Rubber Oligomers

SVP Symposium, March 31, 2022

Presenter: **Dr. Piet Christiaens, Scientific Director**
Nelson Labs Europe

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Content – Rubber Oligomers

1. **Structure**
2. **Formation**
3. **Detection & Identification**
4. **Reactivity**
5. **Toxicity**

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1. Rubber Oligomers: Structure

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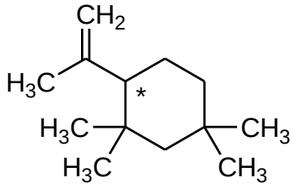
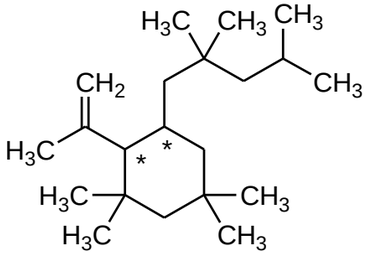
1. Rubber Oligomers: Structure

$C_{13}H_{24}$ and $C_{21}H_{40}$ Oligomers
Not halogenated



C13 oligomer

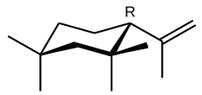


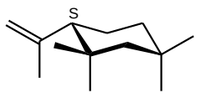
C21 oligomer

- **Formed** both **during the Polymerization** and the **rubber curing** at high temperatures

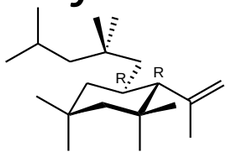
- Considered as
  - **Cyclic aliphatic hydrocarbon** compounds
  - **One double bond**

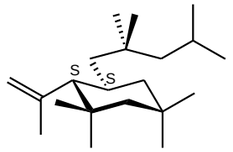
$C_{13}H_{24}$ Oligomer Isomers:
=> 1 pair of enantiomers

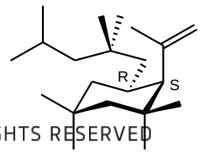


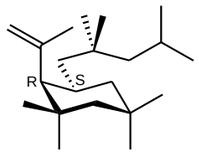


$C_{21}H_{40}$ Oligomer Isomers:
=> 2 pairs of diastereomeric enantiomers









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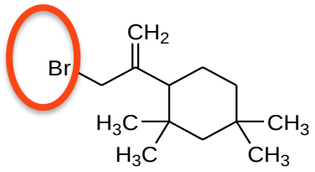
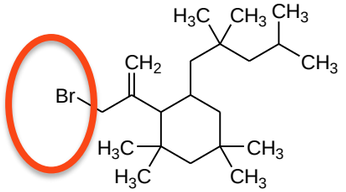
1. Rubber Oligomers: Structure

Halogenated Rubber Oligomers – Compounds of high concern

$C_{13}H_{23}Br$/ $C_{13}H_{23}Cl$ and $C_{21}H_{39}Br$/ $C_{21}H_{39}Cl$ Oligomers





- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrobarbon compounds (**Allyl Halide**)
  - **Alkylating Agents**
  - One double bond

- Structure Activity Relationship (SAR) Assessment:

CARCINOGENICITY IN HUMANS IS PLAUSIBLE

- As **no experimental Literature data** are known about the toxicity of these compounds

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2. Rubber Oligomers: Formation

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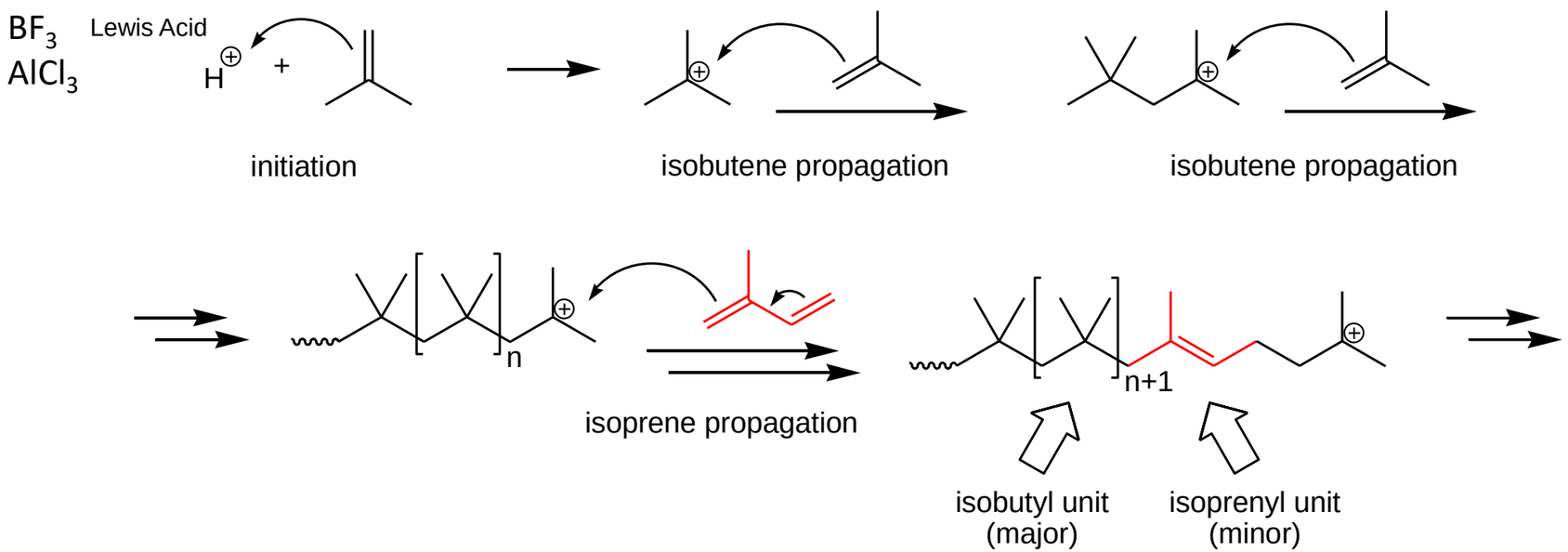
2. Rubber Oligomers - Formation

Formation (polymerization) of a Butyl Elastomer (IIR): Cationic Polymerization



- Note: the Polymerization Starts with an **isobutene** Unit (present in high excess compared to **isoprene**!!)
  - *98 – 99 mol% is isobutylene*
  - *1 – 2 mol% is isoprene*

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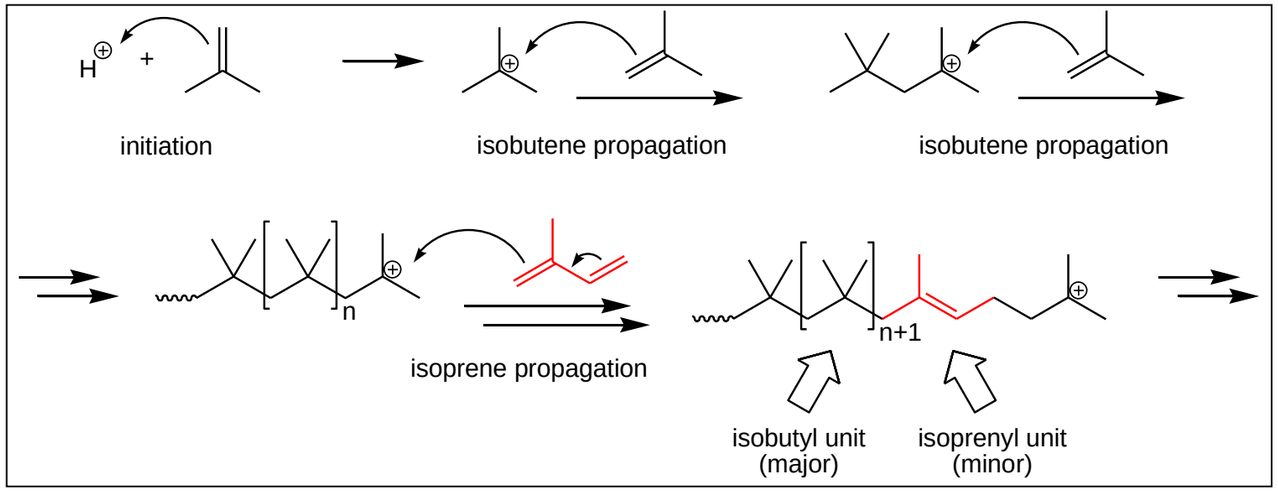
2. Rubber Oligomers - Formation

Formation (polymerization) of a Butyl Elastomer (IIR): Cationic Polymerization



- *98 – 99 mol% is isobutylene*
- *1 – 2 mol% is isoprene*

*Means for **Butyl Elast(IIR)** that approx. **per** **100 C-C bonds** in the backbone, **1 is a double** (C=C) bond (if 2%)*
*Compared with **Polyisoprene: Per 100 C-C bonds** in the backbone, approx. **33 will be double** (C=C) bonds*

Less double bonds in IIR means:

*Butyl Elastomer (IIR) is **less prone to Oxidation/Ageing***

*Butyl Elastomer (IIR) needs a **more efficient crosslinking reaction** compared to Polyisoprene*

*Bromination of the backbone helps to address this (**Br is a good leaving group**)*

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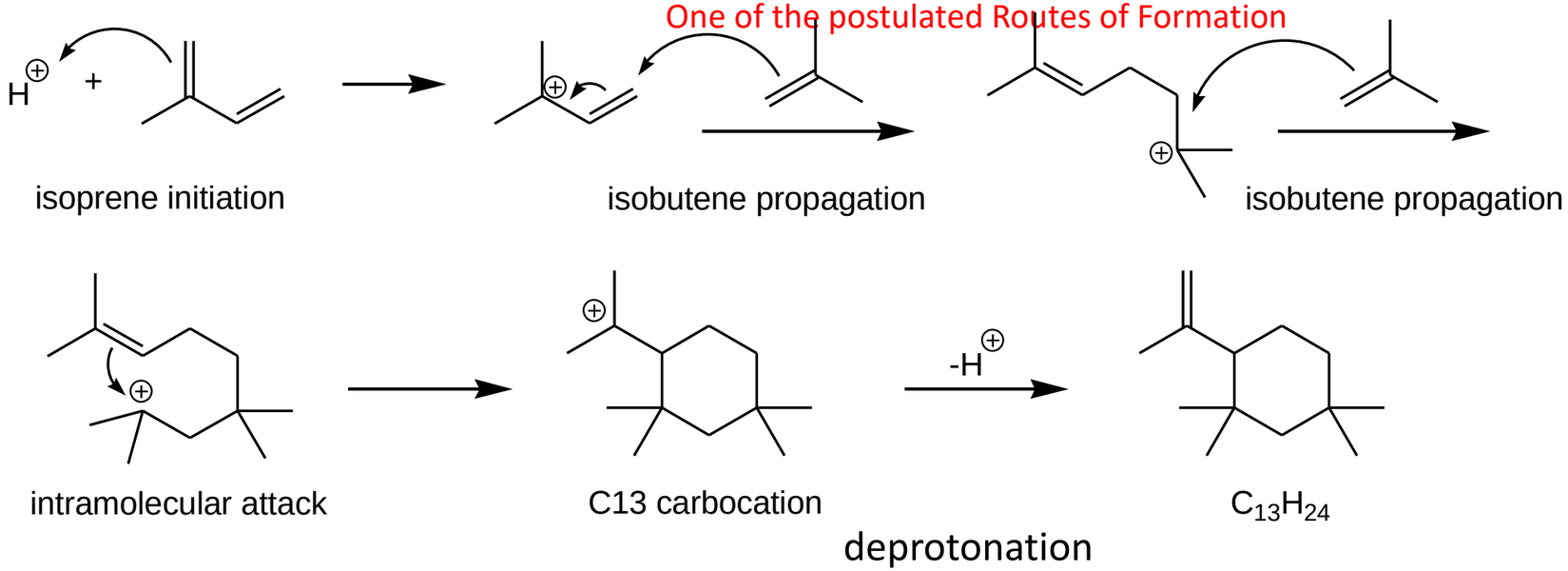
2. Rubber Oligomers - Formation

Formation of the $C_{13}H_{24}$ Oligomer:

One of the postulated Routes of Formation



Also: Backbite reaction during curing (not shown here)

➢ *Note: the polymerization starts with an isoprene unit which provides the double bond which is necessary for the intramolecular ring formation*

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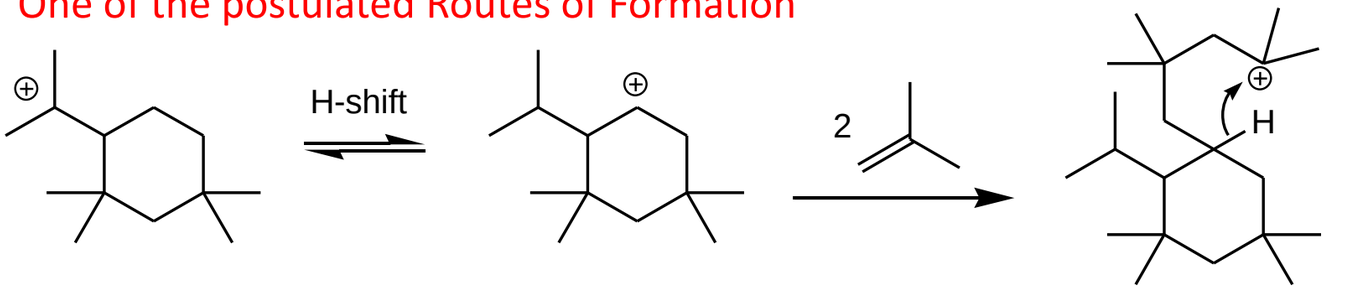
Ref. 2, 3

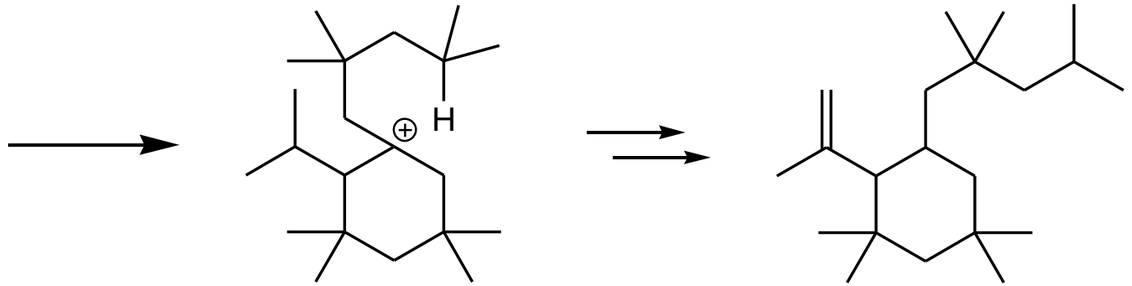
2. Rubber Oligomers - Formation

Formation of the $C_{21}H_{40}$ Oligomer:

One of the postulated Routes of Formation



C13 carbocation — isobutene propagation — intramolecular attack



C21 carbocation — $C_{21}H_{40}$

deprotonation

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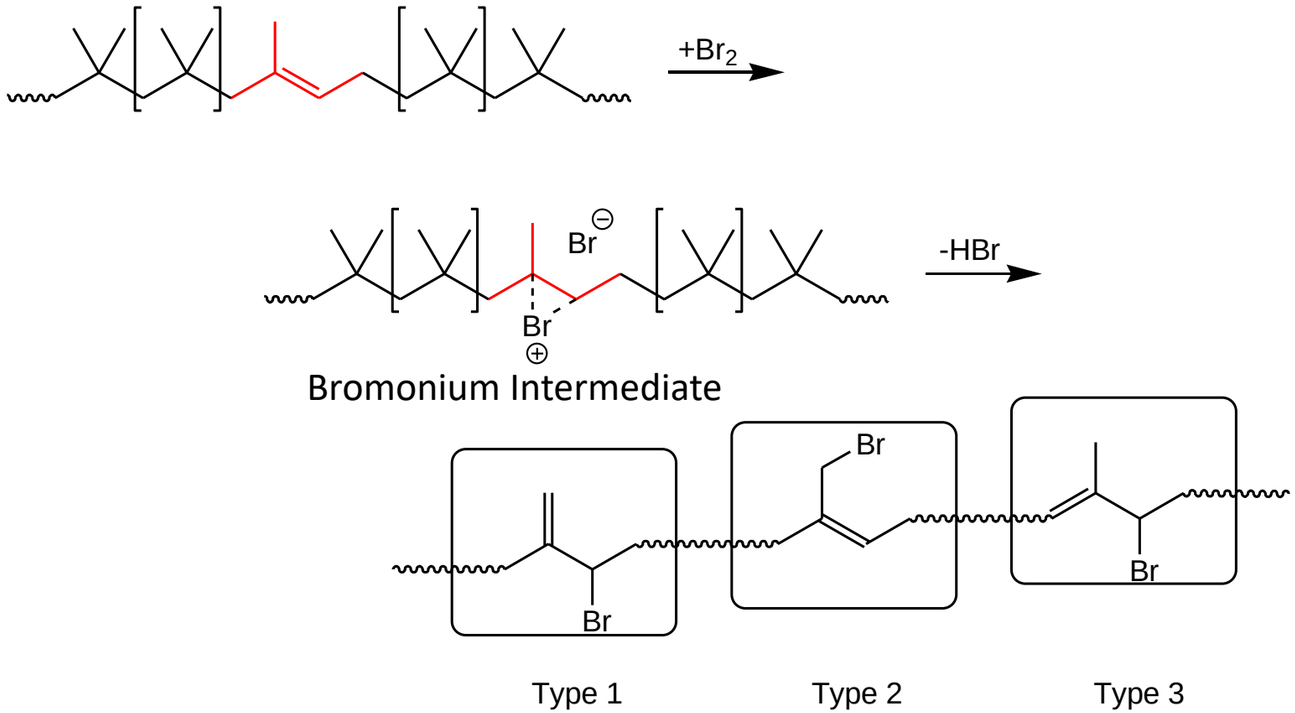
Ref. 2, 3

2. Rubber Oligomers - Formation

Bromobutyl Elastomer: Bromination of a Butyl Elastomer (BIIR)



Explains:

- *Residual Bromide in rubber*
- *Need for Acid Scavenger (eg Ca-Stearate)*

Bromination of the Backbone makes Elastomer

(with a relatively Low N° of double bonds in backbone)

more reactive in vulcanization/cross linking

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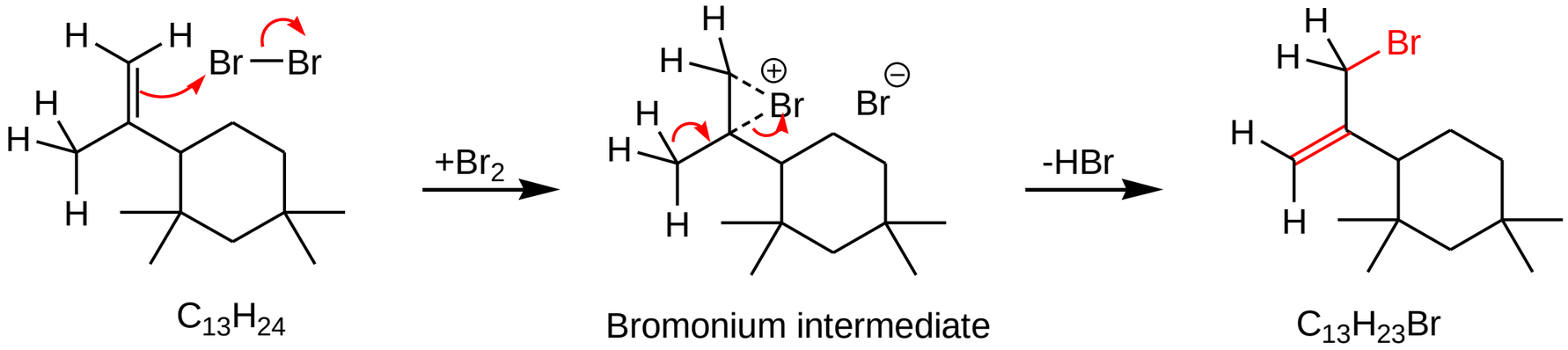
Ref. 9

2. Rubber Oligomers - Formation

Formation of $C_{13}H_{23}Br$, $C_{13}H_{23}Cl$, $C_{21}H_{39}Br$ & $C_{21}H_{39}Cl$:

side reaction in the production of halobutyl elastomer
(halogenation of butyl elastomer)



➢ Note: the halogenation occurs according to classical rubber halogenation chemistry by the substitution of one of the allylic hydrogen atoms

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3. Rubber Oligomers: Detection & Identification

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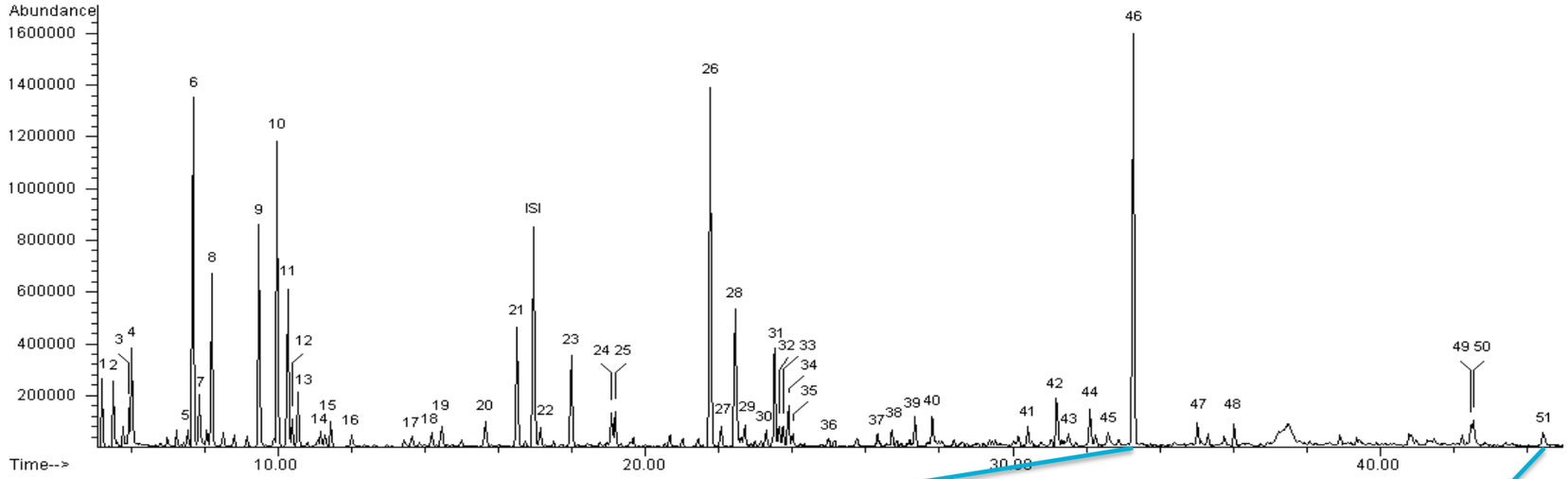
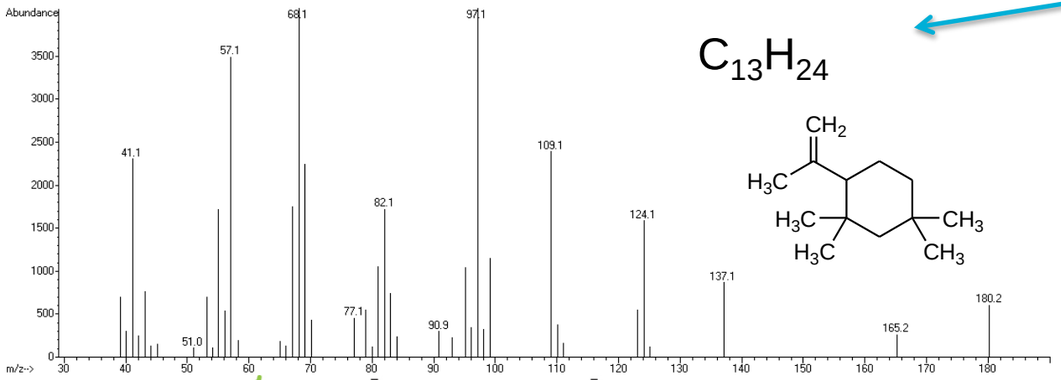
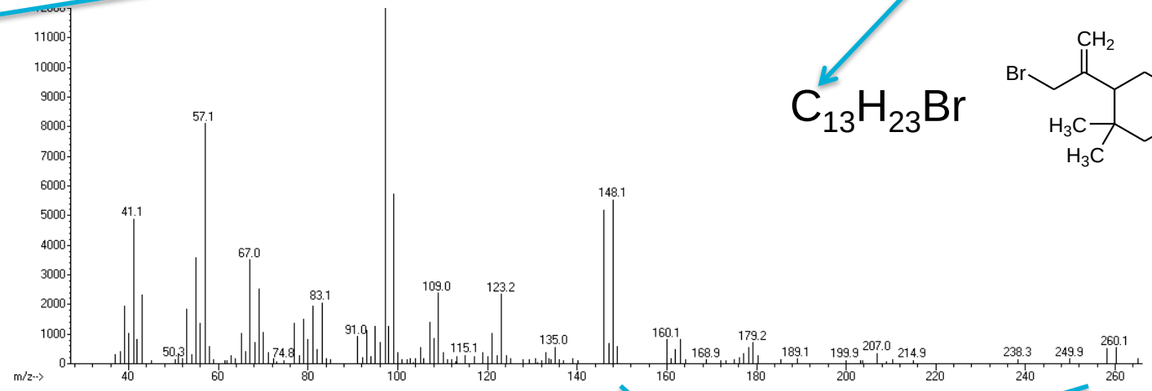
3. Rubber Oligomers – Detection & Identification

Headspace GC/MS on Bromobutyl Rubber Closure:





$C_{13}H_{24}$

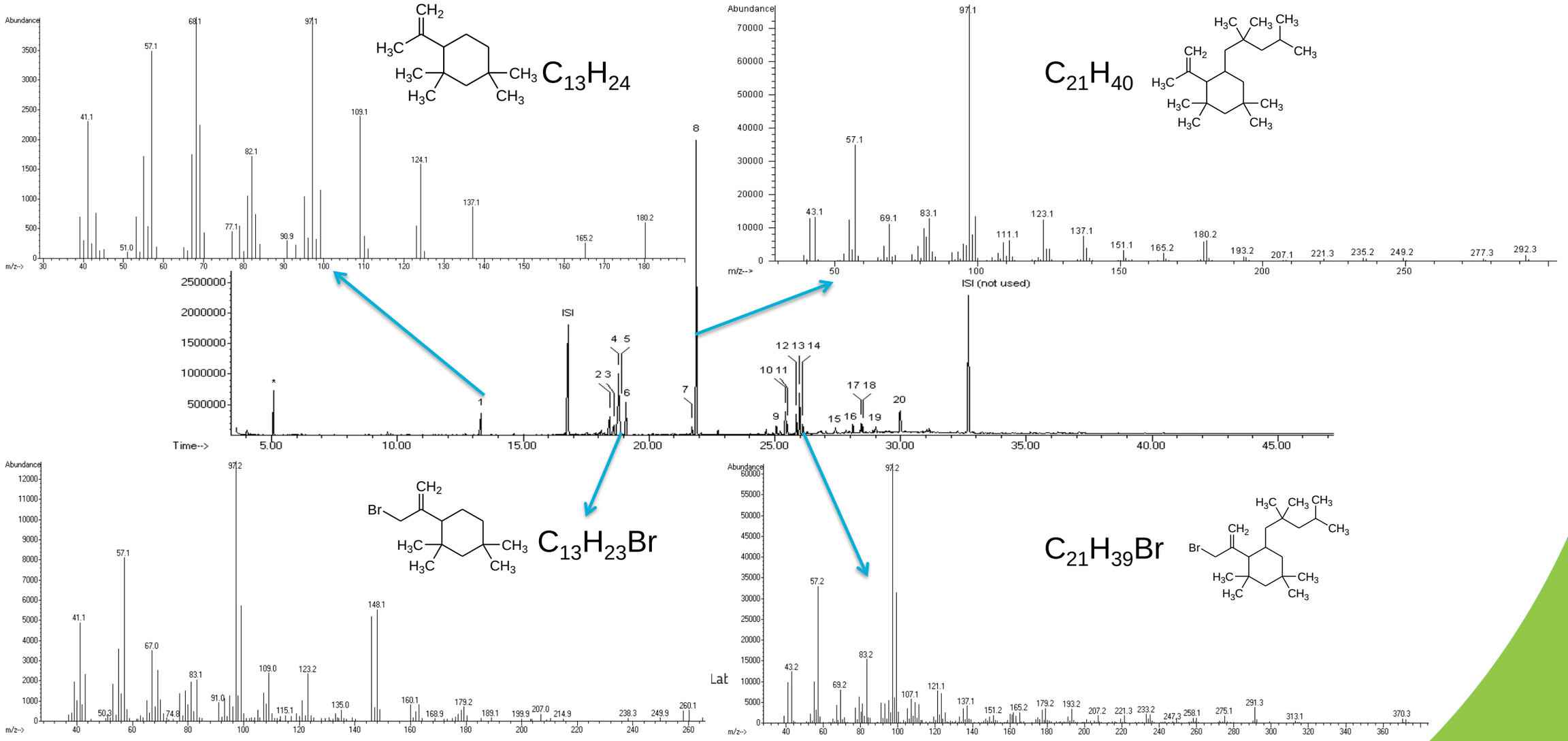


$C_{13}H_{23}Br$

Natural abundancy Br ($^{79}Br/^{81}Br$)

3. Rubber Oligomers – Detection & Identification

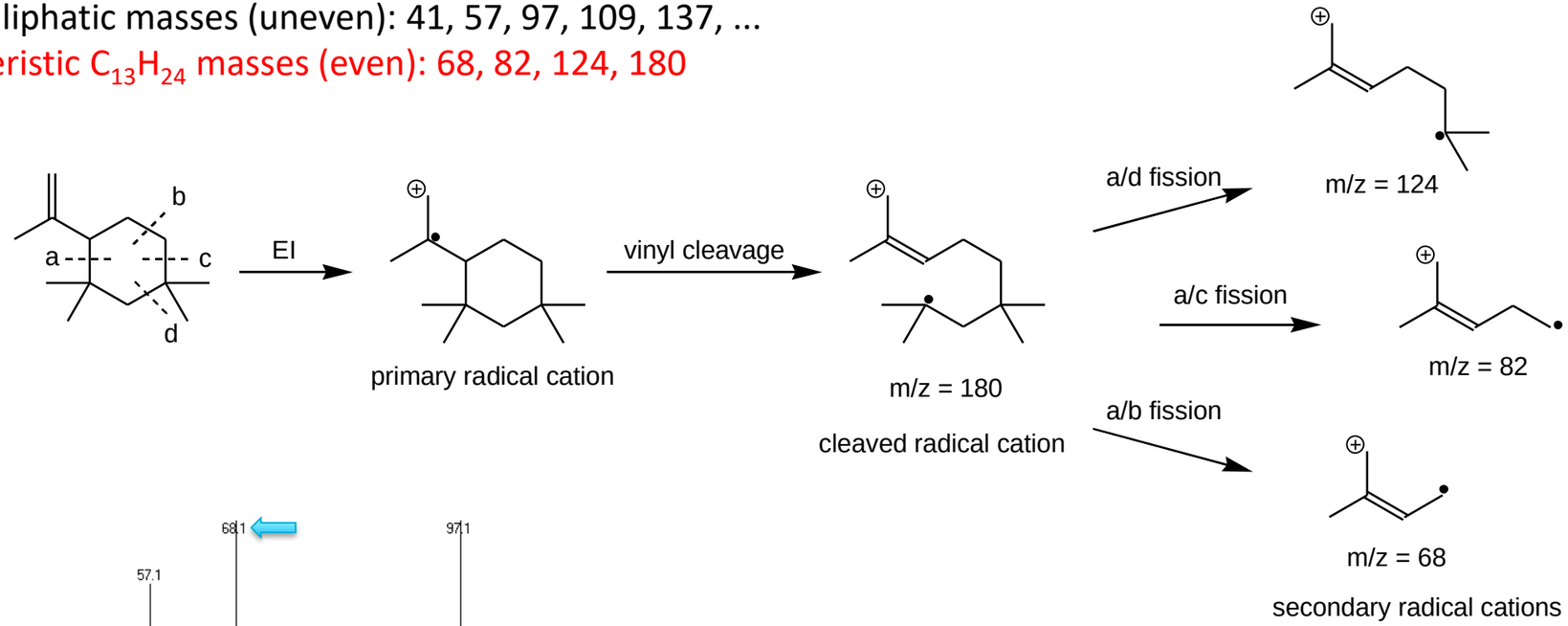
GC/MS on IPA extract of Bromobutyl Rubber Closure:

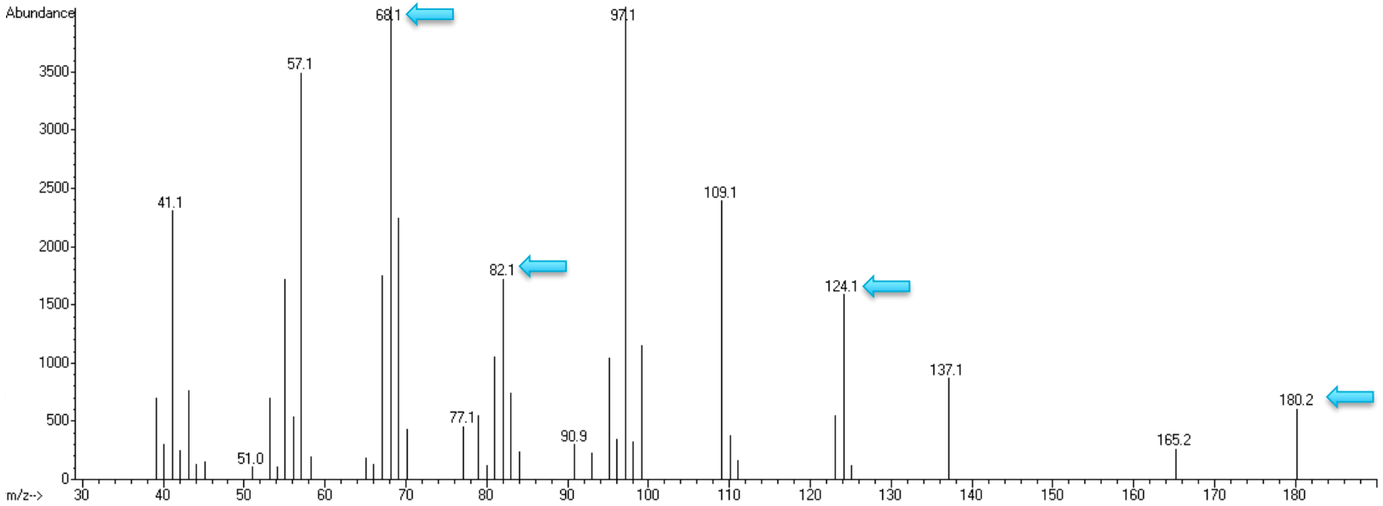


3. Rubber Oligomers – Detection & Identification

GC/MS Mass Spectrum of the $C_{13}H_{24}$ Oligomer

- typical aliphatic masses (uneven): 41, 57, 97, 109, 137, ...
- characteristic $C_{13}H_{24}$ masses (even): 68, 82, 124, 180





4. Rubber Oligomers: Reactivity

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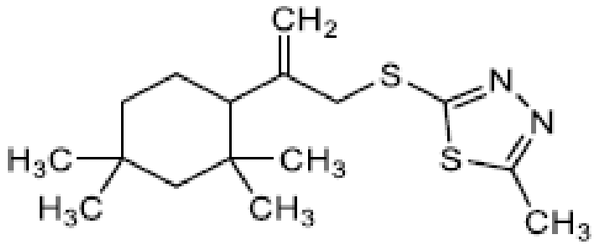
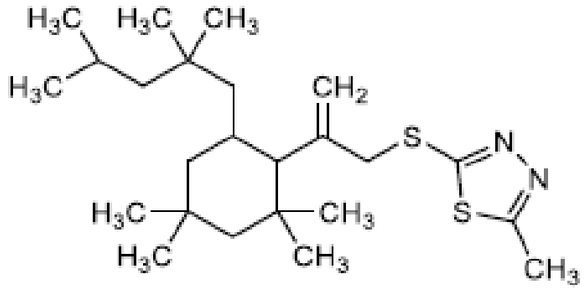
4. Rubber Oligomers – Reactivity

Reactions with API's

Allyl Bromide/Chloride: alkylating agent (nucleophilic substitution)

Adduct Formation of an Small Molecule API adducts with the $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ oligomers





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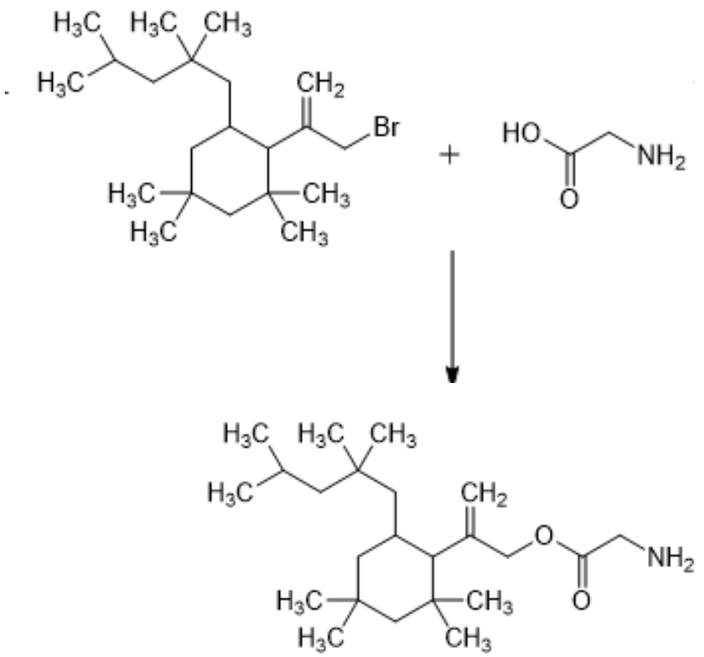
4. Rubber Oligomers – Reactivity

Reactions with Excipients

C21H39Br rubber oligomer source - leachable from a rubber stopper



Glycine (excipient, bulking agent for Lyo DP)

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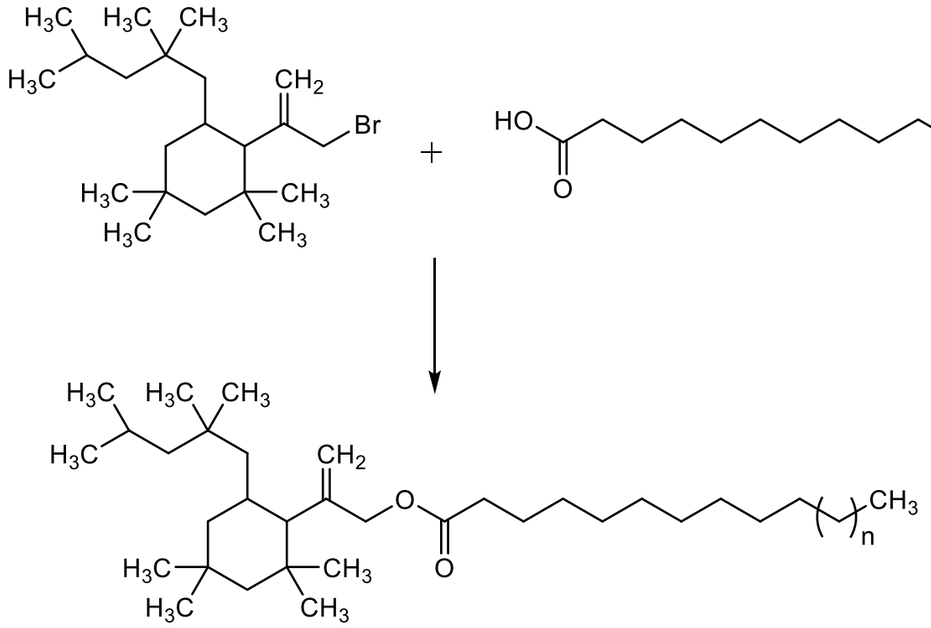
4. Rubber Oligomers – Reactivity

Reactions with Excipient Impurities

C21H39Br rubber oligomer source - leachable from a rubber stopper



Fatty acids source – Polysorbate 20

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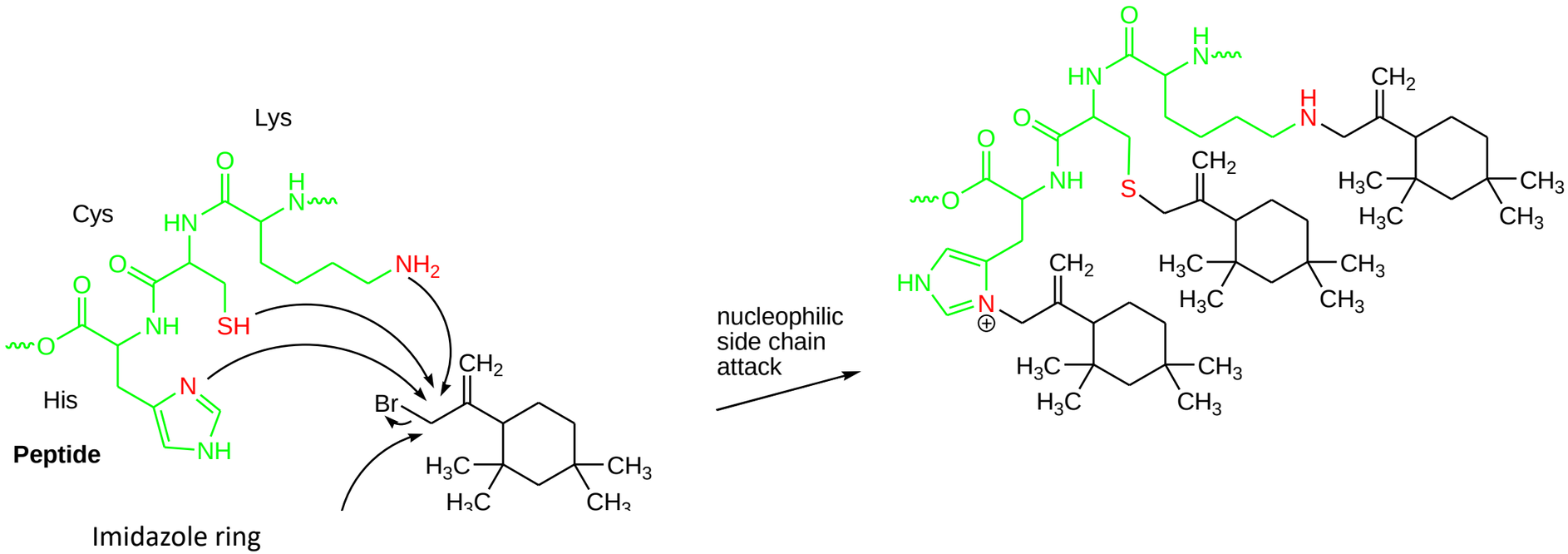
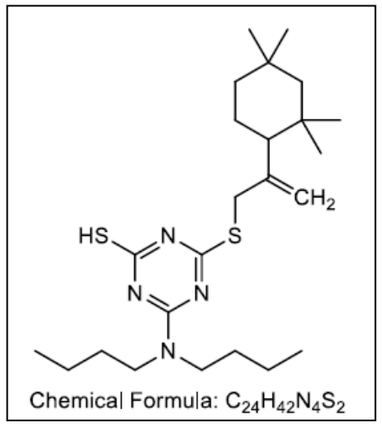
4. Rubber Oligomers – Reactivity

Reactions with peptides and proteins

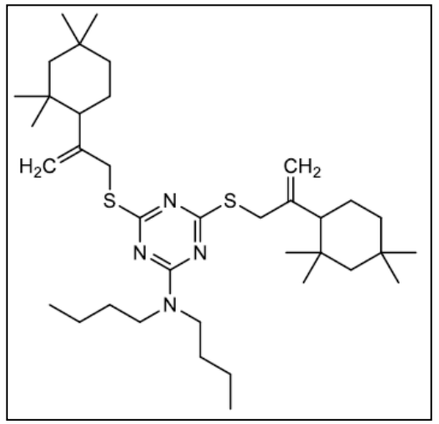


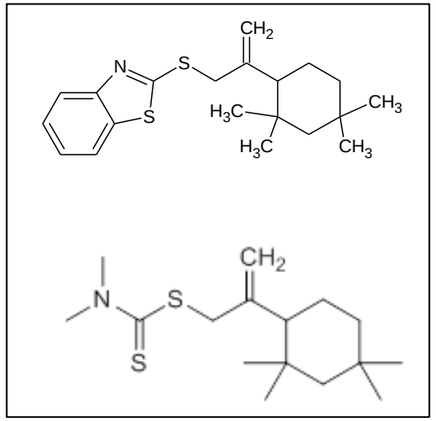
4. Rubber Oligomers – Reactivity

Reactions with other rubber ingredients, formed during the manufacturing process



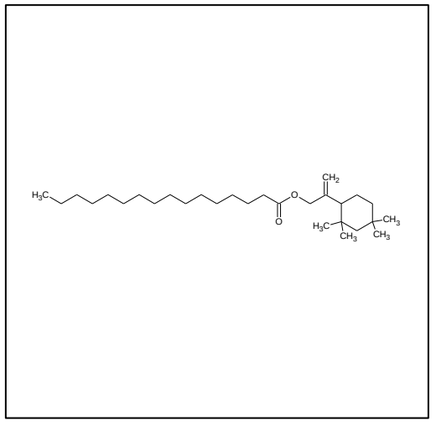
6-(Dibutylamino)-1,3,5-triazine-2,4-dithiol





N-cyclohexyl-2-benzothiazole sulfenamide

Tetramethylthiuram disulfide



Palmitic Acid

$C_{13}H_{23}Br$ /$C_{21}H_{39}Br$ With

- *Antioxidants*
- *ESBO*
- …

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5. Rubber Oligomers: Toxicity

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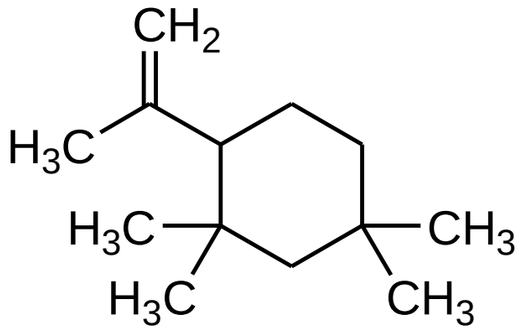
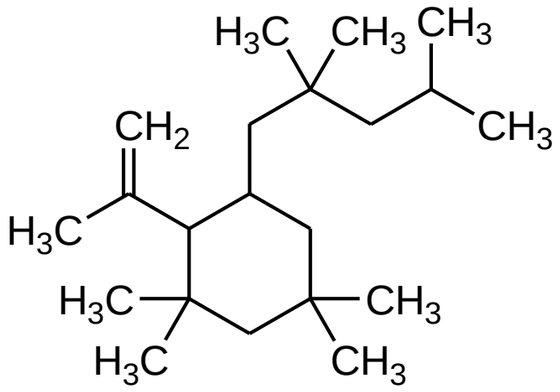
5. Rubber Oligomers – Toxicity





$C_{13}H_{24}$ and $C_{21}H_{40}$ Oligomers

- Considered as
  - **Cyclic aliphatic hydrocarbon** compounds
  - **One double bond**

- Structure Activity Relationship (SAR) Assessment:

NO IMMEDIATE CONCERN

- As no experimental data / Literature data is known about the toxicity of these compounds, a lot of Pharma companies:
  - Rely on the result of a SAR assessment to perform a tox evaluation
  - Conclude that these compounds are of low Concern

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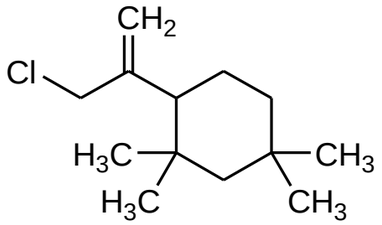
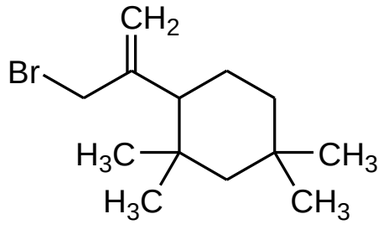
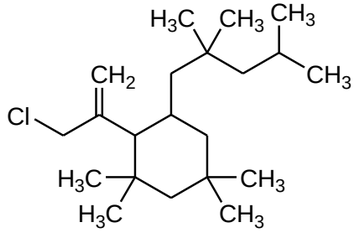
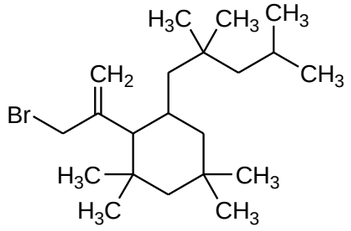
5. Rubber Oligomers – Toxicity









- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrobarbon compounds **(Allyl Halide)**
  - **Alkylating Agents (reactivity!)**
  - One double bond

- Structure Activity Relationship (SAR) Assessment:
  CARCINOGENICITY
  SENSITIZATION

- As no experimental data / Literature data is known about the toxicity of these compounds, a lot of Pharma companies:
  - Rely on the result of a SAR assessment to perform a tox evaluation
  - Conclude that these compounds are of High Concern

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5. Rubber Oligomers – Toxicity

For potential Carcinogenic compounds or Sensitizers:

SCT: 1.5 µg/day (FDA Position for potential Carcinogens) for Chronic Treatments

5 µg/day (FDA Position for potential Sensitizers) for non-Chronic Treatments

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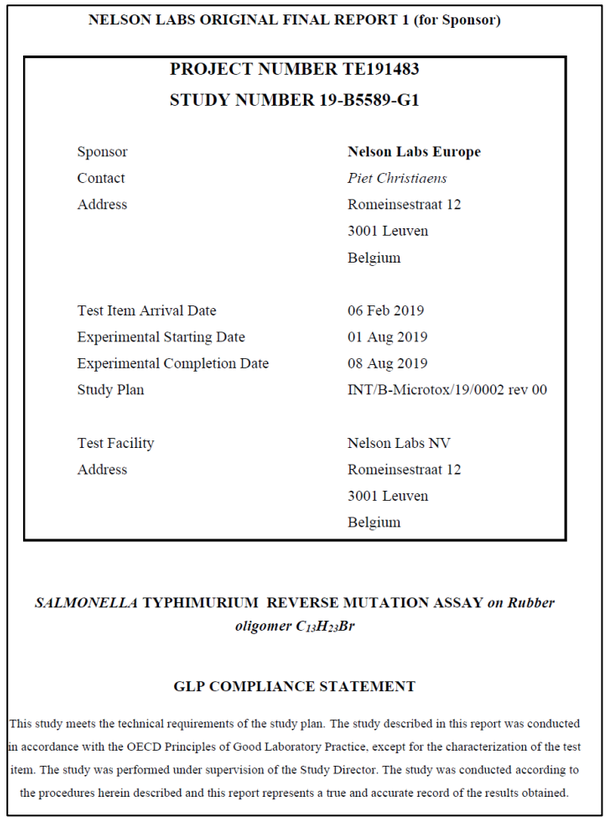
5. Rubber Oligomers – Toxicity



NELSON LABS ORIGINAL FINAL REPORT 1 (for Sponsor)

PROJECT NUMBER TE191483
STUDY NUMBER 19-B5589-G1

Sponsor	**Nelson Labs Europe**
Contact	*Piet Christiaens*
Address	Romeinsestraat 12
	3001 Leuven
	Belgium
Test Item Arrival Date	06 Feb 2019
Experimental Starting Date	01 Aug 2019
Experimental Completion Date	08 Aug 2019
Study Plan	INT/B-Microtox/19/0002 rev 00
Test Facility	Nelson Labs NV
Address	Romeinsestraat 12
	3001 Leuven
	Belgium

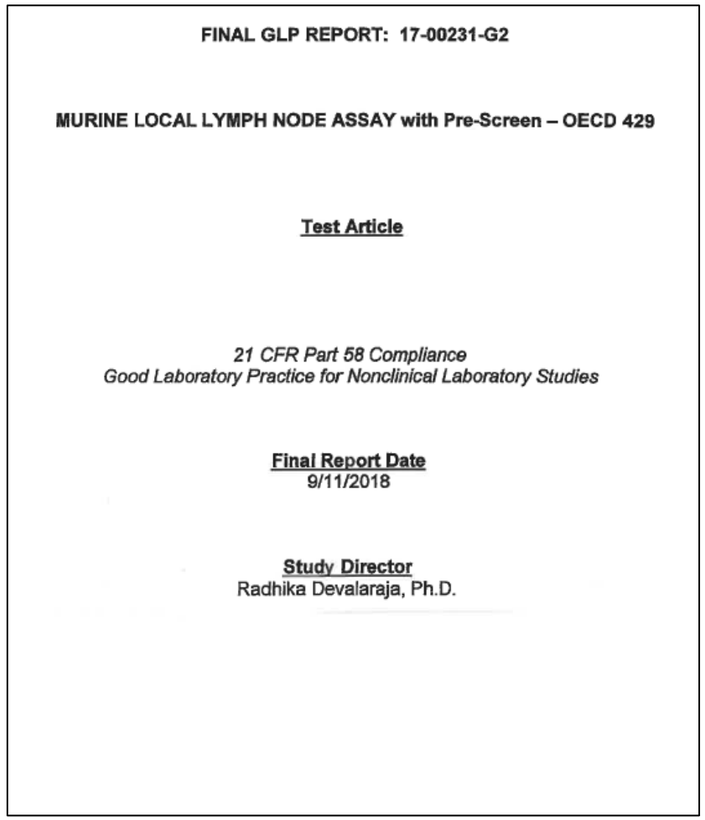
SALMONELLA* TYPHIMURIUM REVERSE MUTATION ASSAY *on Rubber oligomer $C_{13}H_{23}Br$

GLP COMPLIANCE STATEMENT

This study meets the technical requirements of the study plan. The study described in this report was conducted in accordance with the OECD Principles of Good Laboratory Practice, except for the characterization of the test item. The study was performed under supervision of the Study Director. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.

Availability of Rubber Oligomers at Nelson Labs

Allows a **correct assessment** of the **true toxicological risk** of these leachables



FINAL GLP REPORT: 17-00231-G2

MURINE LOCAL LYMPH NODE ASSAY with Pre-Screen – OECD 429

Test Article

21 CFR Part 58 Compliance
Good Laboratory Practice for Nonclinical Laboratory Studies

Final Report Date
9/11/2018

Study Director
Radhika Devalaraja, Ph.D.

NELSON AMES REPORTS (Mutagenicity) for $CH_{13}H_{23}Br$ and $C_{13}H_{23}Cl$

NELSON LOCAL LYMPH NODE ASSAY (LLNA) REPORT for $CH_{13}H_{23}Br$

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Thank you

Questions?

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