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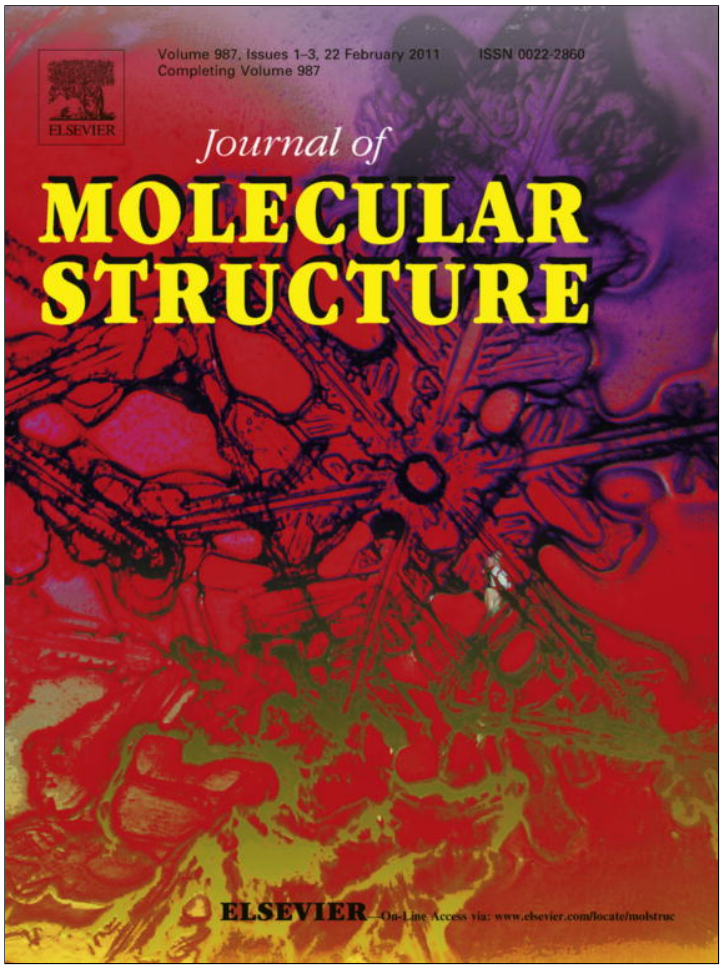

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Decarboxylation of Δ^9-tetrahydrocannabinol: Kinetics and molecular modeling

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ABSTRACT

Efficient tetrahydrocannabinol (Δ^9-THC) production from cannabis is important for its medical application and as basis for the development of production routes of other drugs from plants. This work presents one of the steps of Δ^9-THC production from cannabis plant material, the decarboxylation reaction, transforming the Δ^9-THC-acid naturally present in the plant into the psychoactive Δ^9-THC. Results of experiments showed pseudo-first order reaction kinetics, with an activation barrier of 85 kJ mol^{-1} and a pre-exponential factor of 3.7×10^8 s^{-1}.

Using molecular modeling, two options were identified for an acid catalyzed β-keto acid type mechanism for the decarboxylation of Δ^9-THC-acid. Each of these mechanisms might play a role, depending on the actual process conditions. Formic acid proved to be a good model for a catalyst of such a reaction. Also, the computational idea of catalysis by water to catalysis by an acid, put forward by Li and Brill, and Churchev and Belbruno was extended, and a new direct keto-enol route was found. A direct keto-enol mechanism catalyzed by formic acid seems to be the best explanation for the observed activation barrier and the pre-exponential factor of the decarboxylation of Δ^9-THC-acid. Evidence for this was found by performing an extraction experiment with Cannabis Flos. It revealed the presence of short chain carboxylic acids supporting this hypothesis. The presented approach is important for the development of a sustainable production of Δ^9-THC from the plant.

1. Introduction

At present there is a growing interest in cannabis and its medicinal uses [1,2]. Cannabis contains more than 400 different ingredients, including at least 60 cannabinoids. The major active component, called (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC), does not occur at significant concentrations in the plant, but is formed by decarboxylation of its corresponding acid upon heating.

As described in a patent [3], Δ^9-THC acid (Δ^9-THCA) is obtained from plant material by extraction into an aqueous solvent under basic pH conditions. After acidification of aqueous fraction, the aqueous fraction was extracted using a non-polar solvent, yielding the acid in high purity in organic solvent. Δ^9-THCA is then converted to Δ^9-THC which is further purified and combined with a carrier for pharmaceutical use. The total process includes seven different steps and four purification steps and requires a lot of energy, while producing a lot of inorganic/organic contaminated water. The contaminations are mainly inorganic salts and organic waste; principally organic solvents such as heptane and isopropyl ether. To improve this production process, reducing the number of process steps, energy consumption, water consumption and waste production, is crucially important. In a recent patent [4], both Δ^9-THCA and Δ^9-THC are extracted into an organic solvent followed by decarboxylation with aqueous base in the same solvent. Despite the obvious improvement presented, many process steps are still needed to obtain pure Δ^9-THC. In our view, the ideal process would start from a solid plant source with the highest level of Δ^9-THCA, which then is extracted, decarboxylated, and purified in the minimum number of steps, avoiding water, inorganic salts, and organic solvents.

As most cannabinoids in the plant, including Δ^9-THC, are present as their acid precursor, decarboxylation in the solid phase (i.e. in the plant material) followed by extraction into a neutral solvent, might be considered a viable option. Previous work on the decarboxylation of cannabinoids in the solid phase has been performed in closed reactors [5,6], open reactors and on a glass surface [7]. However, little research has been performed to understand the kinetics and the mechanism of solid state reaction in cannabis, despite the fact that these are crucial for scale-up.

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The first section of this paper presents experimental work to determine the best reaction conditions (i.e. temperature and time) for decarboxylation and its kinetics. Molecular modeling is then used to support or justify proposed mechanism and kinetics parameters for this solid state reaction in accordance with available literature and experimental data herein.

2. Experimental

2.1. Materials

Methanol was HPLC grade and was purchased from J.T. Baker (Deventer, The Netherlands). Medical grade cannabis plant material (female flower-tops) was obtained from Bureau Medicinale Cannabis (The Hague, The Netherlands). It had a Δ^9-THCA content of about 18%, and virtually no free Δ^9-THC. The water content was ~3.6%. The standards of Δ^9-THC (4.2 mg mL^{-1} in methanol – ref number 130-151205x) and Δ^9-THCA (1.0 mg mL^{-1} – ref number 380-250407), with purity higher than 98%, were kindly donated by PRISNA B.V.

2.2. Method

A sample of around 400 mg cannabis was blended in a mixer, and heated at different temperatures in vacuum conditions for a certain time. The temperature range studied was from 90 to 140 °C. To follow the reaction rate, a sample was taken every 5 min for the first hour and then every half an hour until the conversion of Δ^9-THCA to Δ^9-THC was complete. Each solid sample was extracted with 50 mL methanol and sonicated for 15 min before being analysed with HPLC. In a series of extraction experiments it was determined that the extraction process was essentially complete. Calibration lines were determined for both Δ^9-THCA and Δ^9-THC. By this method the solid samples were inherently corrected for weight loss (up to ~30% at 140 °C) during thermal treatment. Balances during the experiments, based on the molalities of Δ^9-THCA and Δ^9-THC, are >95%, indicating that the decarboxylation process itself proceeds with ~100% selectivity. Some skeletal rearrangements however cannot be excluded.

2.3. HPLC analyses

The HPLC profiles were acquired on a Chromapack HPLC system consisting of an Isos pump, an injection valve and a UV–VIS detector (model 340 – Varian). The system is controlled by Galaxie Chromatography software. The profiles were recorded at 228 nm, as absorption by the solute is at its maximum at this wavelength. The analytical column was a Vydac (Hesperia, CA) C_{18}, type 218MS54 (4.6 × 250 mm^2, 5 μm). The mobile phase consisted of a mixture of methanol–water in a concentration gradient containing 25 mM of formic acid (pH ± 3). The methanol/water concentration ratio was linearly increased from 65% to 100% over 25 min, and then kept constant for 3 min. Then the column was re-equilibrated under initial conditions for 4 min, so the total running time was 32 min. The flow rate was 1.5 mL min^{-1} [8].

2.4. Molecular modeling

The Spartan '06 package [9] was used for all calculations. All structures were optimized using DFT B3LYP, level (6- 31G**), starting from PM3 optimized geometries. Transition states were identified and characterised using its unique imaginary vibrational frequency or Internal Reaction Coordinate. Thermodynamical corrections were applied; however activation energies were based on Total Energies, corrected for Zero Point Energy contributions (ZPE-contributions).

3. Results and discussion

3.1. Experimental results

Decarboxylation is a rather common chemical reaction in which a carboxyl group splits off from a compound as carbon dioxide. The reaction for Δ^9-THCA shown schematically in Fig. 1, can be induced by light or heat during e.g. storage or smoking. This reaction transforms the acidic cannabinoids to their psychoactive forms Δ^9-THC. In this article, only thermal decarboxylation will be considered. As described above, the decarboxylation reaction has been studied in the range of 90–140 °C. Under the experimental conditions, the highest yield to Δ^9-THC was obtained at 110 °C and 110 min. Analysis of the data leads to the conclusion that this solid state reaction surprisingly obeys a first order rate law. Raw kinetic data are presented in Fig. 2. Related k values are reported in Table 1. The corresponding ln k versus $1/T$ plots are shown in Fig. 3. This is a straight line, described by the formula:

$$\ln k = \ln k_0 - \frac{E}{RT}$$

from which E and k_0 are determined to be 84.8 kJ mol^{-1} and 3.7×10^8 s^{-1} respectively.

3.2. Literature results

In the literature, only a few liquid phase thermal decarboxylation reactions of carboxylic acids, both aromatic as well as non-aromatic, can be found [10–13]. Li and Brill reported experimental activation energies for the first order decarboxylation of a series of OH substituted benzoic acids under acidic conditions, ranging from 82 to 97 kJ mol^{-1} for 2,4,6-trihydroxybenzoic acid and 2,3-dihydroxybenzoic acid. Their k_0-values range from 3.61×10^{10} s^{-1} to 3.58×10^8 s^{-1}, the latter being similar to the one observed by us [13].

In addition, by applying computational chemistry techniques (B3LYP/6-31G*), Li and Brill found that intra-molecular decarboxylation of the acids via a four membered ring transition state yielded a very high activation barrier, thus suggesting that a real first order process is very unlikely. The calculated activation barriers for four-membered transition state for a series of caboxylic acids ranged from 213 kJ mol^{-1} for 2,4-dihydroxybenzoic acid, to 225 kJ mol^{-1} for 2-hydroxybenzoic acid, and with a constant value of 260 kJ mol^{-1} for 3-hydroxybenzoic acid, 3,5-dihydroxybenzoic acid, and benzoic acid itself.

Li and Brill also found that the addition of one molecule of water in the mechanism transformed the preferred transition state from a four membered ring to a six membered ring with concomitant reduction in the activation barrier to 130 kJ mol^{-1}, a value much closer to the experimental values. However, these values are still far too high, especially if it is realized that these barriers are based on the ~28 kJ mol^{-1} energetically unfavorable anti-conformer of the acid [10–13] which acts as a highly reactive intermediate.

Recently, Chuchev and BelBruno [14] published a study on the mechanism of the decarboxylation of ortho-substituted benzoic acids, wherein they supported the work of Li and Brill that a single water molecule is a potential model for an aqueous environment. In addition, they concluded that the presence of a water molecule forces the reaction through a keto-intermediate in the case of 2-hydroxybenzoic-acid. The keto-intermediate then intramolecularly decarboxylates to yield phenol and CO_2. The overall process is illustrated in Fig. 4. However, their calculated activation barrier for the decarboxylation of salicylic acid is ~150 kJ mol^{-1}, which is still

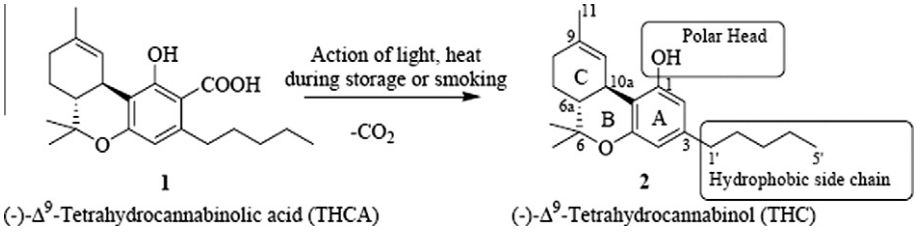

Fig. 1. Model of the decarboxylation reaction of Δ^9-THCA.

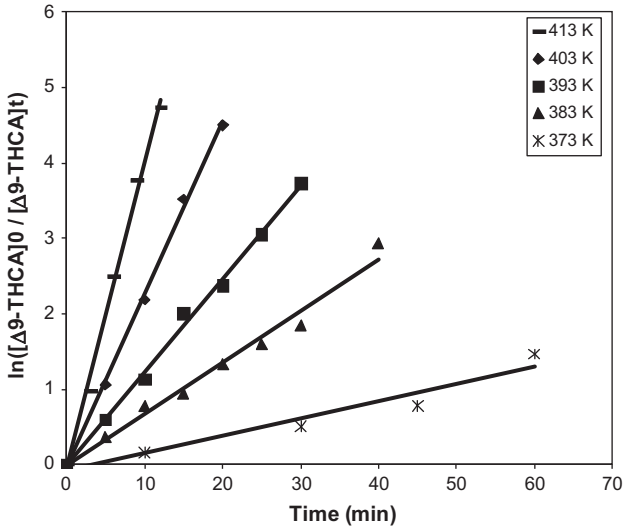

Fig. 2. Plot of $\ln[\Delta^9\text{-THCA}]_0/[\Delta^9\text{-THCA}]$ as a function of time at different temperatures.

Table 1
Values of the constant rate k and of the regression coefficient at different temperatures.

T (K)	$10^3\ k$ (s^{-1})	R^2
413	6.7	0.9949
403	3.8	0.998
393	2.1	0.9958
383	1.1	0.982
373	0.5	0.9426

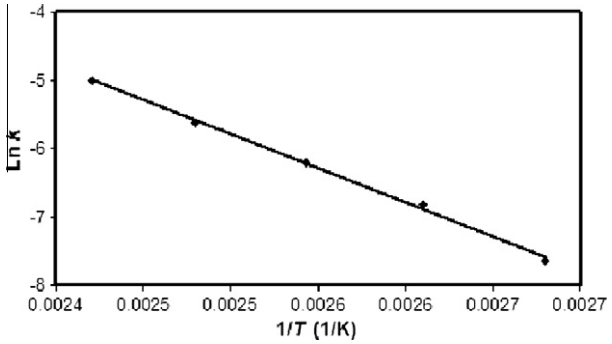

Fig. 3. ln k as a function of $1/T$ – Arrhenius' law.

significantly too high. Hence, it should be noted that the observed first order reaction can only be understood in terms of a pseudo-first order reaction on a molecular level.

For Δ^9-THCA in Cannabis Flos, the reaction takes place in a *solid* phase with a large amount of Δ^9-THCA (18 w% = 0.57 mol kg^{-1})

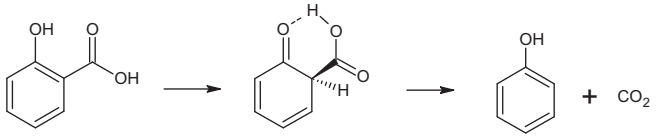

Fig. 4. Decarboxylation of 2-hydroxybenzoic acid via the β-keto acid pathway.

and a low amount of water (3.6 w% = 2.0 mol kg^{-1}). The low value for k_0 might be explained by the fact that it is a solid state reaction, or a catalytic process, leading to a pseudo-first order process. A molecular modeling study has been performed to test this hypothesis.

3.3. Molecular modeling results

Δ^9-THCA is a large molecule and therefore computationally intensive with respect to memory and time. 2-Hydroxybenzoic acid has been used as a suitable, simplest model for Δ^9-THCA. Furthermore both experimental and computational studies have been performed with 2-hydroxybenzoic acid. To allow a meaningful comparison between our work on Δ^9-THCA, and the existing literature on 2-hydroxybenzoic acid, the different options were investigated for 2-hydroxybenzoic acid first.

As a starting point we initially confirmed the computational work of Li and Brill [13], and Chuchev and BelBruno [14] with respect to the geometries of the transition states both for the direct uncatalyzed and one water molecule catalyzed pathways. The geometries look very similar, and important bond lengths are similar within 0.01 Å.

Next, a mechanism was developed in which an organic acid was used as a catalyst to assist in the decarboxylation reaction. This allows the adaptation of the actual acid strength of the catalyst or implicitly the pH of the environment, while avoiding computationally intensive calculations. A disadvantage might be that thermodynamic corrections become meaningless in most cases, except for the ZPE. However, this is already the case, particularly for the entropy contributions, as experiments were carried out in solid phase, but not in the gas phase.

To obtain a good computational model catalyst for the decarboxylation reaction, several acids were investigated and compared in Table 2, for the case of 2-hydroxybenzoic acid. For the decarboxylation of Δ^9-THCA catalysis the work was limited to formic acid and trifluoroacetic acid. As can be seen in Table 2, the differences in activation energies for 2-hydroxybenzoic acid in both pathways with acetic acid, formic acid and trifluoroacetic acid are within 5 kJ mol^{-1}. Thus the acid strength of the catalyst does not seem to be a large discriminator in the calculations. Using formic acid as a model catalyst, two different transition states, shown in Fig. 5, could be located, both leading to the previously mentioned keto-intermediate.

The structure of the transition state with a value of 93 kJ mol^{-1} resembles the geometry of the transition state proposed by Chuchev and BelBruno and illustrated in Fig. 6 [14], with the hydrogen of the acid of the substrate in anti-position. Churchev

Table 2
Calculated activation energies of salicylic acid and Δ^9-THCA with different acids as catalyst.

Acid catalyst	E_a 2-hydroxybenzoic acid (kJ mol^{-1}) Direct keto-enol	E_a 2-hydroxybenzoic acid (kJ mol^{-1}) Indirect keto-enol	E_a Δ^9-THCA (kJ mol^{-1}) Direct keto-enol
Acetic acid	105	89	Not determined
Formic acid	104	93	81, 58[indirect]
Trifluoroacetic acid	100	88	71

et al. reaction pathway presented in [14], shows in fact a three proton transfer process, starting with protonation of the α-C next to the COOH-group, followed by the transfer of the proton in anti-position of the substrate COOH-group to the catalyst, and finally proton transfer of the phenol group to the carboxylate group of the substrate. This mechanism will be referred to as indirect keto-enol pathway.

The pathway with an activation barrier of 104 kJ mol^{-1} resembles a direct keto-enol pathway. Fig. 7 shows the IRC-plots of the formation of the keto-isomer of 2-hydroxybenzoic acid with formic and trifluoroacetic acid as catalyst via the keto-enol pathway. The

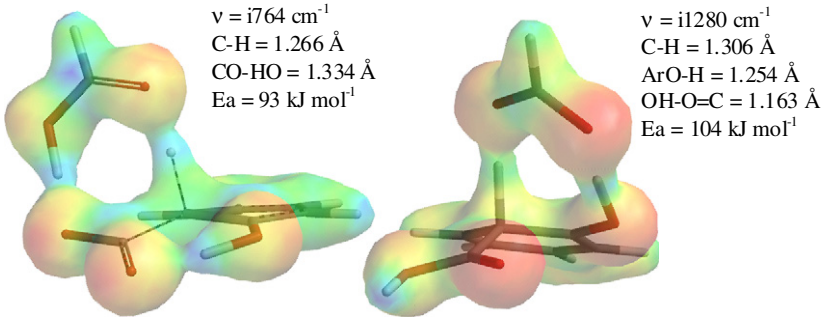

Fig. 5. The two transition states for formic acid catalyzed decarboxylation of 2-hydroxybenzoic acid.

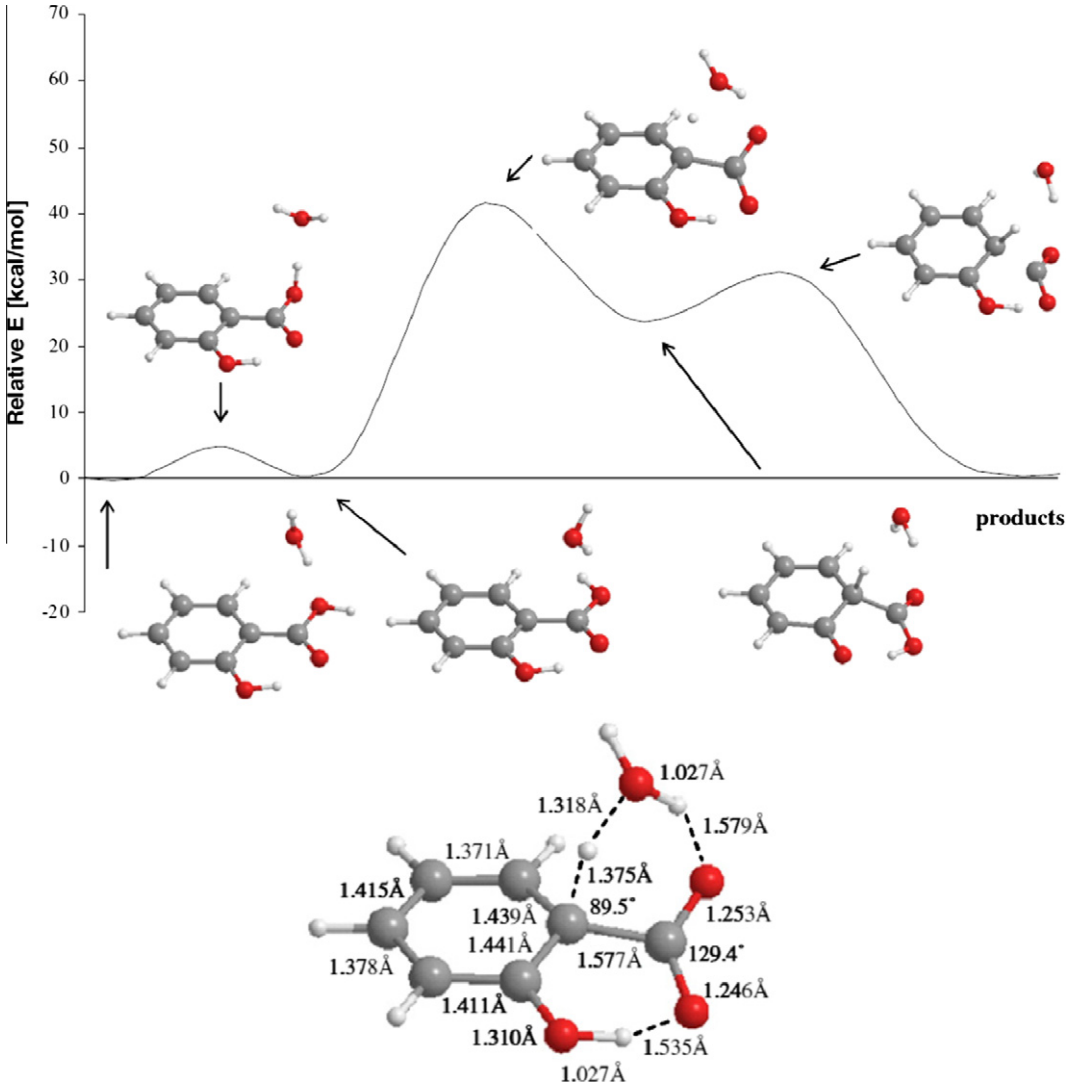

Fig. 6. Indirect keto-enol pathway according to Churchev and BelBruno [14]; structural details of the keto-enol transition state are listed below.

distance between the phenolic O–H atoms was taken as a measure for the reaction coordinate. The reaction starts from the phenol and ends with the keto-isomer. The geometries of the transition states change only slightly.

For Δ^9-THCA decarboxylation, the computed activation barrier for the catalyzed direct keto-enol route with formic acid (81 kJ mol^{-1}) compared well with the experimental value (85 kJ mol^{-1}). However, the computed activation barriers for trifluoroacetic acid (71 kJ mol^{-1}) and the indirect keto-enol pathway (58 kJ mol^{-1}) are much lower than the experimental values. Fig. 8 shows the IRC and the transition state of the first step of the formic acid catalyzed decarboxylation of Δ^9-THCA. Fig. 9 shows the overall reaction energy profile of the entire reaction, including the second step, the intra-molecular proton transfer of the acid to the keto-function.

3.4. Discussion

Aliphatic and aromatic acids are usually present [15] as plant constituents in cannabis. Inspired by the results of molecular modeling, the presence of acids other than Δ^9-THCA was verified experimentally. A sample of around 400 mg of cannabis was blended in a mixer, and extracted with distilled water after sonication for 10 min. The pH of the resulting aqueous solution was 6.1. A sample of 1600 mg of cannabis, yielded an aqueous solution with pH = 5.5. Under these conditions, Δ^9-THCA does not dissolve into water but short chain carboxylic acids do. Thus, acetic acid or formic acid not only can be used as a *model* for acid catalysis, but might be a realistic case from an experimental point of view as well. Furthermore, it offers a plausible explanation for the low value of k_0, as the experimental acidity is low.

To get a better overall understanding of the two different mechanistic options in acid catalyzed decarboxylation, Table 3 shows the comparison of experimental values with computational results obtained for a series of 2-hydroxybenzoic acids with formic acid as catalyst. Experimental data are scarce but, fortunately, well documented [13,14]. For the decarboxylation of 2-hydroxybenzoic acid two experimental activation energies are reported: 97.4 kJ mol^{-1} in catechol (weak acid), and 92 kJ mol^{-1} as an average of two distinct values: 91.4 kJ mol^{-1} in an HCl-solution of pH = 1.3, and 92.7 kJ mol^{-1} in an HCl-solution of pH = 2.7, thus showing a marked influence of both solvent and pH. A similar observation can be made for 2,6-dihydroxybenzoic acid. Here three values are reported: 111.1 kJ mol^{-1} in catechol, 92.7 kJ mol^{-1} at pH = 1.4 and 100.7 kJ mol^{-1} at pH = 2.0. Again, the dependence of the experimental activation energy on solvent type and pH is remarkable.

As can be seen from Table 3, the lowest value for the activation energy of 2-hydroxybenzoic acid, obtained experimentally in a strongly acidic environment, corresponds computationally with the indirect keto-enol pathway yielding an activation barrier of 92 kJ mol^{-1}. The latter requires the presence of a proton (in anti-position) of the substrate acid function. Under strongly acidic conditions this requirement is fulfilled. Under less acidic conditions this is not the case, and then the direct keto-enol pathway comes into play, resulting in an activation barrier of 104 kJ mol^{-1}.

The case of 2,6-dihydroxybenzoic acid is more complicated. It is a significantly stronger acid than 2-hydroxybenzoic acid, so the requirements for the indirect keto-enol pathway are no longer fulfilled in an HCl-solution of pH = 1.4. The direct keto-enol pathway leads to an activation barrier of 92 kJ mol^{-1}, close to the experimental value. The next experimental value of 101 kJ mol^{-1} at pH = 2.0, can be understood as a loss of coordination of one of the phenolic groups to the adjacent acid group due to the higher pH. Calculations for these systems lead to an activation barrier of 102 kJ mol^{-1}. With respect of the experimental work in catechol, computations with either formic acid or catechol itself as an acid catalyst, the indirect keto-enol pathway leads to an activation barrier of 114 kJ mol^{-1} close to the experimental value. The indirect pathway here is rationalized by the fact that 2,6-dihydroxybenzoic acid in catechol will not dissociate. Furthermore, it shows that formic acid can even act as a reasonable model for catechol.

From the computational results obtained it would be tempting to speculate what the activation barrier would become if strongly acidic conditions were applied in the case of Δ^9-THCA. However, the application of strong acids, containing halogens or sulfur would not contribute to the sustainability of the overall process.

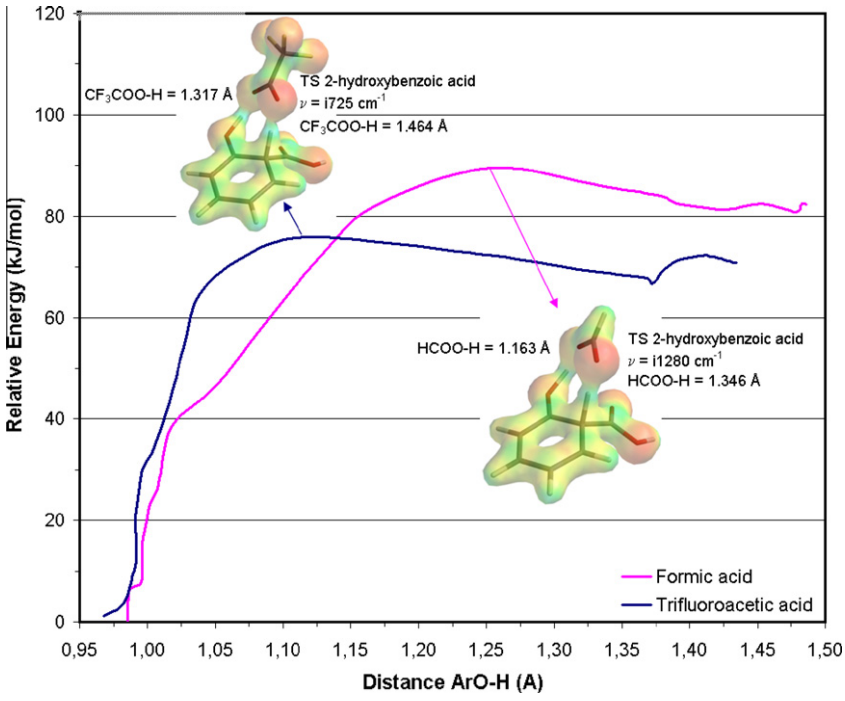

Fig. 7. IRC's of the formation of the keto-isomer of 2-hydroxybenzoic acid decarboxylation catalyzed by trifluoroacetic acid and formic acid via the direct keto-enol pathway.

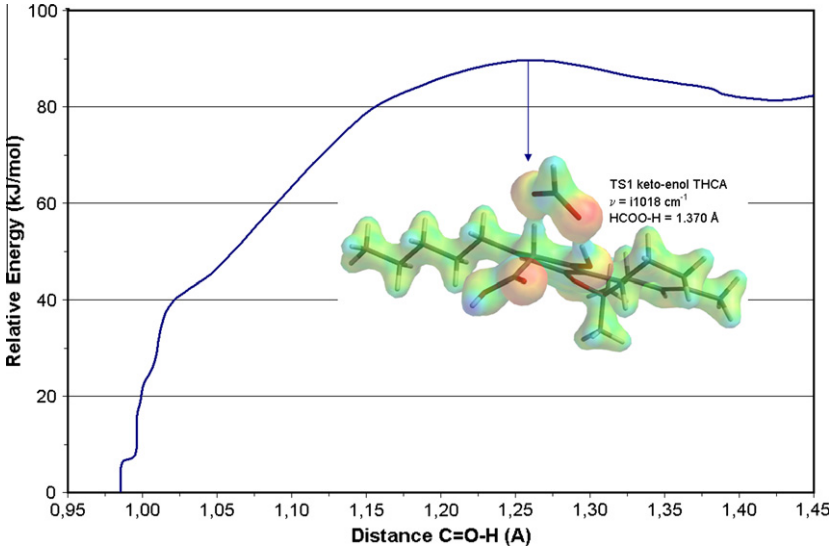

Fig. 8. IRC of Δ^9-THCA decarboxylation catalyzed by formic acid via the direct keto-enol pathway.

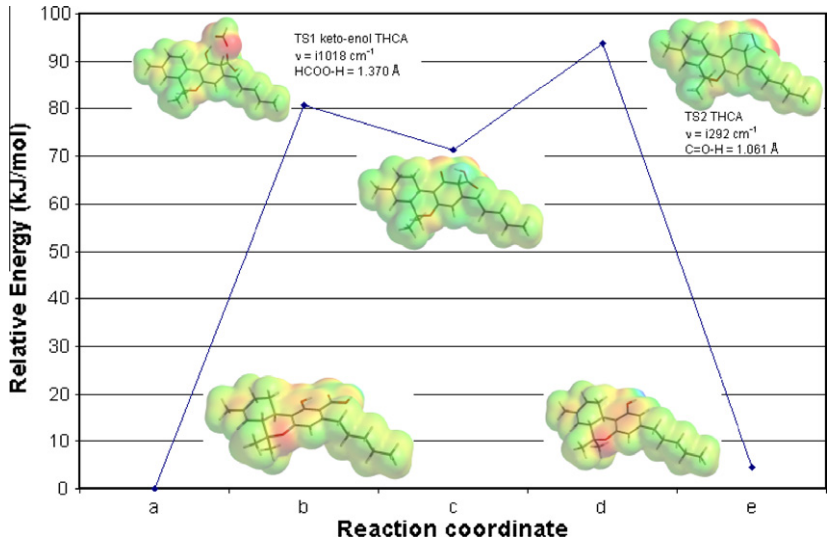

Fig. 9. Energy profile of formic acid catalyzed decarboxylation of Δ^9-THCA.

Table 3
Activation energies of substituted 2-hydroxybenzoic acids with formic acid as catalyst.

Compound	E_a-exp (kJ mol^{-1})	E_a-comp (kJ mol^{-1})
2-Hydroxybenzoic acid	97 [10], 92 [13]	104[a], 92[b]
2,6-Dihydroxybenzoic acid	111 [10], 101, 92 [13]	114[b], 102[c], 92[a],
Δ^9-THCA	85	81[a]

[a] Direct keto-enol pathway.
[b] Indirect keto-enol pathway.
[c] Direct keto-enol pathway with one phenolic OH group not forming an hydrogen bridge with the acid function.

4. Conclusions

Decarboxylation of Δ^9-THCA can be described as a pseudo-first order reaction catalyzed by formic acid, as a model for short chain organic acids present in the flowers of the cannabis plant. The presence of such acids was verified in a series of extraction experiments. Also, the computational idea of catalysis by water to catalysis by an acid, put forward by Li and Brill, and Churchev and Belbruno was extended, and a new direct keto-enol route was found. This route offers the best explanation for the experimental results obtained with Δ^9-THCA, both with respect to the activation barrier and the pre-exponential factor. However both routes can play a role, depending on the exact experimental conditions, as an analysis of available experimental and computational results shows.

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References

[1] R. Baardman, Verkenning Medicinale Cannabis, ZonMw 1 (2003).
[2] E. Russo, J. Cannabis Ther. 3 (2003) 1.

[3] N.J. Goodwin, N.J. Archer, C. Murray, A.K. Greenwood, D. Mchattie, Method and Apparatus for Processing Herbaceous Plant Materials Including the Plant Cannabis, Resolution Chemicals Limited, 2009.
[4] P. Bhatarah, D. McHattie, A.K. Greenwood, Production of Delta-9-tetrahydrocannabinol, US, Patent WO 2009/133376 A1, 2009.
[5] S.L. Kanter, M.R.M. Hollister, J. Chromatogr. 171 (1979) 504.
[6] Vaughan, J. Chromatogr. 129 (1976) 347.
[7] T. Veress, J.I. Szanto, L. Leisztner, J. Chromatogr. 250 (1990) 339.
[8] A. Hazekamp, A. Peltenburg, R. Verpoorte, C. Giroud, J. Liq. Chromatogr. Relat. Technol. 28 (2005) 2361.
[9] Spartan '06 molecular modeling package of Wavefunction, Inc., Irvine, CA. Phys. Chem. Chem. Phys. 8 (2006) 3172.
[10] M.A. Haleem, M.A. Hakeem, Aust. J. Chem. 29 (1976) 443.
[11] R.W. Hay, M.A. Bond, Aust. J. Chem. 20 (1967) 1823.
[12] J. Li, T.B. Brill, J. Phys. Chem. A 105 (2001) 6171.
[13] J. Li, T.B. Brill, J. Phys. Chem. 107 (2003) 2667.
[14] K. Churchev, J.J. BelBruno, J. Mol. Struct. (THEOCHEM) 807 (2007) 1.
[15] M.A. ElSohly, Chemical constituents of Cannabis, in: F.G.-E. Russo (Ed.), Cannabis and Cannabinoids – Pharmacology, Toxicology and Therapeutic Potential, 1984.