Why is THCA decarboxylation faster than CBDA?

an in silico perspective

Weiying He,1 Paul J. Foth,1 Markus Roggen,*1,6 Glenn M. Sammis,*1,6 Pierre Kennepohl*1,2
1 Department of Chemistry, The University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada
2 Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada

Markus Roggen (markus@cbdvl.com)
Glenn Sammis (gsammis@chem.ubc.ca)
Pierre Kennepohl (pierre.kennepohl@ucalgary.ca)

Tetrahydrocannabinol acid (THCA) and cannabidiol acid (CBDA), the two crucial organic components in cannabis and hemp, decarboxylate at different rates to their more active neutral forms. Theoretical calculations are used herein to analyze how the remote annulated ring or pendant substituent influences the rate determining steps of the decarboxylation processes. The uncatalyzed keto-enol tautomerization that precedes decarboxylation is found to be extremely slow in both cases albeit with a ten-fold preference for CBDA. A single molecule of methanol dramatically enhances the reaction rates by allowing for tautomerization through a more favorable six-membered ring transition state. Methanol-catalyzed tautomerization is found to be faster in THCA than in CBDA. This difference results from both the larger dipole moment of the THCA scaffold as well as its greater rigidity relative to CBDA. The greater dipole moment leads to a somewhat better binding of methanol. The lower entropic penalty in THCA towards tautomerization leads to faster decarboxylation.

The cannabis and hemp industries have witnessed exponential growth in the past decade due to changes in their legal status around the globe.1,2 With legalization, consumer interest and demands have evolved from predominantly direct flower sales to a broad range of products including cannabinoïd concentrates and infused products.3 While both the cannabis and hemp extract industries rely on the cannabis plant, the former requires isolates with high tetrahydrocannabinol (THC) concentration and minimal THC contamination.4 Further complicating separation, the naturally occurring form of these cannabinoïds are the acid forms, THCA and CBDA.5 These acids are thermally unstable and undergo decarboxylation upon heating to the neutral, and more potent psychoactive molecules THC and CBD, respectively. It has been reported that THCA decarboxylates at a faster rate than CBDA, but no chemical explanation has been proposed to date.6 There have been a few reported studies on the mechanism of THCA decarboxylation and simplified structural analogs. An early computational study by Ruelle demonstrated that water catalytically lowers the activation energy for the thermal decarboxylation of salicylic acid (Figure 1).7 More recently, Li and Brill explored the role of hydroxyl groups on the aromatic ring in the decarboxylation and found that ortho substitution was critical.8 Chuchev and BelBruno observed the formation of a critical keto-type intermediate and showed the direct role of the o-OH group in the development of the transition state.9 Under acid-catalyzed conditions, Perrotin-Brunel et al. refined this mechanistic proposal and provided further evidence that direct keto-enol tautomerism was the key step in HCOOH-catalyzed decarboxylation of THCA and computed an activation barrier (81 kJ/mol) that is in good agreement with experiment (85 kJ/mol).10 These studies have provided a foundation for understanding the mechanistic pathway of benzoic acid derivatives and even THC decarboxylation. However, there are no studies that mechanistically explain the discrepancy observed for the rate differences between THCA and CBDA.6 Herein, we report a computational study on the decarboxylation of Δ9-THCA and CBDA that identifies the key mechanistic differences that account for the differing decarboxylation rates.

The difference in kinetic reactivity between two similar systems is often a result of minor electronics or stericus near the reaction site. Simultaneously, the conformational space of complex molecules can be extremely large. It can be beneficial to simplify a computational model to remove structural features that may dramatically increase computational cost while having only a minor influence on the process under investigation. Figure 2 summarizes the key features of both Δ9-THCA and CBDA, which must be maintained: the aromatic core, the dihydropyran ring systems in Δ9-THCA, the acyclic isoprenyl fragment in CBDA, and the local steric environment alpha to the carboxylic acid. Deletions in both $T_1$ and $C_1$ involve the removal of the same features: abbreviating the o-pentyl

---

Figure 1. Summary of the state of current knowledge in the decarboxylation of THCA and CBDA via computational studies. The role of remote substitution on the benzoic acid has not been explored and thus the origin of the differing rates of THCA and CBDA decarboxylation have not been elucidated until this work.

Figure 2 summarizes the key features of both Δ9-THCA and CBDA, which must be maintained: the aromatic core, the dihydropyran ring systems in Δ9-THCA, the acyclic isoprenyl fragment in CBDA, and the local steric environment alpha to the carboxylic acid. Deletions in both $T_1$ and $C_1$ involve the removal of the same features: abbreviating the o-pentyl...
sidechain to a methyl group and removing the remote 1-methylcyclohex-1-ene fragment.

Figure 2. Simplified Model of Δ⁹-THCA (T₁) and CBDA (C₁). Atoms in blue were deleted to generate simplified models with significantly fewer degrees of freedom without significantly affecting the overall reaction of interest.

DFT calculations were performed to evaluate both the conformational space of the initial reagents, as well as potential reaction pathways. Gas phase calculations were first performed to evaluate the inherent differences in reactivity between THCA and CBDA towards decarboxylation. The role of solvation and explicit methanol in the reaction mechanism were evaluated in subsequent steps.

A single pathway for decarboxylation was found for both T₁ → T₄ and C₁ → C₄ as shown in Figure 3. In both cases, initial facile rotation of the carboxylic moiety (T₁ → T₂ & C₁ → C₂) precedes rate-limiting formation of the keto form via four-membered ring transition states (T₄ & C₄). Decarboxylation of the keto forms (T₃ & C₃) is calculated to be very rapid compared to the enol/keto rearrangement. Calculated barriers for the uncatalyzed tautomerization are very large, reflecting the high energy required to form the highly strained four-membered ring transition states.

Fig. 4. Detailed gas phase reaction profile for rate determining keto/enol tautomerization in THCA model. Geometry structure of four transition states differs by the location of transfer proton and the relative position of the four-member ring in simplified TCHA model. The products from each pathway (T₃) are enantiomers of each other, which converge to the same decarboxylated product.

The situation is more complex for CBDA as there are now four available reaction pathways from C₂ rather than only two. As with T₂, two isomers are potentially accessible prior to the tautomerism (labelled C₂ₐ and C₂₈) but each of these isomers may now proceed via two distinct reaction paths, which we term cis and trans pathways (Figure 5). In the cis pathway, the proton transfer occurs on the same side as the dangling alkyl sidechain in the meta-position on the ring leading to either the cis-C₂ₐ or cis-C₂₈ transition states. By contrast, proton transfer on the opposite face of the alkyl sidechain leads to either of the trans-C₂₈ or trans-C₂₉ transition states. In contrast to our results with THCA, the energies of the four distinct transition states are very different from each other. Most notably, we find that pathways from the unfavorable C₂₈ isomers are significantly lower in energy than those resulting from C₂₉.
Given that isomerization is rapid compared to the overall process, we must evaluate all potential paths in order to evaluate the relative importance of each pathway and thus provide a better estimate of the overall calculated rates. We therefore performed kinetic modelling using the open-source program COPASI 4.29. Rate constants were derived based on calculated $\Delta G^0$ and $\Delta G^1$ from our DFT calculations (see SI for details). Based on these data, we estimate that the overall rate of tautomerization (and thus of decarboxylation) for CBDA should be about 10× faster than that of THCA, which we attribute to the increased flexibility in CBDA that facilitates formation of the highly strained four-membered ring transition state. Importantly, basal rates of uncatalyzed tautomerization should be extremely low as exemplified by the very large (>150 kJ/mol) calculated transition state energies in all cases.

To mimic commonly used reaction conditions, where alcohols such as ethanol are used in extraction, a methanol molecule was added to evaluate its influence on the kinetics of the tautomerization steps. As has been previously observed with both H$_2$O and HCOOH,$^{7,10}$ the addition of a single molecule of methanol has a dramatic influence on the structure of the calculated intermediates and transition states, as well as the energetics of the tautomerization reaction. Most notably, the $C_2\cdot$MeOH and $T_2\cdot$MeOH transition states now involve a six-membered ring proton-transfer network that allows for proton transfer with negligible ring string, thus lowering the activation energy by >100 kJ/mol for both the THCA and CBDA models.

A closer examination of the reaction pathways reveals similar complexities to those in the gas phase, with multiple relevant pathways for both THCA and CBDA. Two potentially relevant isomers ($T_{2a}\cdot$MeOH and $T_{2b}\cdot$MeOH) are found for THCA leading to two distinct transition states ($T_{2a}\cdot$MeOH and $T_{2b}\cdot$MeOH) at very similar energies ($\Delta \Delta G^\beta < 2 \text{ kJ/mol}$), as shown in Figure 6. Although the presence of the bridging methanol has a profound impact on the overall energy of the rate-limiting transition states, its impact is very similar in both pathways, having only a minor impact on the relative energies of the $T_2$ intermediates and $T_2\cdot$MeOH transition states ($\alpha$ vs. $\beta$).

The situation for the CBDA model is more complex (Figure 6). We now have four different species (cis/trans-$C_{2a}\cdot$MeOH & cis/trans-$C_{2b}\cdot$MeOH) leading to four distinct pathways. In this situation, however, the relative energies of the transition states are all quite similar to each other (<5 kJ/mol), implying that all four paths should contribute to the overall tautomerization process. This differs from the gas phase, where both cis/trans-$C_{2a}$ were ~10 kJ/mol higher in energy than cis/trans-$C_{2b}$. This difference enables the cis/trans-$C_{2a}$ pathway to become more prominent in the overall reaction.
rather than 10× slower in the uncatalyzed reaction (see Figure 8). The shift in preference for THCA relative to CBDA can be attributed to two major factors. Firstly, the conformational flexibility that allows for easier formation of the four-membered ring transition state in the catalyzed reaction becomes a liability in the easier to form six-membered transition state in the catalyzed reaction. In this situation, the entropic penalty in the THCA transition state is much lower since there is a lower conformational range in the fused-ring system. Secondly, the larger dipole moment in the THCA model (4.9D) as compared to the CBDA model (3.7D), which leads to stronger binding of the catalytic methanol, which further accentuates the differences between the two reactions.

As a final step, we applied the SMD solvation model (using MeOH as solvent) to evaluate the influence of a high dielectric medium on the relative rates of the reactions. The overall influence of the solvation model has a relatively subtle influence on the overall energetics but the kinetic model shows that the major impact is a decrease in the kinetic preference for THCA down to only 2× faster than CBDA (Figure 8), indicating that decarboxylation should be quite sensitive to experimental conditions. This result is consistent with the previously discussed influence of the dipole moment between the two molecules. The dipole moment effect is mitigated in high dielectric media, thus impairing the preference towards THCA in the catalyzed reaction.

![Figure 8. Summary of pathways for enol/keto tautomerization and relative importance of each pathway to the overall rate of decarboxylation in CDBA (top) and THCA (bottom). The presence of even small quantities of methanol generates a 4-5 fold preference for THCA decarboxylation over CDBA. This preference is somewhat mitigated by high dielectric solvation of the species (e.g. using MeOH as solvent), leading to a decrease in selectivity for THCA. These studies provide a clear rationale for the observed preference for decarboxylation of Δ9-THCA over CDBA. The differences in reactivity hinge on the greater rigidity of the Δ9-THCA framework as compared to CBDA. The relative conformational flexibility of CBDA is a benefit in the uncatalyzed reaction, but this process is kinetically irrelevant given that it is predicted to be 105× slower than the alcohol-catalyzed reaction. The presence of trace methanol dramatically enhances the overall tautomerization process by enabling a six-membered ring transition state for proton transfer; it further changes the kinetic preference towards the more rigid Δ9-THCA. The greater polarity of the rigid molecule also assists in this process under low dielectric media but is suppressed in high dielectric solvents. These results provide a blueprint for controlling the relative rates of decarboxylation and may serve as a guide for improving current strategies for the processing of hemp and cannabis.

EXPERIMENTAL SECTION Initial geometries for all molecules were constructed from standard models. Geometry optimizations and numerical frequency calculations were performed using version 3.0.3 of the ORCA computational chemistry package.11 Molecular geometries were optimized using the closed-shell B3LYP functional12–15 in combination with the Ahlrichs double-ξ basis set16 with valence polarization for all atoms. Computational efficiency was improved by applying the RI approximation (RJCOSX) for the hybrid functional.17 All calculations were performed with integration grid 4. Reported thermochemical energies are given in kcal/mol and correspond to Gibbs free energies (ΔG0) with zero-point vibrational energy corrections (ZPVE). Statistical mechanics calculations of entropic and thermal effects were performed using the rigid rotor and harmonic oscillator approximations at 298.15 K and 1 atm. Potential energy surface (PES) scans were performed to find intermediate and transition state geometries, and intrinsic reaction coordinates (IRC) were calculated to confirm the connection between all transition states and reactants/intermediates/products. Single point energies were calculated using B3LYP/def2-TZVP with a dense integration grid (Grid 6) and ZORA scalar relativistic corrections. Solvent corrections for methanol were included using the SMD method as implemented in ORCA. All calculations were run on the Abacus computer cluster in the Department of Chemistry at UBC.

ACKNOWLEDGEMENT Financial support for this work was provided by the University of British Columbia (UBC) and the Natural Sciences and Engineering Research Council of Canada (NSERC, 2015-RGPIN-05856 & 2016-RGPIN-05453). Financial support was provided for P.J.F. by the NSERC CREATE Sustainable Synthesis Program and for M.R. by Complex Biotech Discovery Ventures, Ltd.

(11) Neese, F. ORCA v 3.03 – An Ab Initio, DFT, and Semiempirical Electronic Structure Package; Max-Planck-Institut für Kohlenforschung.