Structure-Activity Relationships of Propylene Glycol, Glycerin, and Select Analogs for Carbonyl Thermal Degradation Products

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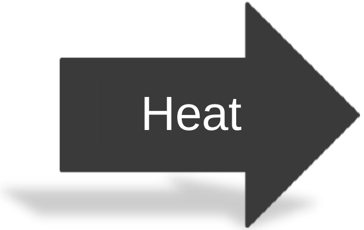
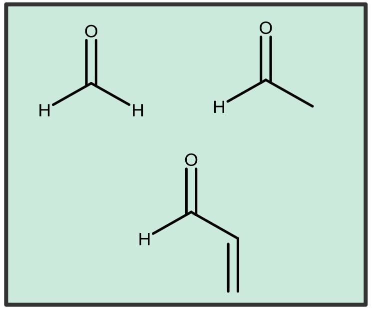
Thermal Degradation of eLiquids

Propylene Glycol
Glycerin
Nicotine
Flavor Systems

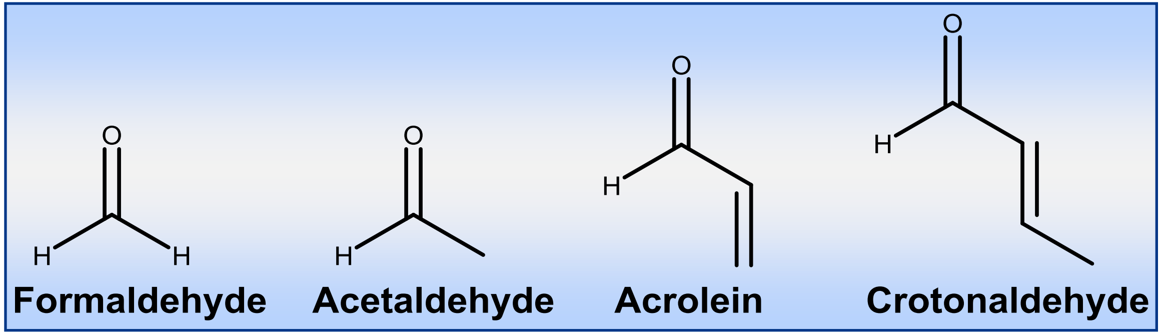




- Propylene glycol (PG) and Glycerine (GLY) can thermally degrade upon heating
  - Formaldehyde, Acetaldehyde, Acrolein[1,2,3]

Carbonyls in E-Cigarettes

- Geiss et al. and Gillman et al. demonstrated that carbonyl formation increased with temperature[1,4]
- US FDA PMTA Draft Guidance for ENDS Products recommends reporting four carbonyls in e-liquid and aerosol[5]



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Objectives and Approach

- Determine the formation pathways of formaldehyde, acetaldehyde, acrolein, and crotonaldehyde:
  1. Identify source of degradation products using $^{13}C_3$-labeled PG and GLY
  2. Determine the role of 3-hydroxypropanal (3-HPA) as an intermediate during the thermal degradation of e-liquids
  3. Propose rational mechanisms based on results
  4. Determine key reaction centers using rationally selected derivatives of PG and GLY

Microwave Model System

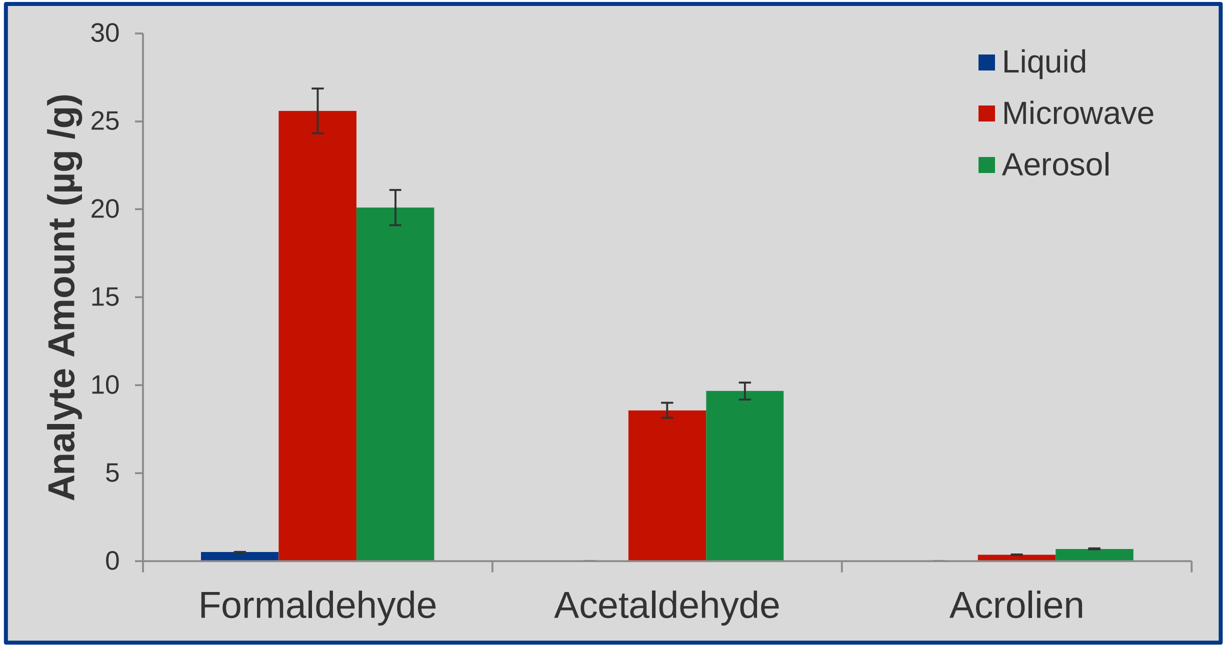
- Model microwave system used to generate target carbonyls
  - Previously used to identify diacetyl and acetyl propionyl formation pathways[6]

- Microwave system evaluated for equivalent yields to e-cigarette
  - Sample = 50% PG : 50% GLY + 2.5 % nicotine (w/w)
  - 140 puffs
  - 55 mL puff volume, 5 sec puff duration, 30 sec puff period, square wave

CEM Discovery SP Hybrid

Analyte Yield Comparison

140 puffs using 55 ml Puff Volume, 5 sec Puff Duration, 30 sec Puff Period; Square Wave



Crotonaldehyde was not detected

Identify Source of Degradation Products Using 13C-labeled PG and GLY

Carbon-13 Labeled PG and GLY

- Samples:
  - 50% **$^{13}C_3$-PG** : 50% GLY + 2.5% nicotine (w/w)
  - 50% PG : 50% **$^{13}C_3$-GLY** + 2.5% nicotine (w/w)

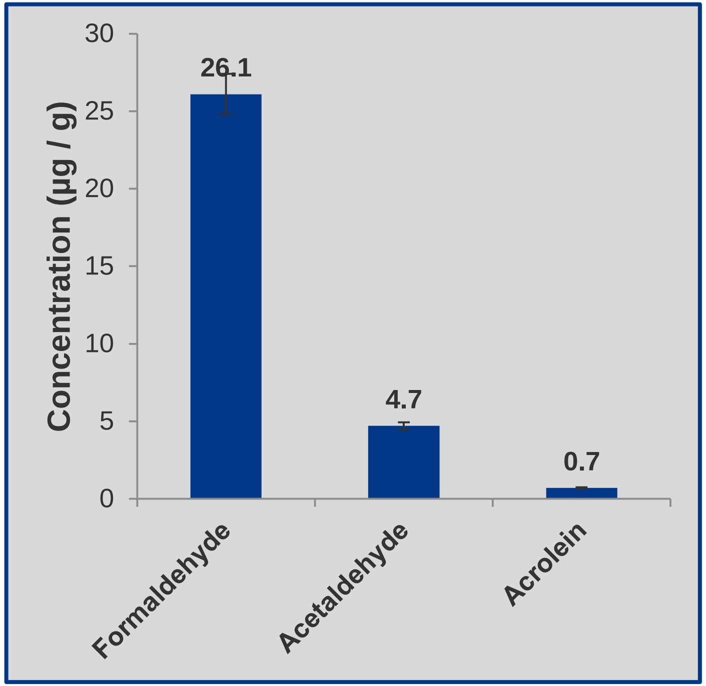
Microwave Heating* → DNPH Derivatization → UPLC-UV-MS/MS → Isotope Distribution

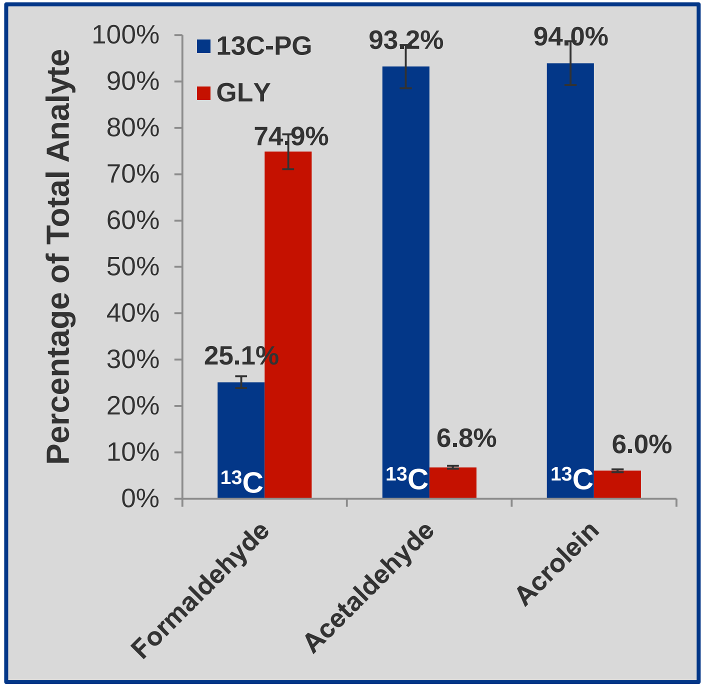
*500 mg of sample heated to 180 °C and held for 3 min

- Labeled products directly traceable to labeled precursor

Product Distribution Using $^{13}C_3$-PG

50% $^{13}C_3$-PG : 50% GLY + 2.5 % Nicotine (w/w)

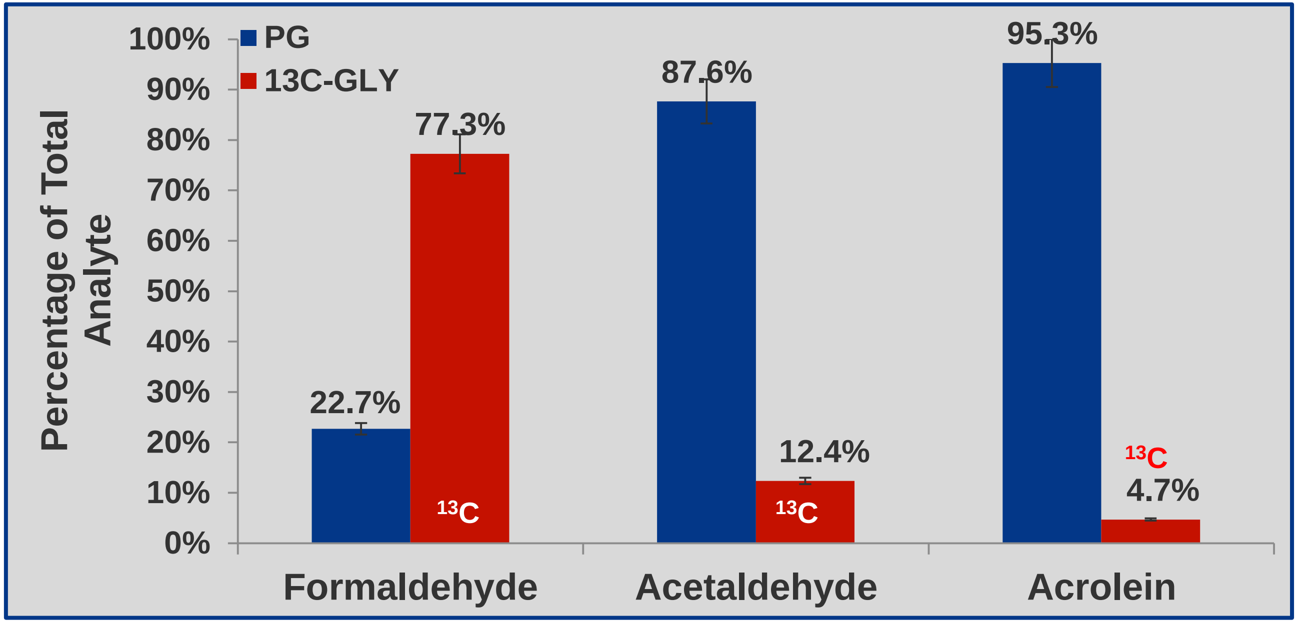




Crotonaldehyde was not detected

Product Distribution using $^{13}C_3$-GLY

50% PG : 50% $^{13}C_3$-GLY + 2.5 % Nicotine (w/w)



Crotonaldehyde was not detected

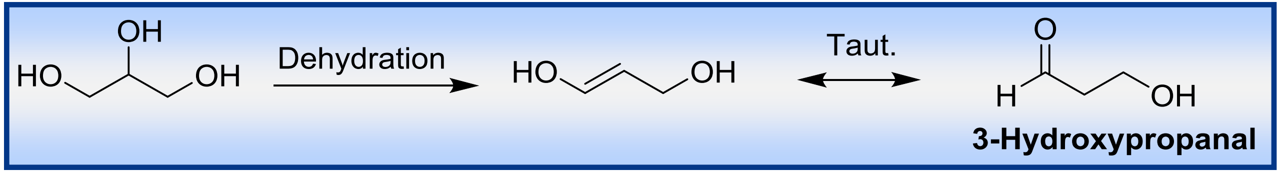
Summary: ^{13}C-Labeling Studies

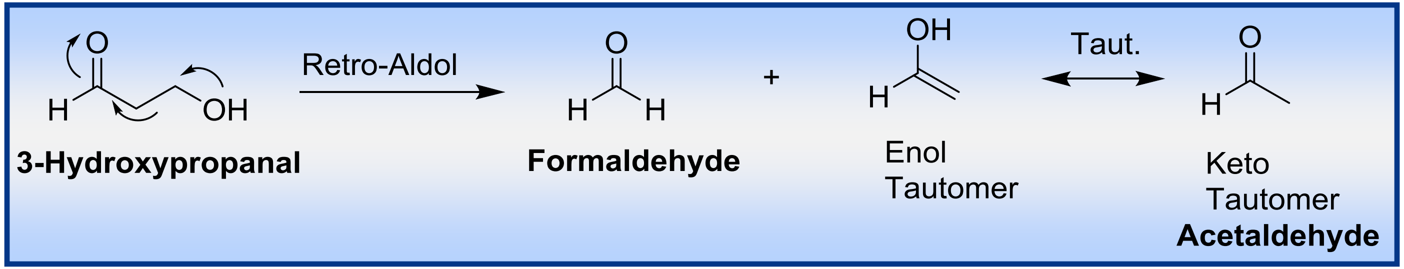
- Formaldehyde was predominantly formed from GLY
- Acetaldehyde and acrolein were predominantly formed from PG
- Crotonaldehyde was not detected

Determine the Role of 3-hydroxypropanal (3-HPA) as an Intermediate During the Thermal Degradation of e-Liquids

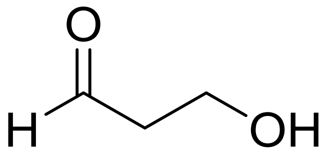
3-Hydroxypropanal Background

- Researchers proposed formaldehyde and acetaldehyde are produced from the retro-aldol condensation of 3-hydroxypropanal (3-HPA)[4,7]





3-HPA Fortification Studies



500 mg e-liquid 50% PG : 50% GLY + 2.5 % nicotine (w/w)

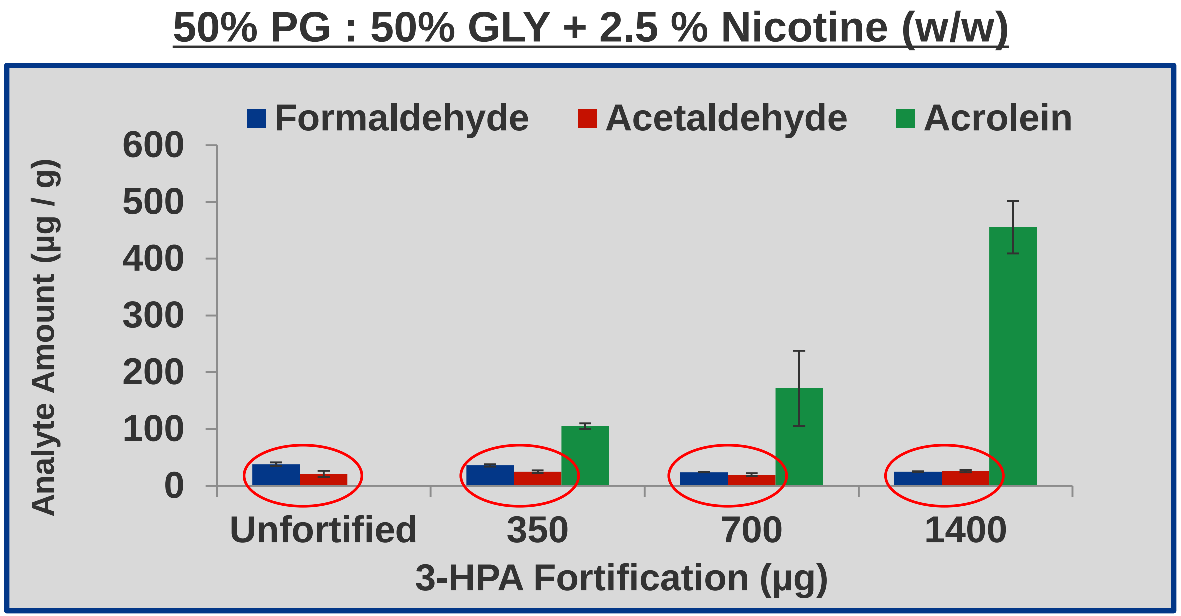
Fortify samples with 3-HPA at 3 levels (300, 700, 1500 µg)

Microwave Heating: 180 °C for 3 min

DNPH Derivatization

UPLC-UV-MS/MS Analysis

Results: 3-HPA Fortification (N=3)



Acrolein Yield ~ 30%

Summary: 3-Hydroxypropanal (3-HPA)

- Unfortified e-liquids
  - 3-HPA, acrolein, and crotonaldehyde were not detected
- E-liquids fortified with 3-HPA
  - Crotonaldehyde was not detected
  - No increase in formaldehyde and acetaldehyde
  - 3-HPA converted to acrolein with ~30 % yield

➢ The retro-aldol condensation of 3-HPA appears to be a negligible pathway for the production of formaldehyde and acetaldehyde under test conditions

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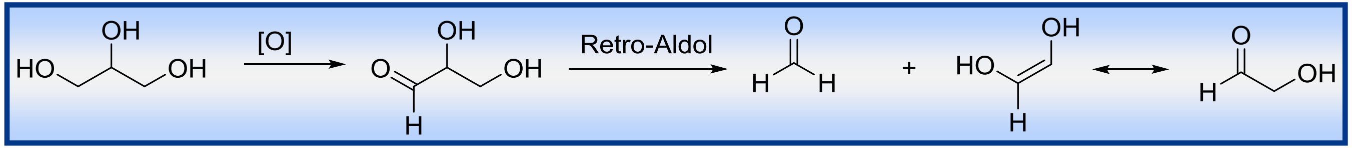
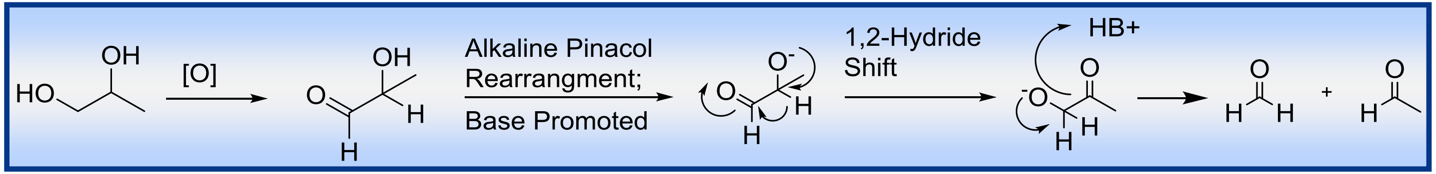
Suggested Formation Pathways in Aerosol

3-HPA was not detected

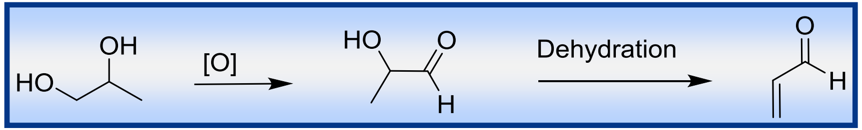
- Formaldehyde from Glycerin



- Acetaldehyde from Propylene Glycol



- Acrolein from Propylene Glycol



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Determine Key Reaction Centers Using Rationally Selected Derivatives of PG and GLY

Experimental: Evaluation of Derivatives

- Derivatives:
  - Methoxy derivatives selected to reduce autoxidation efficiency
  - Methyl derivatives selected to reduce dehydration efficiency

- Samples:
  - 50% PG : 50% **GLY-Deriv** + 2.5 % nicotine (w/w) -> Formaldehyde
  - 50% **PG-Deriv** : 50% GLY + 2.5 % nicotine (w/w) -> Acetaldehyde and Acrolein

- Control = 50% PG : 50% GLY + 2.5% nicotine (w/w)

Microwave Heating: 180 °C for 3 min → DNPH Derivatization → UPLC-UV-MS/MS

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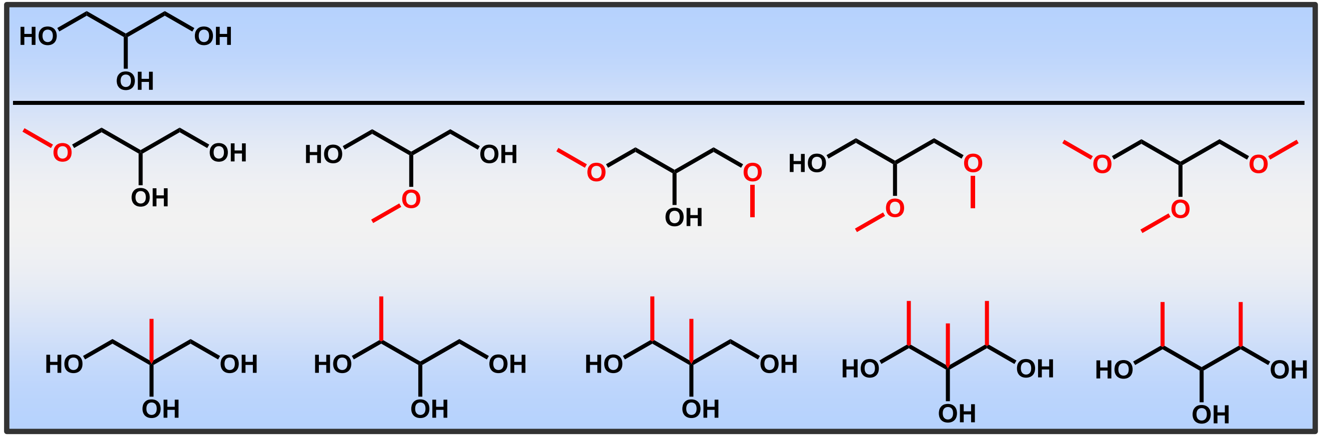
GLY Derivatives: Formaldehyde

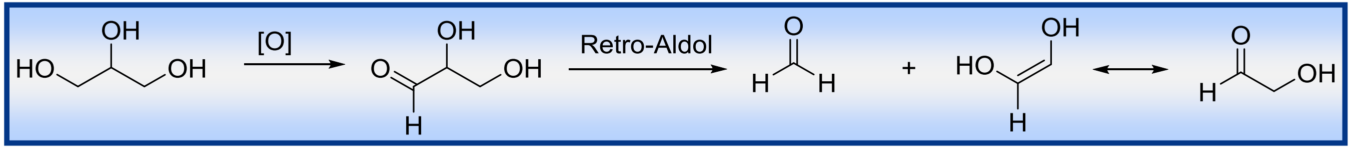
Methoxy Derivatives

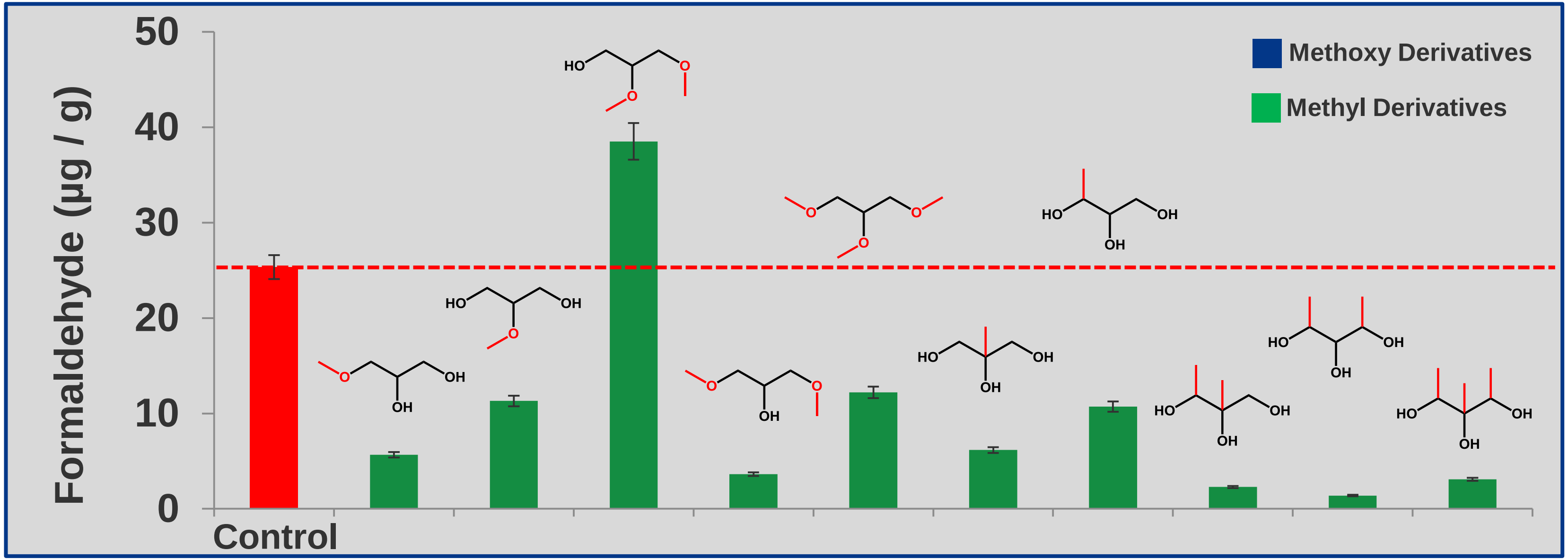
Methyl Derivatives



Formaldehyde: GLY Derivatives

Results support proposed mechanism





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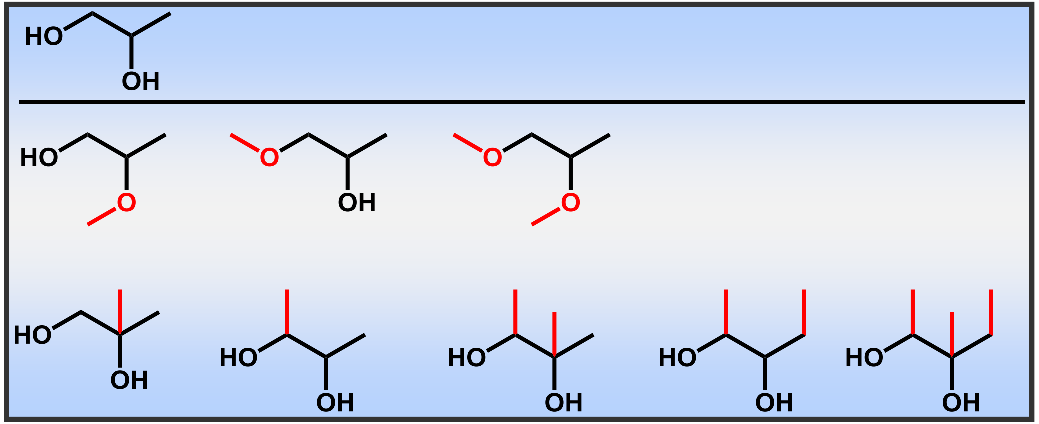
PG Derivatives: Acetaldehyde and Acrolein

Methoxy Derivatives

Methyl Derivatives



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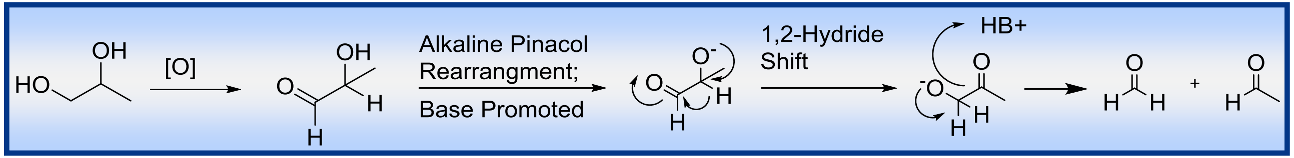
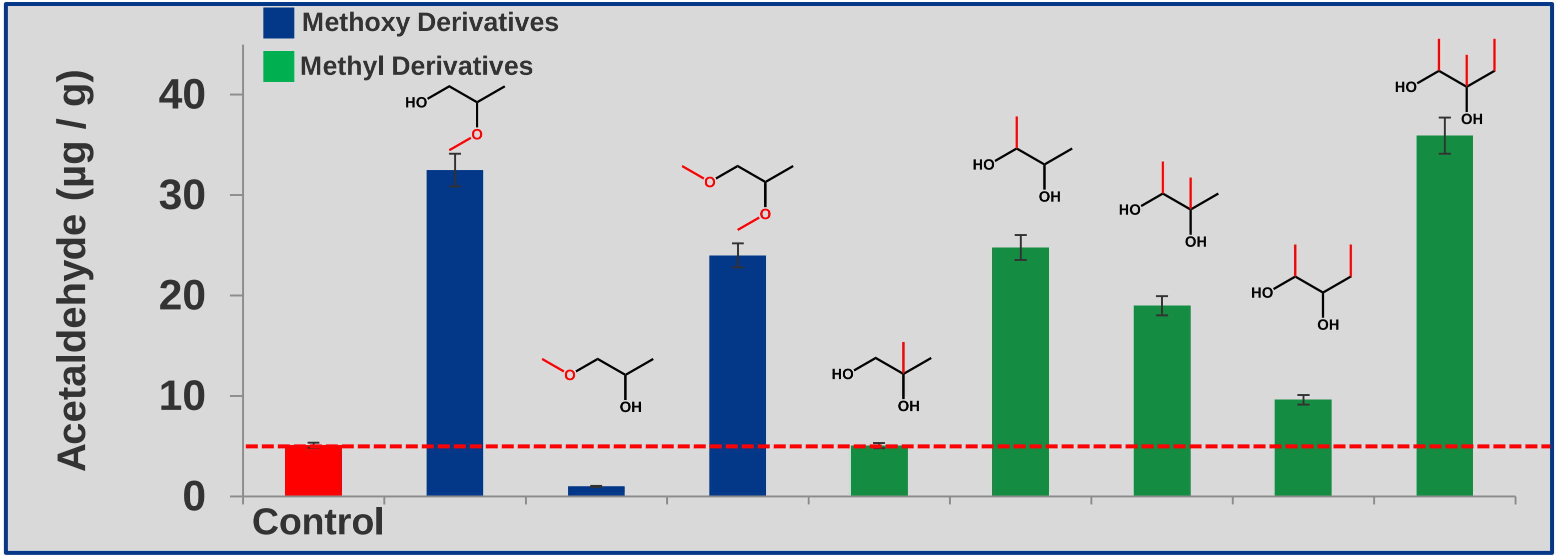
Acetaldehyde: PG Derivatives

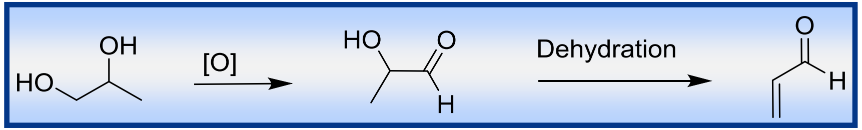
Results do not support proposed mechanism

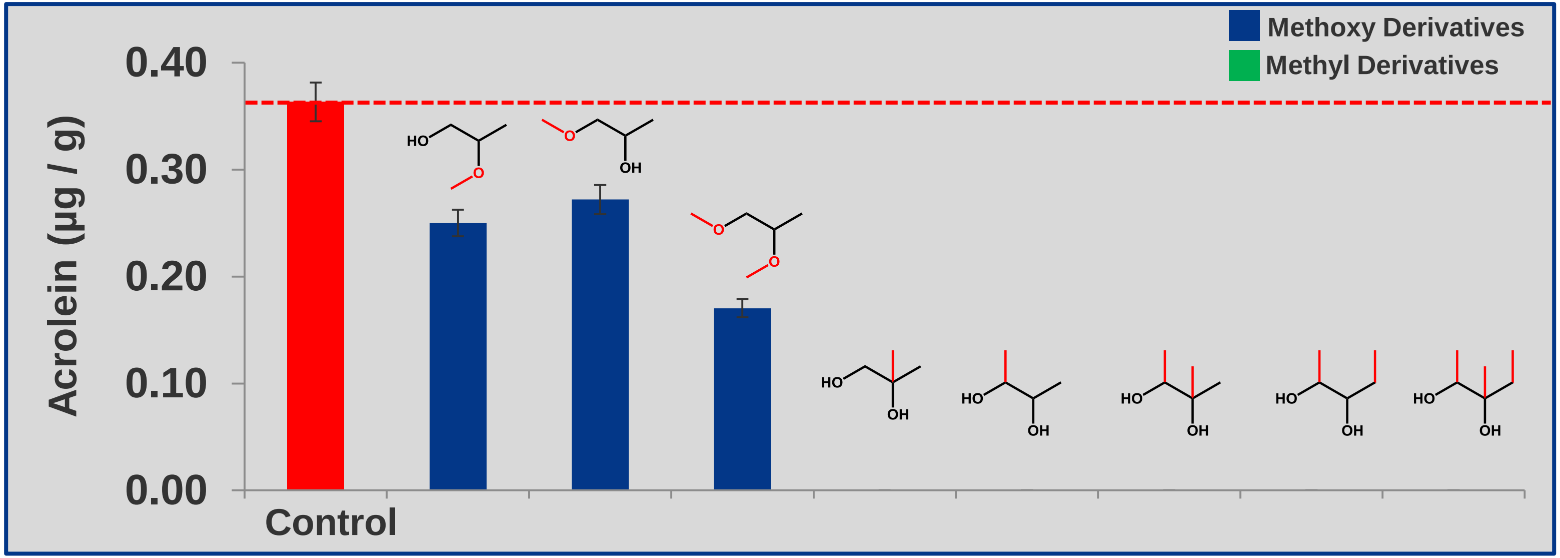




Acrolein: PG Derivatives

Results support proposed mechanism





Summary: Methoxy and Methyl Derivatives

- Formaldehyde: GLY Derivatives
  - Substitution reduced formaldehyde generation
  - Consistent with proposed pathway
- Acetaldehyde: PG Derivatives
  - Substitution increased acetaldehyde production
  - Not consistent with proposed pathway
  - Under further investigation
- Acrolein: PG Derivatives
  - Substitution decreased acrolein generation
  - Consistent with proposed mechanism
- Crotonaldehyde was not detected

Conclusions

- Formaldehyde derived primarily from glycerin
- Acetaldehyde and acrolein derived primarily from propylene glycol
- 3-hydroxypropanal pathway has negligible contribution to formaldehyde and acetaldehyde generation
- Proposed pathways for formaldehyde and acrolein are consistent with experimental results
- Acetaldehyde pathway under further investigation

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