

Organic Synthesis of Raspberry Ketone Analogue

CH3204 Course Project

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April 15, 2025



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Project Objectives

Why did we choose raspberry ketone?



Figure: Because summers are here and we wanted to do something fruity!

Reaction Scheme

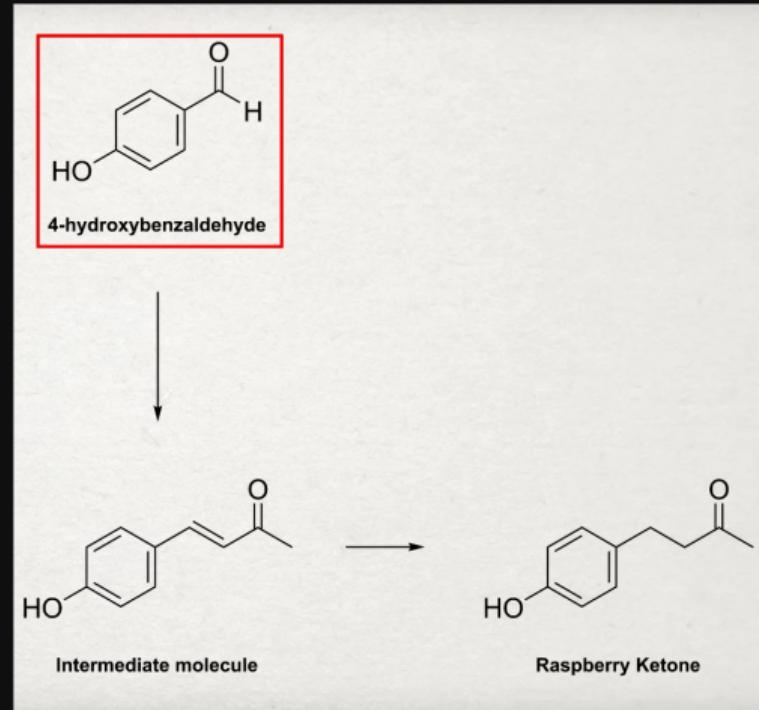


Figure: The Base Reaction Scheme that is generally followed[OnePotSynthesisRK]

Reaction Scheme

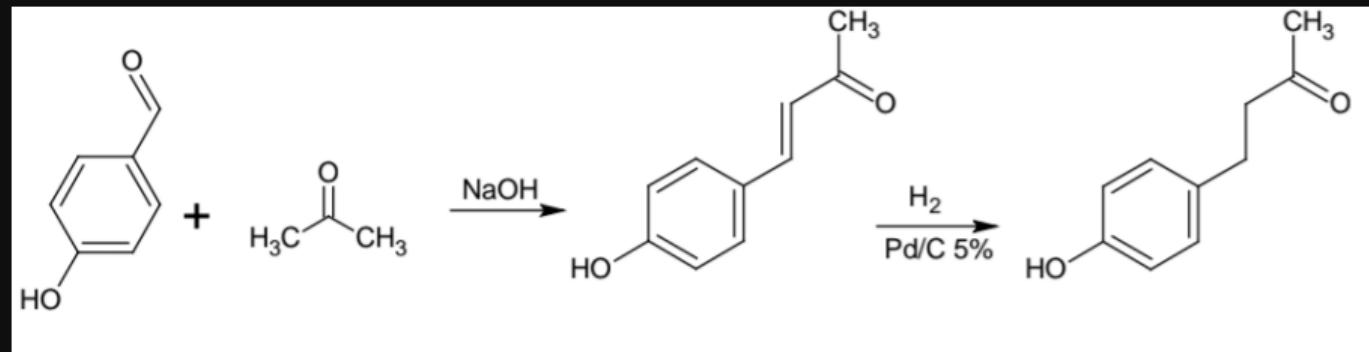


Figure: The Base Reaction Scheme that is generally followed[[OnePotSynthesisRK](#)]

Synthesis of Rhoesmin (Raspberry Ketone)

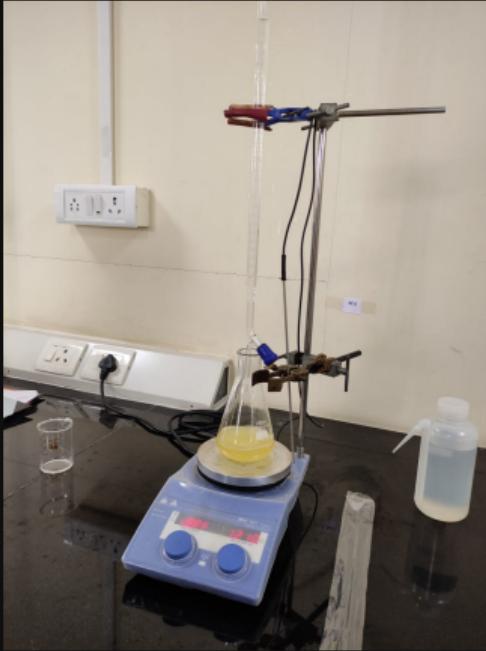
Procedure:

- Dissolve 10g 4-Hydroxybenzaldehyde in 40ml CaO-dried Propanone with stirring.
- Slowly drip in 40ml of 10% NaOH solution (4g in 40ml water). Let stand overnight to form crystals.
- Slurry crystals into 200ml **ice-cold** 10% HCl; crystallisation occurs.
- Filter and recrystallise from boiling water. (Yield: 5g, MP: 124°C sharp)
- **Hydrogenation Setup:** Flask flushed with H₂, attached to upturned gas jar filled with H₂.
- Add intermediate product dissolved in 20ml Ethyl Acetate, 5.125g Sodium Acetate, and 0.5g 5% Pd/C catalyst to the flask.
- Stir and allow H₂ absorption (approx. 800ml over 4 hours until absorption ceases). *Note: Large H₂ uptake may indicate leaks.*
- Once absorption stops, **vacuum filter under Nitrogen flow** to recover catalyst.
- Wash filtrate with 2x20ml Water to remove Sodium Acetate.
- Rotavap Ethyl Acetate to yield oil which crystallises.
- Recrystallise from 10ml boiling water. (Final Yield: 3.43g, MP: 82°C sharp)

Important Points:

- Use CaO-dried Propanone.
- Add NaOH solution slowly.
- Use ice-cold HCl for quenching.
- Ensure proper hydrogenation setup and monitor gas absorption. Be aware of potential leaks.
- Filter catalyst under Nitrogen to prevent side reactions/deactivation.
- Purify final product by recrystallisation for sharp melting point.

The Physical Setup



(a) The setup consists of the reaction mixture of 10ml 4-methoxybenzaldehyde + 40ml Acetone + 40ml 10% w/v NaOH solution(in burette)



(b) The Reaction Mixture being stirred vigorously

Figure: Our Synthesis Setup at the Teaching Lab

The Physical Setup

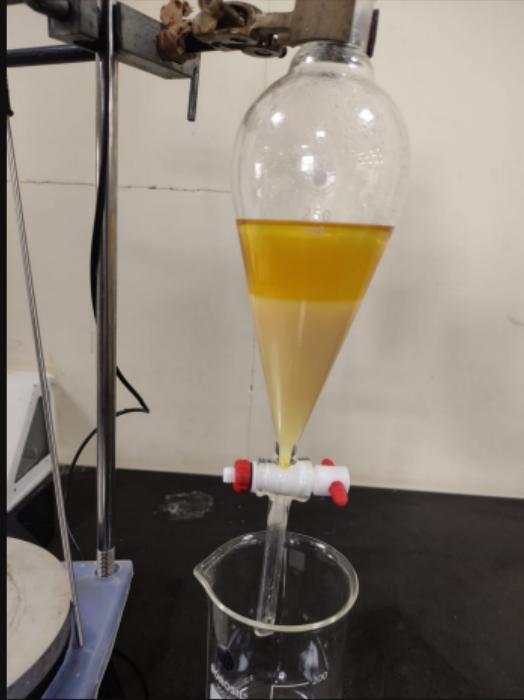


Figure: Separating funnel for separating the aqueous phase from the organic phase (primarily ethyl acetate consisting of the compounds)

Mechanism: Cross Aldol Condensation

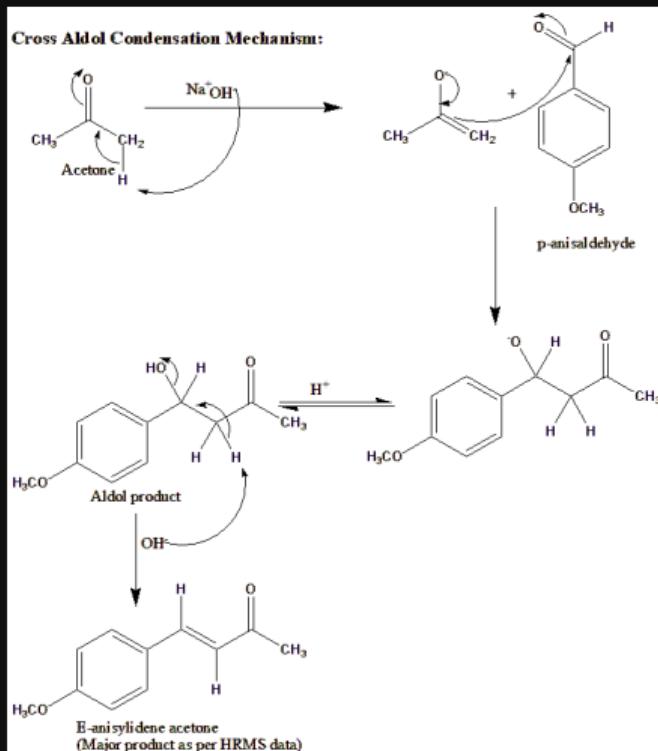


Figure: Mechanism of the desired product

Mechanism: So what's the problem?

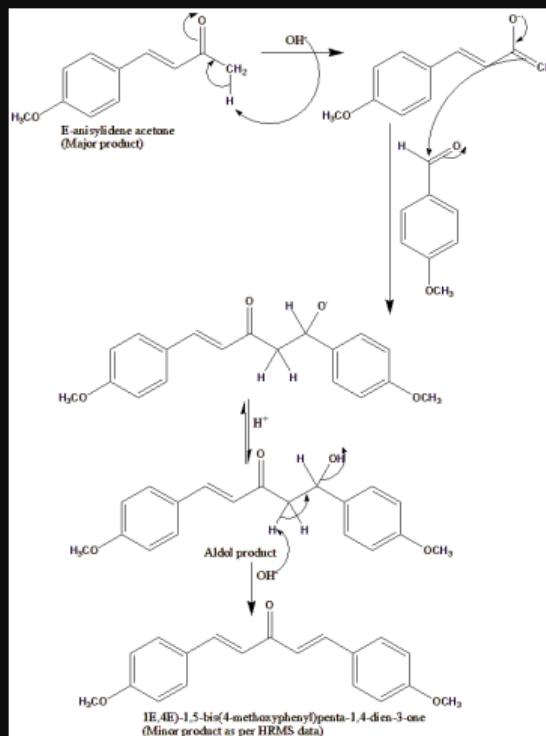
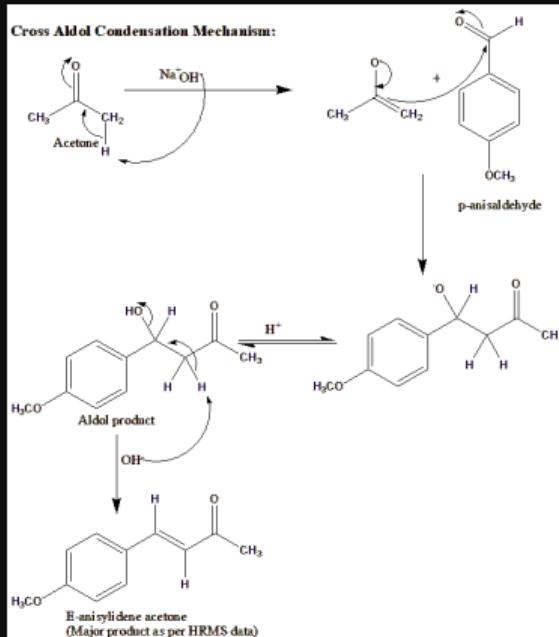
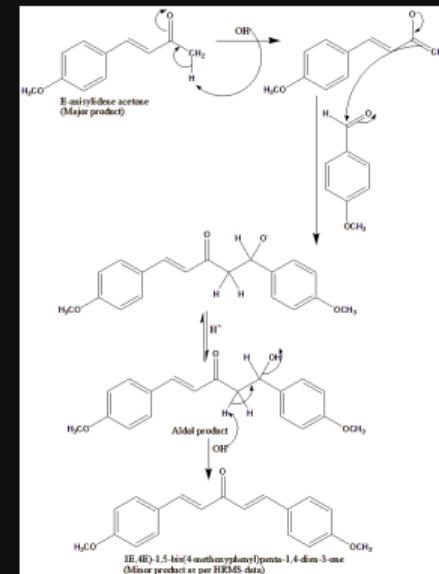


Figure: Mechanism for formation of side product

Mechanism



(a) Mechanism of the desired product



(b) Mechanism for formation of side product

Figure: All the Mechanisms shown here were drawn using ChemDrawPro V8.0

Results:



(a) Recrystallization in Ethanol



(b) The Final Product

Figure: The Fruit of our Synthesis

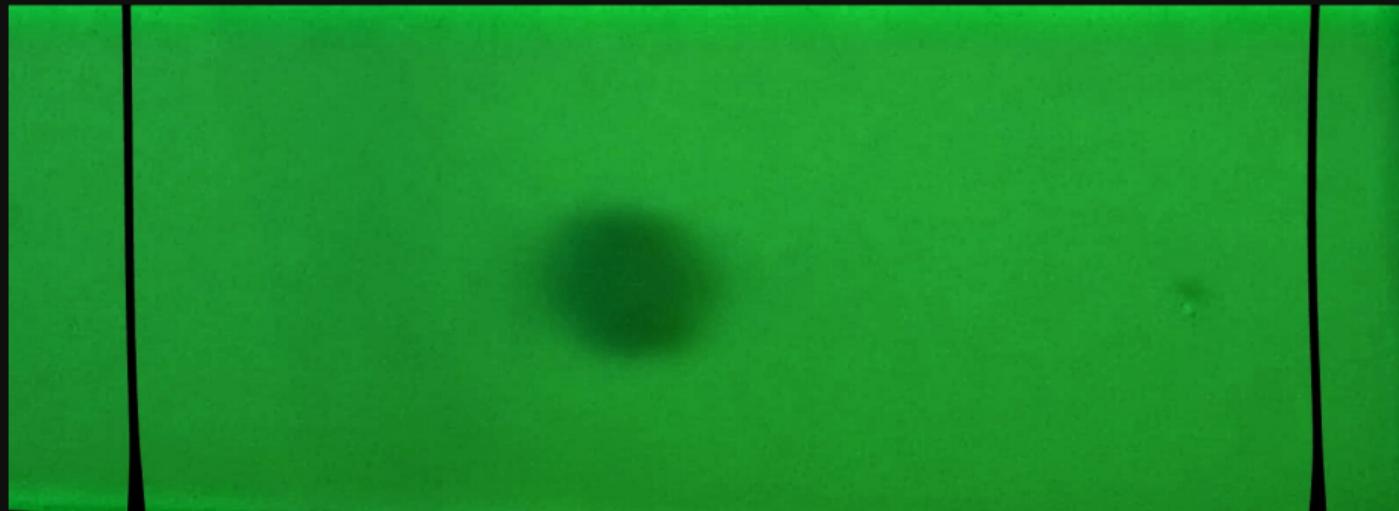


Figure: TLC of the final product mixture in 30% ethyl acetate in hexane, $R_f = 0.63$

Analytical Characterization: ^1H NMR spectra

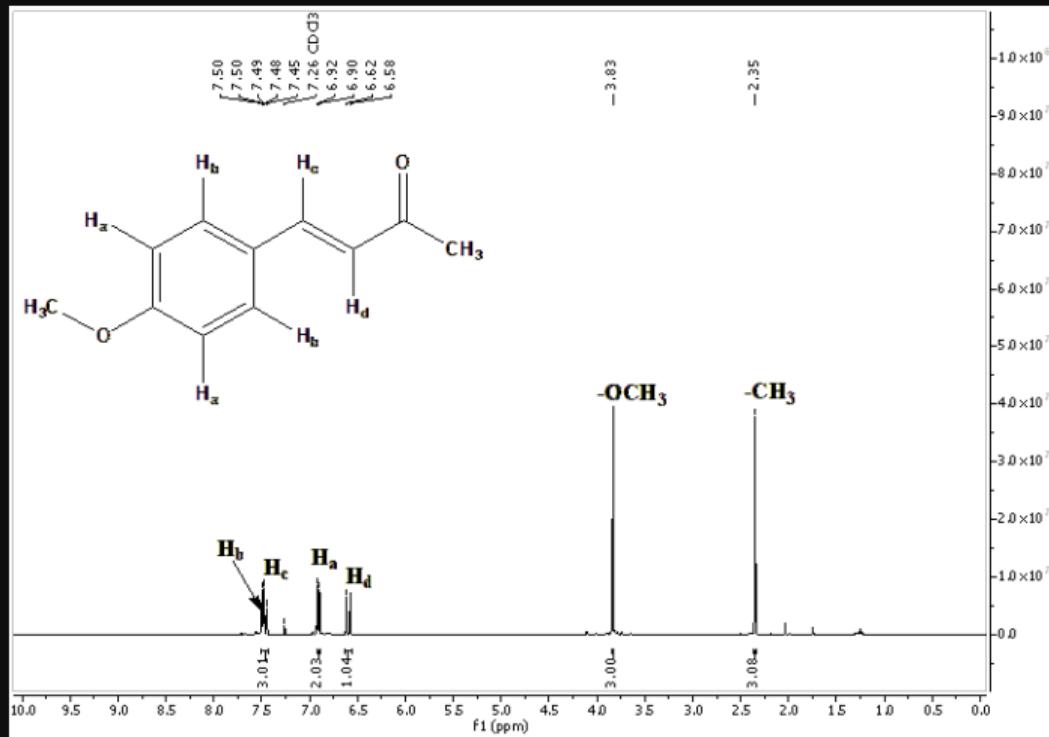


Figure: ^1H NMR data of the formed product

Analytical Characterization: HRMS spectra

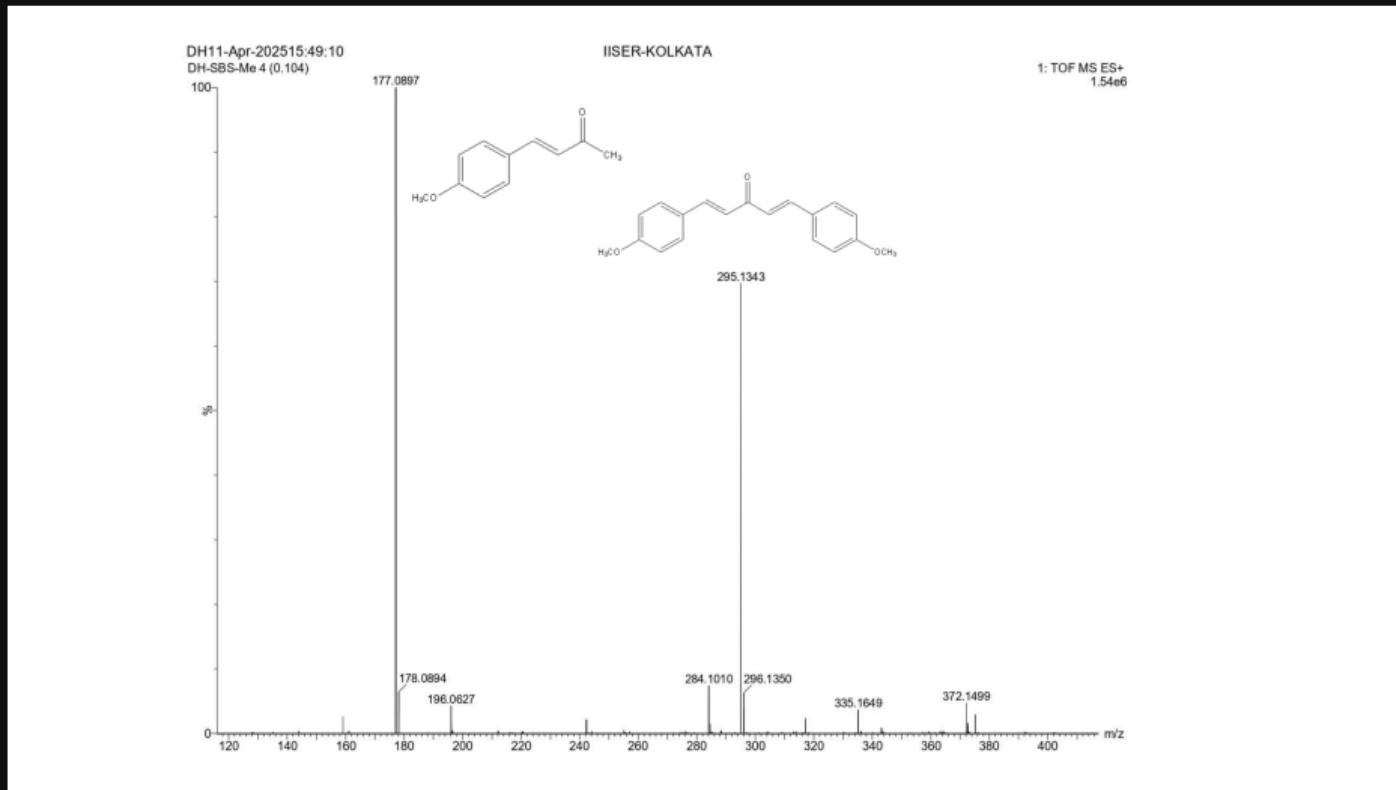


Figure: HRMS data of the formed yellow product

Analytical Characterization: FTIR spectra

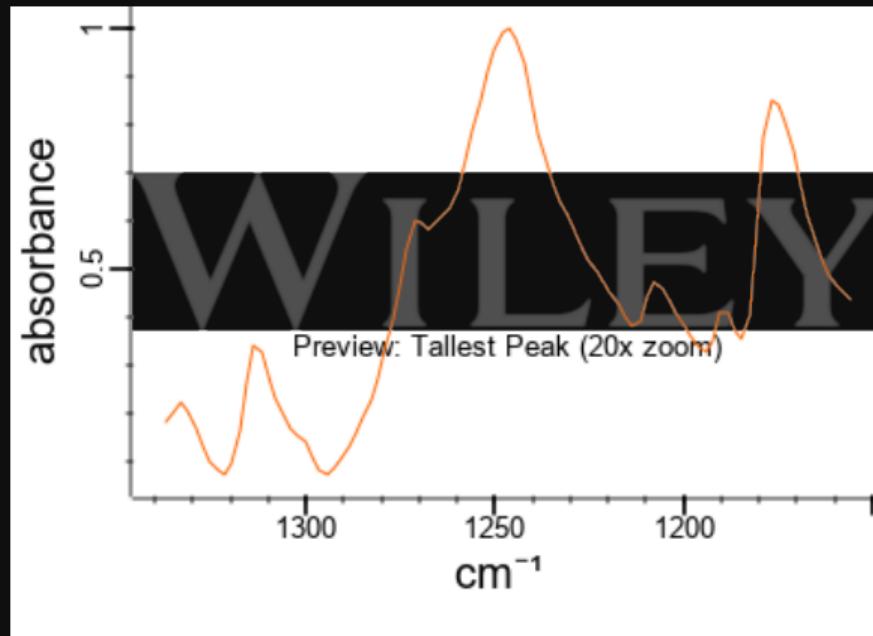


Figure: FTIR data of the major product as per 1989, 1990-2025 Wiley-VCH GmbH

Yield Calculation:

Step 1: Calculate the mass of anisaldehyde used

$$\text{Mass of anisaldehyde} = \text{Volume} \times \text{Density} \quad (1)$$

$$= 10 \text{ mL} \times 1.12 \text{ g/mL} \quad (2)$$

$$= 11.2 \text{ g} \quad (3)$$

Step 2: Calculate moles of anisaldehyde used

$$\text{Molar mass of anisaldehyde} = 136.15 \text{ g/mol} \quad (4)$$

$$\text{Moles of anisaldehyde} = \frac{11.2 \text{ g}}{136.15 \text{ g/mol}} \quad (5)$$

$$= 0.0823 \text{ mol} \quad (6)$$

Step 3: Define variables

$$x = \text{moles of major product} \quad (7)$$

$$0.7x = \text{moles of minor product (from 10:7 ratio)} \quad (8)$$

Yield Calculation:

Step 4: Set up equations based on anisaldehyde consumption

$$\text{Anisaldehyde for major product} = x \text{ mol} \quad (9)$$

$$\text{Anisaldehyde for minor product} = 2 \times 0.7x = 1.4x \text{ mol} \quad (10)$$

$$\text{Total anisaldehyde used} = x + 1.4x = 2.4x \text{ mol} \quad (11)$$

Step 5: Solve for x using the total anisaldehyde amount

$$2.4x = 0.0823 \quad (12)$$

$$x = \frac{0.0823}{2.4} \quad (13)$$

$$x = 0.03429 \text{ mol} \quad (14)$$

Step 6: Calculate moles of each product

$$\text{Moles of major product} = x = 0.03429 \text{ mol} \quad (15)$$

$$\text{Moles of minor product} = 0.7x = 0.7 \times 0.03429 = 0.02400 \text{ mol} \quad (16)$$

Yield Calculation:

Step 7: Calculate actual yield of each product

$$\text{Mass of major product} = 0.03429 \text{ mol} \times 177.0897 \text{ g/mol} \quad (17)$$

$$= 6.073 \text{ g} \quad (18)$$

$$\text{Mass of minor product} = 0.02400 \text{ mol} \times 295.1343 \text{ g/mol} \quad (19)$$

$$= 7.083 \text{ g} \quad (20)$$

$$\text{Total mass of products} = 6.073 \text{ g} + 7.083 \text{ g} = 13.156 \text{ g} \quad (21)$$

Step 8: Adjust calculation based on the actual total yield

$$\text{Actual total yield} = 11.564 \text{ g} \quad (22)$$

$$\text{Correction factor} = \frac{11.564}{13.156} = 0.8790 \quad (23)$$

$$\text{Actual major product yield} = 6.073 \times 0.8790 = 5.338 \text{ g} \quad (24)$$

$$\text{Actual minor product yield} = 7.083 \times 0.8790 = 6.226 \text{ g} \quad (25)$$

Yield Calculation:

Step 9: Calculate theoretical yields

For major product: (26)

Maximum moles from anisaldehyde = 0.0823 mol (27)

Theoretical yield = $0.0823 \text{ mol} \times 177.0897 \text{ g/mol}$ (28)

= 14.574 g (29)

For minor product: (30)

Maximum moles from anisaldehyde = $\frac{0.0823 \text{ mol}}{2} = 0.04115 \text{ mol}$ (31)

Theoretical yield = $0.04115 \text{ mol} \times 295.1343 \text{ g/mol}$ (32)

= 12.145 g (33)

Yield Calculation:

Step 10: Calculate percent yields

$$\% \text{ Yield of major product} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100\% \quad (34)$$

$$= \frac{5.338 \text{ g}}{14.574 \text{ g}} \times 100\% \quad (35)$$

$$= 36.63\% \quad (36)$$

$$\% \text{ Yield of minor product} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100\% \quad (37)$$

$$= \frac{6.226 \text{ g}}{12.145 \text{ g}} \times 100\% \quad (38)$$

$$= 51.26\% \quad (39)$$

Final Answer:

$$\% \text{ Yield of major product} = 36.63\% \quad (40)$$

$$\% \text{ Yield of minor product} = 51.26\% \quad (41)$$

Computational Parameters for Anisylidene Acetone

```
opt freq b3lyp/6-311g scrf=(iefpcm,solvent=acetone) guess=save pop=(mk,nto,savento,savemulliken)  
density=current geom=connectivity
```

opt Geometry optimization to find the minimum energy structure

freq Calculate vibrational frequencies for thermodynamic properties and confirm stationary point

b3lyp Becke's three-parameter hybrid functional with Lee-Yang-Parr correlation

6-311g Split-valence triple-zeta basis set with polarization functions

scrf Self-Consistent Reaction Field for solvation effects

iefpcm Integral Equation Formalism Polarizable Continuum Model

solvent Acetone as the solvent environment

guess=save Save the converged wavefunction for future calculations

pop=mk Merz-Kollman scheme for calculating atomic charges

nto Natural Transition Orbitals analysis

savento Save the Natural Transition Orbitals

savemulliken Save the Mulliken population analysis

density=current Use the current density matrix for population analysis

geom=connectivity Include molecular connectivity in the input file

HOMO Visualization

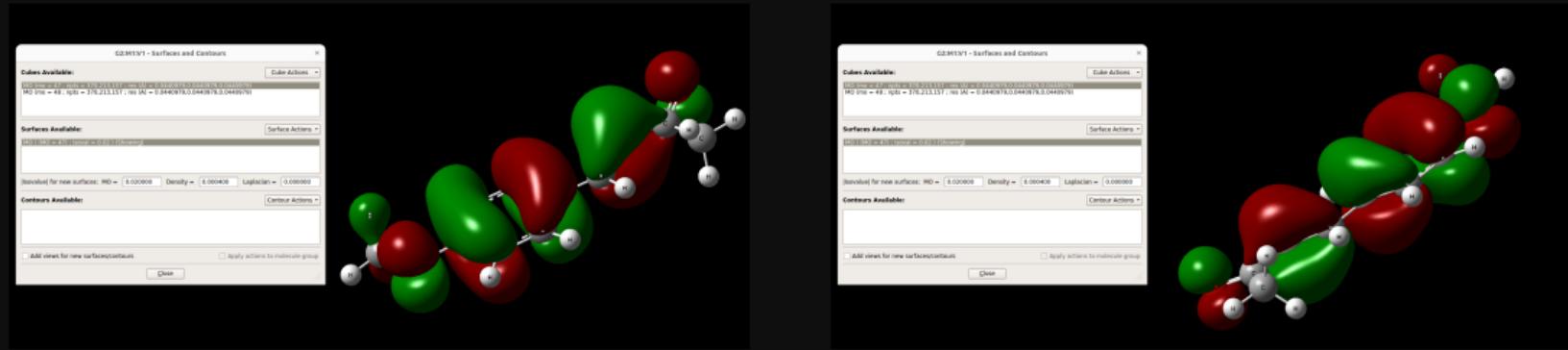


Figure: Visualizing the HOMO

LUMO Visualization

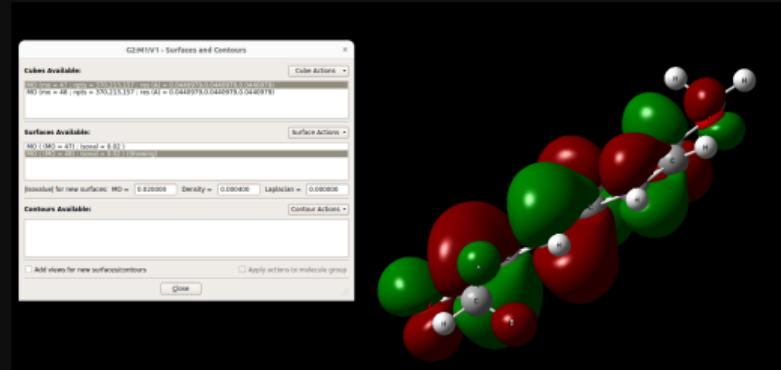
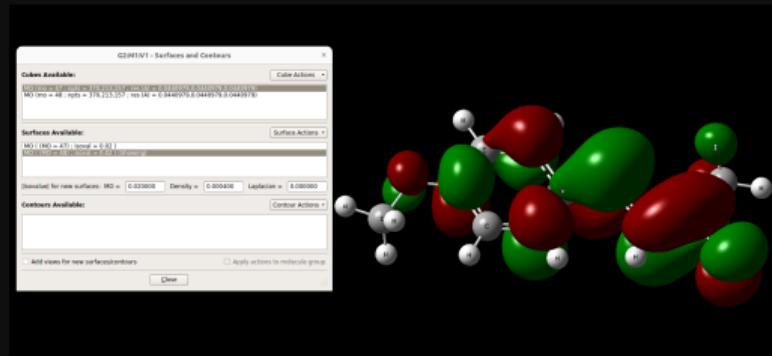


Figure: Visualizing the LUMO

HOMO-LUMO Gap

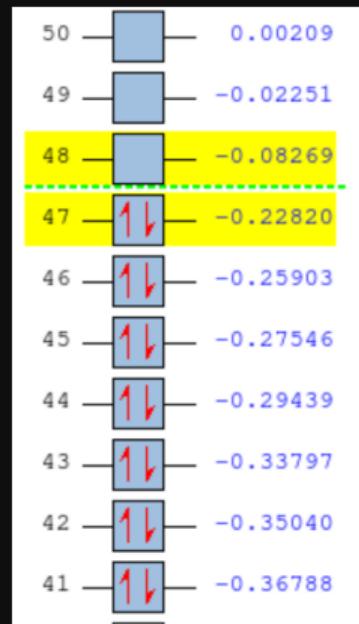


Figure: The HOMO-LUMO Energy Gap in Hartree

Rotational Properties of Anisylidene Acetone

Principal Axis	1	2	3
Moment of Inertia (a.u.)	633.31	6425.00	7035.65
Rotational Temp. (K)	0.137	0.013	0.012
Rotational Const. (GHz)	2.850	0.281	0.257

- Classified as an asymmetric top
- Rotational symmetry number: 1
- Significant difference between axis 1 vs. axes 2 & 3
- Near-planar orientation (X-Y plane)
- Principal axes nearly aligned with Cartesian axes

Vibrational Properties - Zero-Point Energy

Zero-Point Energy	Value
Joules/Mol	535,326.2
Kcal/Mol	127.95
Hartree/Particle	0.203895

- Significant ZPE reflects:
 - Large molecular size
 - Multiple vibrational modes (69 total)
 - Presence of high-frequency C-H stretches
- 19 degrees of freedom considered as vibrations

Vibrational Temperature Distribution

Vibrational Temp. Range (K)	Interpretation
54-200	Low-frequency modes
200-1000	Framework vibrations
1000-2000	Stretching vibrations
2000-3000	Double-bond stretching
4300-4650	C-H stretching modes

- Low-frequency modes:
 - Torsional motions
 - Ring deformations
- Mid-range frequencies:
 - C-C stretching
 - C=C ring modes
- High frequencies:
 - C-H stretching
 - Characteristic of aromatic systems

Thermodynamic Properties

Property	Value (Hartree)
Zero-point correction	0.203895
Thermal correction to Energy	0.216654
Thermal correction to Enthalpy	0.217598
Thermal correction to Gibbs Free Energy	0.163613
Sum of electronic and zero-point Energies	-576.612812
Sum of electronic and thermal Energies	-576.600052
Sum of electronic and thermal Enthalpies	-576.599108
Sum of electronic and thermal Free Energies	-576.653093

Thermodynamic Analysis

Key Insights:

- Significant entropic contribution
 - $T\Delta S = 0.053985$ Hartree
 - 33.9 kcal/mol at 298K
- Thermal energy contribution
 - $E_{thermal} - E_{ZPE} = 0.012759$ Hartree
 - 8.0 kcal/mol

Implications:

- Conformational flexibility
 - Possible rotations around C-C bonds
 - Multiple accessible conformers
- Reaction thermodynamics
 - Free energy guidance for reactions
 - Significant entropic effects
 - Temperature-dependent stability

Structure-Dynamics Relationships

- Molecular shape characterization:
 - Elongated structure ($I_1 \parallel I_2 \parallel I_3$)
 - Nearly planar configuration
 - Rotational constants suggest restricted rotation
- Vibrational signature highlights:
 - Conjugated system (characteristic frequencies)
 - Functional group identification (carbonyl, methoxy)
 - Framework rigidity (high-frequency skeletal modes)
- Thermodynamic behavior:
 - Entropic stabilization at higher temperatures
 - Enthalpic stability from conjugation
 - Thermal mobility of side groups

Electric Dipole Moment of Anisylidene Acetone

Component	Magnitude (Debye)	Direction
Total	6.13	-
X	-0.89	Weak contribution
Y	-5.85	Major contributor
Z	1.59	Moderate contribution

- Significant total dipole moment (6.13 D)
- Strong Y-axis polarization
- Suggests highly asymmetric charge distribution
- Characteristic of conjugated systems with electron-withdrawing groups

Polarizability Analysis

Property	Value ($\times 10^{-24}$ esu)
Isotropic α	28.51
Anisotropic α	34.25

Component	Value ($\times 10^{-24}$ esu)
α_{xx}	26.21
α_{yy}	45.35
α_{zz}	13.98

- High anisotropy ratio (1.20)
- Dominant Y-axis polarizability
- X-axis - moderate response
- Z-axis - least polarizable
- Aligns with molecular structure:
 - Y-axis spans conjugated system
 - Z-axis perpendicular to aromatic plane

Dipole Orientation Analysis

Component	Input Orientation (D)	Dipole Orientation (D)
Total	6.13	6.13
X	-0.89	0.00
Y	-5.85	0.00
Z	1.59	6.13

- In dipole orientation:
 - Z-axis aligns with molecular dipole
 - X and Y components vanish
- Dipole direction indicates electron density distribution
- Points from electron-rich methoxy group toward carbonyl moiety

Key Insights:

- High polarizability ($\alpha_{iso} = 28.51 \times 10^{-24}$ esu)
- Significant dipole moment (6.13 D)
- Strong anisotropy in both properties

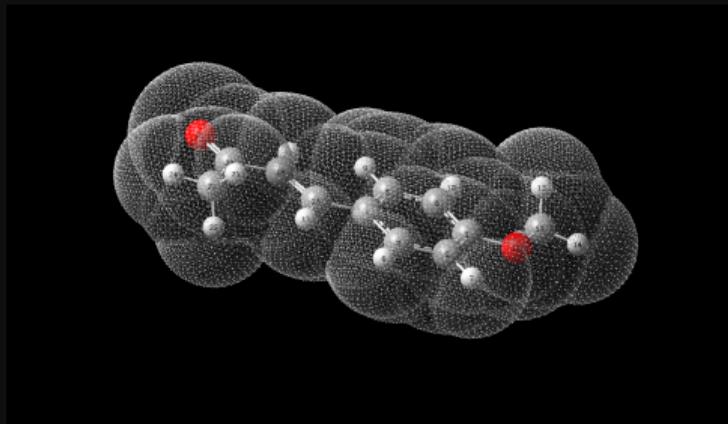
Contributing Factors:

- Conjugated -system
- Electron-donating methoxy group
- Electron-withdrawing carbonyl group

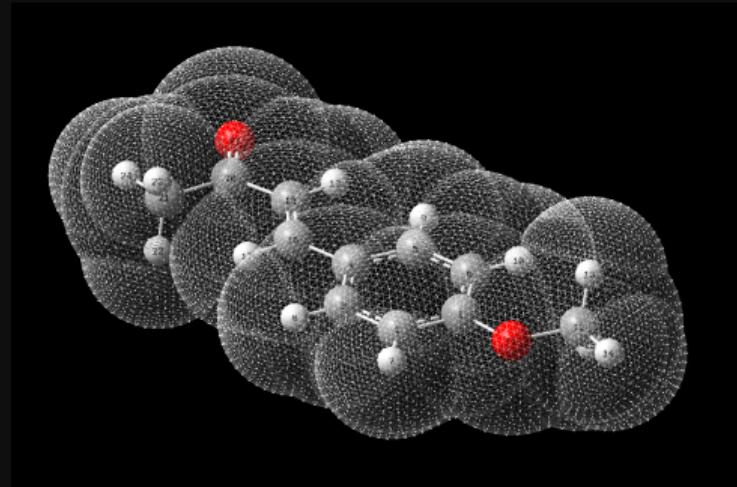
Implications for Molecular Properties:

- Enhanced solubility in polar solvents
- Strong intermolecular interactions
- Potential for hydrogen bonding
- Significant reactivity at carbonyl center
- Possible -stacking interactions
- UV-vis absorption characteristics

PCM Solvation Cavity



(a) A Side View of Solvation Cavity



(b) A $\frac{3}{4}$ th view of the Solvation Cavity

Figure: Model: IEFPCM, Solvent: Acetone, Molecule : Anisylidene Acetone

Computational Method Assessment

- B3LYP/6-311G in IEFPCM (acetone) provides:
 - Reasonable description of electronic structure
 - Accounts for solvent effects on charge distribution
 - Captures -conjugation effects on polarizability
- Population analysis methods (Merz-Kollman, NTO) offer:
 - Insights into charge localization
 - Visualization of electronic transitions
 - Understanding of molecular orbitals involved in excitation
- Results support experimental observations of:
 - Strong UV-vis absorption
 - Solvatochromic behavior
 - Reactivity patterns

Acknowledgments

Research Support

We thank the Department of Chemical Sciences for laboratory facilities and technical support during this project.

Faculty Support

Special thanks to:

- Prof. Suman De Sarkar (for providing anisaldehyde) and Prof. Debashish Halder for guidance and mentorship
- Lab technicians (Saroj Da only) for their constant assistance and cleaning up our mess
- Our classmates for providing entertainment during the course of the project (by Pritam)
- Swapnanil Sur for helping us doing the HRMS while we were not in Campus.
- Sayan da(our TA) for doing the NMR of the sample

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All Sources are Available!!!



Figure: Scan the Code or Click on it to see all the Project data and information

Since we are done!



Figure: Just Enjoy some Raspberry Juice

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