Gas Evolution Analysis: Unexpected Detection & Profile

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Introduction

- Gas evolution is a key hazard when scaling chemical processes
- Important to identify & quantitate evolved gases
- GSK Method: Thermal Mass Flow Meter (TMFM) w/ concurrent Hiden Mass Spec (Hiden)*
- Key Data:
  - Gas evolution
  - Rate (maximum & average)
  - Identify components
  - Duration of gas evolution

* **Frank Dixon (P2SAC Spring 2023):**

Quantitative Gas Evolution Analysis via Combination of Online Thermal Mass flow and Mass Spectrometry Data

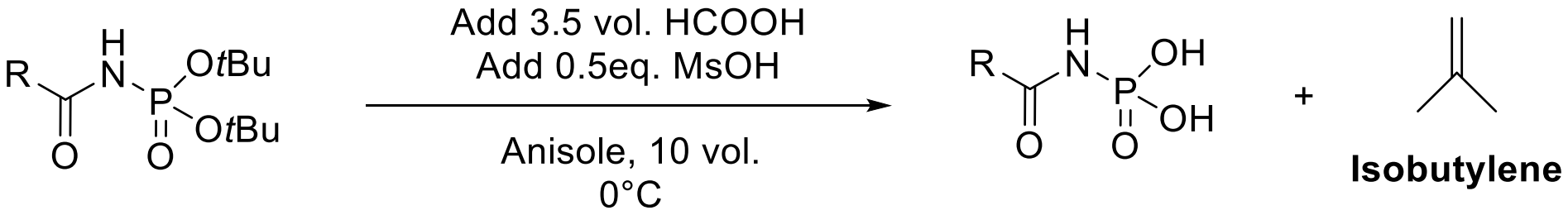
PowerPoint Presentation (purdue.edu)

GSK

Example 1:

Organic acid-mediated hydrolysis of di-tert-butoxy phosphonate amide

- Sequential addition of formic acid followed by methanesulfonic acid (MSA)
- Hold 4 hours then proceed with additional charges
- Chemist hadn't observed or detected off-gassing during development work
- Calorimetry testing with concurrent TMFM & Hiden evaluation:
  - Low-level isobutylene gas evolution measured by Hiden but not by TMFM
  - Observed isobutylene represented only 15% theoretical amount available*



*balance remains in solution

Example 1:

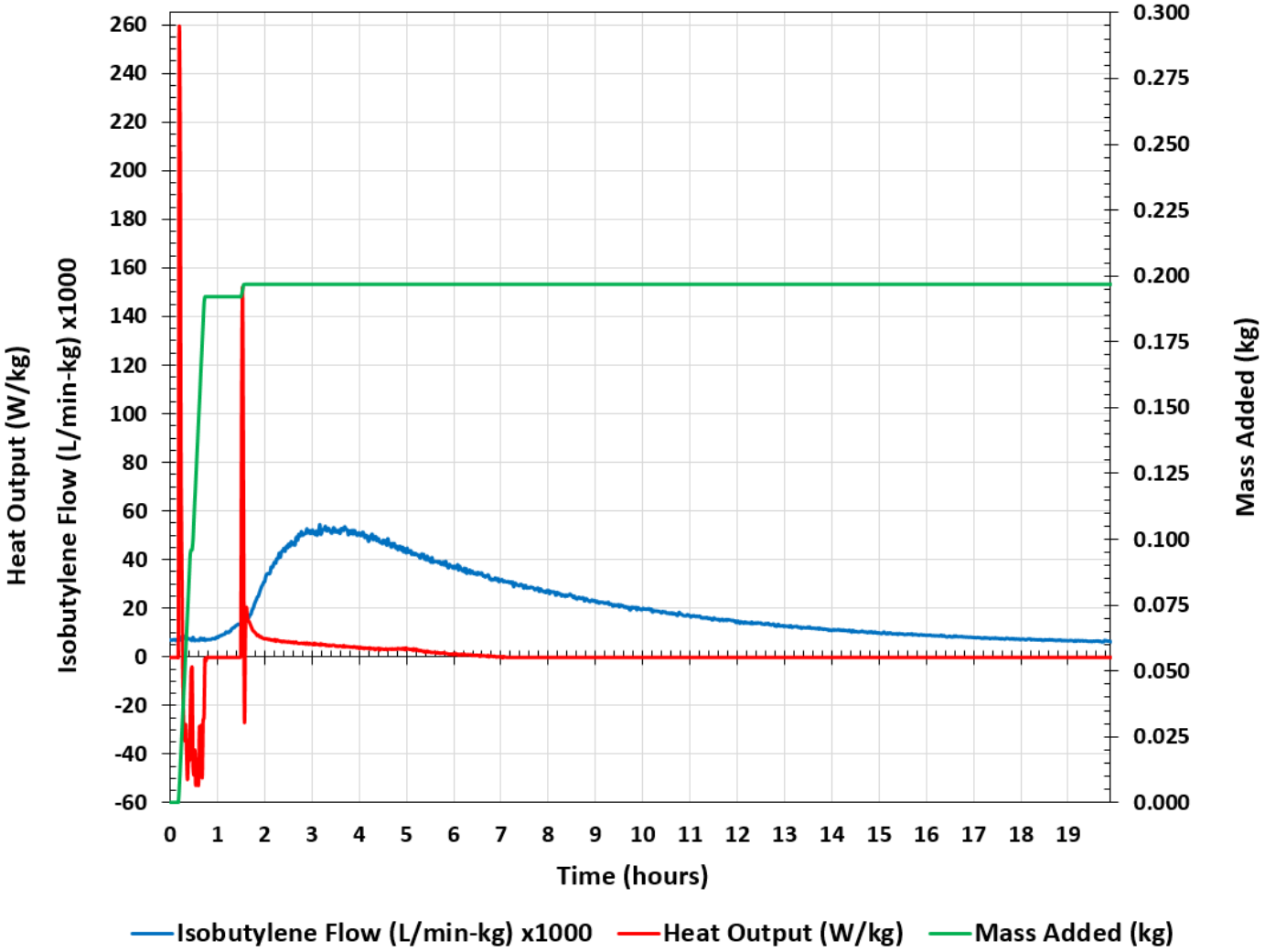
Observations:

- Heat output lasted **~4.5 hours post-MSA**
- Isobutylene gas evolved for **~17 hours**

Theoretical, total gas:	171 L/kg of Starting Material (SM)
Observed, total gas:	25 L/kg of SM
Observed maximum rate of gas output:	0.05 L/min-kg of SM
Observed average rate of gas output:	0.02 L/min-kg of SM

Recommendations:

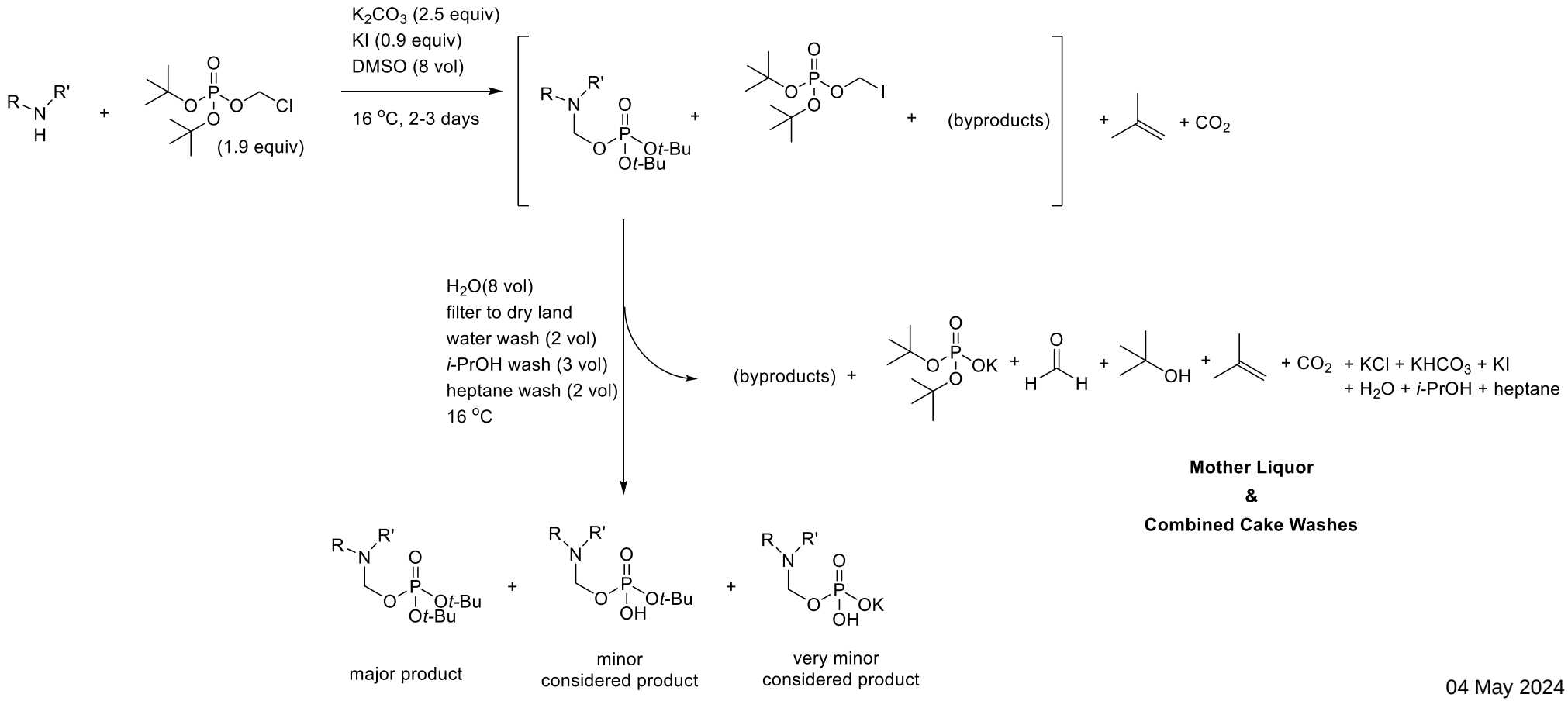
- Extend hold period prior to additional processing
- Safe venting of flammable gas



Example 2:

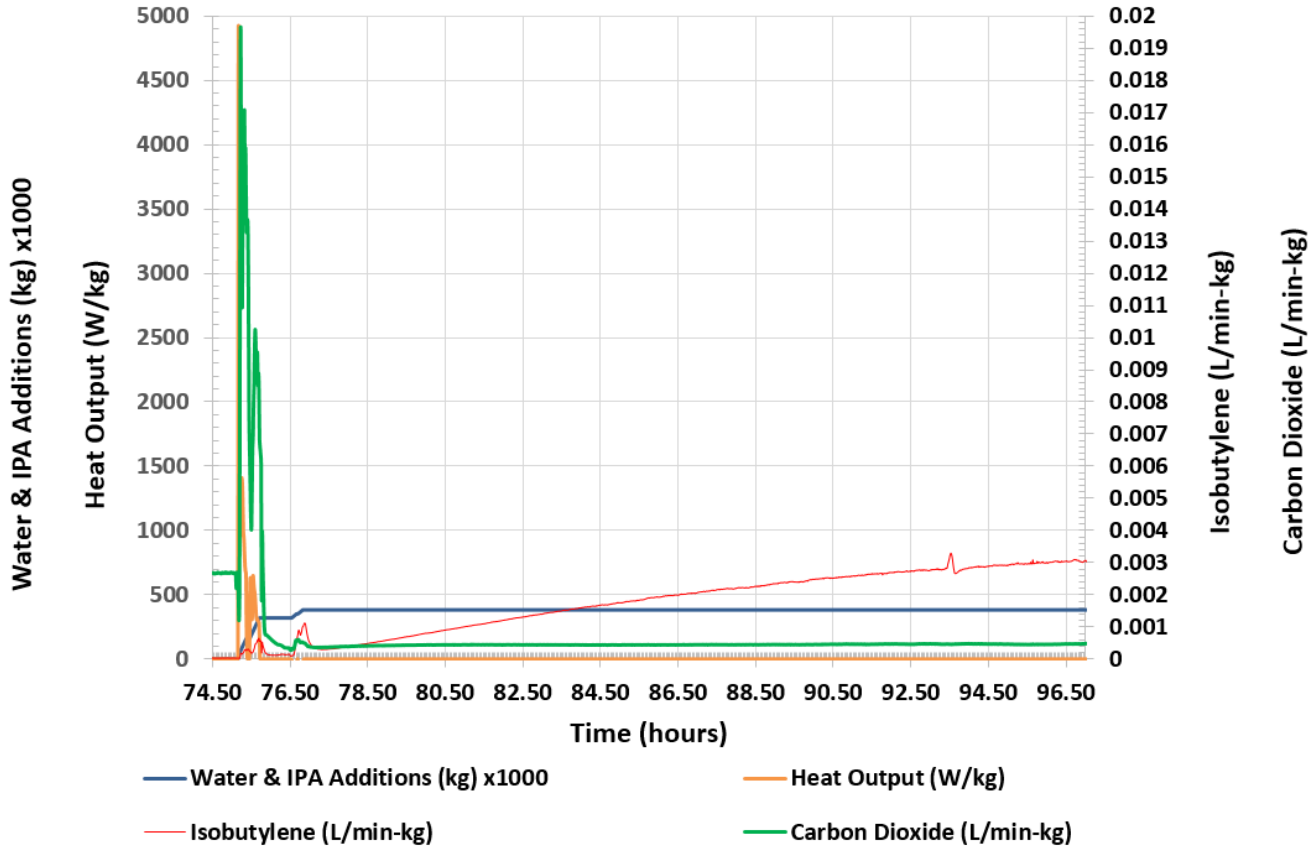
Amine alkylation with di-tert-butyl chloromethyl phosphate

- Low-level CO_2 gas evolution initiated following charge of K_2CO_3
- Very low-level isobutylene gas evolution initiated following charge of the ‘chloromethyl phosphate’ reagent
- Gas evolution persists throughout reaction, work-up, and isolation

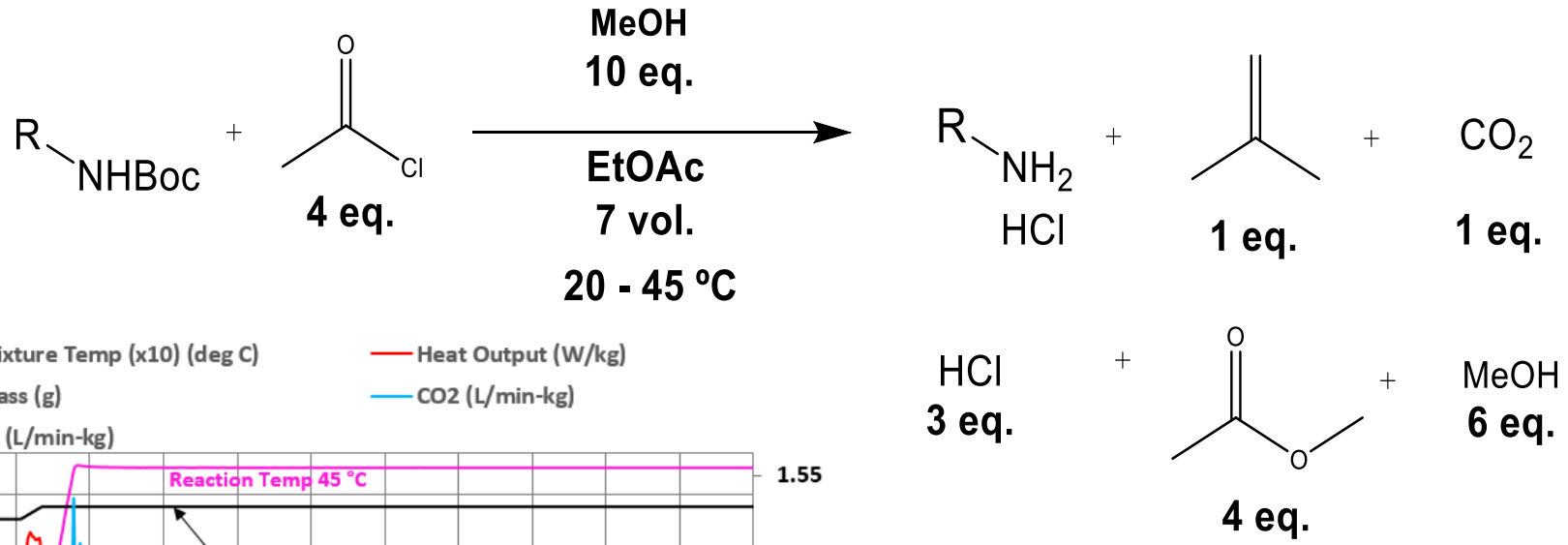


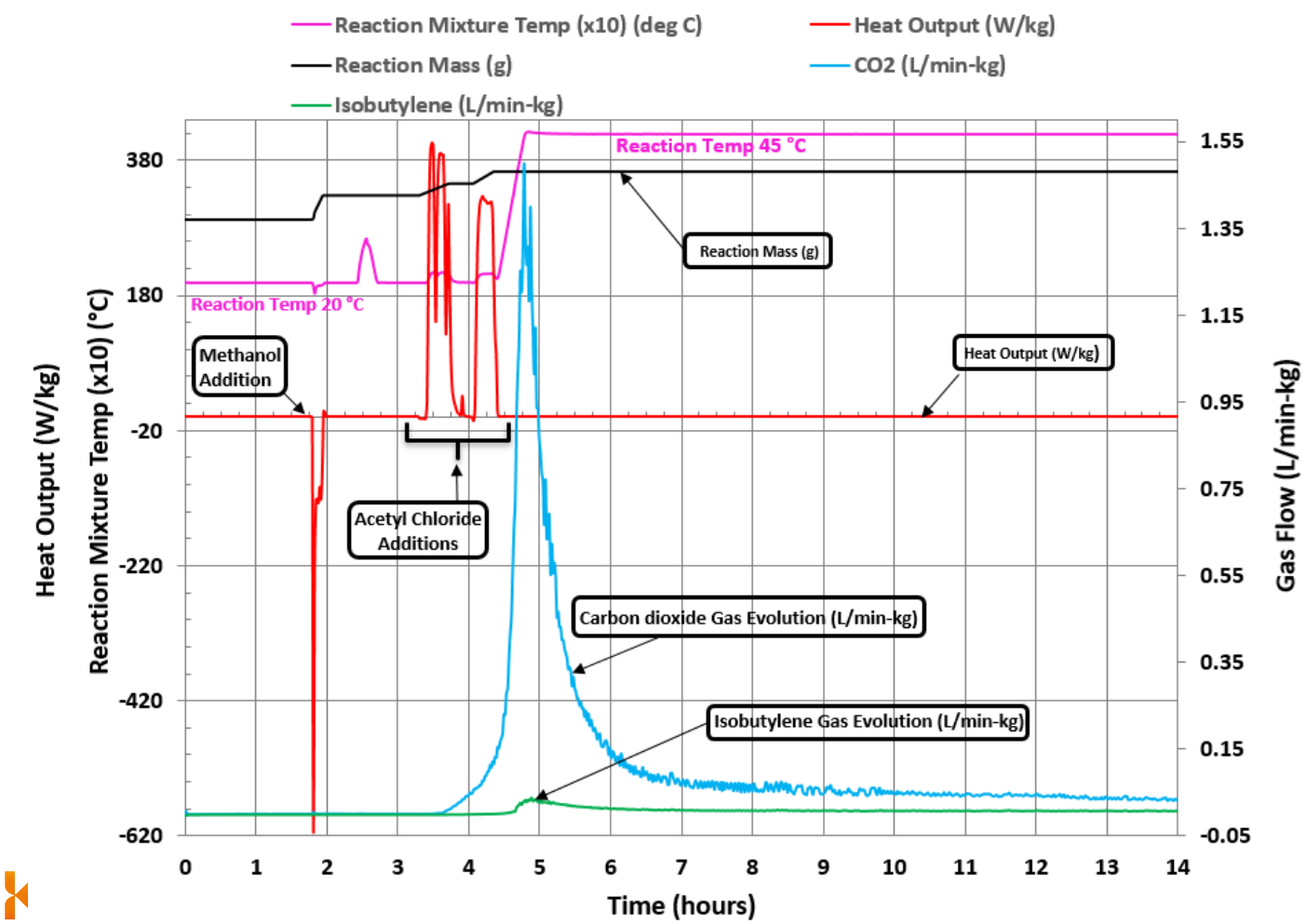
Example 2:

- CO2 and isobutylene gas evolution throughout the process
- Water & IPA additions cause brief spikes in gas evolution
- Typically, stir for 2 hours then filter
- Isobutylene gas evolution increases after 1 hour
  - Evolution levels off after 18 hours
  - Decision made to filter slurry
- Filter product slurry:
  - Mother liquor evolves CO_2 and isobutylene gas
    - Treat with 2M aq. NaOH
- Cake washes w/ Water & TBME:
  - CO_2 and isobutylene gas continue to evolve
    - Stir in collection vessel for 8 hours

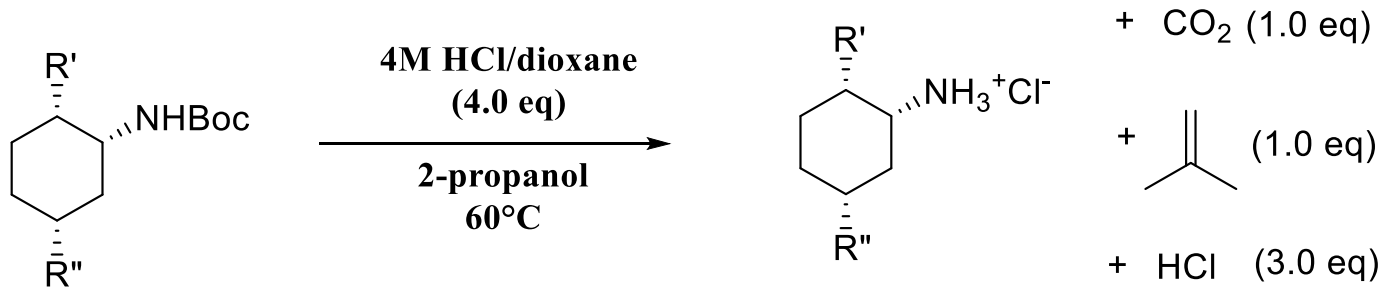


Example 3:

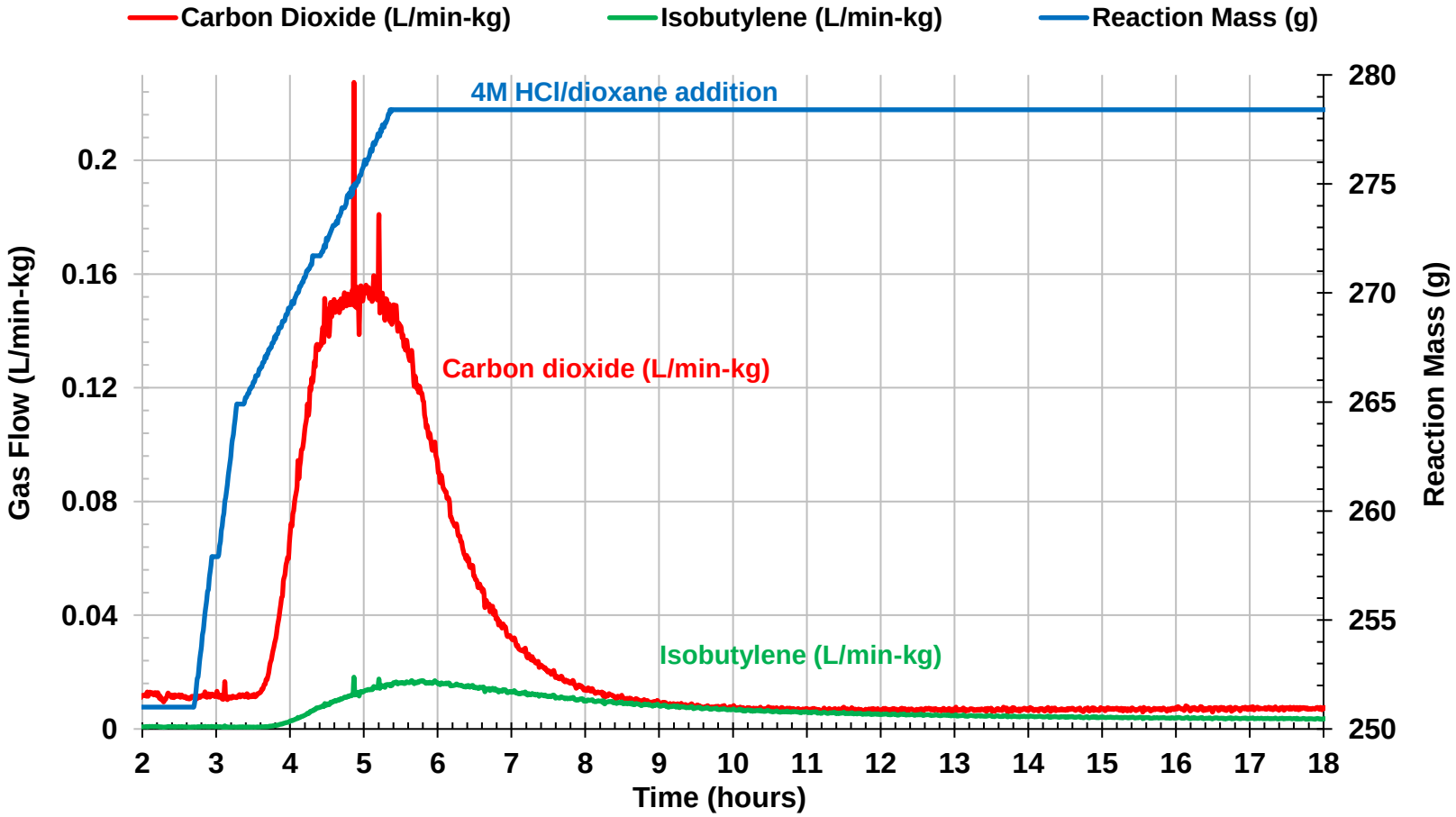

MeOH
10 eq.
EtOAc
7 vol.
20 - 45 ºC
4 eq.
1 eq.
1 eq.
3 eq.
4 eq.
6 eq.
HCl
MeOH


Reaction Mixture Temp (x10) (deg C)
Heat Output (W/kg)
Reaction Mass (g)
CO2 (L/min-kg)
Isobutylene (L/min-kg)
Reaction Temp 45 °C
Reaction Temp 20 °C
Reaction Mass (g)
Heat Output (W/kg)
Methanol Addition
Acetyl Chloride Additions
Carbon dioxide Gas Evolution (L/min-kg)
Isobutylene Gas Evolution (L/min-kg)
Heat Output (W/kg)
Reaction Mixture Temp (x10) (°C)
Gas Flow (L/min-kg)
Time (hours)
380
180
-20
-220
-420
-620
1.55
1.35
1.15
0.95
0.75
0.55
0.35
0.15
-0.05
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14

Example 4:



R' & R" contain secondary amines



Conclusion

- Challenge thinking on possible gas evolution
- Certain functional groups or reagents should prompt closer scrutiny for the generation of gas evolution
- Gas evolution can occur at low-levels, even if not expected
  - Hydrolysis of t-butyl esters may produce isobutylene gas
  - Boc protected compounds can generate CO_2 and isobutylene gas evolution in varying levels
- Predicted gas evolution within a process may not always occur as or when expected
  - May significantly increase and/or not begin until heating
  - May require sequential chemical interactions to initiate gas evolution

Acknowledgement

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- Frank Dixon – Investigator, Global Process Hazard Evaluation Group

Thank-you! – Q&A / AOB