Sealed-Cell Photo-DSC: A New Tool for Process Safety Evaluation of Photochemical Processes

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Outline

- Background: Application of DSC to Photochemical Systems
- Design/Development of a Photo-DSC method
- Proof-of-Concept Data
- Future Direction

But first…. a shameless plug!

Merck currently has a job opening (Assoc. Principal Scientist) for a process safety chemist, posting is open through May 16

Photochemistry

Photochemistry is becoming a key element of the pharma chemistry toolbox

- Novel reactivity, milder conditions, higher selectivity

Photons excite starting materials or transition state

- Can enable new reaction mechanisms (including degradation pathways!)

We cannot keep doing our thermal hazard workflows in the dark!

What is DSC?

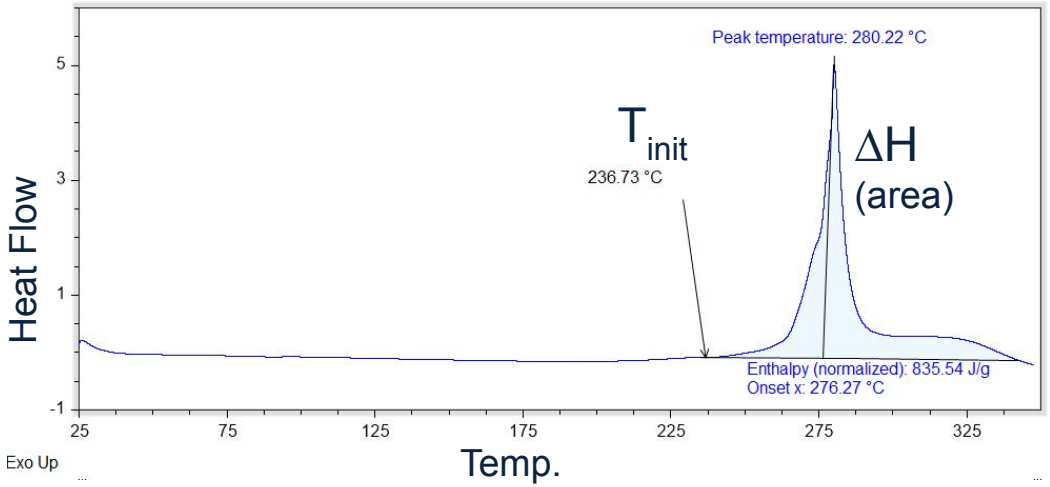
Used to assess processes for overheat upset scenario

- Jacket runaway scenario or loss of cooling in exothermic reaction

DSC

DSC (differential scanning calorimetry) measures the heat flow of a sample vs. a reference when temperature ramps up

- Low sample requirement (~2-5 mg)
- First-pass screening to determine further testing needs



Standard testing:

- Both raw materials and process streams
- Typically scan up to ~350°C
- Jacket runaway scenario can reach up to ~180°C

For reactions with organic solvents, the sample must be sealed in a non-reactive pan for analysis (e.g., gold-plated stainless steel high-pressure crucibles)

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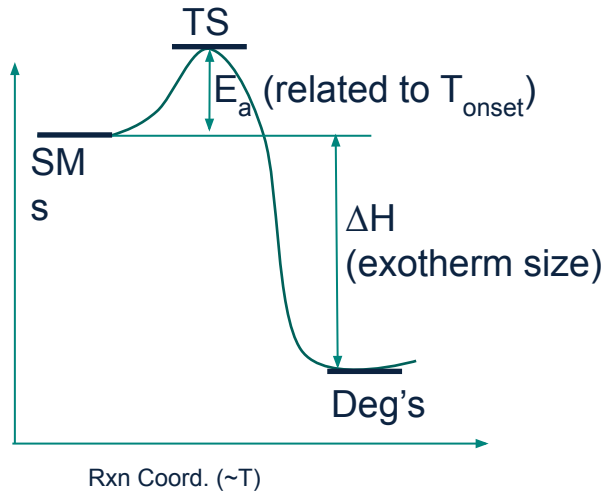
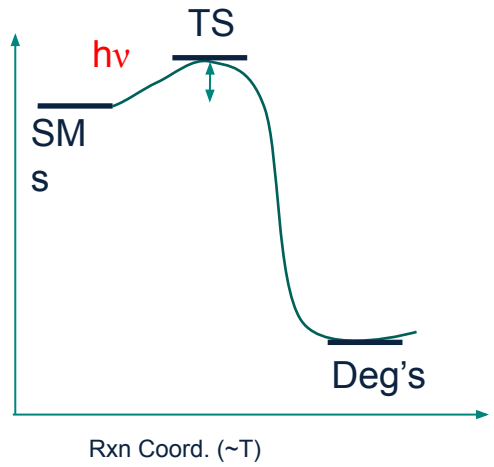
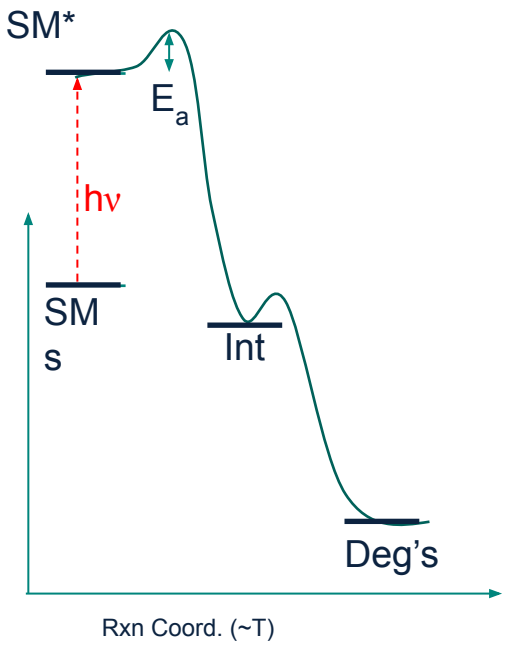
Justification for Photocalorimetry

- Want to characterize magnitude and onset of hazardous exotherms in the presence of the same photons that will be used during a photochemical process







- ΔH may change, and onset T could change significantly if the degradation pathway and/or mechanism is enabled by light
- Jacket runaway is still plausible, but also loss of cooling could lead to batch overheating from the light source

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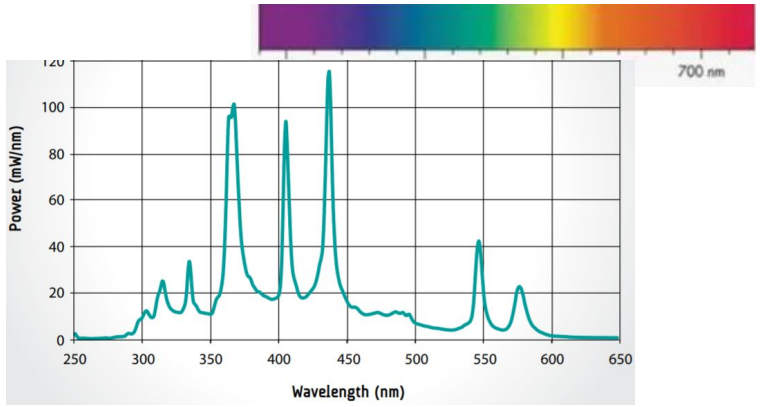
Photocalorimeter Accessory (PCA)

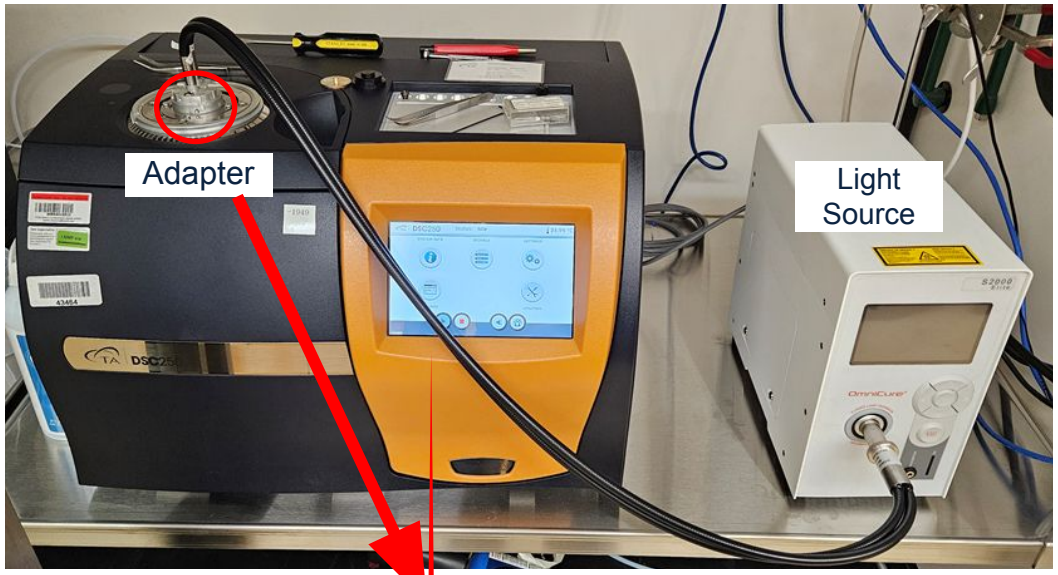
- TA's Photocalorimeter Accessory (PCA) includes a **light source** (Excelitas Omnicure S2000) and **adapter** hardware
  - Two parallel light beams, for sample + reference
  - Independent vertical beam adjustment to equalize intensity
  - Max operating temperature ~250 °C

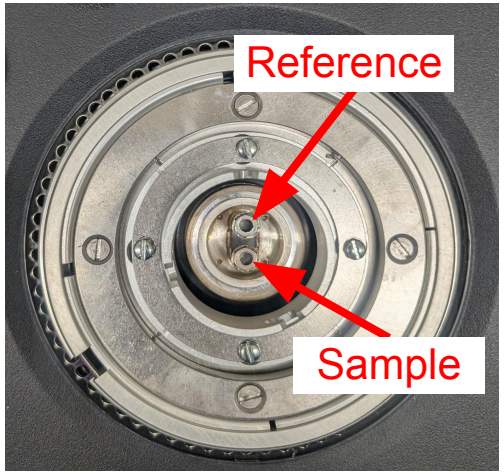


Omnicure S2000 light source output spectrum

- Traditionally, the PCA is used with open DSC pans (e.g., for photo-curing of non-volatile polymers)

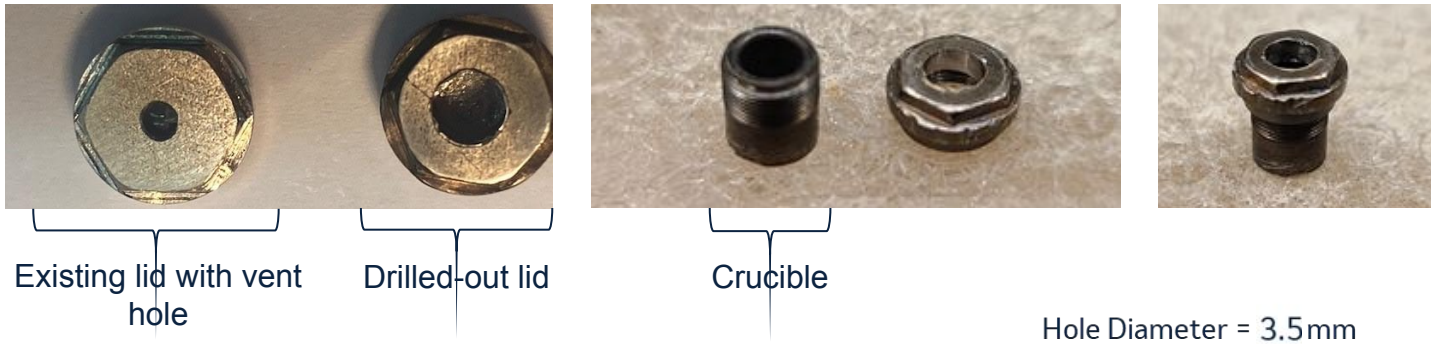
We sought a sealed DSC pan with a transparent "window" to enable irradiation





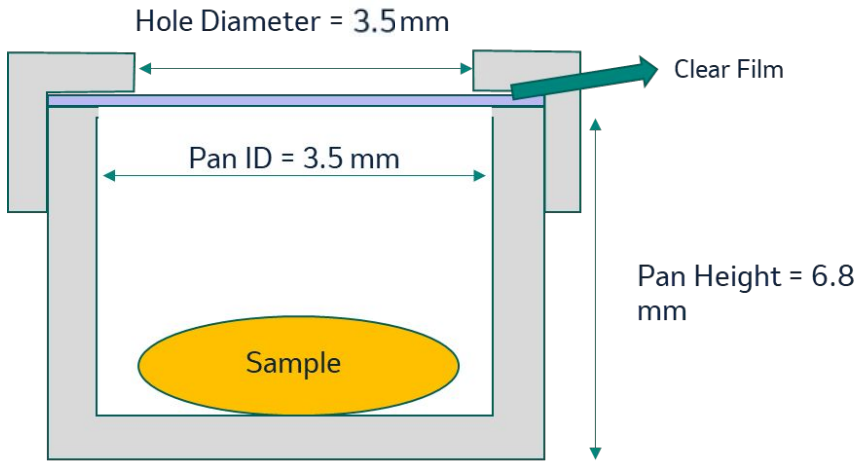
Crucible Design

- Leveraged existing reusable Tantalum-lined Hastelloy crucibles with screw-down lid and vent hole
  - Drilled hole (~3.5 mm) through existing lid to allow for light penetration
  - Punched-out a transparent disc (“window”) of film to insert inside of lid



Film options:

- Glass/Sapphire
- Ethylene tetrafluoroethylene (ETFE)
- Fluorinated Ethylene Propylene (FEP)
- Perfluoroalkoxy (PFA)



Schematic of photo-DSC Crucible Design

Tuma, L. A reusable metal crucible for use in differential scanning calorimetry analysis of closed reaction system samples. *Thermochimica Acta* **1992**, *212*, 179-187. DOI: https://doi.org/10.1016/0040-6031(92)80233-M.

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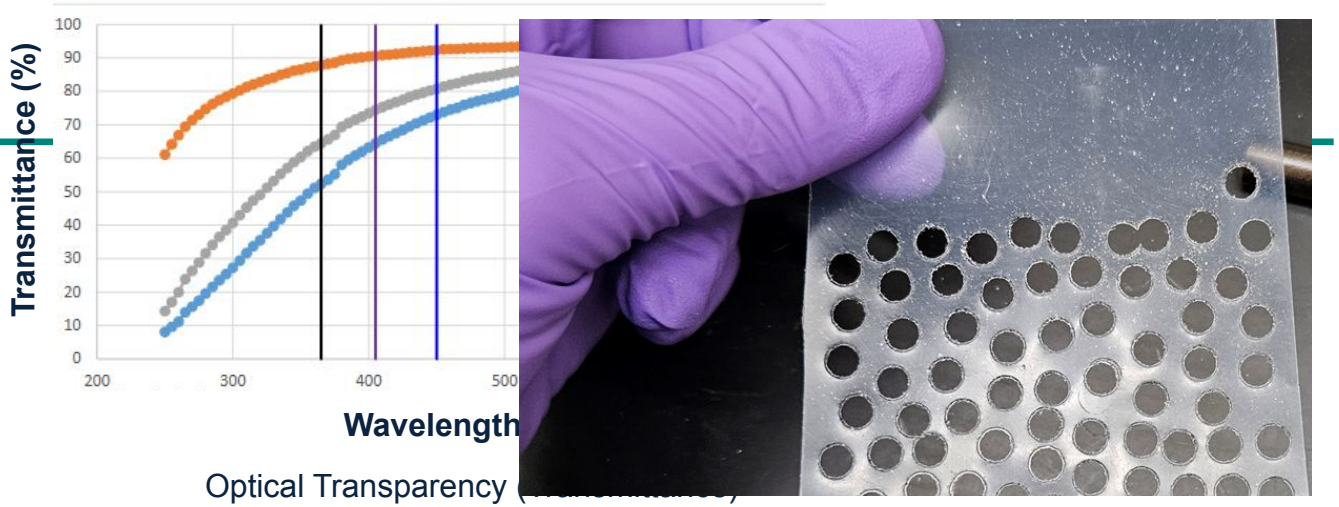
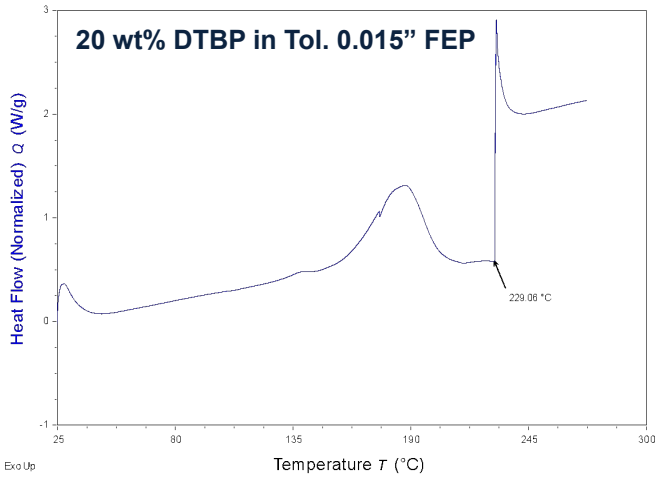
Window Film Selection

Key Requirements:

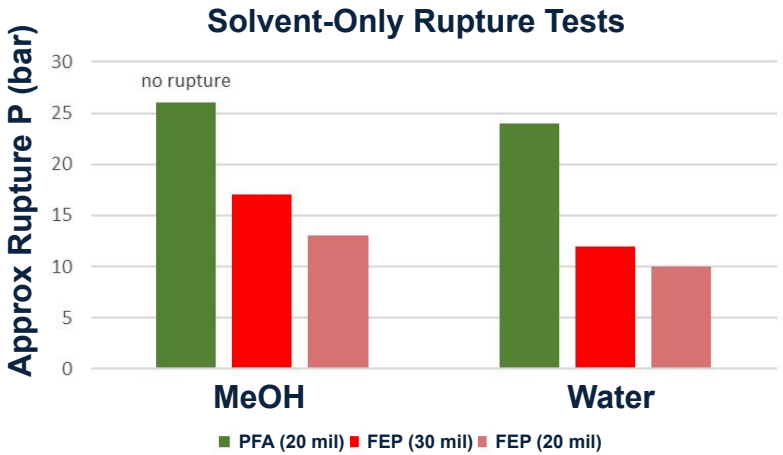
- ✔ Optical transparency
- ✔ Heat resistant (~250ºC)
- ✔ Strength (hold pressure)
- ✔ Pliable
- ✔ Easy to manipulate/install
- ✔ Non-reactive
- ✔ Inexpensive



Optical Transparency (Transmittance) for PFA and FEP Films



Ruptured PFA film

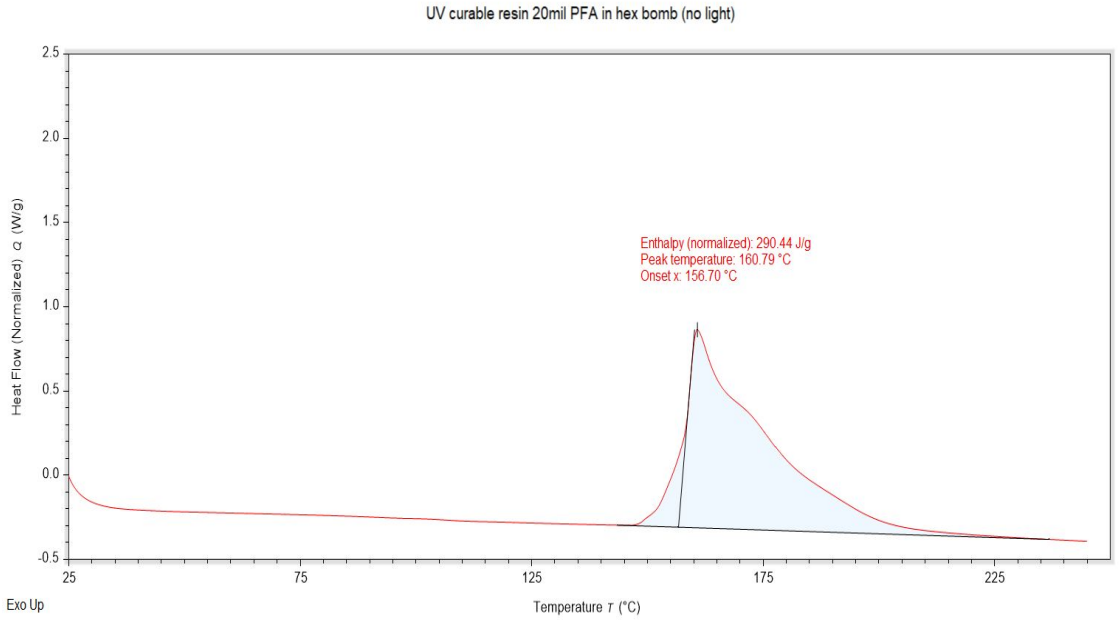


20 mil PFA was selected as the best balance of UV transparency and strength

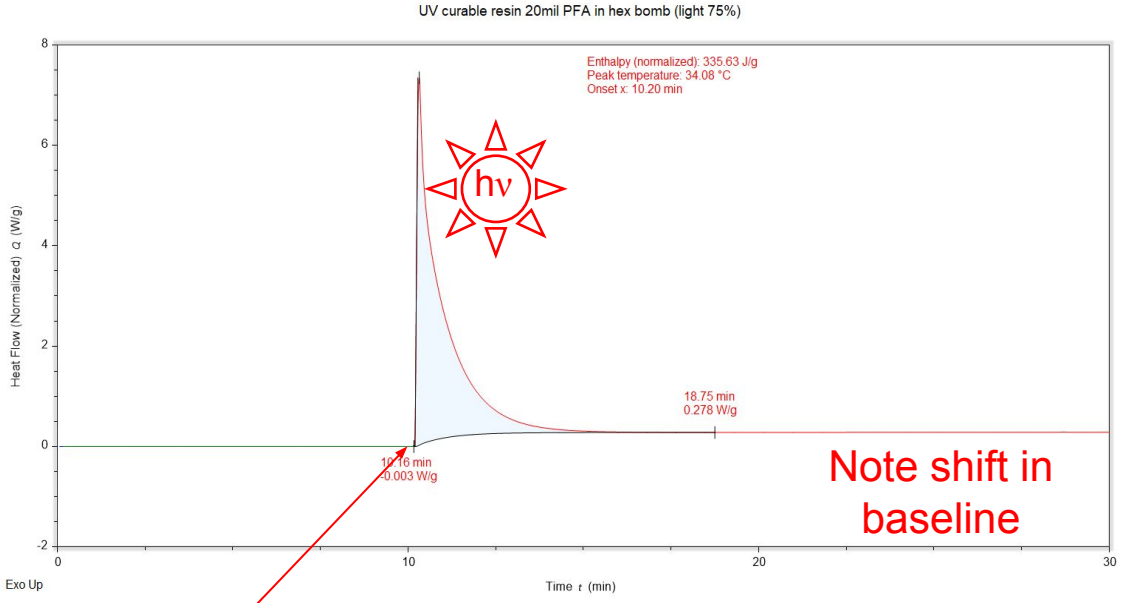
Proof-of-Concept Data

UV-Curing Resin w/ PFA window

No light (temp. ramp)
- Enthalpy: ~300 J/g
- Initiates at ~144 °C



Light on (UV curing, isothermal)
- Enthalpy: ~300 J/g
- Initiates upon illumination



Light source turned ON

Searching for Test Cases…

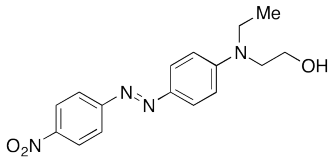
- Criteria:

✔ Commercially-available molecules with known UV-absorbance

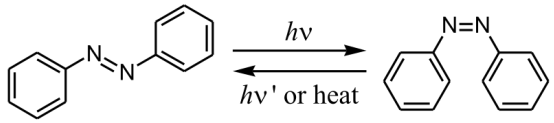
✔ Known or suspected to be energetic (need a DSC signal)

✔ Neat or in solution (DMSO, Cyrene used as solvents – low volatility, high decomp. energy)

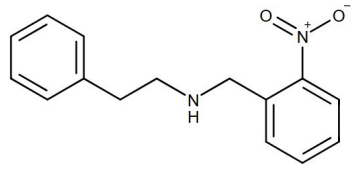
- Candidates
  - Azo, nitro dyes



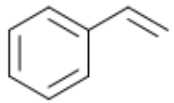
  - Azobenzene “photoswitches”



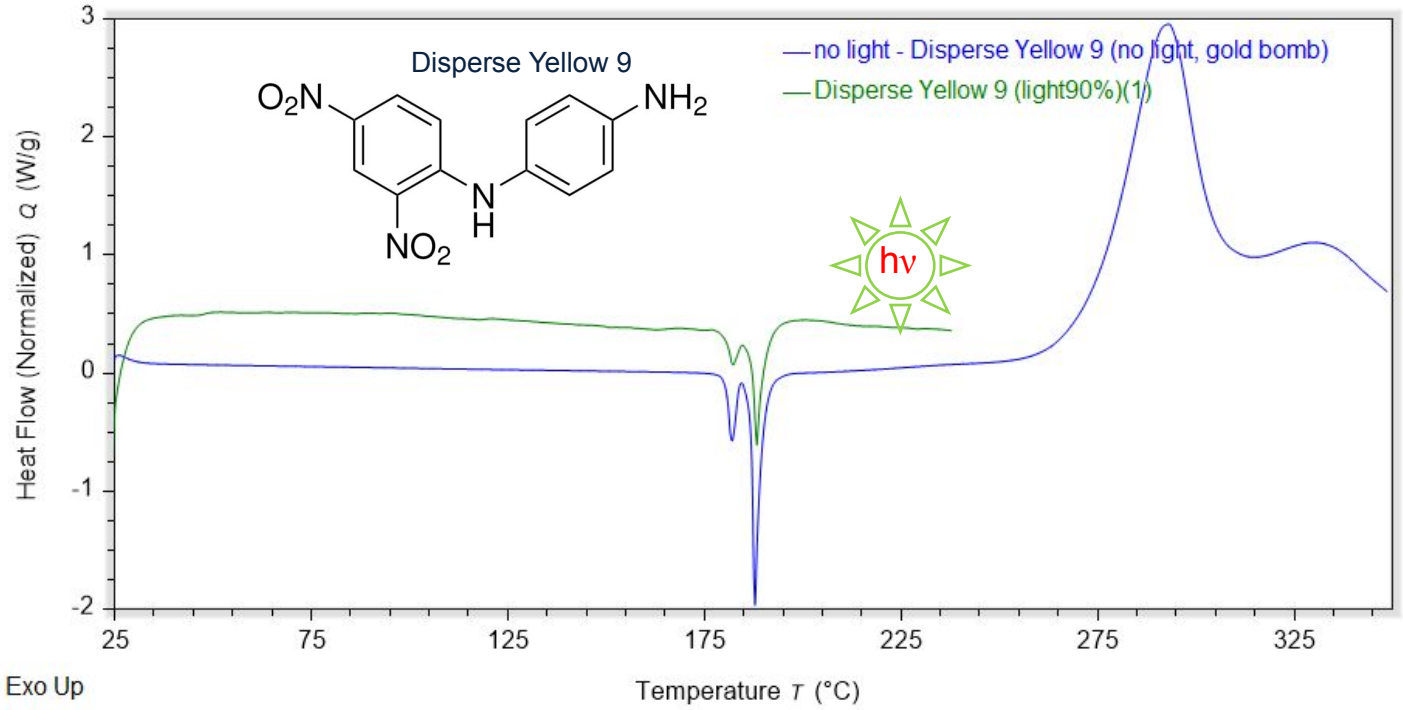
  - Photolabile protecting groups (o-nitrobenzyl)

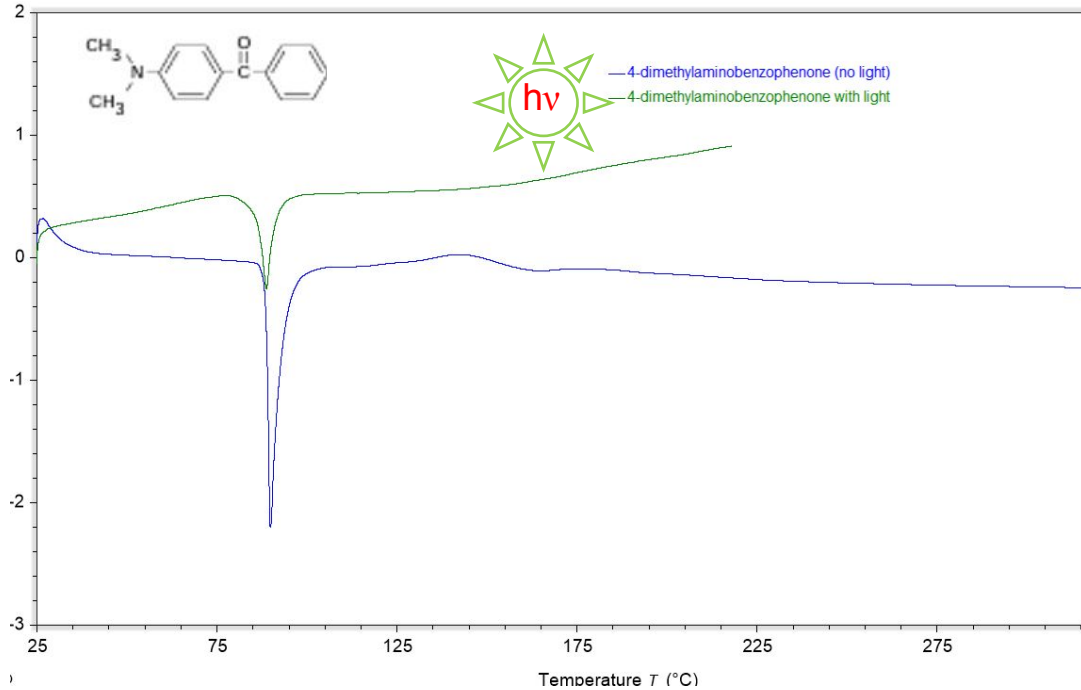


  - Diazo photo-initiators
  - Photosensitive monomers



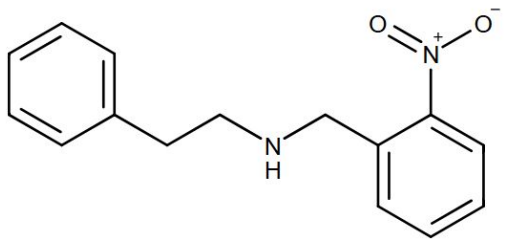
Results vs. M20 gold crucibles





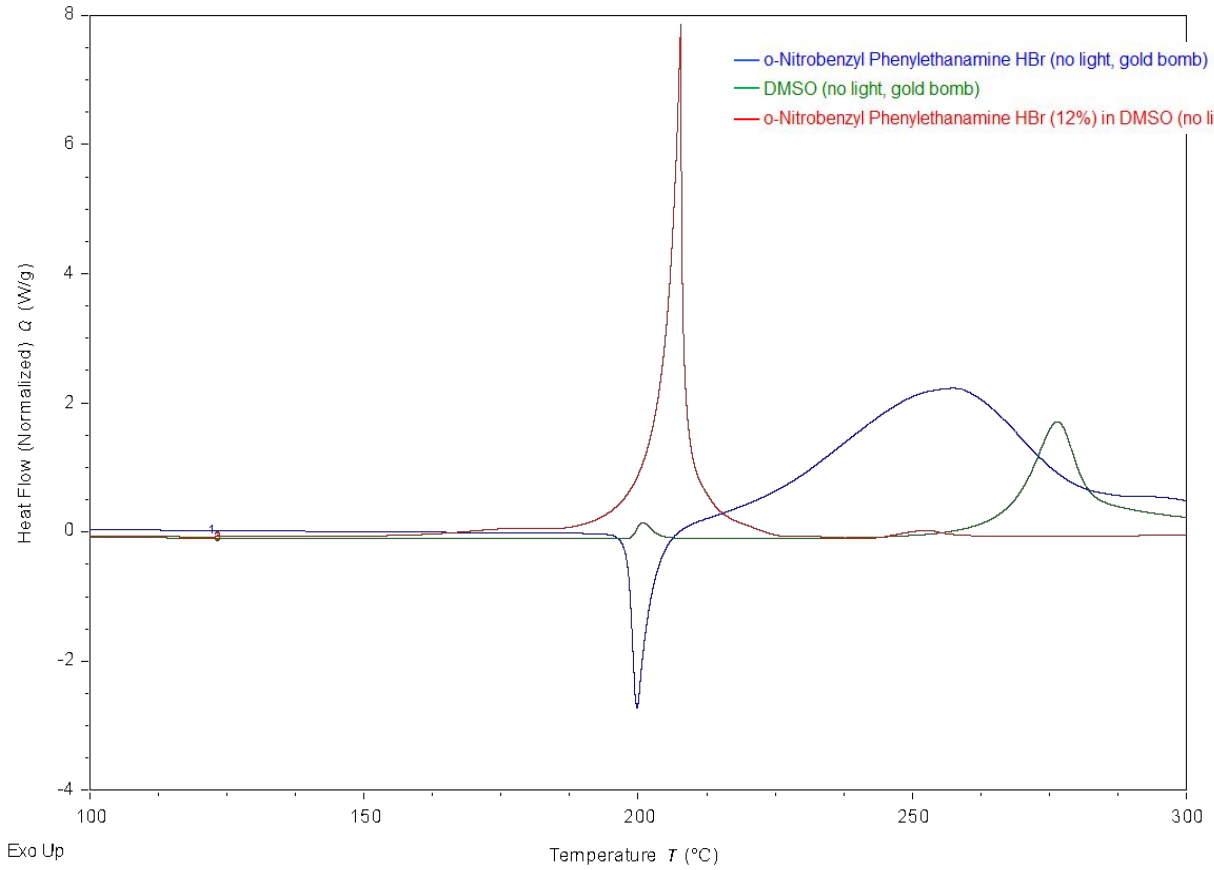
- Generally good thermograms
- Baseline not quite as smooth/level
- Larger sample size typically used (5-10mg) to improve signal/noise
- Cannot exceed 250°C (limited by both PCA and film max temp)

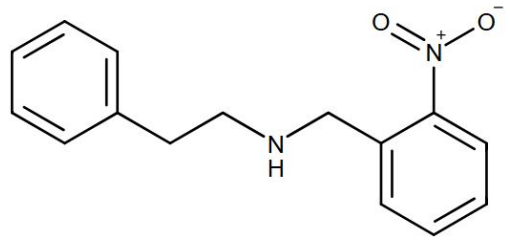
N-(2-nitrobenzyl)-2-phenylethanamine HBr



O-nitrobenzyl is commonly used as a photolabile protecting group

N-(2-nitrobenzyl)-2-phenylethanamine HBr in DMSO





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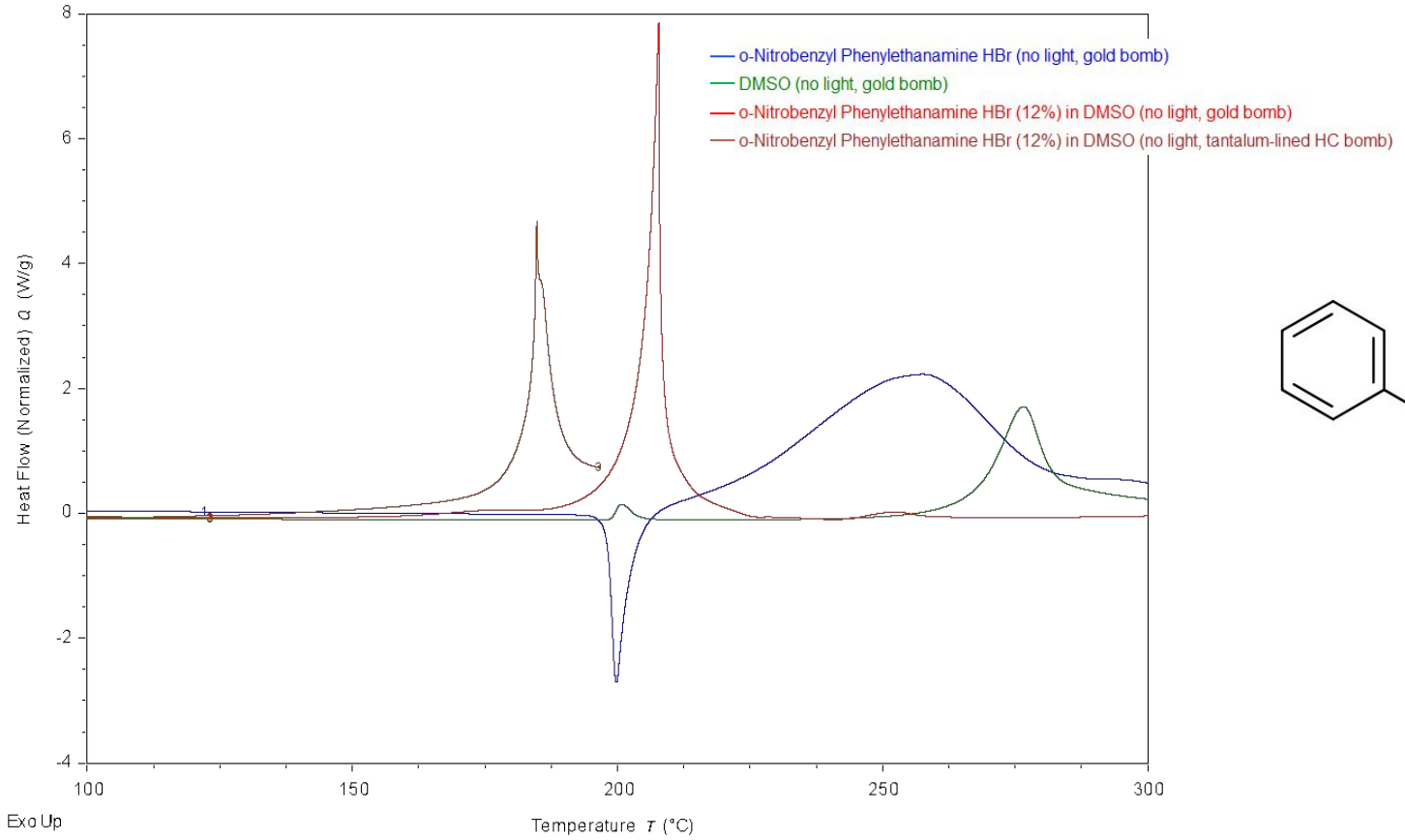

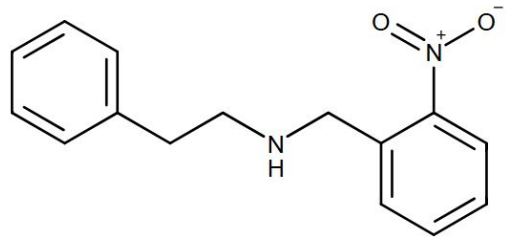

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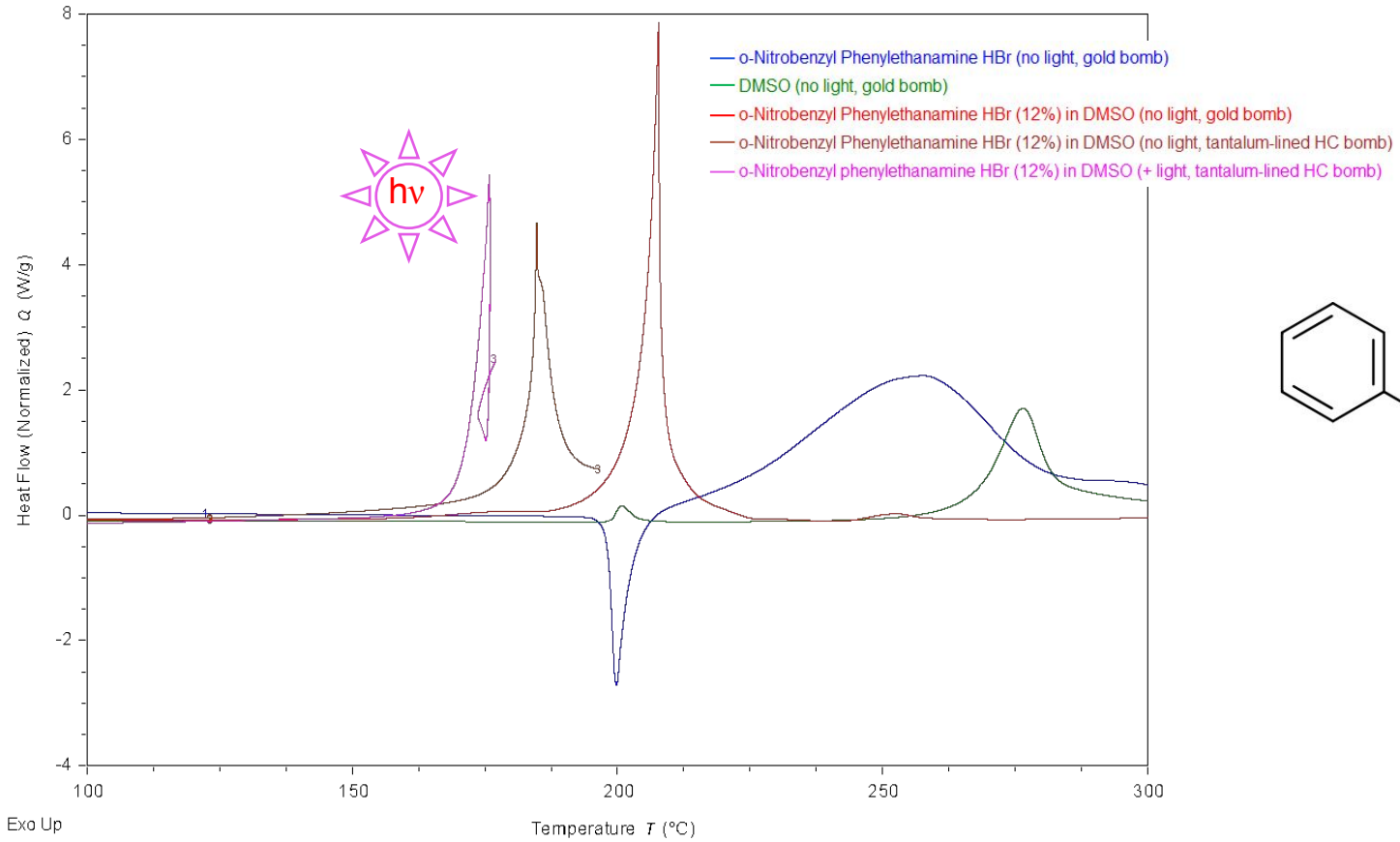
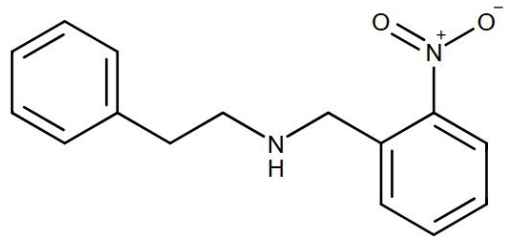
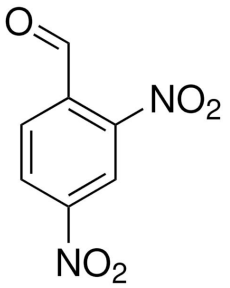


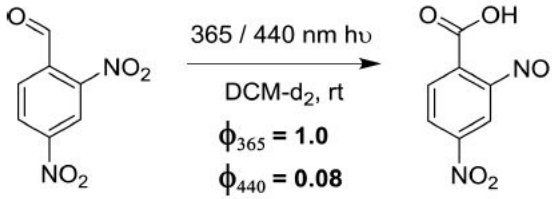


2,4-Dinitrobenzaldehyde

Used as actinometer for photo-NMR at Merck



Scheme 3. Photochemistry of 2,4-Dinitrobenzaldehyde



Org. Lett. 2018, 20, 2156−2159
https://pubs.acs.org/doi/10.1021/acs.orglett.8b00391

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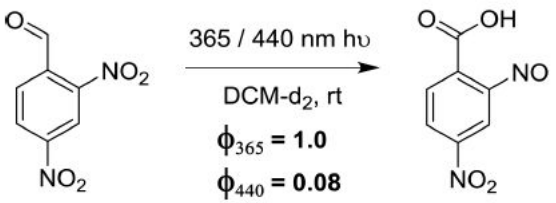
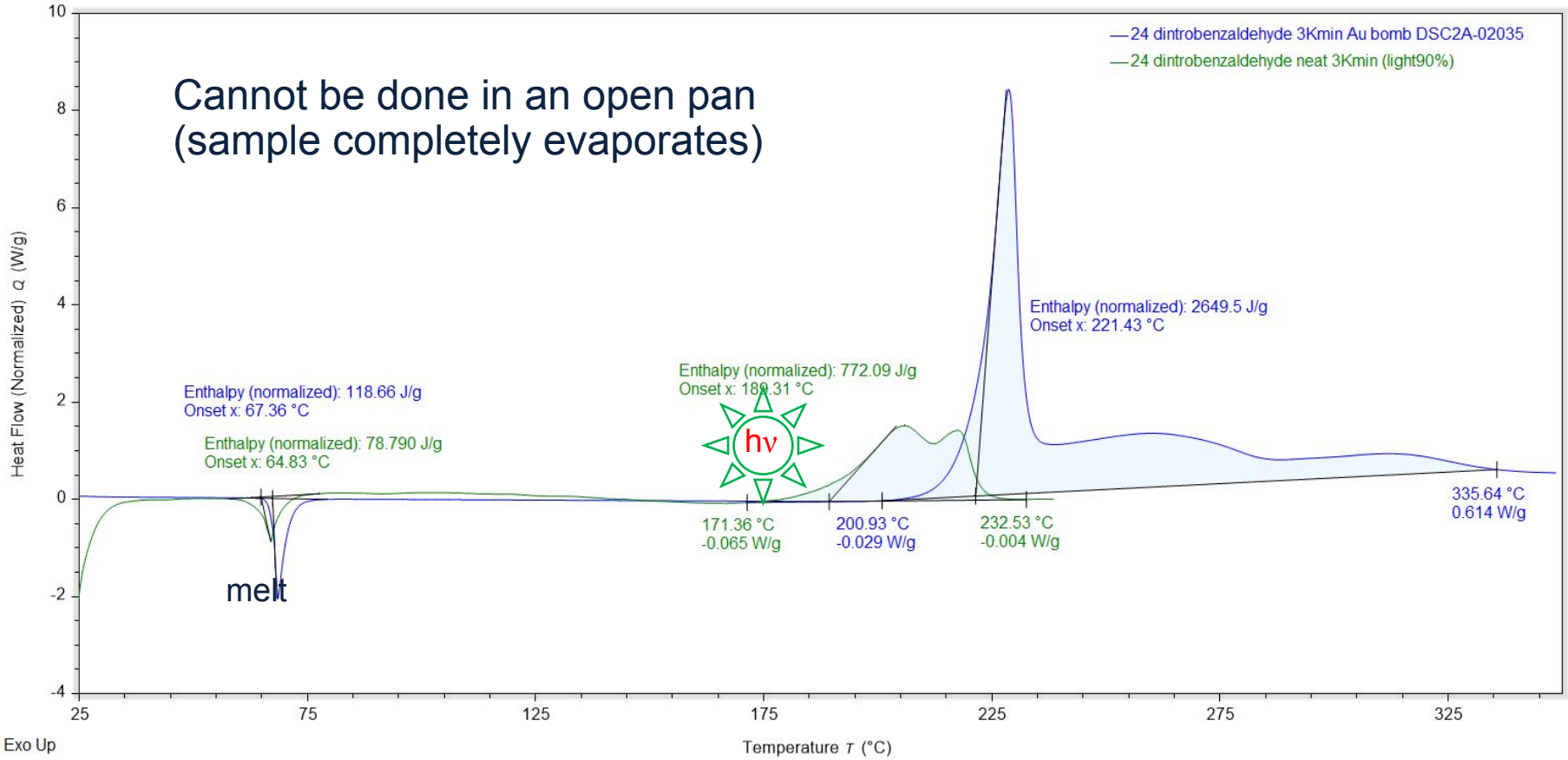
2,4-dinitrobenzaldehyde

Neat,
3K/min

Scheme 3. Photochemistry of 2,4-Dinitrobenzaldehyde



DNB **P**



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Conclusions/Future Direction

- **Conclusions/Summary**
  - Demonstrated proof-of-concept, instrument and technique are sufficient to get meaningful data at relevant wavelengths and photon fluxes
    - Pressure and Temperature are known limitations, but still suitable for our needs
- **Future Directions**
  - Building larger data set, more repeats, understand variability
  - Start using photo-DSC for real reactions
    - First “real” reaction stream was analyzed in March (C-N photoredox coupling)
    - Intern this summer will be working on other reactions/applications
  - Manuscript is in progress
- **Key Message**
  - The field of chemistry is constantly changing. Process safety assessment techniques must evolve to keep up!

Acknowledgements

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