A DFT analysis for synthesizing vitamin A

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Abstract

Vitamin A deficiency (VAD) is a major nutritional concern in lower-income countries. It is responsible for thousands of deaths in those countries every year. Thus, finding the optimal route for vitamin A synthesis is essential, especially for the countries that are influenced by VAD. Three mechanisms of synthesizing Vitamin A have been evaluated by Density Functional Theory (DFT) calculations. This experiment investigated the BASF C_{15} + C_5 Wittig approach, the Rhône-Poulenc C_{15} + C_5 Julia approach, and the Kuraray C_{10} + C_{10} approach. The electronic energy, highest occupied molecular orbital energy, and dipole moments were calculated using the B3LYP functional and the 3-21g basis set. The energy profiles of these synthesis routes were compared to determine the most energetically favorable method. The Julia approach has the lowest energy change, indicating its higher efficiency in terms of energy compared to the Wittig and Kuraray methods. It is shown that other factors such as scalability and raw material availability should also be considered in industrial applications.

Keywords: Synthesis, Vitamin A, Density functional theory, Computational chemistry

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Introduction

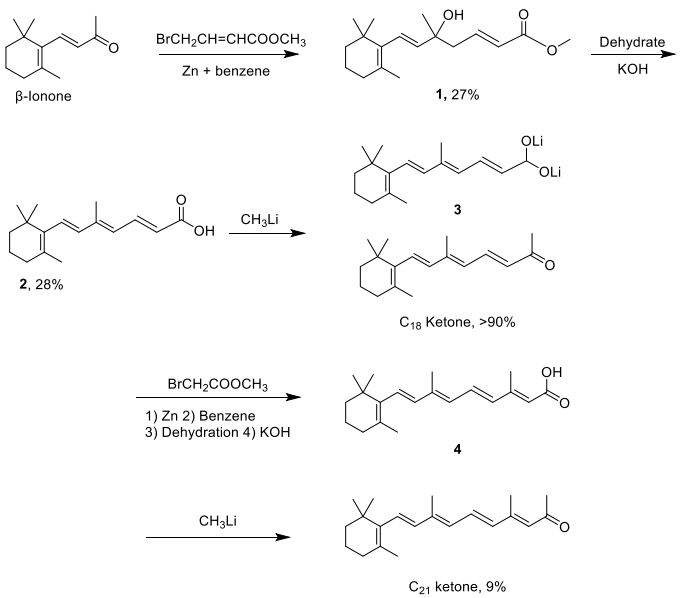
The proper operation of numerous critical metabolic and physiological processes, such as vision, immune system function, gene transcription, and skin cell differentiation, depends on vitamin A. (1) However, some diseases exist due to lack of vitamin A. Vitamin A deficiency (VAD) is a major nutritional concern in poor societies, especially in lower-income countries. Although the percentage is decreasing, in 2013, 30% of children under 5 years old were vitamin A deficient. About 2% of all deaths in this age group are attributable to this disease. Furthermore, vitamin A deficiency was found to be responsible for 94 500 deaths from diarrhea and 11 200 deaths from measles in 2013. This accounted for 1.7% of all deaths in children under the age of five in low-income and middle-income countries. (2) With such severe circumstances, a cost reduction in producing vitamin A would dramatically assist more people suffering from vitamin A deficiency.

The exploration of vitamin A structure and production has persisted for over 140 years. The finding of vitamin A might originate from a study conducted in 1816, the physiologist François Magendie experimented on dogs under nutritional deprivation, a technique that led to corneal ulcers and a high death rate. These results were comparable to the clinical condition commonly observed in undernourished, abandoned infants in Paris. Later, Frederick Gowland Hopkins postulated the existence of "unsuspected dietetic factors" as prerequisites for life in 1906. (3) In 1913, at the University of Wisconsin, Elmer Verner McCollum (1879–1967) and Marguerite Davis recorded an observation involving rats given "the ether extract of egg or of butter." They were given credit for finding what they dubbed "fat-soluble A," the first food

additive to be identified as a vitamin. (4) In 1920, Jack Cecil Drummond (1891–1952) suggested that because the substances are not all amines, they should be named Vitamin A, B, C, etc. (5) Vitamin A's structures were verified by Karrer, P., Morf, R., and Schöpp, K. later in 1931. (6) In 1937, Holmes and Corbet separated it and crystallized it from fish liver oils at Oberlin College.(7)

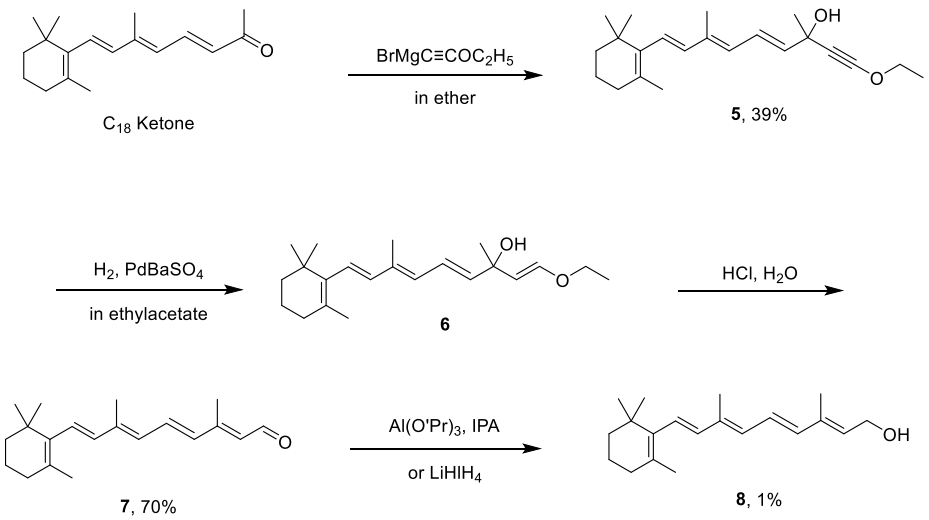
Van Dorp and Arens' synthesis of vitamin A acid and aldehyde

Retinoic acid (vitamin A acid) and retinol (vitamin A aldehyde) were first fully industrially synthesized in 1946 and 1947 by David Adriaan van Dorp (1915–1995) and Jozef Ferdinand Arens (1914–2001). (8)(9) The synthesis provided by Van Drop And Arens is a multistep synthesis from β-Ionone and undergoes the Reformatsky reaction, which symbolizes the process of forming β-hydroxy-esters by adding zinc enolates to aldehydes or ketones. (10) Three crystalline acids were isolated after the synthesis. The reaction mechanism that produces vitamin A acid is provided below (Scheme 1).



Scheme 1. Van Drop and Arens' Synthesis of Compounds with Strong Vitamin A Activity

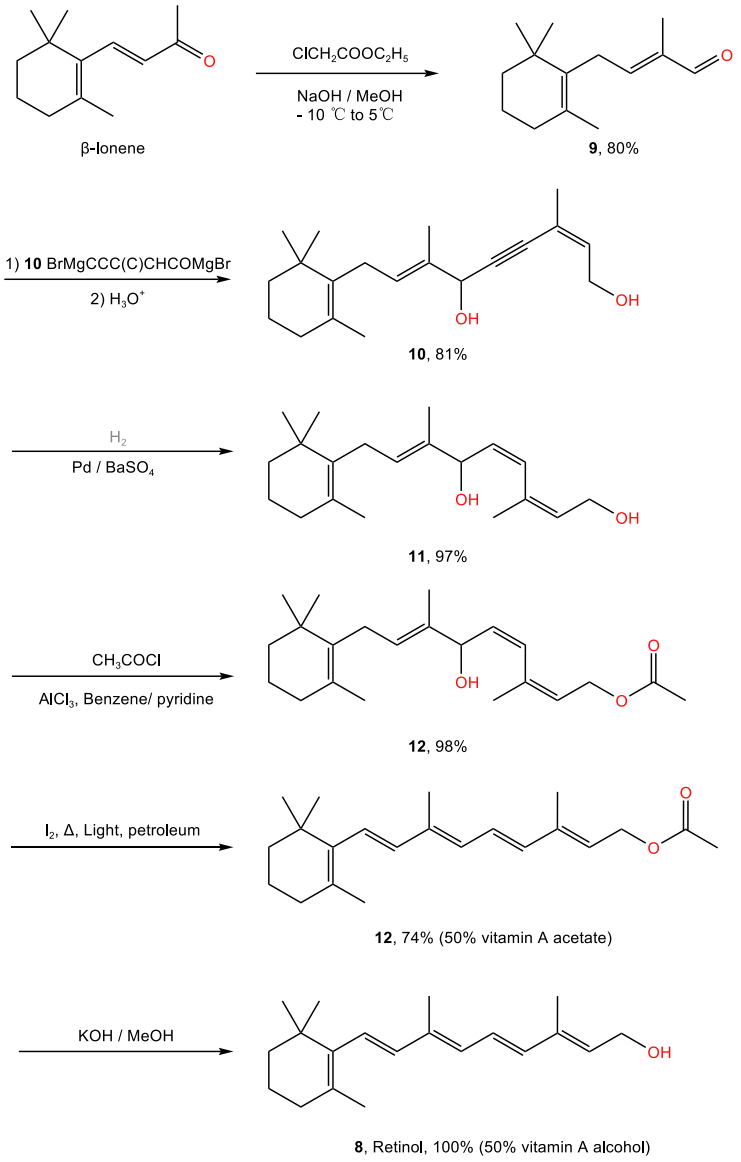
In 1947, vitamin A was synthesized by Van Dorp and Arens starting with the C_{18} Ketone that was synthesized in their 1946 study. The mechanism of the synthesization is provided below (Scheme 2). Vitamin A could be derived by reducing **7** using aluminum isopropoxide and isopropyl alcohol in a Meerwein-Ponndorf-Verley reduction, which 35% of the product is vitamin A. Later in 1949, Van Drop and Arens found that lithium aluminum hydride could also be used to do the reduction. (11) This reaction path increased the production of vitamin A aldehyde to 50%. However, since it is time-consuming, it is not suitable for large-scale production. (10)



Scheme 2. Arens-van Dorp reaction (9)(10)

O. Isler, W. Huber, A. Roneo und M. Kofler's synthesis of vitamin A

The reactions, similar to Van Dorp and Arens' synthesis, start with β-Ionone. However, since it avoids preparing ethoxyacetylene, it is not as time-consuming as the previous one and is thus suitable for large-scale production. (10) The reaction mechanism is shown in Scheme 3.

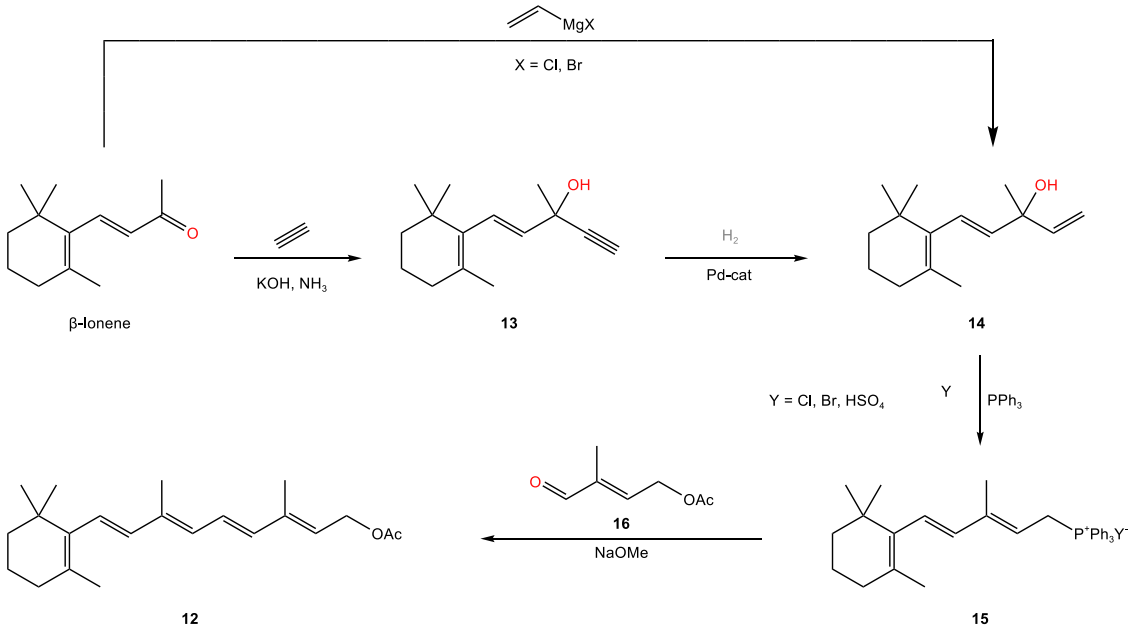


Scheme 3. O. Isler, W. Huber, A. Roneo und M. Kofler's Synthesis of Retinol (10)(12)

Synthesizing vitamin A by Wittig Reaction

The reaction between benzophenone and methylenetriphenylphosphorane, subsequently known as the Wittig reaction or Wittig olefination, was discovered in the 1950s by Wittig and Geissler. (13) Eventually, a method for synthesizing vitamin A was established, which relied on the Wittig olefination of a C_{15}-building block **15** with a C_5-moiety **16**. (14) β-ionone was vinylated using a Grignard reaction. (15) As an alternative, β-ionone can be semihydrogenated

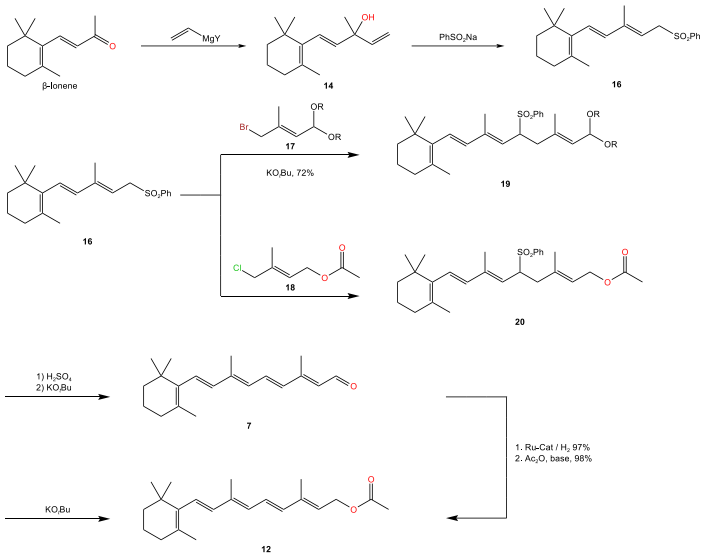
and then added to acetylene to create vinyl-β-ionol **14**. (16) The corresponding C_{15}-phosphonium salt **15** is produced by treating triphenylphosphine with acid. Vitamin A acetate is produced by Wittig olefination of the second essential building block, a C_5-aldehyde **16**, with phosphonium salt. (17) The coupling is carried out in aqueous solutions containing mild bases (such as ammonia or alkali metal carbonates) or in organic solvents like alcohols or DMF. (18)(19) To obtain the desired (all-E) vitamin A acetate, a mixture containing the (11Z)-isomer is obtained. This mixture can be photochemically induced to form the (all-E)-form in the presence of a photosensitizer and visible light, or it can be isomerized at elevated temperatures with Pd/C. (20)(21)(22) The reaction mechanism of synthesizing vitamin A acetate by Witting Reaction is shown in Scheme 4.



Scheme 4. Synthesis of Vitamin A acetate by Wittig reaction (15)(16)

Synthesis of vitamin A by Julia Chemistry

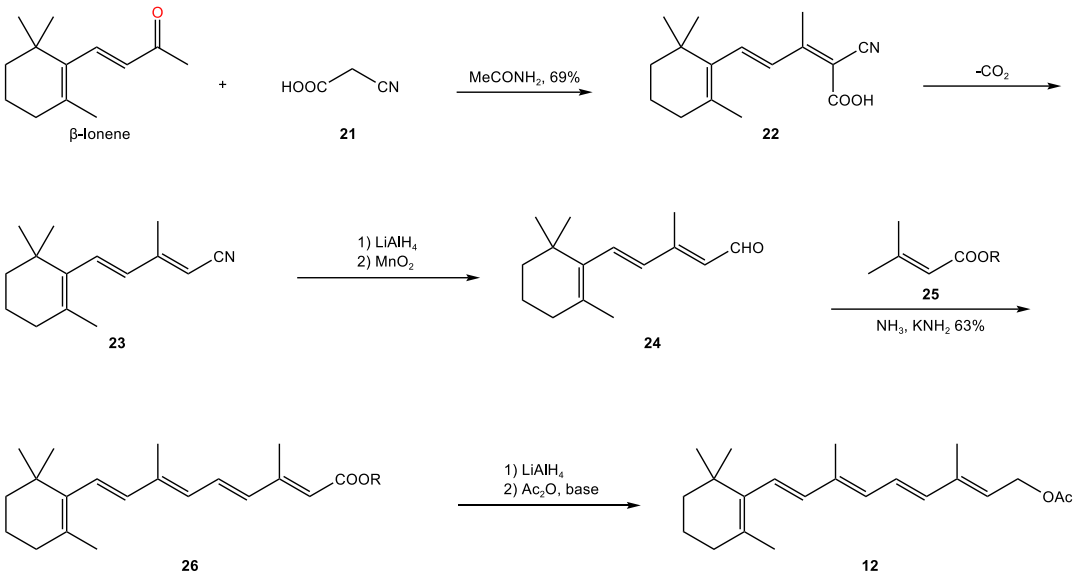
Rhône-Poulenc used the sulfone-based olefin synthesis, initially reported by Marc Julia in the 1970s, in an industrial process for the synthesis of vitamin A acetate. (24) The reaction mechanism is shown in scheme 5. The C_{15}-sulfone 16 is produced by reacting β-Vinylol 14, which is derived from β-ionone, with sodium phenyl sulfonate. (25) This is followed by a reaction with either bromo-acetal 17 or chloride 18 to produce the C_{20}-sulfones 19 and 20. Direct production of vitamin A acetate occurs from the removal of benzenesulfinic acid from 20. On the other hand, 19 is eliminated and hydrolyzed to produce retinal 7, which is then reduced and acylated to produce vitamin A acetate. (26)(27)(28)(29)(30) The overall yield of the C_5-building block synthesis was assumed to be about 90%. (16)



Scheme 5. Synthesis of Vitamin A acetate by Marc Julia's theory

Synthesis of Vitamin A by Sumitomo

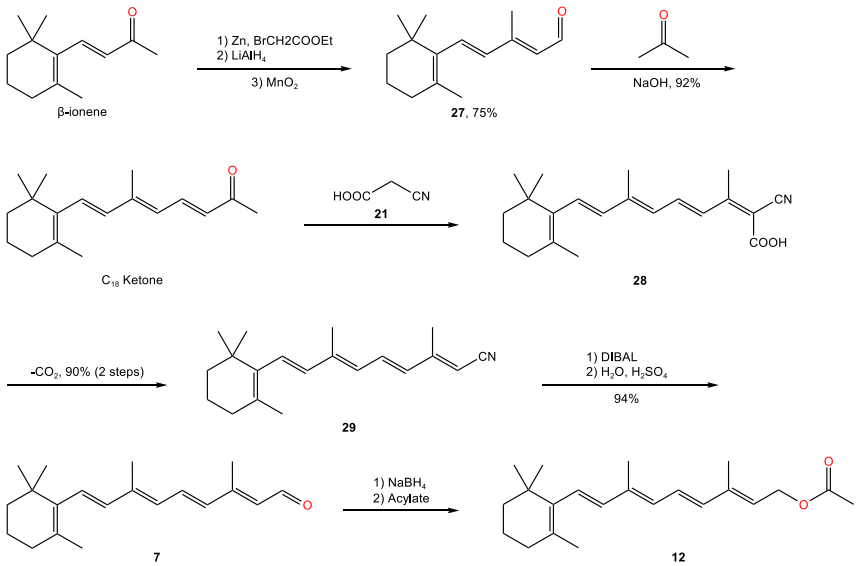
Sumitomo developed a synthesis pathway starting with β-ionone. In the reaction, vitamin A acetate is also formed by the coupling of C_{15} + C_5 building blocks. The mechanism is shown below (Scheme 6).



Scheme 6. Synthesis of Vitamin A Acetate by Sumitomo (25)(32)

Synthesis of Vitamin A by Philips

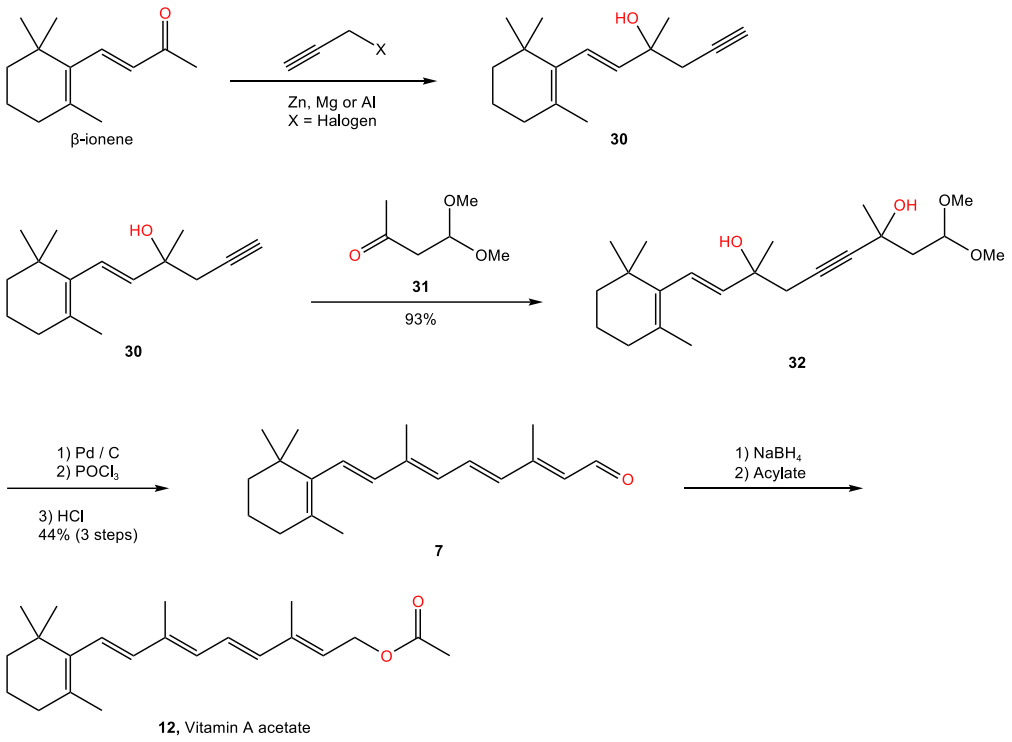
Philip's synthesis of vitamin A also starts with β-ionone and is the coupling of C_{15} + C_5 building blocks. However, its synthesis with C_{18}-ketone to form the corresponding C_{20}-nitrile **28**. (16) The mechanism is shown in scheme 7.



Scheme 7. Synthesis of Vitamin A acetate by Philips (33)(34)

Synthesis of Vitamin A by DPI and Glaxo

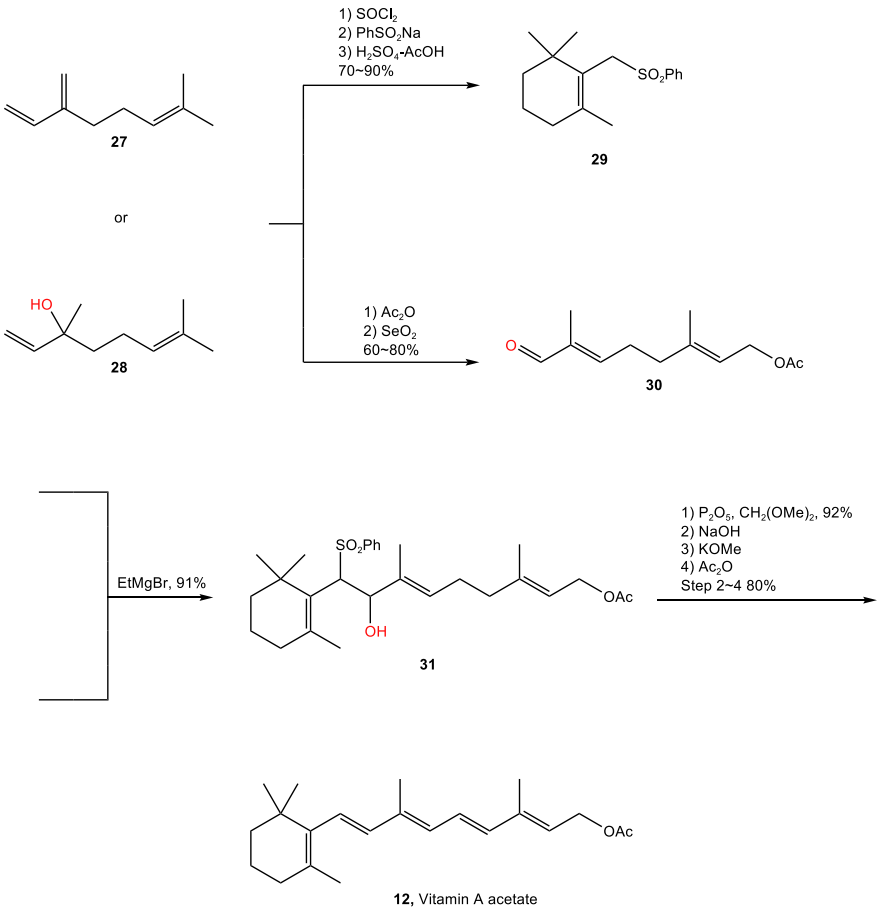
Distillation Products Limited and Glaxo in 1954, however, follows a C_{16} + C_4 approach. This synthesis has a reaction mechanism that is quite different from the previous ones that follow a C_{15} + C_5 approach. (Scheme 8)



Scheme 8. Synthesis of Vitamin A Acetate by Distillation Products Limited and Glaxo (35)(36)

Kuraray's synthesis of vitamin A

From the 1980s to 1990, the Japanese company Kuraray developed a pathway for synthesizing vitamin A by combining two C_{10} blocks. Two distinct C_{10}-compounds, sulfone **29** and aldehyde **30**, were produced from myrcene **27** or linalool **28**. When these two substances are combined, β-hydroxy-sulfone **31** is created, which is then transformed into vitamin A acetate. The mechanism is shown in Scheme 9.



Scheme 9. Synthesis of Vitamin A Acetate by Kuraray (16)(37)(38)(39)(40)(41)(42)(43)(44)

In conclusion, the experiment in this paper will mainly focus on three reaction mechanisms that produce vitamin A acetate: the BASF $C_{15} + C_5$ Wittig approach, Rhône-Poulenc/Adisseo $C_{15} + C_5$ Julia approach, and the Kuraray $C_{10} + C_{10}$ mechanism. The self-consistent field energy and highest occupied molecular orbital energy of intermediates in the mechanisms would be calculated by computational methods. An energy diagram of the production of Vitamin A through each mechanism will be drawn using the self-consistent field energy calculated and compared to find the optimal route from the three mechanisms.

Method

Density Functional Theory Fundamentals

Chemicals obey the laws of quantum mechanics, allowing predictions in-silico of chemical reactions. (46) Quantum chemistry methods such as Density Functional Theory, aim to provide a solution to the Schrödinger equation, shown below:

$$\hat{H}\Psi(r_1, r_2,\ldots,r_N) = E\Psi(r_1,r_2,\ldots,r_N)$$

Where $\hat{H}$ is the Hamiltonian operator, E is the energy, Ψ is the wavefunction, and r_i is the coordinate of each electron. (45) B By using the Kohn-Sham description of many-body systems, the electronic Schrödinger equation of chemical systems can be solved. (47)

We have employed Density Functional Theory (DFT) is being used in this study. In physics and chemistry, DFT has been a major tool for investigating the electronic structure of periodic systems, like crystals, since the last 40 years. (45) Potential energy surfaces (PES) of chemical systems can be computed with DFT.

DFT plays a crucial role in modeling chemical reactions by computing Potential Energy Surfaces (PES of chemical systems). These PES gives details about a chemical's energy at a variety of geometries and degrees of freedom. (45) Analysis of PES enables the evaluation of transition states, activation barriers, or the energy differences between reactants and transition states. Thus, the DFT method described in this work has been used for calculating the electronic (Self-Consistent Field, SCF) energy of transition states to compare the practicability and efficiency of selected vitamin A synthetic routes.

Preparation

Structures in the calculations were prepared using RDKit from SMILES. The Python code to generate the structures can be found in Appendix 1.

All geometries and energies presented in this study were computed using the B3LYP functional theory (DFT) functional and the Grimme's D4 dispersion method as implemented in the ORCA Quantum Chemistry Package (version 6.0). B3LYP stands for "Becke, 3-parameter, Lee-Yang-Parr." This hybrid functional incorporates a portion of exact exchange energy from the Hartree-Fock theory along with exchange-correlation energies derived from other sources, specifically the local spin density approximation (LSDA) and the correlation functional developed by Lee, Yang, and Parr (LYP). (48)

Geometry optimizations were performed using the 3-21G basis set, A split-valence double-ζ basis set. A double-ζ basis set consists of two basis functions for each atomic orbital, allowing for greater flexibility in representing the electron density around atoms. This contrasts with a minimal basis set, which uses only one function per orbital. The term "ζ" refers to the exponent in Slater-type orbitals (STOs), and having two functions enables better modeling of the variations in electron distribution due to chemical bonding and molecular interactions. The RIJCOSX method with auxiliary basis sets was used to speed-up the calculations. An example of an optimized geometry employing this approach is shown in Figure 1.

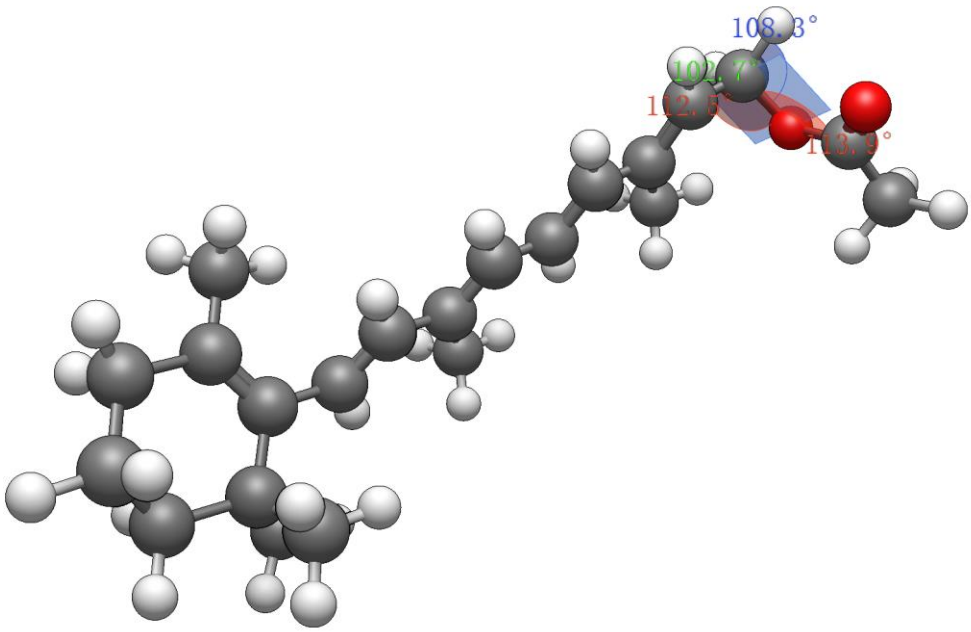


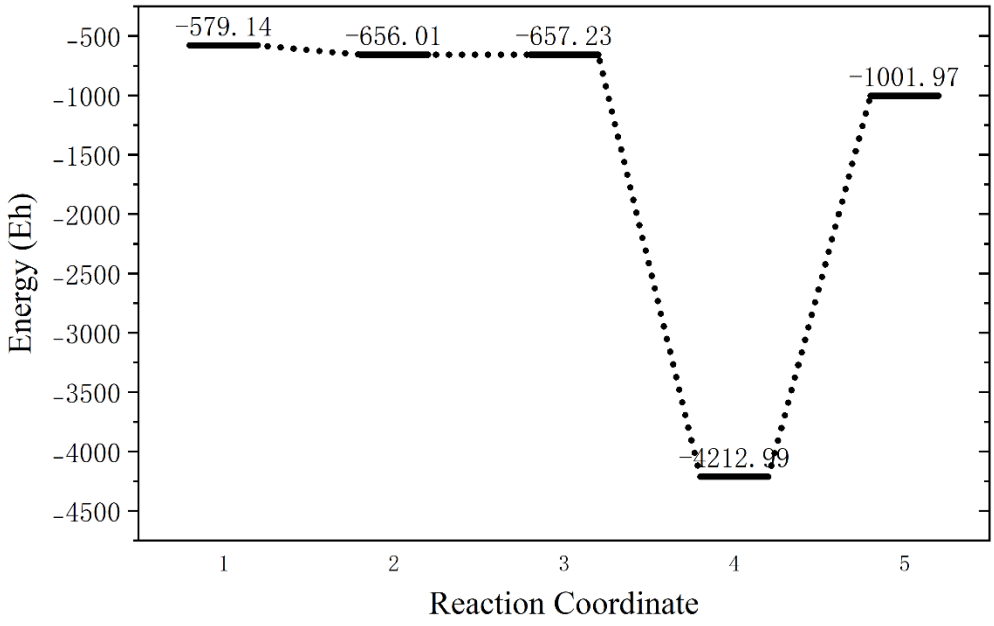
Figure 1. Optimized structure of vitamin A acetate

Self-Consistent Field (SCF) energies, orbital energies, and dipole moments were extracted from the ORCA output files. (49)(50)(51)(52)(53)(54)(55)(56)(57)(57)(58)

Results

BASF C15 + C5 Wittig approach

The reaction mechanism of the DASF synthesis of vitamin A acetate by using the Wittig approach is already shown in Scheme 4. The following scheme is the reaction energy change of the vitamin A acetate synthesis by the Wittig reaction.



Scheme 10 Schematic representation (energy V.S. reaction coordinate) of the reaction mechanism by Wittig approach

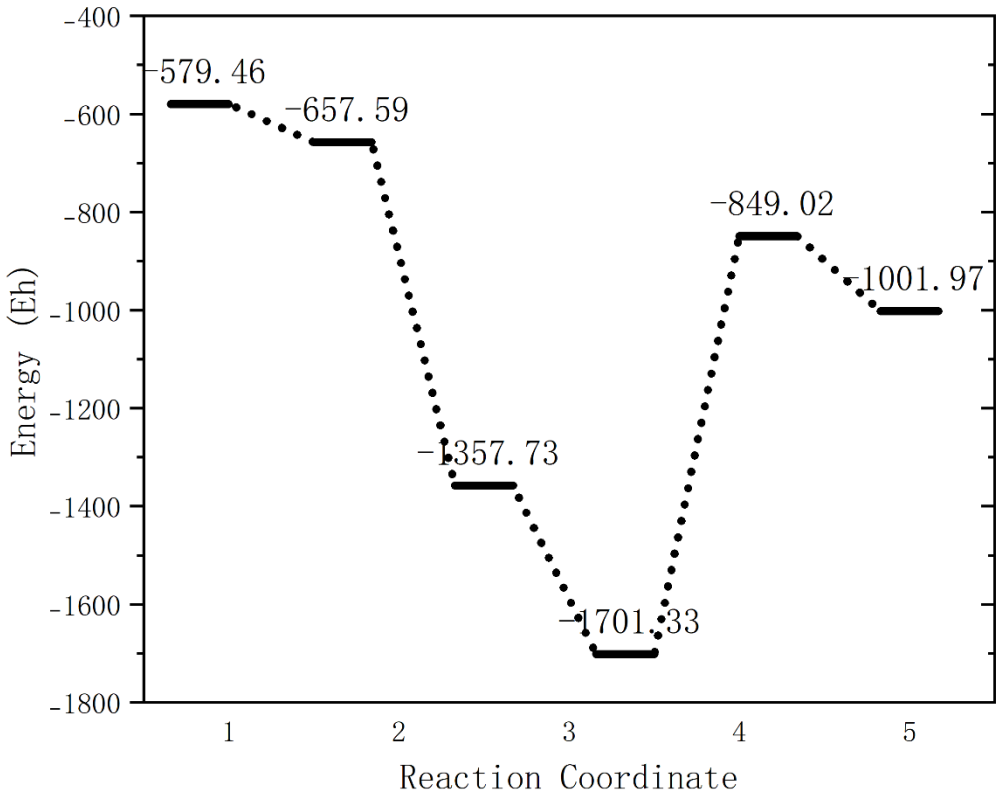
The specific final single energy, HOMO energy, and dipole magnitude are given in Table 1.

Table 1. Values calculated through the Density Functional Theory of synthesizing vitamin A by Wittig reaction

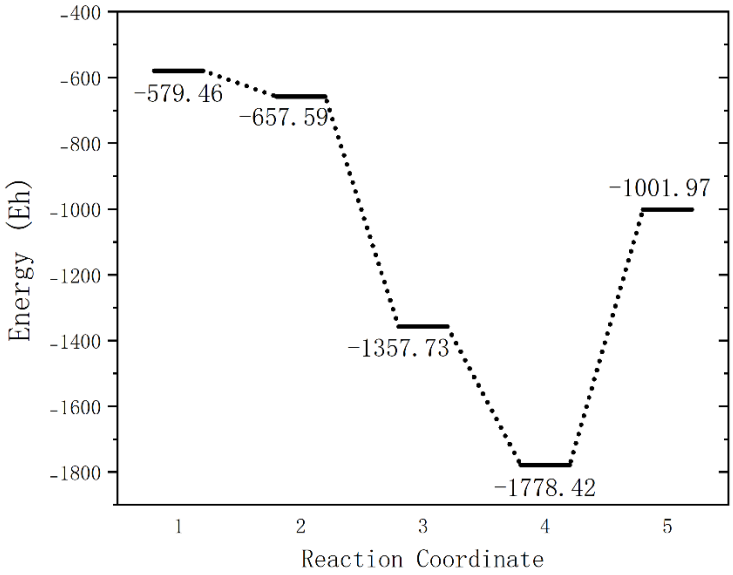
Compound name	***SCF Energy (Hartree)***	***HOMO energy (Hartree)***	***Dipole magnitude (Debye)***
β - Ionone	-579.13963	-0.218577	3.208074944
No.13	-656.01099	-0.208618	1.399691435
No.14	-657.22755	-0.195693	1.134328777
No.15	-4212.9864	-0.131678	12.07898961
Vitamin A Acetate	-1001.974713	-0.182186	1.794558566

Julia reaction (Rhône-Poulenc)

The reaction mechanism developed by Julia has two possible reaction routes, as shown in Scheme 5. The first path is through the direct synthesis of sulfone **20**. After eliminating the benzenesulfinic acid from compound **20** it will directly produce compound acetate **12**. The second path would include the synthesis of sulfone **19**. Sulfone **19** will go through both hydrolysis and elimination of benzenesulfinic acid to produce retinal **7**. Eventually, retinal **7** would convert to acetate **12** by acylation and reduction. The schematic representation of the energy of the routes is shown in schemes 11 and 12 separately. The specific final single energy, HOMO energy, and dipole magnitude are given in Tables 2 and 3.



Scheme 11. Schematic representation (energy V.S. reaction coordinate) of the first reaction mechanism developed by Marc Julia



Scheme 12. Schematic representation (energy V.S. reaction coordinate) of the second reaction mechanism developed by Marc Julia

Table 2. Values calculated through the Density Functional Theory of synthesizing vitamin A acetate by Julia's method 1

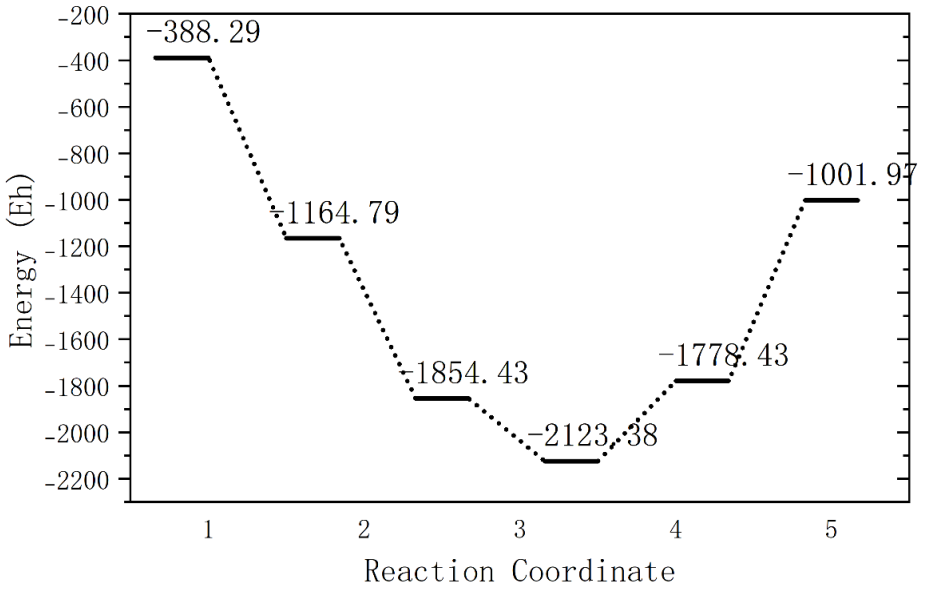
Compound name	***SCF Energy (Hartree)***	***HOMO energy (Hartree)***	***Dipole magnitude (Debye)***
β - Ionone	-579.46179	-0.218577	3.212844591
No. 14	-657.59455	-0.195693	1.13266856
No.16	-1357.7324	-0.20089	4.545812364
No. 19	-1701.3313	-0.203717	5.332725768
No. 7	-849.02156	-0.195027	5.997955331
Vitamin A Acetate	-1001.974713	-0.182186	1.794558566

Table 3 Values calculated through the Density Functional Theory of synthesizing vitamin A acetate by Julia's method 2

Compound name	***SCF Energy (Hartree)***	***HOMO energy (Hartree)***	***Dipole magnitude (Debye)***
β - Ionone	-579.46179	-0.218577	3.212844591
No. 14	-657.59455	-0.195693	1.13266856
No.16	-1357.7324	-0.20089	4.545812364
No. 20	-1778.4217	-0.204485	5.08082873
Vitamin A Acetate	-1001.974713	-0.182186	1.794558566

Kuraray synthesis of vitamin A acetate

Kuraray's synthesis includes a combination of two C_{10} building blocks. Sulfone **29** and aldehyde **30**, were produced from myrcene **27** or linalool **28**. When these two substances are combined, β-hydroxy-sulfone **31** is created, which is then transformed into vitamin A acetate. The mechanism is shown in Scheme 9. The schematic representation of the energy of the mechanism is presented in Scheme 13. The values calculated are presented in Table 4.

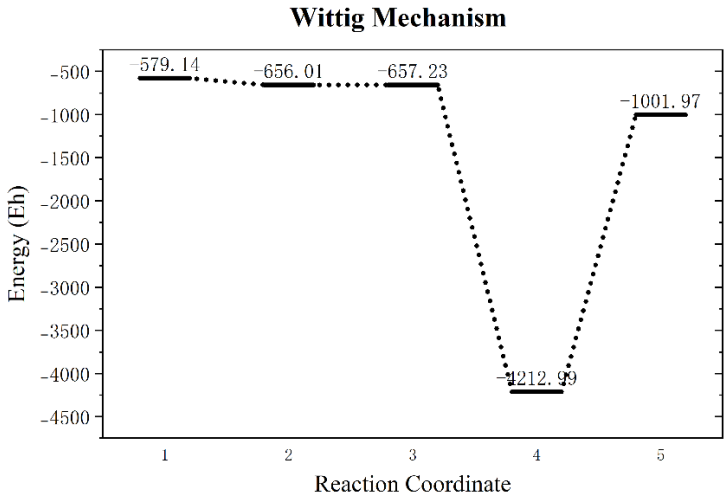


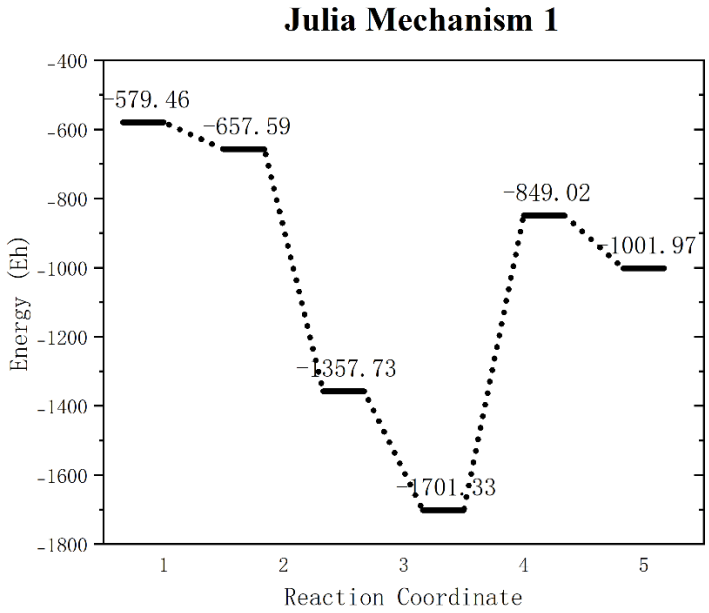
Scheme 13. Schematic representation (energy V.S. reaction coordinate) of synthesis of vitamin A acetate developed by Kuraray

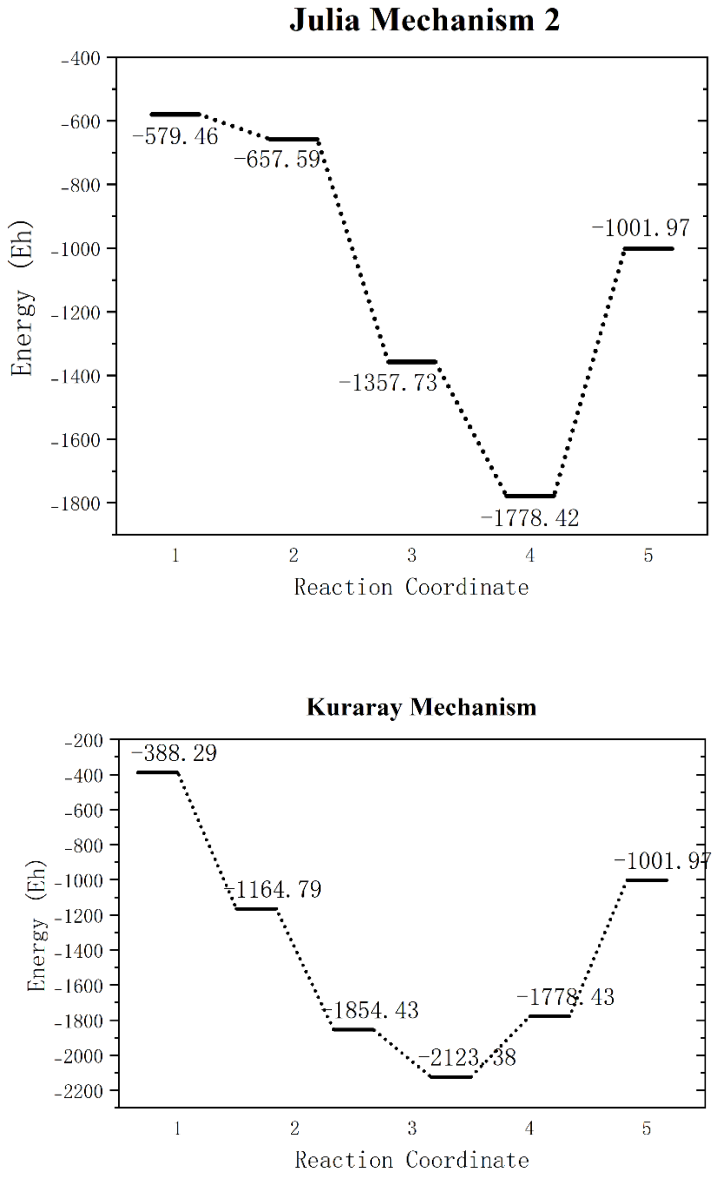
Table 3 values calculated through the Density Functional Theory of synthesizing vitamin A acetate by Kuraray

Compound name	***SCF Energy (Hartree)***	***HOMO energy (Hartree)***	***Dipole magnitude (Debye)***
No. 27	-388.28719	-0.219925	0.39529421
No. 29	-1164.791914	-0.220583	4.669811213
No. 31	-1854.43498	-0.22186	4.70231496
No. 32	-2123.384953	-0.208417	6.409372827
No. 33	-1778.43284	-0.213869	3.843230534
Vitamin A Acetate	-1001.974713	-0.182186	1.794558566

Overall, the synthesis of vitamin A acetate through the Wittig approach is the one that has the highest energy change, whereas the first approach developed by Marc Julia has the lowest energy change. The schematic representation of all reaction mechanisms is shown in scheme 14.







Scheme 14. Schematic representation (energy V.S. reaction coordinate) of all reaction mechanisms of synthesizing vitamin A acetate

Discussion

This DFT study compared three synthesis pathways for Vitamin A Acetate, which includes the Wittig approach, Julia Chemistry, and Kuraray's approach. Through the calculations, we could compare the energy change of all three mechanisms.

The Wittig approach, which involves the olefination of a C15 building block with a C5 moiety, resulted in the highest energy changes throughout all three reaction mechanisms, which should be one of the reasons why this method is not widely used as other reaction mechanisms. In contrast, the first approach by Marc Julia exhibited the lowest energy changes, making it the most energetically efficient pathway among all three. These results aligned with its continued use in industrial processes, especially in large-scale production of vitamin A. The second route developed by Julia, although less energetically favorable than the first one, still performs comparably to other synthesis methods. Kuraray's C_{10} + C_{10} approach, while innovative, presented an intermediate energy change between the Wittig and Julia methods. Thus, in terms of energy, Julia's method of synthesizing vitamin A is the most efficient.

However, the experiment still has plenty of limitations. Other factors such as scalability, raw material availability, and industrial preferences must be considered when selecting the optimal synthesis route for Vitamin A acetate. The results from this DFT study only give a reference to evaluating the synthetic pathways and for further optimization in industrial applications.

Appendix

Appendix 1: Python code for generating chemical structures from SMILES

```
!pip install --prefer-binary pyscf
!pip install pyberny
#!pip install geometric
!pip install fortecubeview pythreejs
!pip install --upgrade traitlets
!pip install rdkit
!pip install py3Dmol


from google.colab import output
output.enable_custom_widget_manager()
import pathlib
# RDKit imports:
from rdkit import Chem
from rdkit.Chem import (
    AllChem,
    rdCoordGen,
)
from rdkit.Chem.Draw import IPythonConsole
IPythonConsole.ipython_useSVG = True  # Use higher quality images for molecules
# For visualization of molecules and orbitals:
import py3Dmol
import fortecubeview
# pyscf imports:
from pyscf import gto, scf, lo, tools
# For plotting
import matplotlib
from matplotlib import pyplot as plt
import seaborn as sns
%matplotlib inline
sns.set_theme(style="ticks", context="talk", palette="muted")
# For numerics:
import numpy as np
import pandas as pd
pd.options.display.float_format = "{:,.3f}".format


molecule_name = "Bicarbonate"
molecule = Chem.MolFromSmiles("")  # Generate the molecule from smiles
molecule


def get_xyz(molecule, optimize=False):
    """Get xyz-coordinates for the molecule"""
    mol = Chem.Mol(molecule)
    mol = AllChem.AddHs(mol, addCoords=True)
    AllChem.EmbedMolecule(mol)
    if optimize:  # Optimize the molecules with the MM force field:
        AllChem.MMFFOptimizeMolecule(mol)
    xyz = []
    for lines in Chem.MolToXYZBlock(mol).split("\n")[2:]:
        strip = lines.strip()
        if strip:
            xyz.append(strip)
    xyz = "\n".join(xyz)
    return mol, xyz


molecule3d, xyz = get_xyz(molecule)
print(xyz)


view = py3Dmol.view(
    data=Chem.MolToMolBlock(molecule3d),
    style={"stick": {}, "sphere": {"scale": 0.3}},
    width=300,
    height=300,
)
view.zoomTo()
```

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