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Cannabinoid spoilage, metabolism and cannabidiol(CBD) conversion to Tetrahydrocannabinol(THC) mechanisms with energetic parameters

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Abstract

Chemical redox mechanisms and thermodynamic parameters of the Cannabinoids Δ^9 -Tetrahydrocannabinol (THC) and cannabidiol (CBD) were determined theoretically and using activated complex theory then compared to physical experimentations of chemical spoilage by Pholsiri T et al. and intramolecular conversion of CBD to thc by Daniels. R. et al. Thermodynamic parameters were derived from activated complex theory using standard bond enthalpy data from the elements of Physical Chemistry by Atkins ((Atkins, Elements of Physical Chemistry, 2001)). Situations where psychotropic cannabinoids found in CBD based products were also understood due to the parameters that drive the reduction process of conversion to THC. The metabolism process of cannabinoids has been detailed from consumption to excretion with mechanistic support to deactivation and glucuronidation in order to have a cannabis standard established.

Keywords Tetrahydrocannabinol (THC), Cannabidiol (CBD), Cannabinol (CBN), Storage, 11-nor-9-carboxy, Glucuronidation

Introduction

Δ^9 -THC undergoes oxidation which converts to CBN (cannabinol) which is a more stable thermodynamic compound compared to 11-OH THC a more potent cannabinoid. As the product of oxidation at isobaric conditions, cannabidiol follows a similar oxidation pathway to CBND however the cannabinoid undergoes proton catalysis to form THC, a more feasible compound. A pathway is proposed for the decomposition of Δ^9 -tetrahydrocannabinol (I) and its Δ^8 -isomer (IX) with the eventual formation of cannabinol (II) through epoxy and hydroxylated intermediates (Turner and Elsohly 1979). The goal is to

fully understand the metabolism process using thermodynamic parameters to supplement the pharmacokinetics of the enzyme substrate complex cytochrome P450 enzymatic cycle while maintaining charge neutrality during molecular transformation of the cannabinoid during and after the enzyme complex metabolism. The activation energies for the redox of the cannabinoids CBD and Δ^9 - THC were sought after by means of activation energy complex theory to simulate a theoretical value and rate constants for the chemical change. Standard data was then to be compared to experimental energy changes of the cannabinoids CBD and Δ^9 - THC respectively as redox from Polori and Omir respectively. Provided with the energy changes by each mechanism, pharmacokinetics essays and chemical spoilage experimentation could

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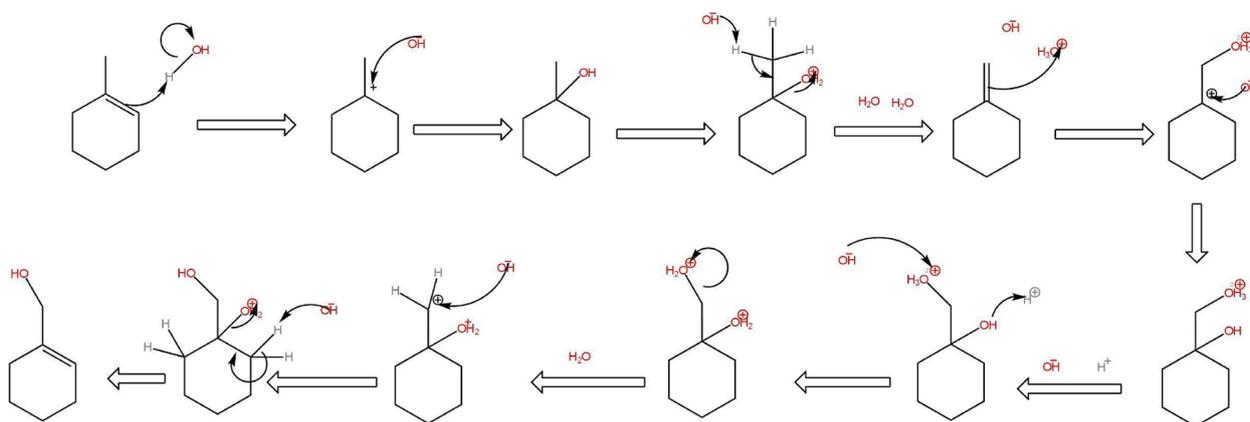


Fig. 1 Mechanism of Δ^9 -Tetrahydrocannabinol (THC) reduction to 11-OH-THC

Free energy change vs entropy change

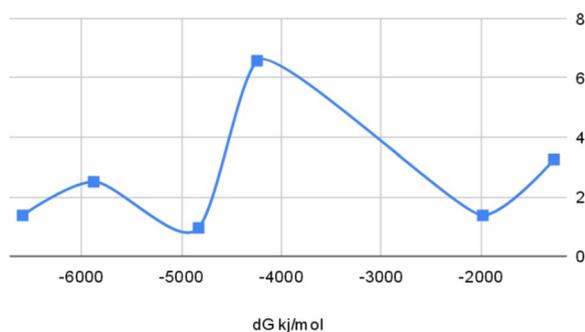


Fig. 2 Energy diagram of formation of 11-OH-THC

CBD to CBND, the model of mammalian metabolism of Δ^9 -THC and CBD in stomach acid and deactivation to 11-nor-carboxy-THC and 7-OH-CBD as primary metabolites, lastly the conversion of CBD to Δ^9 -THC consuming water in an acidic condition.

Method

Applying bond enthalpy mechanistic change data from Elements of Physical Chemistry by Peter Atkins (Figs. 1, 2, 3, 4, 5, 6, 7 and 8).

Δ^9 -THC to 11-OH THC:

$$\Delta G_{total} = -6588.751 \text{ kJmol}^{-1}$$

$$\Delta S_{total} = +16.064 \text{ kJmol}^{-1}$$

Applying thermochemical equation: $\Delta G = -nFE$.

As a 6 step electron transfer at equilibrium, $\Delta G_{11-OH} = -nFE_{eq}$

have more understanding in regards to the order of the reactants.

Data provided propose mechanisms and thermodynamic parameters; oxidation of Δ^9 - THC to CBN and

$$E_{eq} = -(\Delta G)/nF = -(-6588.749 \text{ kJmol}^{-1} / (6 \text{ mol} \times 96500 \text{ JC} - 1 \text{ mol}^{-1})) = +11.380 \text{ mV}$$

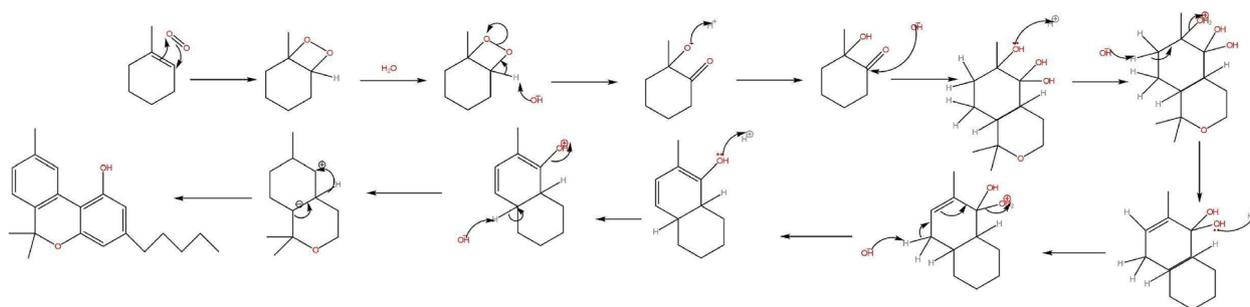


Fig. 3 Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) oxidation mechanism to cannabinol (CBN)

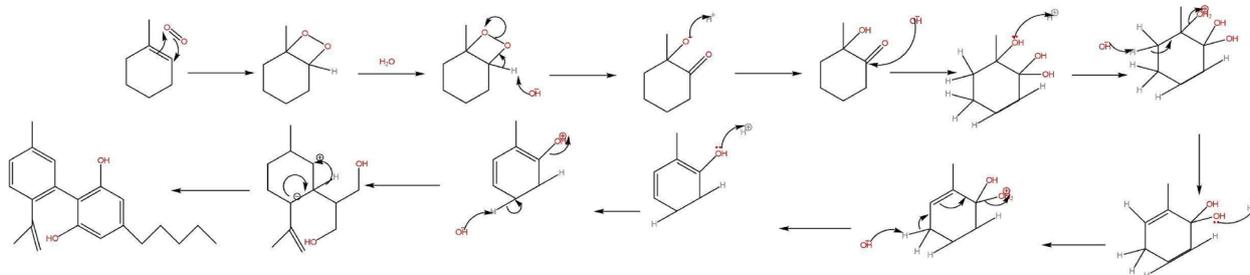


Fig. 4 CBD oxidation to CBND mechanism

Gibbs free energy change vs entropy

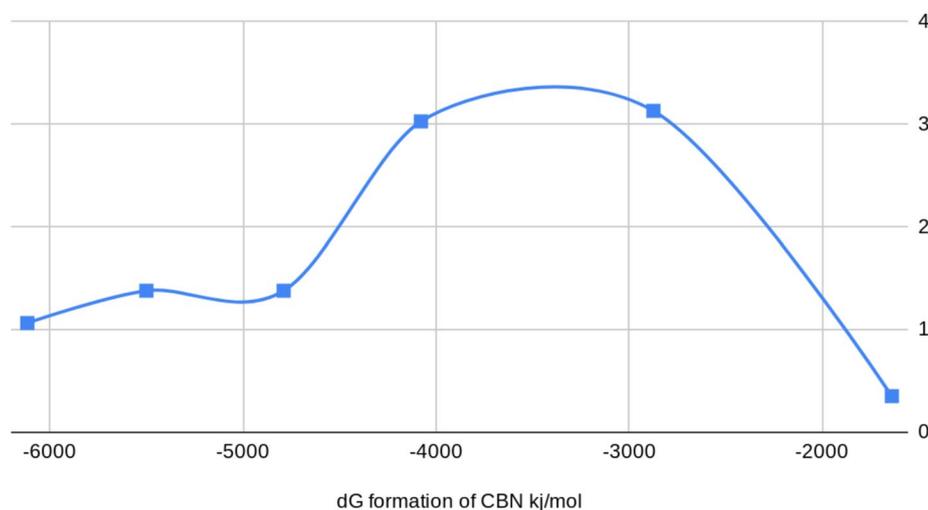


Fig. 5 Energy diagram of formation of CBN

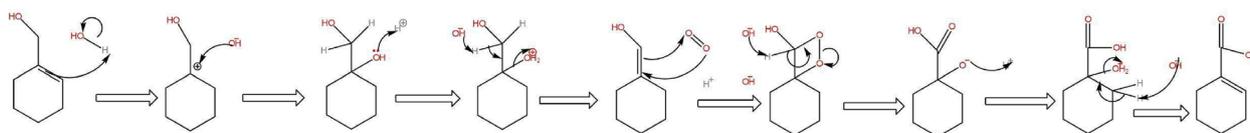


Fig. 6 Formation of 11-nor-carboxy-THC from Δ^9 -Tetrahydrocannabinol mechanism

$\Delta G_{redox} = RT/nF - \ln K$, where $K = \text{product/reactant}$ each index was calculated as product/reactant in mechanism and of the cannabinoids considered with respect to the concentration of itself at equilibrium.

$K = \frac{[11\text{-OH-THC}]}{[\Delta^9\text{-THC}][\text{H}_2\text{O}]}$ as equilibrium constant,

$-RT \ln K = \Delta G = \Delta H - T\Delta S$. Activated theory complex determines the rate constant from the thermodynamic functions of entropy and energy to determine

the partition of energy within time that determines the chemical kinetic rate. This derives the rate constant of formation of products (Atkins 2001) (Tables 1, 2, 3 and 4).

Activation energy = $-RT \ln K = \Delta G = e^{-\Delta G/RT}$

$$E_A = 14.268 \text{ kJmol}^{-1}$$

$$k_{rate} = (kT/h)e^{-(\Delta H - T\Delta S)/RT}$$

Gibbs free energy change vs entropy of 11-carboxy-THC

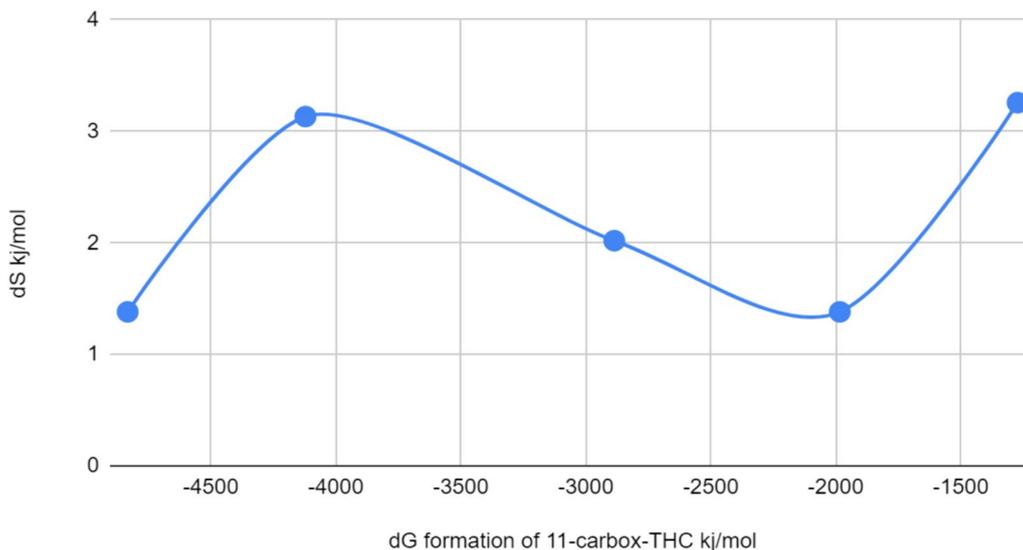


Fig. 7 Free energy diagram of formation of 11-nor-carboxy-THC

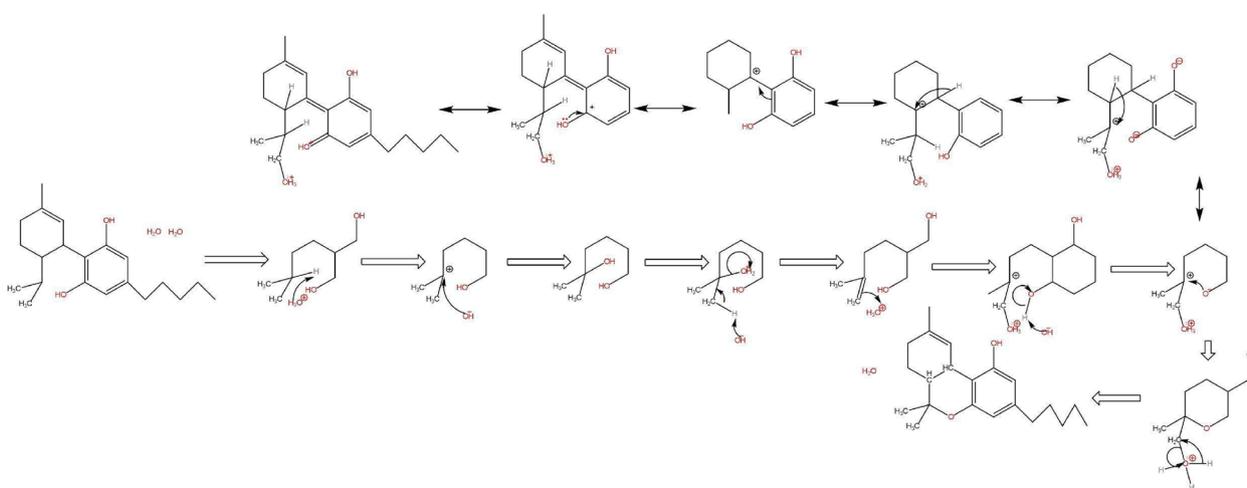


Fig. 8 Formation of Δ^9 -THC from cannabidiol

$$k_{rate} = (1.38066JK^{-1} \times 298.15K / 6.626 \times 10^{-34} Js) \times e^{-(-4788.98kJ/mol - (298.15K \times 16.064kJ/mol) / (8.314J/mol/K \times 298.15K))}$$

$$k = 6.21255 \times 10^{35} \times e^{1.93216} = 4.28854 \times 10^{36} \text{seconds}$$

$$\Delta S_{total} = +10.338 \text{kJmol}^{-1} K^{-1}$$

Where the rate expression for the chemical reaction can also be deduced from the mechanism where:

$$E_A = 7.167 \text{kJmol}^{-1}$$

Δ^9 -THC to CBN:

$$k_{rate} = 4.4525 \times 10^{36} \text{seconds}$$

$$\Delta G_{total} = -4882.049 \text{kJmol}^{-1}$$

Table 1 Thermodynamic energy changes of the mechanism Δ^9 -Tetrahydrocannabinol to 11-OH-THC

ΔH kJmol^{-1}	ΔH sum kJmol^{-1}	ΔG kJmol^{-1}	ΔE mV	ΔS kJmol^{-1}
-971	-971	-1272.407	13.186	3.257
-411.66	-1382.66	-711.191	7.370	1.381
-1960	-3342.66	-2259.531	23.415	6.574
-285.83	-3628.49	-584.939	6.062	0.959
-748.83	-4377.32	-1049.492	10.876	2.512
-411.66	-4788.98	-711.191	7.370	1.381

Table 2 Thermodynamic oxidation energy changes of the cannabinoids THC and CBD to CBN and CBND respectively

ΔH kJmol^{-1}	ΔH sum kJmol^{-1}	ΔG kJmol^{-1}	ΔE mV	ΔS kJmol^{-1}
-105	-105	-403.502	4.181	0.352
-933.83	-1038.83	-1235.112	12.799	3.132
-903	-1941.83	-1204.179	12.479	3.027
-411.66	-2353.49	-711.191	7.370	1.381
-411.66	-2765.15	-711.191	7.370	1.381
-317.66	-3082.81	-616.874	6.392	1.065

Table 3 Thermodynamic energy changes of the deactivation of Δ^9 -Tetrahydrocannabinol to 11-nor-carboxy-THC

ΔH kJmol^{-1}	ΔH sum kJmol^{-1}	ΔG kJmol^{-1}	ΔE mV	ΔS kJmol^{-1}
-971	-971	-1272.40675	13.186	3.256749958
-411.66	-1382.66	-711.1907144	7.370	1.380714406
-602	-1984.66	-902.1691179	9.349	2.019117894
-933.83	-2918.49	-1235.112081	12.799	3.132081167
-411.66	-3330.15	-711.1907144	7.370	1.380714406

Table 4 Thermodynamic energy changes of the reductive conversion of CBD to Δ^9 -Tetrahydrocannabinol

ΔH kJmol^{-1}	ΔH sum kJmol^{-1}	ΔG kJmol^{-1}	ΔE mV	ΔS kJmol^{-1}
-411	-411	-710.5285008	7.363	1.378500755
-411.33	-822.33	-710.8596076	7.366	1.37960758
-1485	-2307.33	-1788.130714	18.523	4.980714406
-182.85	-2490.18	-481.6132819	4.991	0.6132819051
-337.83	-2828.01	-637.1130874	6.602	1.133087372

As 6 step nucleophilic transfer to equilibrium:

$$E_{eq} = -(\Delta G)/nF = -(-6117.16 \text{ kJmol}^{-1} / (6 \text{ mol} \times 96500 \text{ JC}^{-1} \text{ mol}^{-1})) = +10.565 \text{ mV}$$

$$\Delta G_{redox} = RT/nF - \ln K, \text{ where } K = \text{product/reactant},$$

$$K = [\text{CBN}]/[\Delta^9 - \text{THC}][\text{O}_2][\text{H}_2\text{O}]$$

As 5 step nucleophilic transfer to equilibrium:

$$E_{eq} = -(\Delta G)/nF = -(-4832.069 \text{ kJmol}^{-1} / (5 \text{ mol} \times 96500 \text{ JC}^{-1} \text{ mol}^{-1})) = +10.015 \text{ mV}$$

K=product/reactant,

$$K = [11 - \text{nor} - \text{carboxy} - \text{THC}]/[\Delta^9 - \text{THC}][\text{O}_2][\text{H}_2\text{O}]$$

$$\Delta G_{total} = -4832.07 \text{ kJmol}^{-1}$$

$$\Delta S_{total} = +11.169 \text{ kJmol}^{-1} \text{K}^{-1}$$

$$E_A = 7.024 \text{ kJmol}^{-1}$$

$$k_{rate} = 4.364 \times 10^{36}$$

$$E_{eq} = -(\Delta G)/nF = -(-4328.245 \text{ kJmol}^{-1} / (5 \text{ mol} \times 96500 \text{ JC}^{-1} \text{ mol}^{-1})) = +8.970 \text{ mV}$$

$$\Delta G_{total} = -4328.246 \text{ kJmol}^{-1}$$

$$\Delta S_{total} = 9.48519 \text{ kJmol}^{-1} \text{K}^{-1}$$

$$E_A = 5.73216 \text{ kJmol}^{-1}$$

$$k_{rate} = 3.561 \times 10^{36} \text{ seconds}$$

$$K = [\Delta^9 - \text{THC}]/[\text{CBD}][\text{H}_2\text{O}]$$

Discussion

The mechanism proposed intramolecular interactions with the alkene, the deduced synthesis yielded thermodynamic parameters that explains the probability of the difference in the cannabinoid reduction routes.

The restriction in the rotation of the cyclohexene ring of CBD was caused by the difference in the intramolecular OH- π bonds of the alkenes of both cyclic vs aliphatic interaction within the symmetry of the phenols in the aromatic ring (Daniels et al. 2023, Fig. 9). The redox routes of both cannabinoids were similar based on their functional groups however the location of the reaction was of importance which would determine the outcome of chemical reactions; spoilage through oxidation in storage to aromatization stability of CBN or CBND or reductions

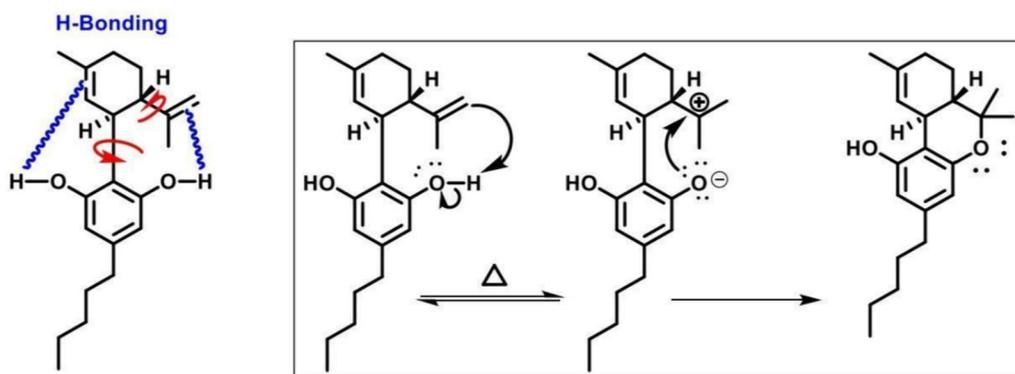


Fig. 9 Proposed mechanism for the intermolecular isomerization of CBD to Δ^9 -THC

via conversion of THC to higher energies of CBN comparative to CBND, or metabolism in the animal body as reduction.

Where the reduction for CBD can occur as an intramolecular reaction converting to THC a different reduction can occur as metabolism in a mammalian body by the liver being more feasible and producing higher energies of thermodynamic parameters forming 7-OH-CBD to further metabolise to 7-COOH-CBD to deactivate the cannabinoid similar to THC of both isomers Δ^8 and Δ^9 -THC. Oxidising the cannabinoids after reductive hydroxy intermediate formation through peroxide intermediates, enzymatic catalysis in the liver by the cytochrome P450 has the ability to further increase the rate routes of both cannabinoids metabolism to the carboxylic acids (Harvey and Brown 1991) from peroxides display a similar functional activities producing similar energetic parameters of pharmacokinetics.

The problem of intramolecular conversion of CBD was observed in storage of CBD in sunflower oil resulting in detection of CBN in most samples however THC was not detected due to possible limitations. In addition, several

oxidation products of CBD eluted at various retention times in partially degraded samples (Kosović et al. 2021). The oxidative degradation of both samples in oil and as powder is reflected in the functionality of CBN and of CBND having longer elution times being more aromatic with a stronger affinity with the non polar stationary phase. Where majority of the cannabinoids underwent protic conversion in sunflower oil via THC intermediate compared to relatively smaller concentrations and energies of CBND formation represented by Fig. 10. As CBD reduces to THC it is well understood that THC oxidises to CBN as proposed by Turner and Elsohly.

A pathway for the oxidation of Δ^9 -THC proposed by Turner and Elsohly using water and oxygen as reactants and product making CBN implies the cannabinoid as a lipid is undergoing oxidation with motifs of water in oxygen oxidation and proton reduction making water for free energy potential gains (Turner and Elsohly 1979). The mechanism in the proposal applied a quantized thermochemical mechanism to determine the electrochemical redox driven by the hydroxyl potential of water similarly as proposed by Turner (Fig. 11).

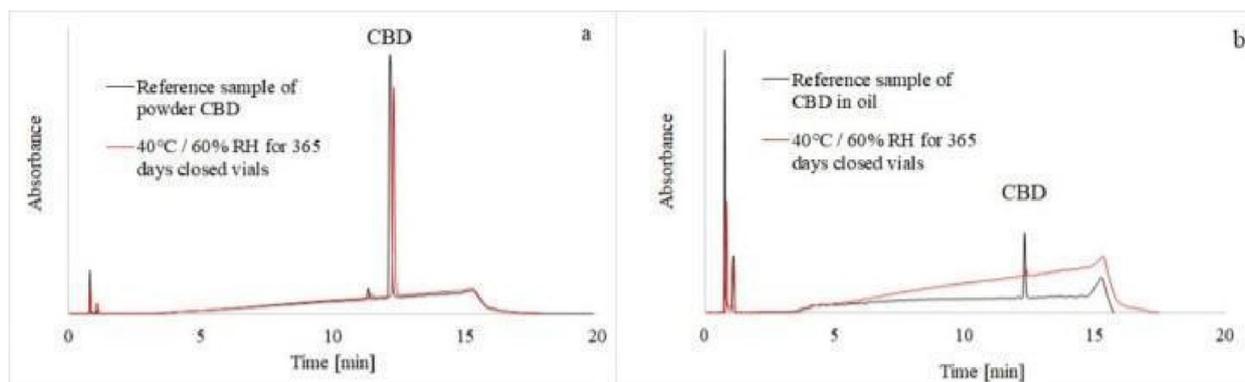


Fig. 10 HPLC-UV chromatograms of CBD reference samples (black line) and CBD samples stored for 365 days (red line) in the stability chambers. The CBD powder was measured at 225 nm (a) and the CBD oil solution at 210 nm (b)

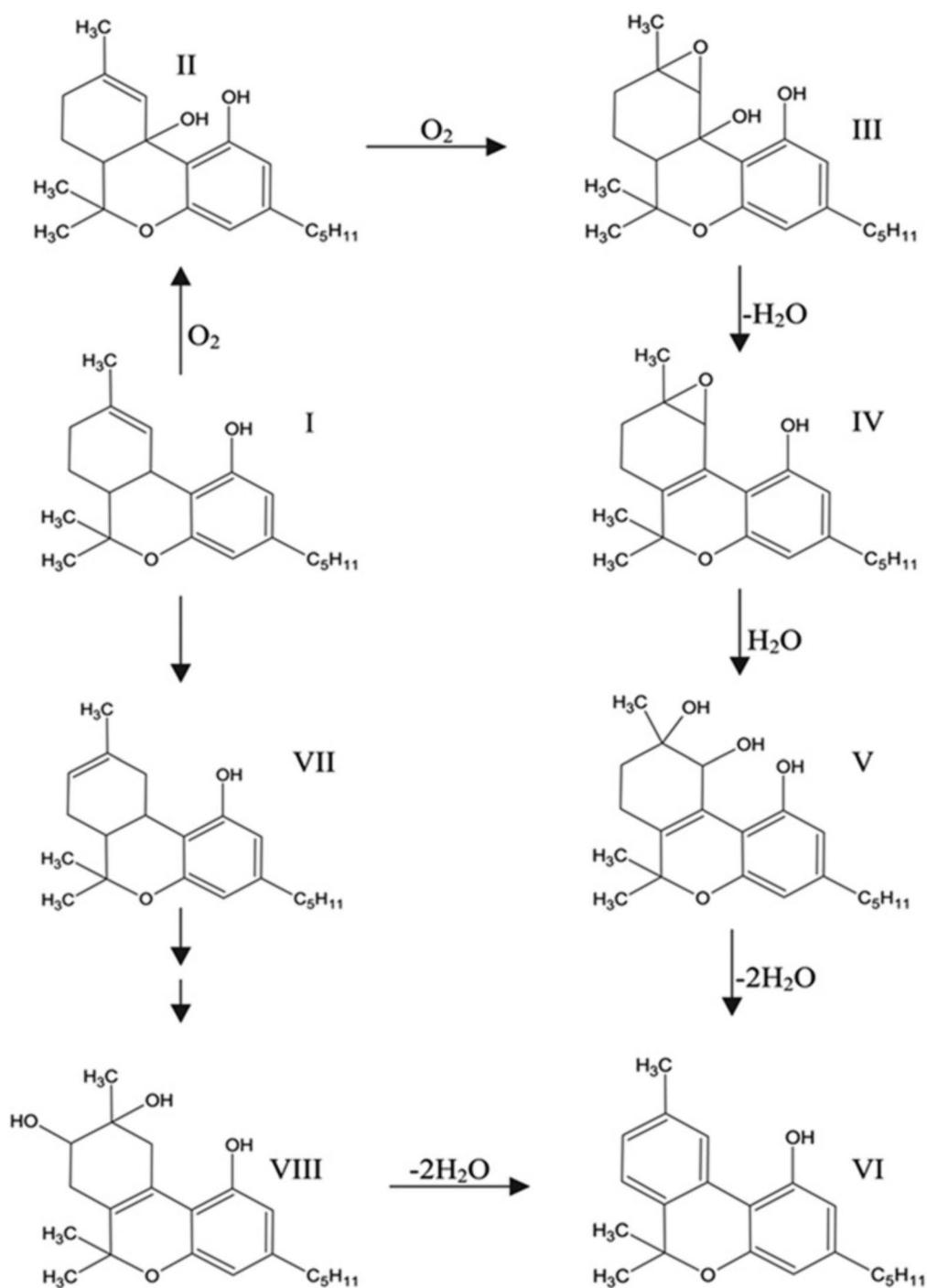


Fig. 11 Proposed Pathway for Decomposition of THC (I) to Its Primary Degradant, Cannabinol (VI). (Adapted by Turner & ElSohly, 1979)

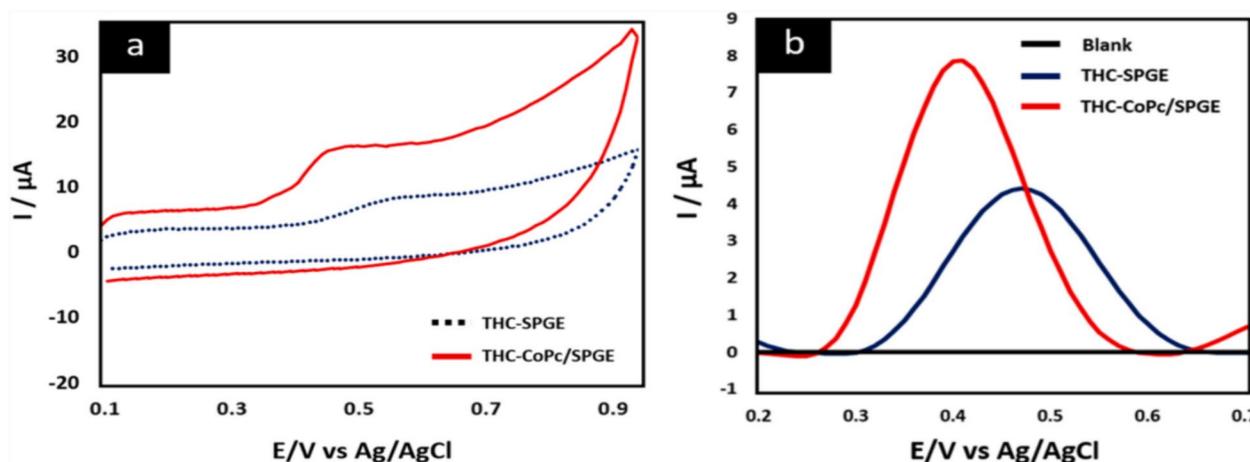


Fig. 12 CVs and DPVs of 500 µg/mL THC in 0.1 M PBS buffer pH 7 at SPGE (blue line) and CoPc/SPGE (red line) on cPED. Buffer of 0.1 M PBS at pH 7 was measured using CoPc/SPGE (black line) as blank signal

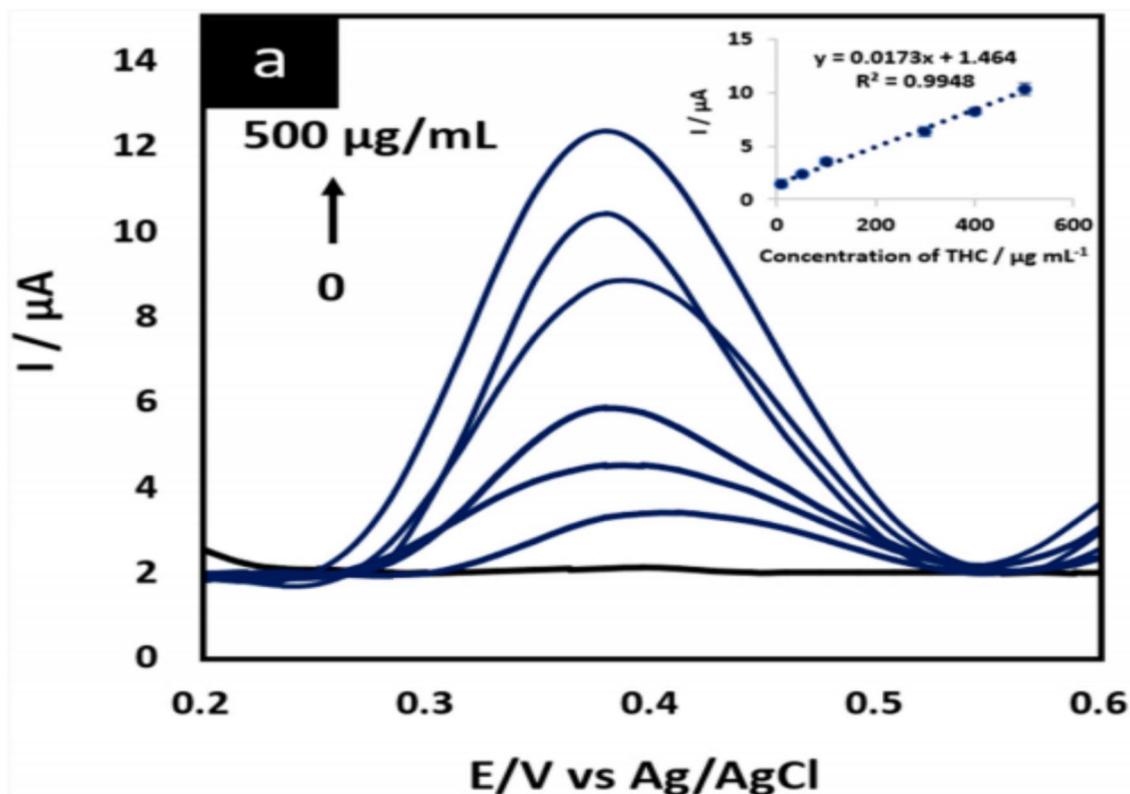


Fig. 13 DPVs of THC (a) at a CoPc/SPGE in 0.1 M PBS pH 7 using cPED device at concentrations between 10 and 500 µg/mL. Inset: linear relationship of current signals vs. THC concentration. Experiment conditions: -0.5 V vs. Ag/AgCl preconditioning potential, 15-s preconditioning time, 0.2 – 0.6 V vs. Ag/AgCl in the working range for THC determination

Pholsiri. T et al. had designed a chromatography paper-based electrochemical device as a means to electrochemically detect a chemical change through the use of a chemical sensor and actuator, to detect the chemical oxidation of THC. Where experimental values were

detected by Pholsiri. T et al. in a buffer of pH 7 at equilibrium and a value of +18 mV was detected in a 2 s phase pulse for THC in a chemical cell (Pholsiri, et al. 2022) represented in Figs. 12 and 13 the theoretical quantised value was calculated as +10.565 mV as the oxidation

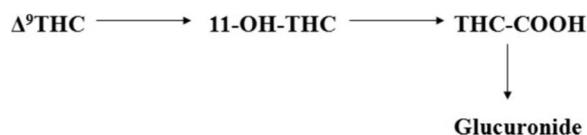


Fig. 14 Metabolic route of -tetrahydrocannabinol ($\Delta^9\text{-THC}$), its primary active metabolite 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) and the primary inactive metabolite, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol(THC-COOH)

formation of CBN using standard bond enthalpy data from Elements of Physical Chemistry.

The degradation activation energies of resin cannabinoids CBD and $\Delta^9\text{-THC}$ were 3.86 kJmol^{-1} and 11.63 kJmol^{-1} respectively with degradation orders of zero and pseudo first orders respectively [(Jaidee et al. 2021)]. From mechanistic extensive change activation energies were $5.73216 \text{ kJmol}^{-1}$ and 7.167 kJmol^{-1} $\Delta^9\text{-THC}$ from CBD and to CBN respectively, the parameter of intramolecular conversion were found to be within of each other as physical and theoretical values however CBN formation activation energies observed from Jaidee W. et al. were derived from increase in temperatures and different mass samples being smaller comparative to standard conditions which inturns influence the functions of energies as thermodynamic functions. It was observed that energies required for degradation were within the energies of formation suggesting the energies of oxidation were easily accessible to provide free energy releasing protons forming water. As a result of the freely feasible thermodynamic nature of conversion of CBD to $\Delta^9\text{-THC}$ it was found that consumer products with active ingredients of CBD had contamination of $\Delta^9\text{-THC}$ a psychotropic (Seccamani et al. 2021), the nature of C11 as an intermediate between 11-OH-THC, $\Delta^9\text{-THC}$ and $\Delta^8\text{-THC}$ isomerization proton catalysis in water driving stability of equilibriums the pH would be the determinant of the cannabinoids relative formations as chemical reduction. A proposed pathway of the deactivation of THC to nor-carboxy THC along with the final detectable metabolite (Sharma et al. 2012) (Fig. 14).

Conclusion

Preservation of cannabinoids from oxidation can be synthesised by deactivation of the acidic proton of the phenol selectively with base as means of conversion to prevent the free energy change of spoilage and to prevent the conversion of non psychotropic CBD to $\Delta^9\text{-THC}$ contamination. Metabolites from the consumption of cannabis follow the pharmacokinetic route both theoretically and from bioassays presented as clinical trials.

Abbreviations

THC	Tetrahydrocannabinol
CBD	Cannabidiol
CBN	Cannabinol
CBND	Cannabinodiol
11-OH-THC	11-Hydroxy tetrahydrocannabinol
11-nor-carboxy-THC	11-Nor-carboxy tetrahydrocannabinol
COOH	Organic acid functional group
G	Gibbs free energy
S	Entropy
H	Enthalpy
mV	Millivolt
K	Equilibrium constant
n	Number of mols
F	Faraday constant
R	Gas constant
T	Temperature
k	Rate constant
k	Boltzman constant
h	Planck constant
e	Euler number
E	Energy
HPLC	High pressure liquid chromatography
UV	Ultraviolet
MS	Mass spectrometry

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Authors' contributions

The corresponding author is the sole contributor of the manuscript.

Author's information

The corresponding author is affiliated with the University of the West Indies through academic enrollment and however did not complete the process. Mobile contact: 876-476-8728.

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Availability of data and materials

Standard data had been provided by the elements of Physical Chemistry, Atkins 3rd edition in regards to bond energy data.

Declarations

Ethics approval and consent to participate

N/A

Consent for publication

N/A.

Competing interests

The corresponding author currently does not hold an academic qualification from a tertiary institution (University of the West Indies).

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