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Cannabinoid Decarboxylation: A Comparative Kinetic Study

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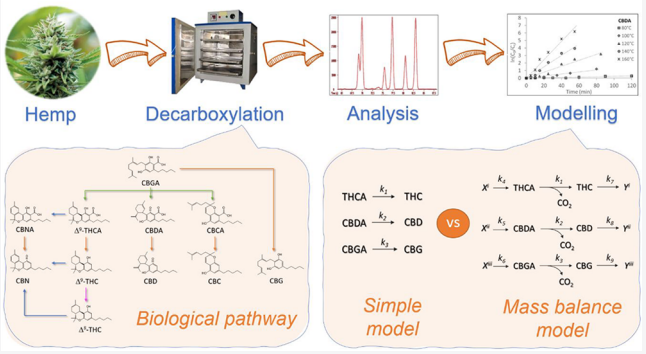
ABSTRACT: Cannabinoids like Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG) are considered the main active components in *Cannabis sativa* L. and are obtained through the decarboxylation of their acid analogues (THCA, CBDA, and CBGA), which are the forms naturally present in the plant. The kinetics of this reaction were studied for hemp plant material in an oven at different temperatures (80−160 °C) and reaction times (5−120 min). The effect of oxygen and the amount of plant material on the reaction rate was also studied. The reactions follow first-order kinetics, with THCA showing the fastest decarboxylation rate. In all cases, a significant loss of neutral cannabinoids was observed at elevated temperatures and reaction times, although this can be minimized in the absence of oxygen. Two different kinetic models were used to fit the experimental data and to predict the optimum decarboxylation conditions to maximize THC or CBD concentration.



INTRODUCTION

Cannabis sativa L. is an ancient crop that has recently gained much international attention due to the increasing demand for phytocannabinoids for therapeutic use. Of the more than 100 phytocannabinoids identified in the plant, only a handful have been researched in varying degrees of detail.[1−4] Of these, psychoactive Δ^9-tetrahydrocannabinol (Δ^9-THC or THC) and nonpsychoactive cannabidiol (CBD) are the most prevalent in the plant and therefore have traditionally attracted the most interest. THC can interact with cannabinoid receptors 1 (CB_1) and 2 (CB_2) in the human endocannabinoid system and has a number of known pharmacological properties (modulation of pain, spasticity, sedation, appetite, and mood; bronchodilator; neuroprotective antioxidant and anti-inflammatory);[2] however, its psychoactive effects greatly restrict access to this substance. CBD, on the other hand, has no psychoactive activity and offers a plethora of interesting neuroprotective properties such as antioxidant, anti-inflammatory, anticonvulsant, and antipsychotic.[2,3] It has a very low affinity for CB receptors but is believed to have significant CB_1- and CB_2-independent mechanisms of action. Cannabigerol (CBG) is a relatively unknown nonpsychoactive phytocannabinoid with analgesic, antiproliferative, and antibacterial activity as well as anticancer properties (in basic research models) and the ability to relieve intraocular pressure.[2] It is gaining traction as a potential candidate for the treatment of glaucoma, inflammatory bowel disease, and colon cancer.[3] CBG is normally a relatively minor component, but certain *cannabis* chemotypes have been developed to express 100% of their cannabinoid content as CBG.[2] Cannabinol (CBN) is a relatively minor constituent in fresh plant material, as it is an oxidation product of THC.[4] CBN content increases as THC degrades during storage and is usually considered a chemical marker for poor or lengthy storage conditions.[3,5] Other compounds, such as cannabichromene (CBC), Δ^8-tetrahydrocannabinol (Δ^8-THC, an isomer of Δ^9-THC), Δ^9-tetrahydrocannabivarin (Δ^9-THCV, the propyl homologue of Δ^9-THC), or cannabidivarin (CBDV, the propyl homologue of CBD) are considered minor components and are not studied in this work.

Interestingly, none of these phytocannabinoids occurs naturally in the *cannabis* plant at significant concentrations.[3,6] It is the carboxylic acid containing forms of these compounds, i.e. Δ^9-tetrahydrocannabinol acid (THCA), cannabidiol acid (CBDA), and cannabigerol acid (CBGA), that are biosynthesized and accumulated in the glandular trichomes of the plant. THCA and CBDA are biosynthesized from the common precursor CBGA through the action of unique oxidoreductases (THCA synthase and CBDA synthase, respectively), whereas CBGA itself is synthesized by the alkylation of olivetolic acid.[7] These acid forms undergo a nonenzymatic decarboxylation process in which the carboxyl group is lost to release carbon

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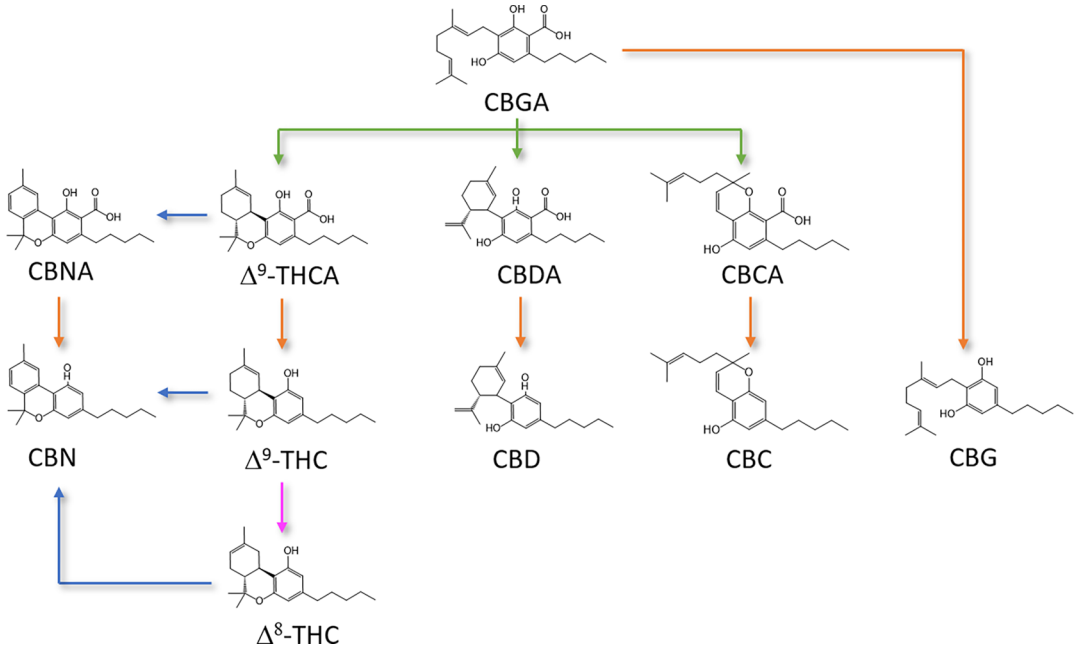
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

Scheme 1. Cannabinoid Synthetic Pathway: Decarboxylation (orange), Biosynthesis (green), Oxidation (blue), and Isomerization (pink)



dioxide (CO_2), and the neutral forms are produced in a solid-state reaction that is accelerated by environmental factors like temperature, light, and oxygen (Scheme 1).[3] Albeit much slower, decarboxylation also occurs naturally at room temperature, and storage time and conditions can, therefore, have an important impact on the cannabinoid composition found in the plant prior to extraction.[8]

Although specific pharmacological properties have been attributed to CBDA and THCA,[3] it is generally the neutral forms that are considered of therapeutic interest since they can more easily cross the blood−brain barrier.[2] Decarboxylation has, therefore, become a crucial step in the *cannabis* industry. *Cannabis* recreational users have traditionally achieved decarboxylation through smoking, vaping, or baking,[3] but as the therapeutic aspect of the plant gains popularity, the industry is developing multiple new products based on extracts. These new products target consumers who seek a medicine-like experience, away from the stigmas associated with recreational use. Industrially, the extraction of cannabinoids can be carried out using different solvents, but supercritical CO_2 ($scCO_2$) is one of the most commonly used due to its high affinity for cannabinoids, mild processing conditions, and lack of solvent residues in the extract.[9,10] The decarboxylation process can be performed either on the plant material prior to extraction or directly on the extracted oleoresin; however, the former is generally preferred as it offers two key advantages when coupled with a $scCO_2$ extraction: (i) moisture present in the plant is removed during decarboxylation, and (ii) cannabinoid acids are more polar than their neutral analogues, and therefore less soluble in $scCO_2$.[11] Despite the importance of the decarboxylation reaction to optimize extraction yield and ensure complete extraction of cannabinoids from the plant, very little data on its kinetics are publicly available.

The decarboxylation process was mentioned as early as 1970 by Kimura and Okamoto,[12] when they applied heat (110 °C) to different fractions of the *cannabis* plant to determine the distribution of THCA as a function of THC. Kanter et al.[13] described the decarboxylation process as a necessary step in the determination of THC by HPLC, and determined the optimum conditions to be at relatively high temperature (200 °C) and short reaction time (3 min). The first kinetic study was performed by Veress et al., who investigated the decarboxylation of THCA and CBDA on a glass surface as well as on different sorbent surfaces in an open oven and described it as a first-order reaction.[14] Perrotin-Brunel et al. studied the decarboxylation of THCA in *cannabis* plant material using a vacuum oven. They described it as a pseudo-first-order reaction catalyzed by short-chain organic acids present in the flowers.[15] Citti et al. studied the decarboxylation of CBDA in hemp seed oil in both open and closed reactors.[16] To the best of our knowledge, the only published study covering the decarboxylation of the three main cannabinoid acids (THCA, CBDA, and CBGA) was performed by Wang et al., who investigated the decarboxylation of cannabis extracts in a vacuum oven to obtain the correspondent first-order rate constants.[17] Although a less common occurrence, the decarboxylation process can be carried out on the extracted oleoresin instead of the plant material, and real-time monitoring of the reaction progress can be performed using IR spectroscopy in order to optimize the process.[18]

In this study, the effect of several parameters (i.e., temperature, time, presence of oxygen, and amount of plant material) on the decarboxylation of THCA, CBDA, and CBGA in hemp has been investigated. Reaction kinetics have been characterized using two different first-order models: a simple approach considering only the decarboxylation reaction itself, and a modification with a mass balance correction to account for the loss of cannabinoids observed at high temperatures. A more complex model that considers the whole reaction matrix and the interactions between different cannabinoids is discussed. The difference between these models is analyzed, and a comparison with previously reported results was also performed.

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

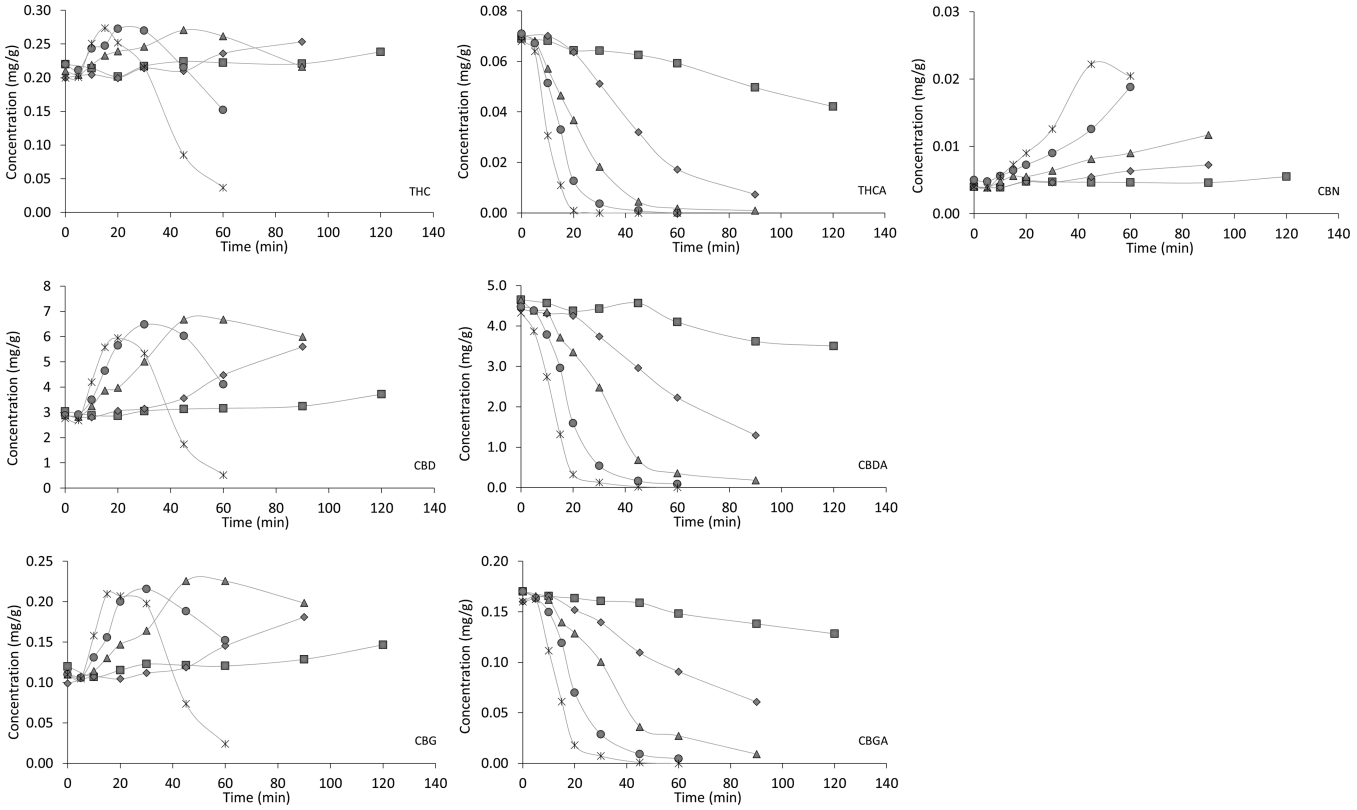

Figure 1. Cannabinoid concentration plots as a function of time and temperature. (■) 80 °C; (◆) 100 °C; (▲) 120 °C; (●) 140 °C; (*) 160 °C.

EXPERIMENTAL SECTION

Materials. Hemp plant material (flower buds) of *Ferimon12* cultivar was supplied by a New Zealand hemp grower. It was milled using a PM-3 pin mill from Mill Powder Tech Solutions (Taiwan) with a 2 mm mesh screen attached and stored in a sealed bag at room temperature until its use. Since the composition of the plant material can change during storage, it was characterized before each experiment. THC, THCA, deuterated THC, and CBD standards were obtained from Cerilliant (Round Rock, Texas). CBDA, CBG, and CBN standards were obtained from Lipomed (Arlesheim, Switzerland). CBGA standard was obtained from SPEX (Metuchen, New Jersey).

Decarboxylation Method. Typically, samples of 10 g of milled hemp were placed in a 75 mm diameter, 90 mm high beaker and heated in an oven at different temperatures (80–160 °C). The depth of plant material in the beaker was approximately 9 mm. In one trial, 40 g of material were used to test the effect of the depth of the bed of material with a depth of approximately 35 mm in the beaker. For the trials in the absence of oxygen, 10 g samples were placed in a small foil bag, flushed with nitrogen, and sealed before being introduced in the oven. Each sample was taken out of the oven after a specific time (between 5 and 120 min) and allowed to cool down in a vacuum desiccator before being weighed.

Cannabinoid Analysis. Quantification of cannabinoids was performed by the New Zealand Institute of Environmental Science and Research using liquid chromatography. Duplicate samples of plant material, of about 0.5 g, were accurately weighed into a hexane rinsed silanized glass test tube. A 5 mL aliquot of methanol (analytical grade from Fisher Scientific) was added to the tube, and the sample was vortexed for 10 min. The samples were stored refrigerated overnight. Samples were removed from refrigeration, allowed to come to room temperature, vortexed for 10 min, and centrifuged for 5 min.

Each sample was further diluted with methanol, as required, to ensure all the major cannabinoids present in the extract fell within the calibration curve.

The analysis was carried out in a Sciex (Framingham, Massachusetts) 5500 Q-Trap quadrupole mass spectrometer operating in multiple reaction monitoring (MRM) mode with an electrospray ionization (ESI) source in positive ionization. Mobile phases consisted of 0.1% formic acid in H_2O (mobile phase A) and 0.1% formic acid in methanol (mobile phase B). A Kinetex Biphenyl (2.1 mm × 50 mm, 2.6 μm particle size) column with SecurityGuard ULTRA Biphenyl guard holder-cartridge assembly from Phenomenex (Torrance, California) was used. A calibration curve including certified reference standards for THC, THCA, CBD, CBDA, CBG, CBGA, and CBN was developed, and deuterated THC was used as an internal standard.

All results were corrected for the weight loss which occurred during decarboxylation (up to 11% at 160 °C) and are reported on the weight basis of the original milled plant material.

Kinetic Modeling. The differential equations were integrated using the Runge–Kutta method, RK4, with time steps of 0.1 min. The mean square difference between the experimental and modeled concentrations was minimized. For the simple model, the fitting was weighted only to the conversion of the acid form. The acid and neutral forms were both considered in the complex (mass balance) model, where the parameters for the Arrhenius equation and the starting concentration of the precursor were the fitted parameters.

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Ind. Eng. Chem. Res. XXXX, XXX, XXX–XXX

RESULTS

Decarboxylation Reactions. The evolution of the concentration of different cannabinoids in the plant material as a function of time and temperature are shown in Figure 1. At the lower temperature (80 °C), the conversion of THCA, CBDA, and CBGA into their respective neutral forms is still relatively slow, but it increases considerably as the temperature increases: at 120 °C, THCA is completely decarboxylated after 90 min, whereas only 20 min are required at 160 °C. The decarboxylation leads to a corresponding increase in THC concentration; however, as the temperature increases, and particularly above 100 °C, THC reaches a maximum, and the concentration then begins to drop. An increase in the concentration of CBN, a known oxidation product of THC, is observed but does not fully account for the quantity of lost THC as the sum of the molar concentrations of THC + THCA + CBN does not remain constant: for example, it decreases by 78% after 60 min at 160 °C (Figure 2).

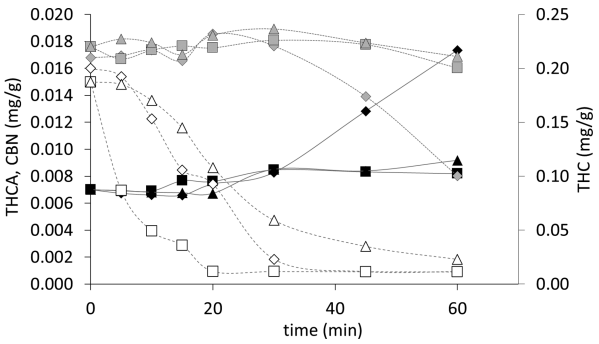

Figure 2. THC (gray), THCA (empty) and CBN (black) concentrations during decarboxylation at 140 °C: (◆) open beaker, thin bed; (▲) open beaker, deep bed; (■) N_2-sealed pouch.

This loss of total cannabinoid content was also observed for CBD and CBG, and in both cases the sum of their acid and neutral form molar concentrations decreased by over 90% after 60 min at 160 °C. This suggests that the formation of unidentified byproducts may be occurring, coupled with the evaporation of the neutral forms at the higher temperature end—the boiling point for THC has been determined at 157 °C, and the boiling point range for CBD sits between 160 and 180 °C.[5]

This effect has previously been reported by other authors.[19] Citti et al. studied the decarboxylation of CBDA in hemp seed oil and observed a loss of total molar concentration of CBD + CBDA of about 60% at 120 °C in an open reactor.[16] Wang et al. observed a similar unexplained disappearance of neutral forms in the decarboxylation of THCA, CBDA, and CBGA in *cannabis* extracts in a vacuum oven at up to 145 °C.[17] Veress et al. observed a decrease in the amount of CBD and THC at 122 and 145 °C and attributed it to evaporation losses.[14] Lindholst studied the stability of THCA and THC in *cannabis* resin over several years under different storage conditions and found that the increase in total CBN did not correspond to the decrease in total THC, indicating that THC may also degrade into compounds other than CBN.[8] Taschwer and Schmid also studied the effect of storage temperature on stability of THCA and THC in *cannabis* plant material and found that a temperature of 100 °C or above led to an accelerated and complete decarboxylation of THCA followed by rapid loss of THC.[20]

In order to study the influence of oxygen in these reactions, an additional test was run at 140 °C using nitrogen-flushed, sealed foil pouches, along with a second test using an open beaker. The absence of oxygen was demonstrated by minimal production of CBN, a known oxidation product of THC (see Figure 2). Interestingly, Figure 2 shows that decarboxylation of THCA in the sealed pouches occurs faster than in the open beakers, while decomposition of THC into CBN and other unknown components is significantly slowed down. This effect is also observed for the other neutral cannabinoids: the rate at which the total molar concentration of a specific cannabinoid (sum of acid and neutral forms) disappeared was significantly reduced, suggesting that decomposition of the neutral cannabinoid forms is oxygen-dependent or that evaporation is suppressed by use of a sealed container (see Figure 3). However, given that Wang et al. observed a similar disappearance of neutral forms when studying the decarboxylation reaction in a vacuum oven,[17] we believe the losses can be attributed to evaporation.

The amount of plant material placed in the beaker also has an influence on the process. A test was carried out at 140 °C using four times the amount of material in the same beakers, which resulted in a 4-fold increase in depth of the bed of material to be decarboxylated. The increase in depth resulted in a slower overall process: conversion of THCA, CBDA, and CBGA after 60 min was 88%, 89%, and 85%, respectively, whereas it was practically complete after that time with a shallower bed, and the loss of total molar concentration was also much slower (Figure 3). This effect could be attributed to the slower heat transfer rates through a deeper bed of plant material, or to the reduced surface area exposed to air circulation and evaporation.

Kinetic Modeling: Simple Model. The reaction matrix considered in this model is shown in Scheme 2. The decarboxylation of cannabinoid acids into their neutral forms

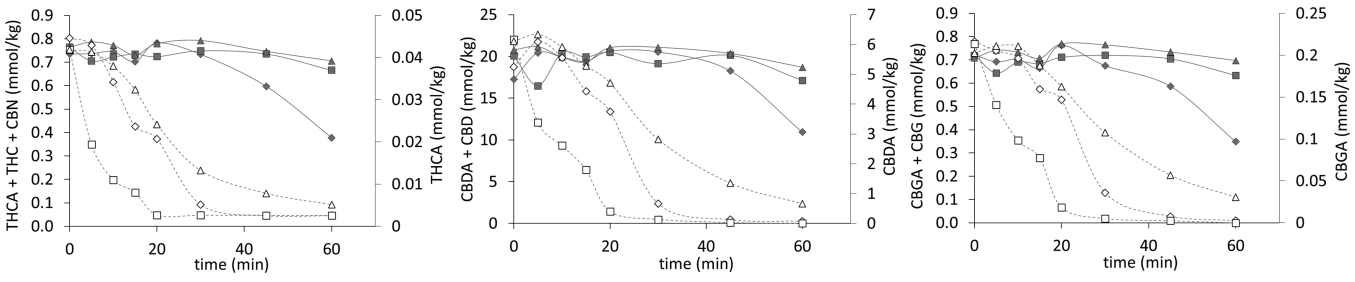

Figure 3. Cannabinoid molar concentration plots as a function of time during decarboxylation at 140 °C: (◆) open beaker, thin bed; (▲) open beaker, deep bed; (■) N_2-sealed pouch (empty symbols indicate acid concentration, solid symbols indicate neutral + acid concentration).

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

Scheme 2. Reaction Matrix (Simple Model)

$$\text{THCA} \xrightarrow{k_1} \text{THC}$$
$$\text{CBDA} \xrightarrow{k_2} \text{CBD}$$
$$\text{CBGA} \xrightarrow{k_3} \text{CBG}$$

has previously been described to follow first-order reaction kinetics. Perrotin-Brunel et al. described the decarboxylation of Δ^9-THCA as a pseudo-first-order reaction catalyzed by short-chain organic acids present in the flowers of the *cannabis* plant.[15] Similar conclusions were reached for CBDA[14,16,17] and CBGA.[17] The three decarboxylation reactions considered here would, therefore, be described as

$$\frac{d[\text{THCA}]}{dt} = -k_1[\text{THCA}] \quad (1)$$

$$\frac{d[\text{CBDA}]}{dt} = -k_2[\text{CBDA}] \quad (2)$$

$$\frac{d[\text{CBGA}]}{dt} = -k_3[\text{CBGA}] \quad (3)$$

In this simplified modeling approach, the decarboxylation reaction rate constant for each cannabinoid, k, can be calculated according to the integrated eq 4:

$$\ln\left(\frac{[C]_0}{[C]_t}\right) = kt \quad (4)$$

where $[C]_0$ and $[C]_t$ represent the concentration of cannabinoid acid at time 0 and t minutes, respectively. The decarboxylation rate constant, k, can, therefore, be calculated from the gradient of $\ln\left(\frac{[C]_0}{[C]_t}\right)$ vs time. The linearity of these plots supports the assumption of first-order kinetics for the cannabinoid acids studied (Figure 4). For reaction temperatures ≥100 °C, an induction period was observed while the temperature of the plant material reached the reaction temperature. During this time, the decarboxylation rate was lower than the decarboxylation rate at the target temperature (see Figure 1). Therefore, the first experimental time point for temperatures ≥100 °C was not used in the fit, to allow for this heating period before the reaction begins.

The gradients were calculated using the *solver* function in MS Excel to minimize the square sum of the difference between experimental and calculated $[C]_t$ for a given value of k.

Once the decarboxylation kinetic constants for each temperature are known, the Arrhenius equation can then be used to calculate the activation energy, E_a, and the pre-exponential or frequency factor, A, according to eq 5:

$$\ln k = \ln A - \frac{E_a}{RT} \quad (5)$$

where R is the universal gas constant (8.3144 J mol^{-1} K). The calculated values of all kinetic constants, as well as the activation energies and the pre-exponential factors, are included in Table 1. THCA has the highest decarboxylation rate at all temperatures, generally followed by CBDA. This trend agrees with the results by Wang et al., who reported THCA decarboxylation rates between 2.2 and 3.6 times higher than for CBDA, and between 1.8 and 3 times higher than for CBGA.[17] Veress et al. also reported a THCA decarboxylation rate up to 2.2 times higher than for CBDA,[14] and a recent preprint study attributes the faster decarboxylation rate of THCA over CBDA to steric effects.[21]

In absolute terms, however, the rate constants reported by these authors are generally higher than the ones in this work with the simple model, particularly for the higher temperatures. This could be explained by the methodology employed: while in our work we used ground samples of plant material, Veress and Wang used small amounts of concentrated extracts (obtained with organic solvents) that were then placed either on the surface of a glass tube[14] or in small vials and into a vacuum oven.[17] Similarly, Perrotin-Brunel et al. observed considerably higher decarboxylation rates for THCA when using small amounts of *cannabis* plant material (400 mg) in a vacuum oven.[15]

In our work, we found that both the amount of material to be decarboxylated and the presence of oxygen during the reaction have an impact on the kinetics of the process. At 140 °C, the decarboxylation rates observed for THCA, CBDA, and CBGA in the samples in absence of oxygen were 122%, 102%, and 98% higher than those obtained in open beakers, respectively. On the other hand, the use of a larger amount of sample slowed down the observed reaction rate in an open beaker by about 38% for all cannabinoids. Since the largest deviations occur at the highest temperatures, this phenomenon also affects the relationship between the reaction constants and the temperature, and as a result, the activation energies obtained in this work are in all cases lower than those reported in the above-mentioned studies. This can be observed from the slopes obtained in Figure 5, where the correlation between the logarithmic values of the reaction constants as a function of the inverse of temperature as dictated by eq 4 is shown.

Kinetic Modeling: A Simple Model with Mass Balance Correction. The simple model described above is a basic first approach to the kinetics of the reaction system, but it neglects the consecutive reaction of the neutral forms that were

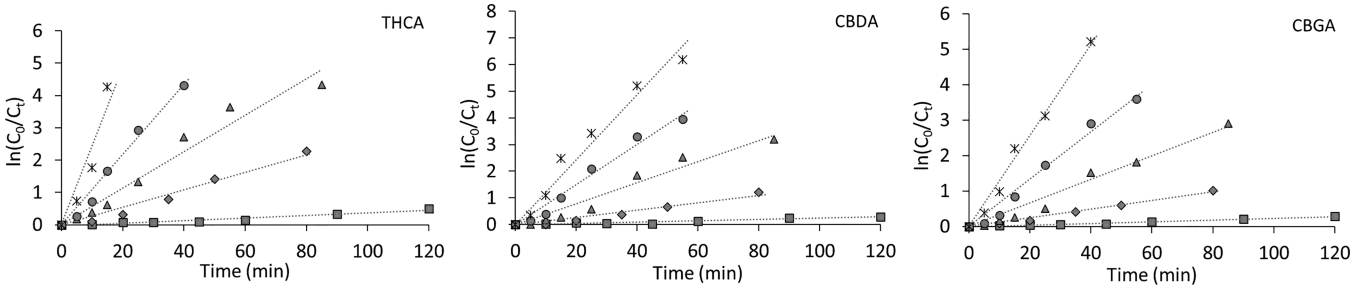

Figure 4. Decarboxylation kinetics at different temperatures. (■) 80 °C; (◆) 100 °C; (▲) 120 °C; (●) 140 °C; (*) 160 °C.

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

Table 1. Simple Model: Rate Constants, Activation Energies, and Pre-Exponential Factors for the Three Cannabinoid Acids Studied

		80 °C	100 °C	120 °C	140 °C	160 °C	E_a (kJ/mol)	$A \times 10^5$ (s^{-1})	R^2
THCA	$k_1 \times 10^3$ (s^{-1})	0.057	0.376	0.795	1.410	2.819	58.7	0.41	0.954
CBDA	$k_2 \times 10^3$ (s^{-1})	0.038	0.203	0.489	0.989	1.816	60.0	0.38	0.973
CBGA	$k_3 \times 10^3$ (s^{-1})	0.037	0.195	0.439	0.862	1.743	58.9	0.25	0.976

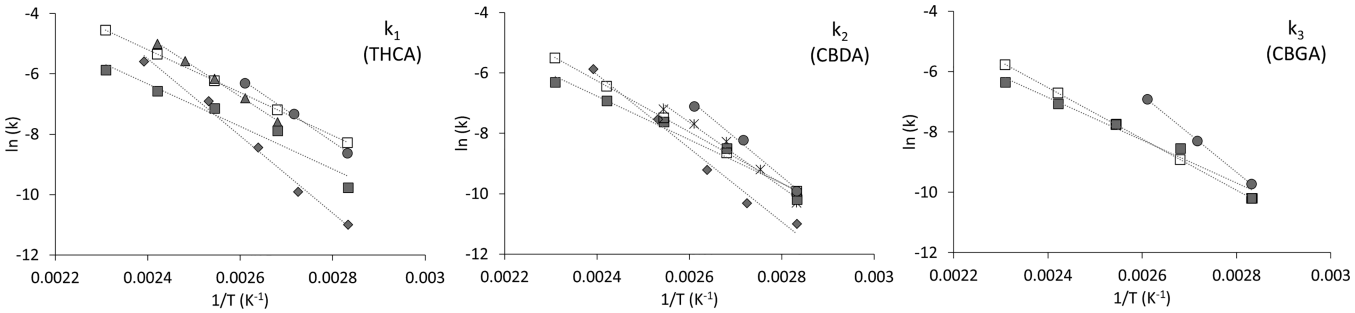
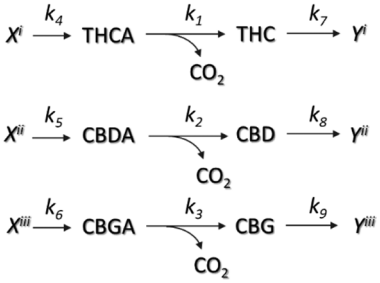


Figure 5. Arrhenius plots for THCA (left), CBDA (middle), and CBGA (right). (■) This work (simple model); (□) this work (mass balance model); (●) Wang et al.;[17] (◆) Veress et al.;[14] (▲) Perrotin-Brunel et al.;[15] (*) Citti et al.[16]

observed in the experimental data. A slightly more comprehensive model was developed (Scheme 3) incorporating a correction for the mass losses observed experimentally by including the presence of CO_2 produced during the decarboxylation reaction. This model still considers the first-order reactions independently, but there is a supply of a hypothetical cannabinoid precursor (X), and consideration of degradation products (Y) that can be formed.

Scheme 3. Reaction Matrix (Simple Model with Mass Balance Correction)



$$\frac{d[X^i]}{dt} = -k_4[X^i] \quad (6)$$

$$\frac{d[X^{ii}]}{dt} = -k_5[X^{ii}] \quad (7)$$

$$\frac{d[X^{iii}]}{dt} = -k_6[X^{iii}] \quad (8)$$

$$\frac{d[THCA]}{dt} = k_4[X^i] - k_1[THCA] \quad (9)$$

$$\frac{d[CBDA]}{dt} = k_5[X^{ii}] - k_2[CBDA] \quad (10)$$

$$\frac{d[CBGA]}{dt} = k_6[X^{iii}] - k_3[CBGA] \quad (11)$$

$$\frac{d[THC]}{dt} = k_1[THCA] - k_7[THC] \quad (12)$$

$$\frac{d[CBD]}{dt} = k_2[CBDA] - k_8[CBD] \quad (13)$$

$$\frac{d[CBG]}{dt} = k_3[CBGA] - k_9[CBG] \quad (14)$$

$$\frac{d[Y^i]}{dt} = k_7[THC] \quad (15)$$

Table 2. Simple Model with Mass Balance Correction: Rate Constants, Activation Energies, and Pre-exponential Factors for the Three Cannabinoid Acids Studied

		80 °C	100 °C	120 °C	140 °C	160 °C	E_a (kJ/mol)	$A \times 10^5$ (s^{-1})
THCA	$k_1 \times 10^3$ (s^{-1})	0.256	0.754	1.992	4.787	10.610	59.2	1.46
	$k_4 \times 10^3$ (s^{-1})	0.085	0.241	0.615	1.430	3.079	57.0	0.23
	$k_7 \times 10^3$ (s^{-1})	0.035	0.077	0.158	0.303	0.546	43.9	0.00
CBDA	$k_2 \times 10^3$ (s^{-1})	0.049	0.179	0.566	1.606	4.138	70.4	12.7
	$k_5 \times 10^3$ (s^{-1})	0.000	0.000	0.000	0.000	0.000	–	–
	$k_8 \times 10^3$ (s^{-1})	0.000	0.002	0.015	0.080	0.364	112.6	139199
CBGA	$k_3 \times 10^3$ (s^{-1})	0.037	0.135	0.430	1.223	3.156	70.5	10.1
	$k_6 \times 10^3$ (s^{-1})	0.000	0.000	0.000	0.000	0.000	–	–
	$k_9 \times 10^3$ (s^{-1})	0.001	0.007	0.030	0.118	0.410	92.4	574.8

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

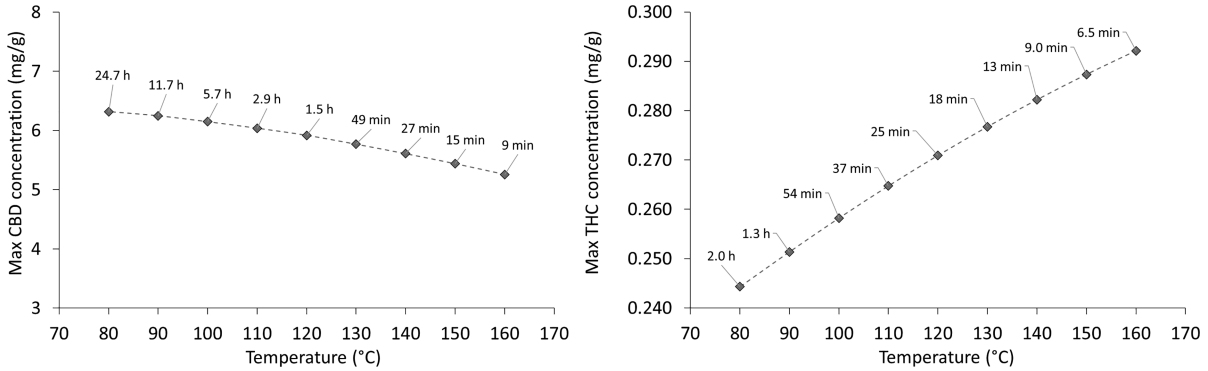

Figure 6. Prediction of maximum CBD (left) and THC (right) concentrations achievable at different temperatures and decarboxylation times, based on the mass balance model.

$$\frac{d[Y^{ii}]}{dt} = k_8[CBD] \quad (16)$$

$$\frac{d[Y^{iii}]}{dt} = k_9[CBG] \quad (17)$$

$$\frac{d[CO_2]}{dt} = k_1[THCA] + k_2[CBDA] + k_3[CBGA] \quad (18)$$

This model can be solved using two different approaches. In one approach, the fitted parameters are the three reaction rates from the precursor X to the cannabinoid acid form (k_{4-6}), from the acid form to the neutral form (k_{1-3}, decarboxylation), and from the neutral form to the degradation product Y (k_{7-9}). This applies to all temperatures, leading to a total of 45 parameters. Since the amount of experimental data available was limited, and in order to minimize the number of fitted parameters, an alternative approach was used in which the parameters of the Arrhenius equation 5; i.e., the activation energy E_a and the pre-exponential factor A were fitted for each reaction constant, leading to a total of 18 parameters. The initial concentration of the precursors was also fitted. The specific reaction rates for each temperature were then calculated with the fitted Arrhenius parameters and are shown in Table 2.

The formation of CBDA and CBGA from the precursor (k_5 and k_6 respectively) was found to be negligible, with reaction rates close to zero, suggesting that the simple first-order reaction model is a good fit without needing to consider more complex reaction pathways or reaction kinetics. THCA, however, fitted the model with a comparatively high formation rate from its hypothetical precursor (k_4), particularly at high temperatures. This indicates that there could be some additional THCA forming during the decarboxylation process, but could also be interpreted as other nonlinearities or complexities in the reaction pathway that result in the data for THCA decarboxylation not fitting as well to the simple first-order model as CBDA and CBGA.

The decarboxylation rates (k_{1-3}) obtained with this model are higher than the ones obtained in the simple model, particularly for THCA as a consequence of the high fitted formation rate (k_4). This also affects the fitted decomposition rate of THC into its byproduct, which is higher than for CBD and CBG across all temperatures. The activation energies obtained with this model for CBDA and CBGA decarboxylation are higher than those obtained with the simple model, whereas it is slightly lower for THCA. This can be observed in Figure 5, which shows the Arrhenius plots for the mass balance model along with the simple model.

The model can be used to predict the most favorable decarboxylation conditions to maximize the concentration of a target compound. Optimizing the decarboxylation reaction involves a delicate balance between reaction temperature and time. Figure 6 shows the maximum concentration of CBD and THC that can be achieved at each temperature according to the mass balance model, along with the time required to reach that concentration. In the case of decarboxylation of CBDA, it is preferable to maintain a low temperature for a longer period of time, since the decomposition reaction (k_8) is greatly minimized at low temperatures and the activation energy for this reaction is considerably higher than that for the decarboxylation. According to the model, the optimum conditions to maximize CBD concentration are 80 °C and around 25 h, although a 10 °C increase in temperature would halve the required reaction time without a significant decrease in maximum CBD concentration. By contrast, decomposition of THC is significant even at low temperatures, and the increase in decarboxylation rate obtained as temperature rises is preferable to maximize the concentration of THC (note that the activation energy of the decomposition reaction is lower than that of the decarboxylation reaction). The optimum decarboxylation temperature for maximum THC concentration would therefore be 160 °C, and the required time is very short. It is worth noting, however, that the exact optimum conditions in each case are not just a function of time and temperature, and will be dependent on the specific cultivar and the cannabinoid profile present in the plant material, as well as other parameters such as the ones discussed in this study (presence of oxygen and amount of plant material).

Kinetic Modeling: Complex Model. While the simple models described above can provide a first approximation to the kinetics of the process, their main limitation is that they consider each cannabinoid independently. In reality, the biological pathway of the cannabinoids in the plant material is highly complex (Scheme 1) and the three reactions described in this work are likely interconnected. However, the exact mechanism is not known, and more data would be required in order to develop a suitable model. The reactions described in Scheme 1 show what is believed to be the synthetic pathway happening in the plant material, and it does not necessarily match the reactions that occur in an oven at elevated temperatures.

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

CONCLUSIONS

This work studies the decarboxylation reaction of THCA, CBDA, and CBGA in hemp plant material at temperatures between 80 and 160 °C. The reactions follow first-order kinetics, with the conversion of THCA into its neutral form being faster than for the other two compounds. A significant loss of neutral cannabinoid concentration was observed for all three compounds at elevated temperatures and reaction times, suggesting the formation of unidentified byproducts or evaporative losses. This loss is greatly reduced in the absence of oxygen, hinting at possible oxidation reactions. The amount of plant material being decarboxylated is another variable to be considered, since it will influence the heat transfer mechanism and oxygen exposure in the oven and will slow down the process, leading to apparently lower reaction rates. The experimental data were fitted using two different kinetic models of increasing complexity, which provided the reaction rates and the activation energies of each reaction, and the results were compared to existing results in the literature. The values obtained for the activation energy, E_a, for the decarboxylation reaction of THCA using both kinetic models were similar (58.7 and 59.2 kJ/mol for the simple and mass balance model, respectively), whereas the values obtained for decarboxylation of CBDA and CBGA were higher in the mass balance model (70.4 and 70.5 kJ/mol for CBDA and CBGA respectively in the mass balance model, and 60.0 and 58.9 kJ/mol in the simple model). Although it is an oversimplification, the kinetic model needs to consider the decarboxylation reactions independently, since a complex model including the interaction between all the cannabinoids studied and based on the biological pathway for the cannabis plant is not suited for this reaction system. The kinetic model used allowed the calculation of the optimum decarboxylation conditions for maximum CBD or THC concentration, indicating that longer reaction times at a low temperature are preferred for CBD whereas a shorter reaction at a higher temperature is preferable for THC.

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Notes

The authors declare no competing financial interest.

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Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX