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ORIGINAL RESEARCH

Re-Examining Cannabidiol: Conversion to Tetrahydrocannabinol Using Only Heat

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Abstract

Introduction: In the last decade, the market for Cannabidiol (CBD) has grown to become a near $2 billion dollar industry in the United States alone. This growth can be attributed to a growing social acceptance of marijuana, a more detailed understanding of many health benefits attributed to cannabinoids, and the low cost and wide availibility of hemp-derived cannabinoids. Due to the complex legal histories of marijuana and cannabinoids, the stability and safety of CBD is still an area of interest as research has been restricted globally. Conversion of CBD to its psychoactive isomers, most notably delta-9-Tetrahydrocannabinol (Δ9-THC), presents a significant safety issue for consumers and producers of CBD products.

Methods: Previous studies investigating the stability of CBD have focused mainly on replicating conditions experienced during long-term storage at room temperature or lower. Here, we report the thermal stability of CBD at 175°C. Dynamic ^{1}H-NMR experiments and computational electronic structure calculations were used to characterize possible reaction paths from CBD to THC.

Results: After 30 minutes of heating, Δ9-THC was produced in detectable amounts in aerobic and anaerobic conditions without an acid catalyst.

Conclusions: Our findings support an energetically feasible reaction route that is favorable due to both an increase in phenol acidity at high temperatures and the presence of intramolecular OH-π hydrogen bonding.

Keywords: cannabidiol; tetrahydrocannabinol; intramolecular conversion; DFT; dynamic NMR; E-cigarette

Introduction

Cannabis Sativa, marijuana, has been used medicinally and recreationally for centuries.[1] Its effects have been attributed to >100 naturally occurring chemical compounds found within the plant, known as cannabinoids. For the past several decades, marijuana has been and remains illegal in most countries, as its use induces intoxicating psychoactive effects. Recently, however, countries around the world including the United States and Canada have begun to legalize marijuana in various degrees, allowing for the research and production of cannabis products to expand tremendously.

Δ9-Tetrahydrocannabinol (Δ9-THC), the main pharmacologically active component of the cannabis plant, is responsible for many of the clinical effects associated with marijuana, both beneficial and intoxicating.[2] Some trace cannabinoids, including Δ8-tetrahydrocannabinol (Δ8-THC) and tetrahydrocannabivarin (THCV), have been shown to induce similar intoxicating effects; however, their low natural abundance has caused them to be largely ignored.[3–6] Cannabidiol (CBD), a well-studied cannabinoid, has been shown to therapeutically benefit conditions, including anxiety, neuropathic pain, and epilepsy.[7,8]

Combined with a lack of psychoactive response, the benefits of CBD have made it the major focus of recent studies and caused a high demand for products containing CBD.[9,10] In 2018, the United States legalized the cultivation and use of the hemp,[11] a marijuana plant containing <0.3% Δ9-THC by dry weight and up to 18% CBD,[12] resulting in a flood of goods containing "hemp-derived" CBD. The rise in popularity and increased availability of CBD-containing products

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worldwide have caused much debate about the safety and stability of CBD. While several research trials have shown CBD to resist conversion to THC *in vivo*,[13] it is well known that both Δ8-THC and Δ9-THC can be synthesized under acidic conditions.[14,15]

Recent studies have been conducted on the stability of CBD as a powder, in extracts, and as a plant material. Trofin et al. reported a decrease in the concentration of CBD and Δ9-THC in cannabis oil when stored over 4 years, while the concentration of cannabinol (CBN) increased over the same time.[16] A more pronounced increase of CBN was observed for samples maintained at 22°C than those maintained at 4°C. They postulated a biochemical cyclization of CBD to Δ9-THC, followed by further oxidation of Δ9-THC to CBN.

A similar study from Kosović and coworkers found substantial degradation of CBD as a powder and dissolved in a solution of sunflower oil over a period of 1 year.[17] Powder samples, heated at 25°C and 40°C, showed ∼10% concentration loss after 1 year, while samples dissolved in oil had significantly higher concentration loss, 40–100%, depending on storage conditions. CBN was identified as a degradation product; however, they did not detect any Δ9-THC.

Citti et al. performed accelerated stability testing of CBD. They monitored the formation of both Δ8-THC and Δ9-THC as a function of temperature and humidity, showing an increase in total THC concentration of samples heated to 50°C at 75% humidity. The amount of THC detected at the same temperature with 55% humidity was slightly lower; however, when heated to 60°C at 25% humidity the total amount of THC peaked above the total concentration of the other samples before degrading, which implies further chemical reactions.

Unfortunately, degradation products of the accelerated stability experiments were not identified in this report due to the complexity of the acquired chromatograms.[18] The stability of cannabinoids in dry cannabis plant material was also investigated by Meija et al. Their results showed an overall decrease in concentrations of THC and CBD, with an increase in the concentration of CBN when heated at 40°C for a period of 1 year.[19]

Based on these reports, the stability of CBD depends on a variety of conditions, including light exposure, storage temperature, and the physical state of CBD. In each study, higher temperatures resulted in an increased CBD degradation. The tendency of CBD to isomerize could be the cause of inaccurate labeling of many CBD-containing products on the market and presents a potential hazard for consumers.[20–23]

An underexplored aspect of CBD stability is the potential for conversion of CBD when heated at elevated temperatures that are typical of e-cigarettes and baking. In this work, we examine the thermal stability of CBD at 175°C to reflect these conditions. Based on our experimental and computational results, we present a thermodynamically feasible route for the conversion of CBD to THC caused by the presence of intramolecular OH-π hydrogen bonds and aided by the increase in phenol acidity with an increase in temperature.

A simple heating procedure produced detectable amounts of Δ9-THC from CBD after ∼30 min in both aerobic and anaerobic conditions, without the need of any additional reagents or acid catalysts. Our results bring questions to the safety and risk of tampering for products containing CBD, especially those with high concentrations, including vape liquids, hemp extracts, and cannabinoid isolates.

Materials and Methods

Materials

CBD was purchased from EcoGen BioSciences and used as received. All other chemicals were purchased from Sigma-Aldrich and used as received. ^{1}H-NMR was collected using a Bruker Avance 500 MHZ instrument.[13] C-NMR was collected using a Bruker Avance 500 (126 MHz carbon monitoring) instrument. Ultra performance liquid chromatography (UPLC) analysis was conducted using a Waters Acquity UPLC-triple-quadrupole mass spectrometer with a photo diode array detector and a standard 90:10 Acetonitrile: Water AmF/FA mobile phase.

Dynamic NMR

NMR samples of CBD at concentrations of 1 mg/mL were prepared using either $CDCl_3$ or CD_3OD. Spectra were collected at temperatures ranging from 230 to 320 K in 10 K increments. On approaching the coalescence temperature, as indicated by peak flattening, spectra were collected in finer temperature increments. The probe temperature was allowed to stabilize for 30 min between each temperature change.

Lineshape analysis

After collecting the variable temperature data, more precise analysis was done using the dnmr package included in TopSpin 4.1.3. First, a method was developed to best fit the line signal by manually identifying two distinct signals with exchanging protons, in this case the aromatic hydrogens of CBD. After developing the

method, 10,000 simulations were modeled against each spectrum to predict an energy minimum and exchange rate for that temperature. Those exchange rates were plotted against the temperature to produce the Eyring plot.

Thermal stability experiments

Samples of 100 mg of CBD were weighed into 50 mL round bottom flasks. The flasks were stoppered and heated for 30 min at 175°C in a laboratory convection oven. Samples heated under argon were first subjected to 10 freeze pump thaw cycles in which the samples were chilled using liquid nitrogen and allowed to warm slowly under vacuum. Between each cycle, the samples were backflushed with argon to thoroughly exchange the atmosphere within the flask. The flasks were filled with dry argon before being heated.

Results

The thermal stability of CBD was examined by heating samples of CBD isolate at 175°C for 30 min under ambient air and argon atmosphere. After heating, the residues were initially analyzed using ^{1}H-NMR, which showed the appearance of new proton signals between 3.2 and 3.5 ppm with splitting patterns similar to those found in THC, Figure 1.[24] Further analysis using UPLC revealed detectable levels of Δ9-THC in the samples heated under argon when compared with a standard solution of several cannabinoids, Supplementary Figure S1a and b.

Our results contradict the findings of Citti et al. who reported a lack of Δ9-THC when heated in an inert atmosphere, which they attributed to the removal of water and carbon dioxide from the samples preventing the formation of carbonic acid.[18] It is important to note that the temperatures used in their studies were below the melting point of CBD, which could have limited the reactivity of the system.

A more recent study characterizing by-products formed by CBD e-cigarettes was conducted by Czegeny et al. showing significant amounts of THC production when heated under both oxidative and inert conditions at high temperatures, directly supporting our results.[25] In direct response to this work, Hindelang et al. have

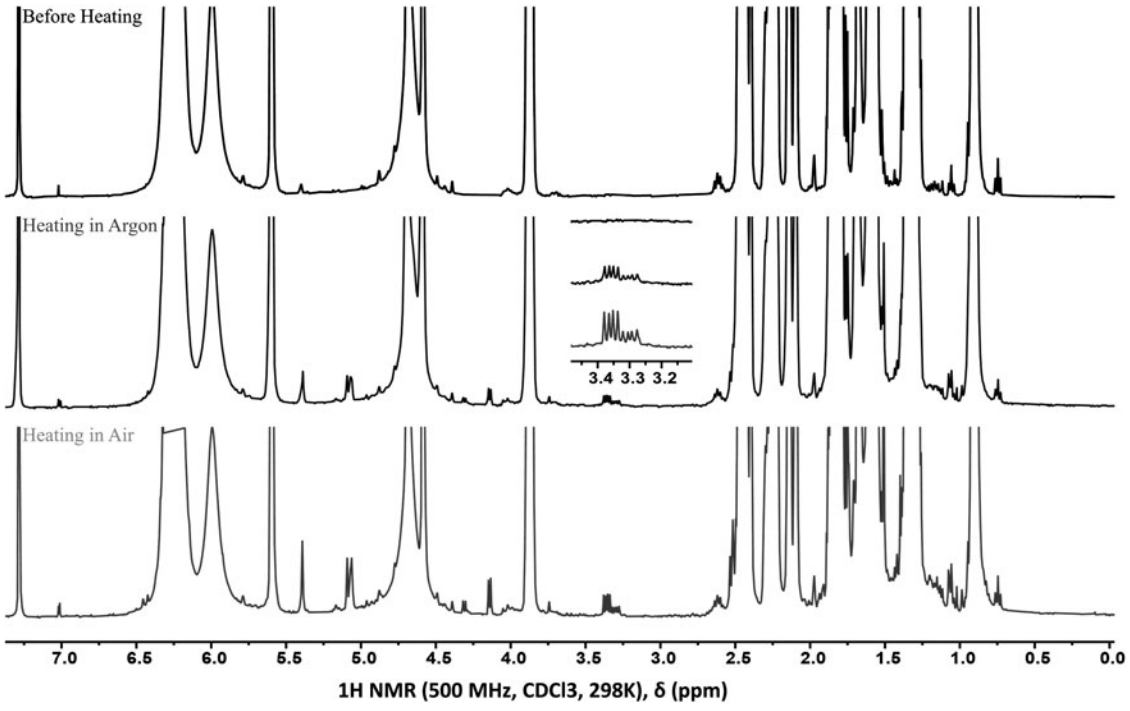

FIG. 1. ^{1}H-NMR analysis of CBD residue heated at 175°C for 30 min under an atmosphere of air and argon. CBD, cannabidiol.

published work refuting that of Czegeny, showing no detectable amounts of THC formed after vaporization of e-liquids.[26]

While investigating literature precedence for the intramolecular cyclization of cannabinoids, a spectral phenomenon in the ^{1}H-NMR peak signals of CBD's aromatic hydrogens was observed. At about room temperature (295 K), the aromatic hydrogen peak of CBD separates into a broad doublet, as shown in Figure 2A. This peak splitting was reported by Mechoulam et al. to be temperature dependent, converging to one peak at ~298 K, and attributed to a restricted rotation of the cyclohexene ring.[27]

The splitting was further explored by Choi et al, who suggested the restricted rotation to be caused by intermolecular hydrogen bonding, which they supported by using deuterated methanol to remove the splitting.[24] To better understand the thermally restricted rotation, a series of ^{1}H-NMR were collected for CBD at temperatures ranging from 230 to 320 K, Figure 2B, and analyzed using the Eyring equation, which can be written as follows[28]:

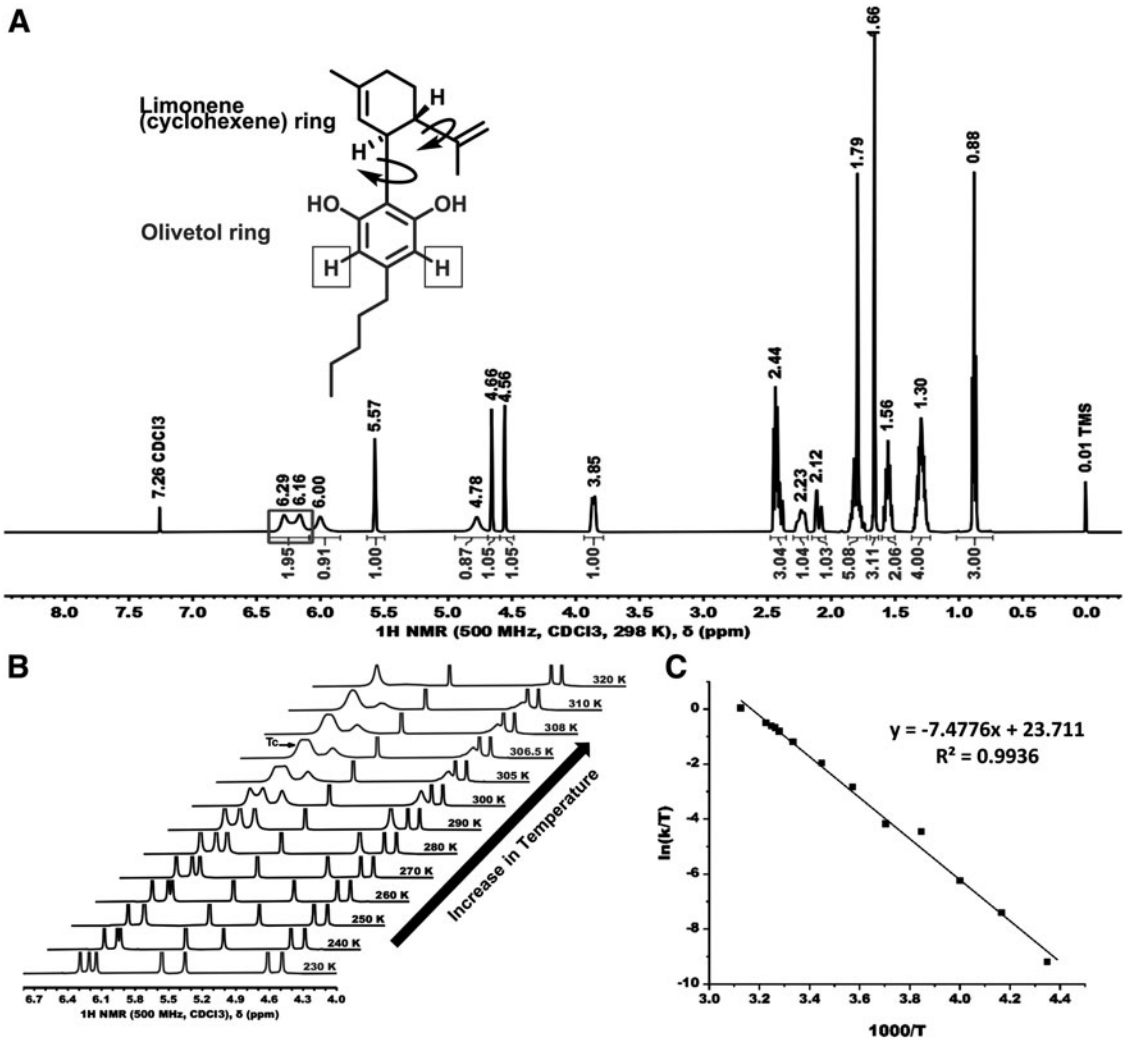

FIG. 2. **(A)** ^{1}H-NMR (R.T.) of CBD showing the splitting of highlighted aromatic protons caused by the restricted rotation of limonene. **(B)** Temperature dependence of the NMR lineshape of the aromatic protons in CBD, coalescence temperature (T_c = 306.5 K), Supplementary Figure S2. **(C)** Eyring plot of exchange rates versus temperature derived from DNMR lineshape analysis Topspin 4.1.3 software.

$$k_e = \frac{k_B T}{h} \exp(-\frac{\Delta G^{\ddagger}}{RT}), \quad (1)$$

$$\ln\left(\frac{k_e}{T}\right) = \ln\left(\frac{k_B}{h}\right) - \frac{\Delta G^{\ddagger}}{RT}, \quad (2)$$

where k_B is Boltzmann's constant, h is Plank's constant, and R is the gas constant. The Eyring equation describes chemical exchanges within molecular systems passing through a transition state at temperature, T, with a defined kinetic barrier, $\Delta G^{\ddagger}$, such as rotation.[29]

Experimentally, $\Delta G^{\ddagger}$ is estimated by collecting spectra for the compound of interest at various temperatures to determine a coalescence temperature where two separate peaks become a single flat-topped peak.[30] As discussed by Bain, the rate of exchange at the temperature of coalescence ($k_c = k_e$) can be calculated using the following equation[31]:

$$k_c = \frac{\pi(\Delta v)}{\sqrt{2}}, \quad (3)$$

where Δv represents the difference in Larmor frequencies of the two exchanging protons.

The Gibbs free energy of rotation was determined by plugging the exchange rate calculated from Equation (3) and the temperature of coalescence, determined experimentally, into Equation (1). Using this method, the coalescence temperature for CBD in deuterated chloroform was identified experimentally at 306.5 K, resulting in a $\Delta G^{\ddagger}$ of 14.88 kcal/mol.

A more detailed analysis was conducted using the Dynamic NMR (DNMR) lineshape analysis feature included with Topspin 4.1.3, which predicted exchange rates at each temperature by simulation. A linear Eyring plot was then generated using Equation (2) by plotting $ln\left(\frac{k_e}{T}\right)$ *vs* $\frac{1}{T}$, Figure 2C. Using this method, $\Delta G^{\ddagger}$ was determined to be 14.89 kcal/mol, which is in excellent agreement with the experimental coalescence temperature method.

Variable temperature ^{1}H-NMR measurements were repeated for CBD in deuterated methanol, Supplementary Figures S3 and S4. While the aromatic hydrogen peak presented as a singlet at room temperature (295 K), peak splitting of the aromatic hydrogens was observed < 245 K. If the restricted rotation of the cyclohexene was dependent solely on intermolecular hydrogen bonds between CBD units, a small protic solvent should have eliminated any observed splitting due to hydrogen bonding with the solvent. Additional NMR spectra are included in the Supplementary Figures (S5–S11) and used to determine purity and assign peak positions.

In addition, samples used for this study were prepared at the low concentration of 1 mg/mL (3.2 mmol) CBD to further reduce intermolecular H-bonding between CBD molecules. We can therefore hypothesize that the restricted rotation of the cyclohexene ring of CBD is caused by intramolecular OH-π hydrogen bonding between the phenolic hydrogens and at least one alkene within CBD. This hypothesis is confirmed by electronic structure calculations (*vide infra*) and supported by the work of Denhez et al.[32]

Figure 3 shows the proposed mechanism of this reaction, which is further substantiated by the work of

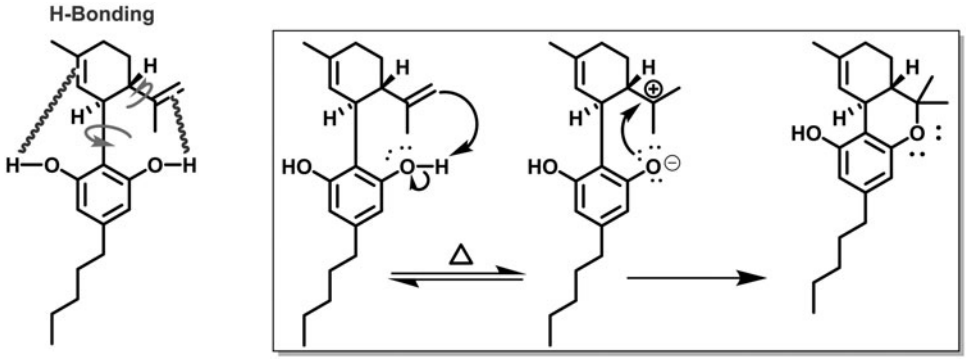

FIG. 3. Proposed mechanism for the intramolecular isomerization of CBD to Δ9-THC. Δ9-THC, delta-9-tetrahydrocannabinol.

Geresh et al. who systematically explored the mechanism of cyclization of substituted allylphenolic compounds to cyclic ethers when irradiated with light. Their study confirmed the presence of intramolecular H-bonds in these systems by monitoring a change in the chemical shift of the hydroxyl hydrogens. The cyclization of their compounds was attributed to a drastic increase in the acidity (*ca.* $10^6\times$increase) of phenolic compounds upon excitation to singlet or triplet excited states using light.[33–35]

Similar excitation is known to happen at high temperatures.[36] The increase of phenolic acidity would reduce the pKa of CBD below a value of 6, making it comparable in strength with carbonic acid, which was suggested by Citti et al. to catalyze the cyclization.[18] More recently, intramolecular cyclization of alkenophenolic compounds has been reported using copper and silver catalysts,[37] as well as the cyclization of flavonoids using light.[38] It is therefore likely that CBD undergoes cyclization to THC that is favorable due to both an intramolecular OH-π hydrogen bond, which holds the reacting species near each other, and an increased acidity of the phenolic hydrogen when heated.

Given the observation that CBD intrinsically isomerizes to THC at elevated temperatures, theoretical characterization of possible reaction paths from CBD to THC was done through electronic structure calculations. The structure of CBD was obtained from the Cambridge Crystallographic Data Bank (CCDC No. 1533487).[39] To reduce the conformational search space and make the electronic structure calculations more tractable, the n-pentyl group of CBD was truncated.

The truncated equivalent of CBD was expected to present an equivalent ranking of conformational energies within the manifold of rotatable bonds connecting the cyclohexene with the resorcinol and with the propylene group. Given this initial structure, a conformational search was performed with Macromodel[40] using the force field Oplsa3e,[41] and the lowest energy conformers were selected within a range of 5 kcal/mol from the global minimum.

These conformers were then resorted using density functional theory (DFT) at the B3LYP-D3/6–31g** theory level with implicit solvent. Solvation was treated within the conductor-like polarizable continuum model with ethanol selected to mimic the dielectric effect of CBD. While in the liquid phase, CBD is likely to stabilize charged intermediates in a similar manner to ethanol, as they are both polar protic solvents. All quantum chemistry calculations were performed with Jaguar within the Schrodinger Suite.[42,43]

Figure 4A shows the two lowest energy conformers (**1** and **2**) according to the DFT ranking. Conformers **1** and **2** are equal in energy, and differ only in the rotation of the propylene group. Most notably, they present an OH-π hydrogen bond. In **1**, there are two such H-bonds, the strongest of which is between the OH and the double bond of hexene.

The distance between the hydrogen (in OH) and the nearest sp2 carbon is 2.04 Å in both **1** and **2**. For the weaker H-bond, this distance is 2.29 Å. As the resorcinol group rotates around the dihedral angle φ, it encounters a local minimum (**3**) 8.1 kcal/mol higher in energy. This conformer presents an H-bond with the sp2 carbon of the propylene group and can potentially form a carbocation by proton transfer from the proximal OH. The transition state ($\mathbf{7}^{\dagger}$) for such proton transfer is 43.8 kcal/mol higher than **3**.

Interestingly, as the proton is placed on the sp2 carbon to form the carbocation, the DFT energy optimization spontaneously generates ring closure, forming isomer **6**, which is the truncated model of THC. The thin black tube overlay in Figure 4A, placed on top of **6**, corresponds to the structure of Δ9-THC deposited in PubChem (CID 2978). A similar set of calculations was repeated starting now from **1**; that is, a transition state ($\mathbf{4}^{\dagger}$) was calculated by transferring the proton of the OH toward the nearest sp2 carbon. This transition state is 35.2 kcal/mol higher than **1**.

Again, after placing the proton on the sp2 carbon to form the corresponding carbocation, ring closure is formed spontaneously during the optimization. This new isomer (**5**) is $\sim$1.3 kcal/mol higher in energy than **6**. It should be noted that **5** and **6** can easily interconvert by changes in ring conformation at room temperature or higher. An estimate of the time scale of these reactions can be obtained by calculating the half-life of the reactions ($t_{1/2}=0.693/k$) and the rate constant (k) according to transition state theory, where $k=(k_BT/h)\exp(-E^{\dagger}/k_BT)$, where $E^{\dagger}$ is the activation energy.

To obtain an estimate of the rate constant, $E^{\dagger}$ was approximated by the difference in the electronic ground state energy between a minimum and transition state. With the activation energy of 35.2 kcal/mol, the half-life was estimated to be $t_{1/2}\sim 3$ h at $T=175$°C (448.2 K), in line with the experimental findings. On the contrary, at room temperature $t_{1/2}$ would be $\sim$230,000 years. The path involving the higher transition state (43.8 kcal/mol) corresponds to a $t_{1/2}\sim 5$ years at $T=175$°C, although at higher temperatures (e.g., a temperature of 230°C), $t_{1/2}\sim 159$ h. Thus,

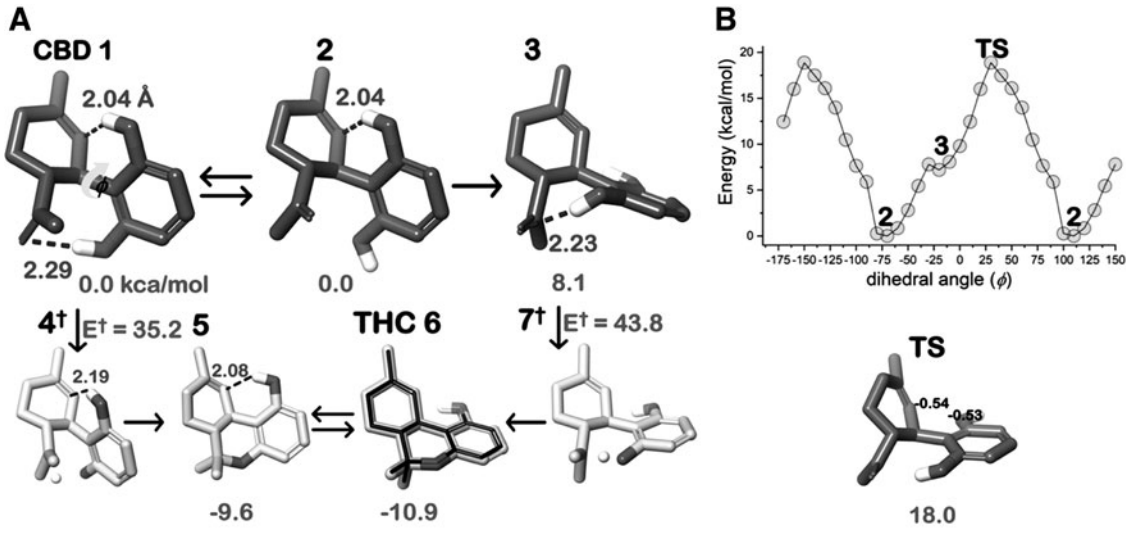

FIG. 4. **(A)** Isomers along the transformation between **1** and **6**, which represents models of CBD and Δ9-THC, respectively. H-bond distances are shown near their respective bonds, values in energies of stable states are shown beneath their respective structures, and values in transition state energies are marked as $E^{\dagger}$. The thin tube overlay on top of isomer **6** corresponds to the structure of Δ9-THC deposited in PubChem (CID 2978). **(B)** Relaxed energy scan along the dihedral angle ϕ connecting **2** with **4** and back to **2**. The transition state along this path is also depicted and includes ESP charges that are critical to the destabilization of this conformation. Structures $\mathbf{4}^{\dagger}$ and $\mathbf{7}^{\dagger}$ represent transition states for each respective pathway. ESP, electrostatic potential.

while at room temperature no transformation from CBD to THC is expected, such reaction is clearly feasible at higher temperatures, likely through the path **1** > $\mathbf{4}^{\dagger}$ > **5** > **6**.

Figure 4B shows a relaxed energy scan rotating ϕ from **2** to **3** and back to **2**. To make results comparable with the NMR experiments, which determined the coalescent temperature and the energy barrier, this energy scan was performed with chloroform as the implicit solvent. The transition state along this rotation is 18 kcal/mol higher than **2**, in good agreement with the estimated barrier obtained by exchange rate NMR experiments with the same solvent. This transition state is destabilized by an electrostatic repulsion between the oxygen atom ($q = -0.53e$) and the nearest sp2 carbon of the cyclohexene double bond ($q = -0.54e$). These charges were obtained through an Electrostatic Potential fitting scheme.

Conclusions

Investigation of the thermal stability of CBD has revealed a feasible path for its conversion to THC without the presence of an external acid. After heating for 30 min at 175°C in an inert atmosphere of argon, Δ9-THC was detected by ^{1}H-NMR and UPLC. Electronic structure calculations further support these results. Our findings present a safety concern for dozens of CBD-containing products, especially those sold with high concentrations such as vape liquids, hemp extracts, and cannabinoid isolates.

Simply heating CBD can produce observable levels of THC whether intentional or unintentional. Producers, consumers, and law makers should be aware of possible means by which these products may be tampered when deciding how they should be regulated and stored. As CBD becomes more widely available, it is not unreasonable to imagine people obtaining and heating these products to produce high concentrations of THC. Preventing the isomerization of CBD to THC, using preservatives or chemical modification, could greatly increase the safety and efficacy of CBD-containing products.

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Authors' Contributions

R.D. contributed to conceptualization, methodology, investigation, formal analysis, validation, writing—original draft/review and editing, visualization; O.A.Y. performed investigation and formal analysis; J.M.T. carried out writing—review and editing, validation; J.A.G. contributed to conceptualization, methodology, investigation, formal analysis, writing—review and editing; G.S. assisted with conceptualization, supervision, and writing—review and editing.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4
Supplementary Figure S5
Supplementary Figure S6
Supplementary Figure S7
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Supplementary Figure S11

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Abbreviations Used

Δ8-THC = Δ8-tetrahydrocannabinol
Δ9-THC = delta-9-tetrahydrocannabinol
CBD = cannabidiol
CBN = cannabinol
DNMR = dynamic NMR
THCV = tetrahydrocannabivarin
DFT = density functional theory
ESP = electrostatic potential