VERTEX
THE SCIENCE of POSSIBILITY

BICYCLO[1.1.1]PENTANE – A RISING PROCESS SAFETY CHALLENGE

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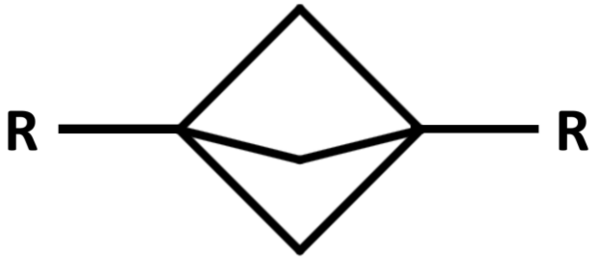
DECEMBER 7, 2021

INTRODUCTION

- Bicyclo[1.1.1]pentane (BCP) is a small, 3-dimensional, strained ring structure
- BCPs have found increased use as a bio-isostere in the pharmaceutical industry
- Publications have emerged describing methods for making BCPs and methods for implanting the structure within molecules



Iridium-Catalyzed Enantioselective Synthesis of α-Chiral Bicyclo[1.1.1]pentanes by 1,3-Difunctionalization of [1.1.1]Propellane

Songjie Yu, Changcheng Jing, Adam Noble, and Varinder K. Aggarwal*

doi.org/10.1021/acs.orglett.0c02017

Direct catalytic asymmetric synthesis of α-chiral bicyclo[1.1.1]pentanes

Marie L. J. Wong, Alistair J. Sterling, James J. Mousseau, Fernanda Duarte & Edward A. Anderson

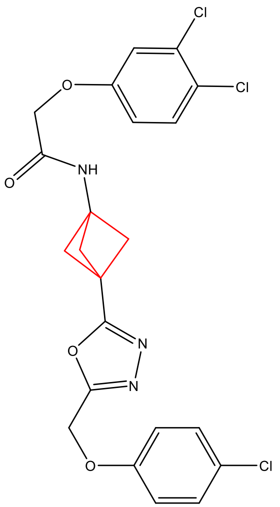
doi.org/10.1038/s41467-021-21936-4

1,2-Difunctionalized bicyclo[1.1.1]pentanes: Long–sought-after mimetics for *ortho*/*meta*-substituted arenes

Jin-Xin Zhao, Yu-Xuan Chang, Chi He, Benjamin J. Burke, Michael R. Collins, Matthew Del Bel, Jeff Elleraas, Gary M. Gallego, T. Patrick Montgomery, James J. Mousseau, Sajiv K. Nair, Matthew A. Perry, Jillian E. Spangler, Julien C. Vantourout, and Phil S. Baran

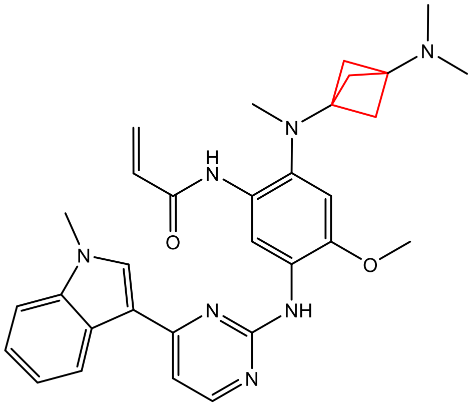
doi.org/10.1073/pnas.2108881118

PHARMACEUTICAL UTILIZATION OF THE BCP SCAFFOLD



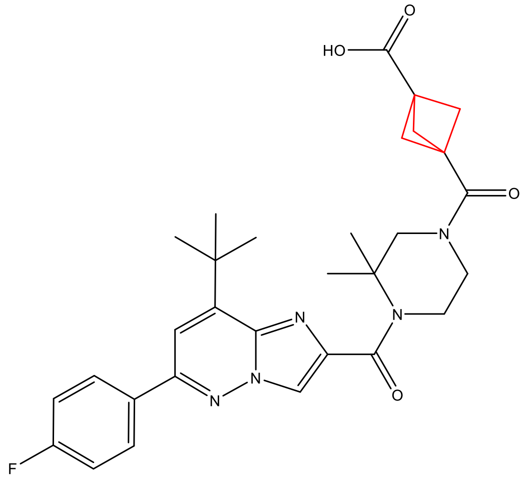
Calico Life Sciences

WO 2017/193030 A1



Kalyra Pharmaceuticals

WO 2017/205459 A1



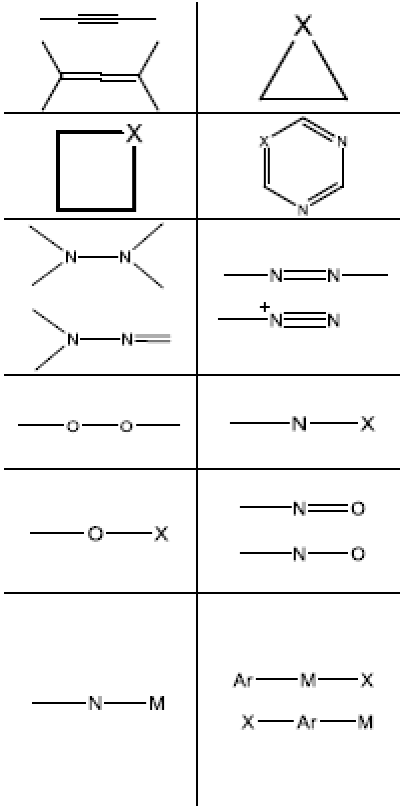
Vertex Pharmaceuticals

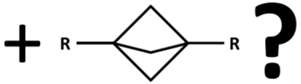
WO 2015/048245 A1

HIGH ENERGY FUNCTIONAL GROUPS (HEFG)

- A HEFG list is a valuable guide for flagging potentially energetic compounds
- Testing at earlier stages allows potential issues to be identified before larger scale reactions are performed
- HEFG lists are NOT exhaustive. The list needs to be a living document

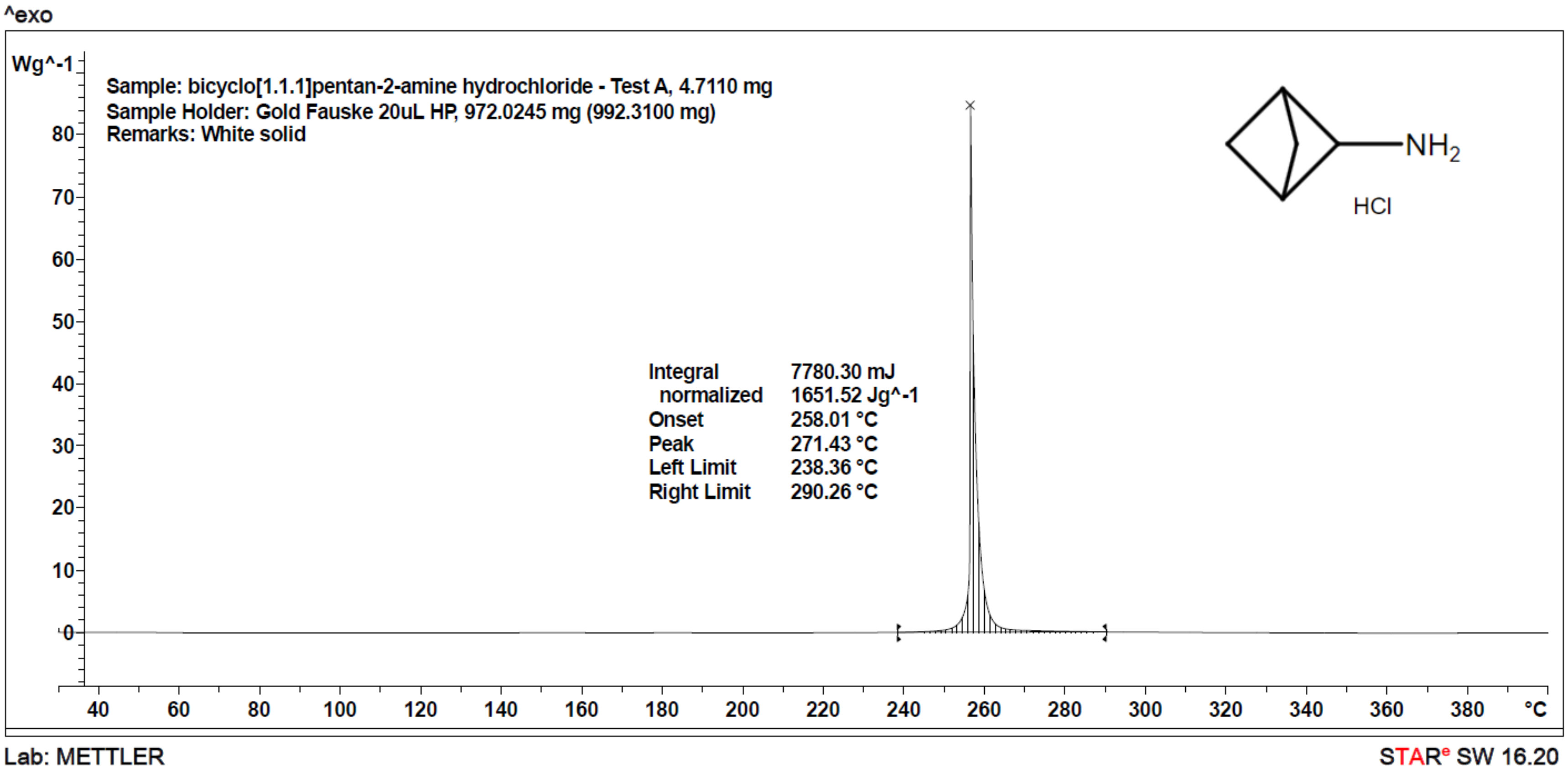
Is bicyclo[1.1.1]pentane a HEFG?





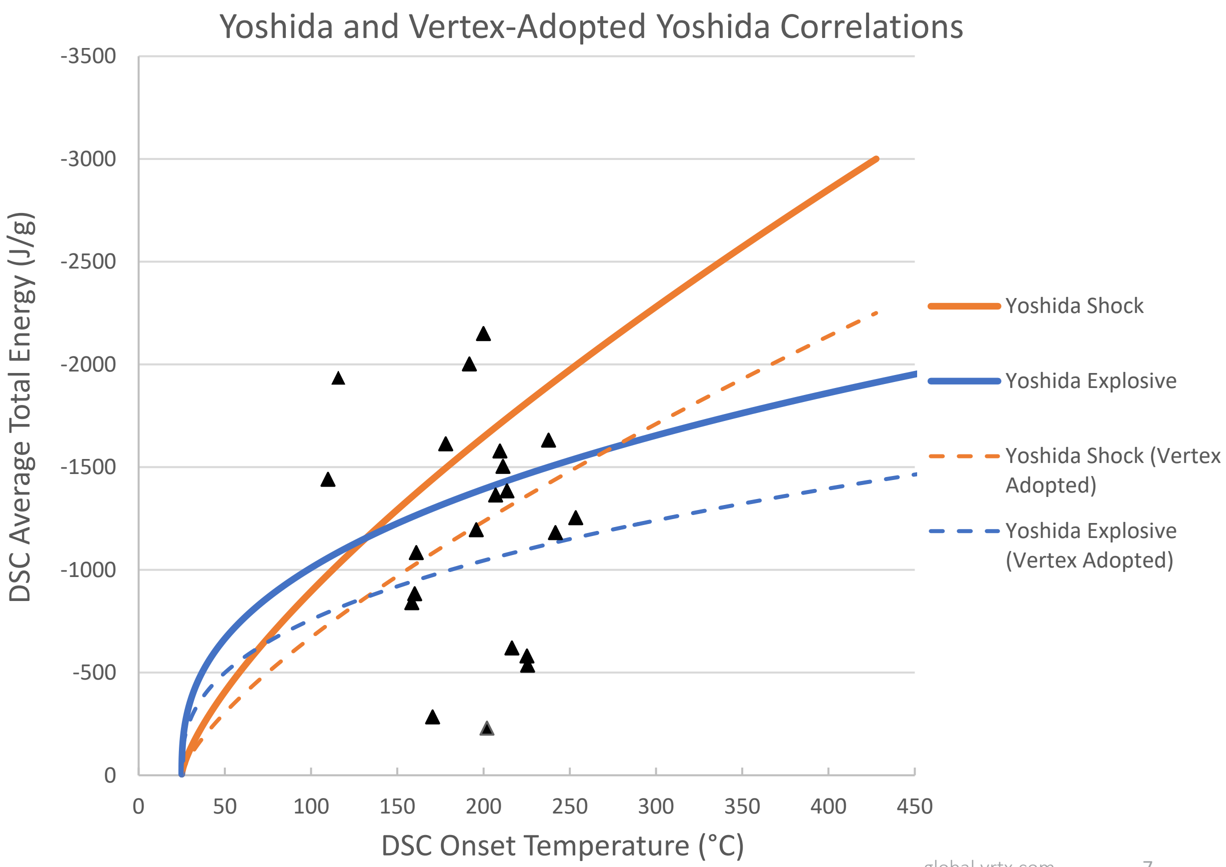
DIFFERENTIAL SCANNING CALORIMETRY (DSC)

- DSC testing offers rapid screening of materials for thermal decomposition hazards
- The speed and low-sample requirement have made the DSC a common starting point in process safety studies
- DSC testing of a readily available BCP showed a high-energy decomposition but more testing was needed to study the thermal stability of BCPs.


^exo
Wg^-1
Sample: bicyclo[1.1.1]pentan-2-amine hydrochloride - Test A, 4.7110 mg
Sample Holder: Gold Fauske 20uL HP, 972.0245 mg (992.3100 mg)
Remarks: White solid
Integral 7780.30 mJ
normalized 1651.52 Jg^-1
Onset 258.01 °C
Peak 271.43 °C
Left Limit 238.36 °C
Right Limit 290.26 °C
NH2
HCl
80
70
60
50
40
30
20
10
0
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 °C
Lab: METTLER
STARe SW 16.20

YOSHIDA CORRELATION

- The Yoshida Curve is used to predict impact sensitivity and the potential to propagate an explosion
- Several of the first BCP compounds tested flagged on the Vertex-modified Yoshida Curve
- Testing was expanded to readily available commercial BCP compounds
- 14 of the compounds tested flagged explosive, 10 of those flagged shock sensitive

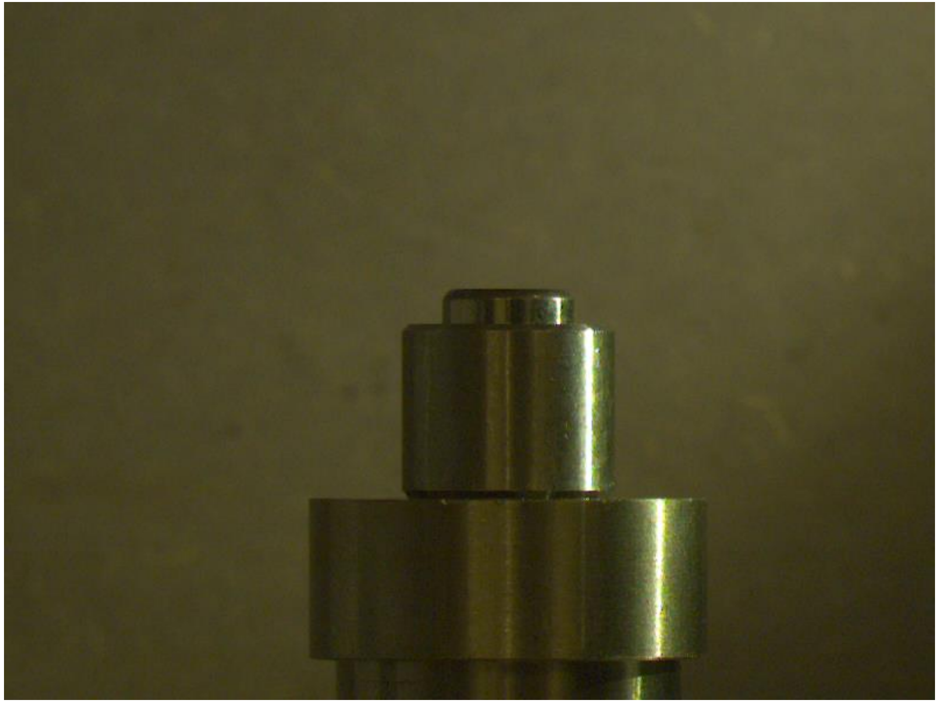


IMPACT SENSITIVITY TESTING

- BAM Fallhammer apparatus was used for testing
- The BAM Fallhammer was designed for the screening of potential high explosives prior to shipment
- While most materials tested are not explosive, the test still offers information on sensitivity to degradation or decomposition without detonation

BCP'S ARE SENSITIVE TO IMPACTS

- Impact sensitivity testing was performed on available samples that flagged on the Vertex-modified Yoshida Curve
- 6 of 10 BCPs tested showed sensitivity to decomposition from impacts. 3 of those samples decomposed with smoke
- No flames, audible reactions, or detonations were detected



OREOS METHOD

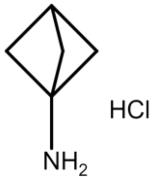
- The OREOS Method helps characterize potentially explosive materials by assigning point values for various properties. The resulting number offers guidance on testing that is either required or recommended
- The Method takes into account the **O**xygen Balance, **R**ule of 6, **E**xplosive Functional Groups, **O**nset Temperature, and the **S**cale.

	Points			
	1	**2**	**4**	**8**
Oxygen Balance Hazard		Low	Med	High
Rule of 6 calculation		Pass		Fail
Explosive Functional Group?	No			Yes
Onset temperature	>300	200-300	125-200	<125
Scale	1mg to 5g	5g to 100g	101g to 500g	>500g

O.R.E.O.S. Total:

Points:	Low Hazard 7 to 17	Medium Hazard 18 to 27	High Hazard 28 to 40
Testing:	No additional testing is required. ARC testing is recommended to understand pressure generation.	ARC testing is **required**. UN TS1 testing is recommended.	ARC testing is **required**. UN TS1 testing is **required**. Alternatives are encouraged.

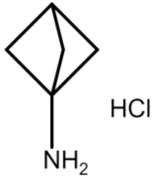
BCP-1-AMINE HCL OREOS



$$\text{Oxygen Balance} = \frac{\left[-1600\left(2X+\frac{Y}{2}-Z\right)\right]}{MW}$$

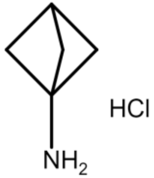
$C_XH_YO_Z$

BCP-1-AMINE HCL OREOS



$$\text{Oxygen Balance} = \frac{\left[-1600\left(2X+\frac{Y}{2}-Z\right)\right]}{MW} = \frac{\left[-1600\left(2(5)+\frac{(10)}{2}-0\right)\right]}{119.59}$$ = -201 = **Medium (4 pts)**

$C_XH_YO_Z$



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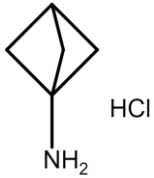
$C_XH_YO_Z$

Rule of 6 – No explosive functional groups = **Pass (2 pts)**



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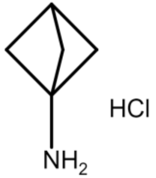
$C_XH_YO_Z$

Rule of 6 – No explosive functional groups = **Pass (2 pts)**

ExFG – No explosive functional groups = **No (1 pt)**

BCP-1-AMINE HCL OREOS



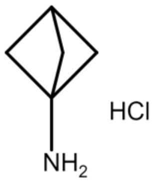
$$\text{Oxygen Balance} = \frac{\left[-1600\left(2X+\frac{Y}{2}-Z\right)\right]}{MW} = \frac{\left[-1600\left(2(5)+\frac{(10)}{2}-0\right)\right]}{119.59} = -201$$ = **Medium (4 pts)**

$C_XH_YO_Z$

Rule of 6 – No explosive functional groups = **Pass (2 pts)**

ExFG – No explosive functional groups = **No (1 pt)**

Onset Temperature = 178°C = **Medium (4 pts)**



BCP-1-AMINE HCL OREOS

$$\text{Oxygen Balance} = \frac{\left[-1600\left(2X+\frac{Y}{2}-Z\right)\right]}{MW} = \frac{\left[-1600\left(2(5)+\frac{(10)}{2}-0\right)\right]}{119.59} = -201 = \textbf{Medium (4 pts)}$$

$C_XH_YO_Z$

Rule of 6 – No explosive functional groups = **Pass (2 pts)**

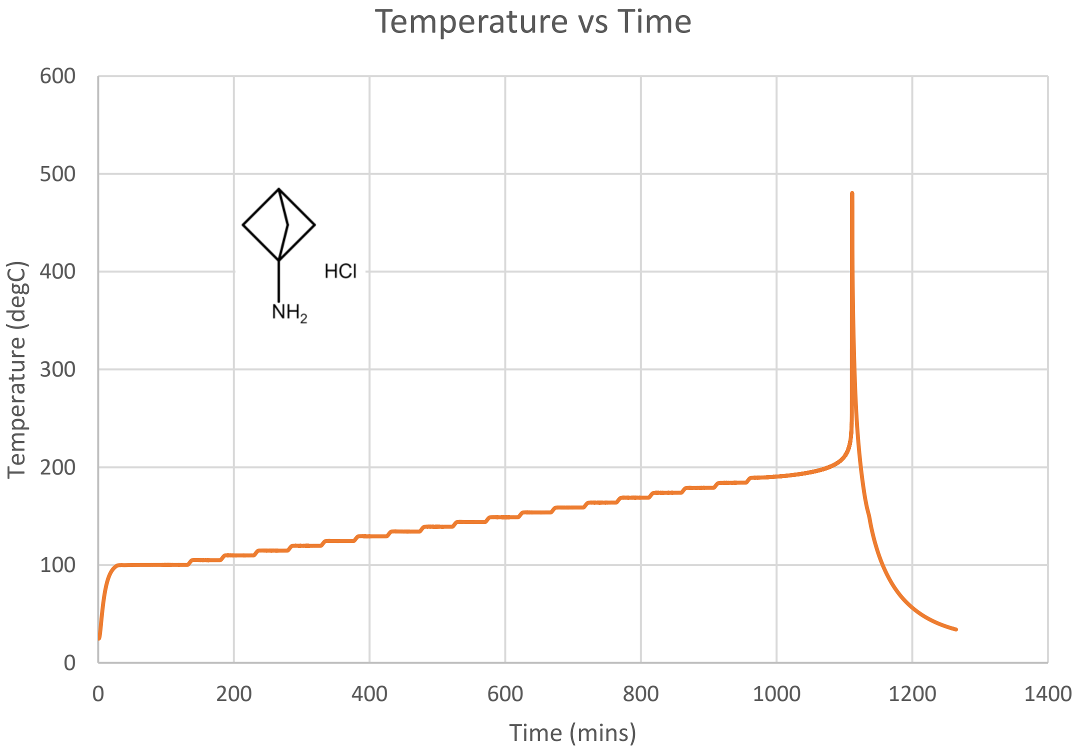
ExFG – No explosive functional groups = **No (1 pt)**

Onset Temperature = 178°C = **Medium (4 pts)**

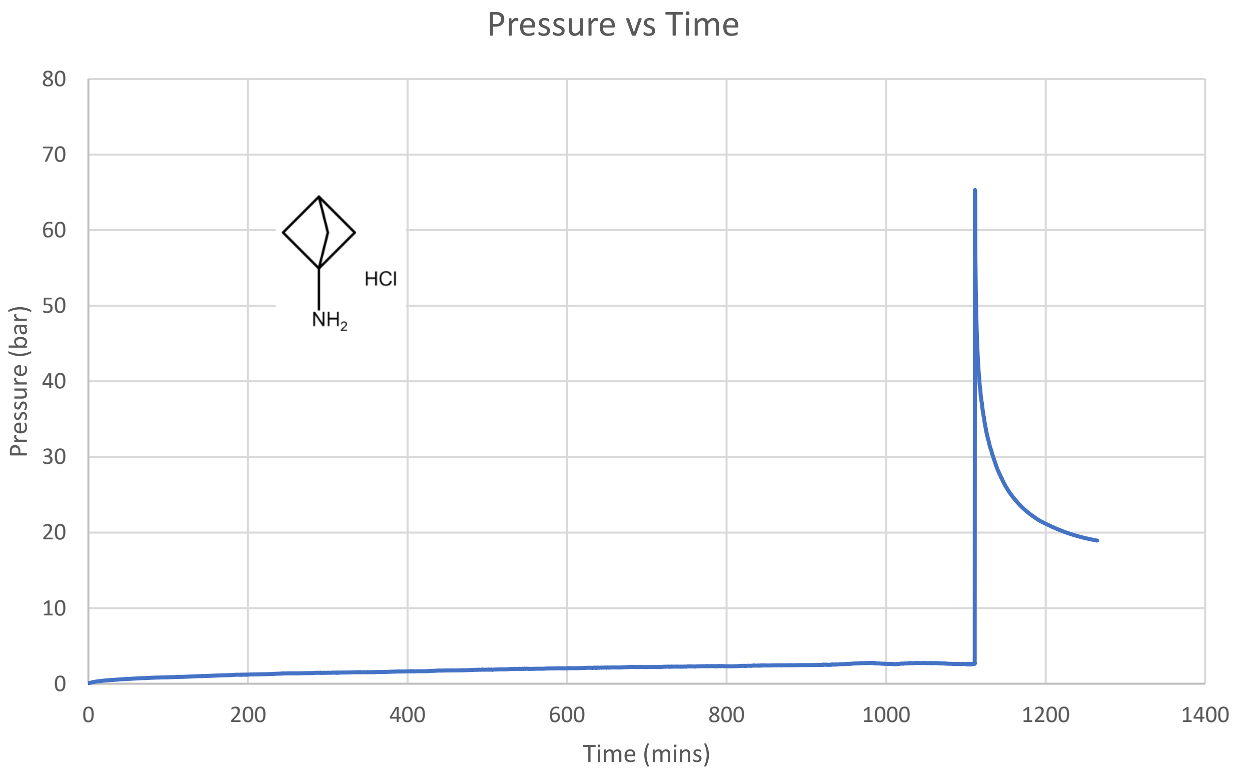
Scale	<5g	5g to 100g	100g to 500g	>500g
Points	**1**	**2**	**4**	**8**
Total	**12**	**13**	**15**	**19**
	Low Hazard	Low Hazard	Low Hazard	Medium Hazard

ACCELERATING RATE CALORIMETRY (PHITEC-1)

- ARC testing was performed to get a better idea of the onset temperatures and to generate data on pressure rise rates and/or non-condensable gas generation
- Each of the 5 compounds tested showed rapid temperature and pressure rise resulting in a loss of adiabaticity
- Each compound produced a moderate amount of non-condensable gas with 6 – 18 bar remaining after cooldown

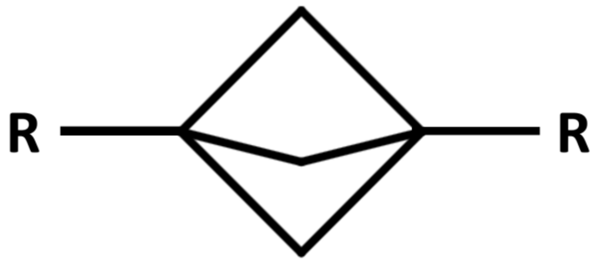


ACCELERATING RATE CALORIMETRY (PHITEC-1)

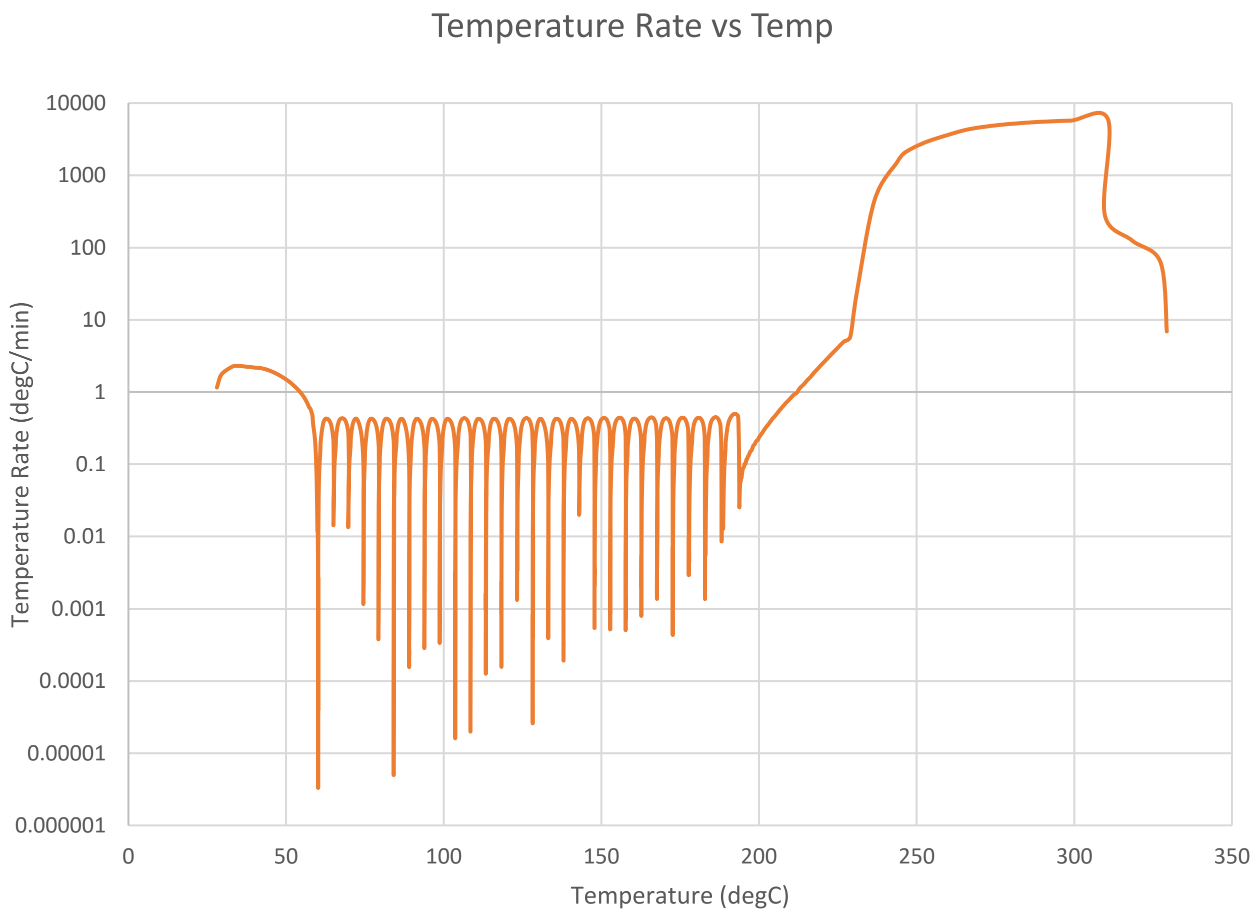


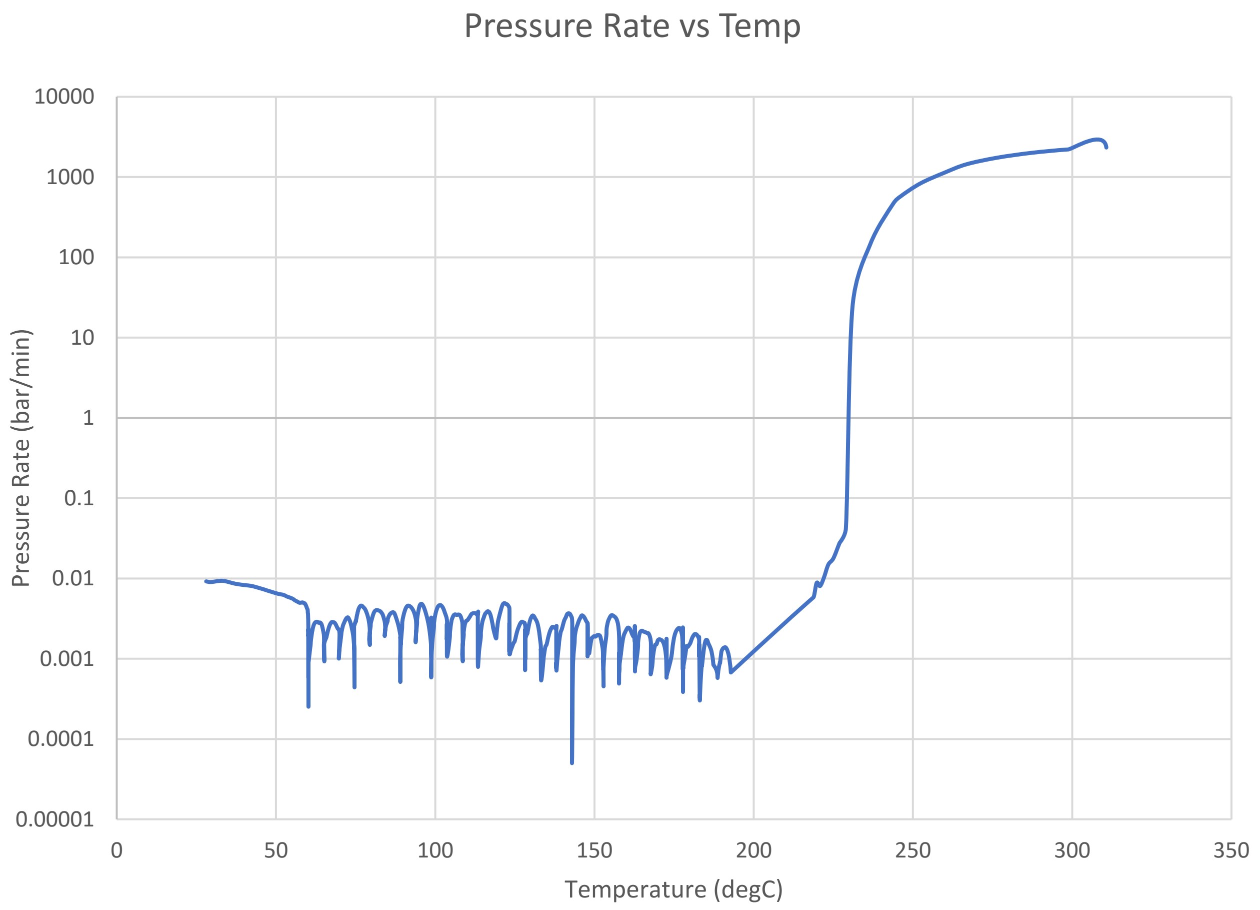
CONCLUSION

- The BCP structure is high energy and caution is needed when using compounds containing BCPs, especially low molecular weight building blocks – “test what you don’t know”
- Having a testing workflow to triage potentially energetic compounds is critical. Methods like the OREOS method help guide testing



POSSIBLE SLIDES TO BE USED


Temperature Rate vs Temp
Temperature Rate (degC/min)
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0
50
100
150
200
250
300
350
Temperature (degC)


Pressure Rate vs Temp
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Pressure Rate (bar/min)
0
50
100
150
200
250
300
350
Temperature (degC)

SMALLER, LIGHTER SAMPLES ARE MORE ENERGETIC