)	R (X = OEt)	R (X = OEt)	R (X = OEt)	R (X = OEt)
Me	4-OMe	3- CF_3	3-Me	3-OMe
Et	4-Me	2-OMe	3-F	4-NO_2
tBu	4-F	2-F	3-Cl	3,4-Me
CH_2Cl_3	4-Cl	2-Cl	3,4-OMe	4-Ph
	4-Br	2-CF_3	3,4,5-OMe	4-OPh
	4- CF_3	3,4-Cl	4-OPh	



V_{min} provides an easy estimate of decomposition temperature for diazo compounds

Org. Process Res. Dev. **2020,** *24*, 67

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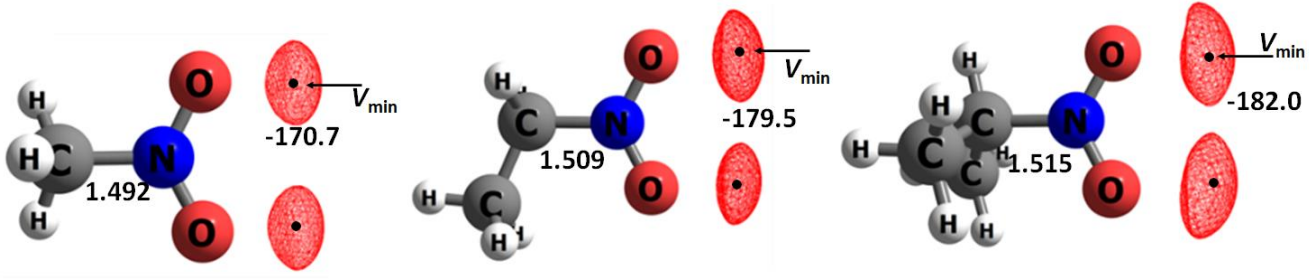
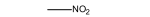
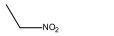
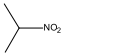
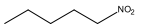
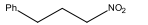
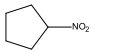
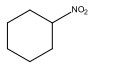
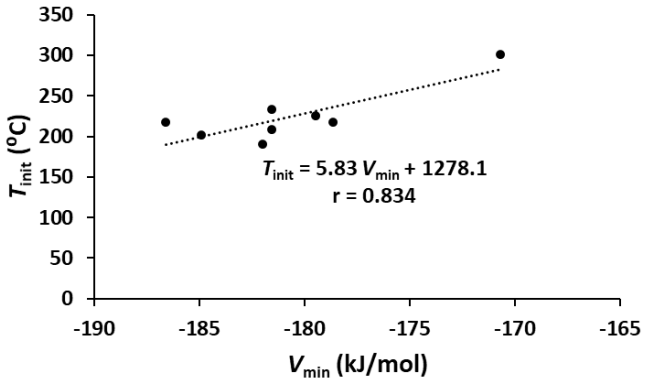
Thermal stability of Nitroalkanes



Nitro methane | Nitro ethane | Nitro propane

Nitro alkane	V_{min} (kJ/mol)	T_{init} (°C)[a]
	−170.7	301
	−179.5	225
	−182.0	191
	−181.6	233
	−181.6	208
	−178.7	218
	−184.9	202
	−186.6	217



V_{min} provides an easy estimate of decomposition temperature for Nitroalkanes

Org. Process Res. Dev. **2021,** *25*, 781

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Summary

- QM calculations provide accurate early phase thermal hazard risk assessment.
- Role of reagents and solvent is important for accurate predictions.
- ΔH_r can be used as a tool to predict thermal stability of salts.
- Structure-stability relationships can be derived using MESP descriptor.

We thank leadership of Synthetic Molecules Design and Development (SMDD) at Eli Lilly and Company for support of this work

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Questions?

Thank you for your Attention!!

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