

## Thermal Isomerization of Cannabinoid Analogues

Angie Garcia, Dan Borchardt, Chia-En A. Chang,\* and Michael J. Marsella\*

Department of Chemistry, University of California, Riverside, California 92521

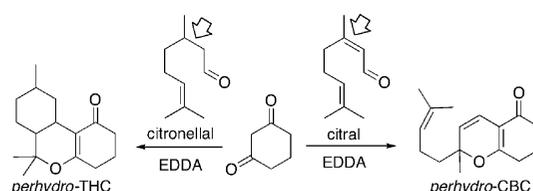
Received August 20, 2009; E-mail: michael.marsella@ucr.edu

Most pharmacotherapeutic and psychoactive effects of marijuana (*Cannabis sativa*) are attributed to a small subset of the ~60 known plant cannabinoids, namely  $\Delta^1$ -tetrahydrocannabinol (THC) and cannabidiol (CBD); nonpsychoactive cannabinoids such as cannabichromene (CBC; a focus of this paper) have garnered less interest.<sup>1</sup> As exogenous CB<sub>1</sub> and/or CB<sub>2</sub> cannabinoid receptor ligands, THC and CBD are believed to mediate central nervous system (CNS) disorders, pain, inflammation, digestive disorders, and immune response.<sup>2</sup> Although traditional pharmaceutical preparations of these cannabinoids are available (e.g., Marinol and Sativex), the concept of “medical marijuana” (i.e., dosing plant cannabinoids by smoking marijuana) has become a legal option for many patients. Unlike oral dosing, smoking exposes cannabinoids to temperatures sufficient to promote thermal reactions, thereby influencing the composition of marijuana smoke. Herein we report the thermal isomerization of nonaromatic cannabinoid analogues CBC<sub>an</sub> and THC<sub>an</sub> (Scheme 2). Our aim is twofold: (i) to demonstrate thermal isomerization as an efficient synthetic tool for interconverting cannabinoid analogues, and (ii) to propose and support a mechanism for the analogous conversion of CBC (a nonpsychoactive plant cannabinoid) to the major psychoactive cannabinoid, THC.

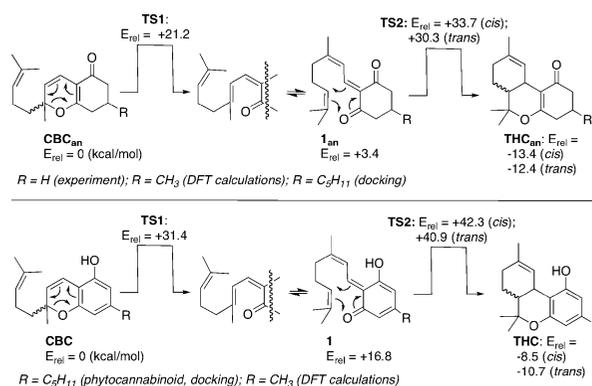
Synthetically, olivetol is often employed to establish the 1,3-dioxo-5-alkylbenzene counterpart moiety of THC.<sup>3–6</sup> An alternate approach utilizes a Knoevenagel/Diels–Alder reaction sequence between citronellal and 1,3-cyclohexadione to yield *perhydro*-THC, a nonaromatic THC analogue lacking the  $\Delta^1$   $\pi$  bond.<sup>7</sup> Attempts to replace citronellal by citral result in a different sequence of reactions (Knoevenagel/oxo  $6\pi$  electrocyclicization) to yield *perhydro*-CBC.<sup>8</sup> Both reaction conditions (Scheme 1) include ethylenediaminediacetate (EDDA), which is believed to catalyze both the Knoevenagel and oxo  $6\pi$  electrocyclicization reactions.<sup>9</sup>

We propose that controlling the competition between the hetero-Diels–Alder and oxo  $6\pi$  electrocyclicization pathways (see Schemes 1 and 2) could establish a strategy for synthesizing THC analogues via isomeric CBC analogues as well as support our hypothesis that CBC may thermally isomerize to THC during the process of smoking marijuana. At present, there are no comprehensive analyses of marijuana smoke for the distribution of cannabinoid stereoisomers; indeed, the presence of nonplant stereoisomers in marijuana smoke would imply thermal isomerization. A paucity of information in this area may reflect restricted access to cannabinoids, all of which maintain Schedule I status in the United States. We addressed this issue by limiting Schedule I compounds (THC, CBC; R = C<sub>5</sub>H<sub>11</sub>) to in silico studies. Furthermore, compounds CBC<sub>an</sub>, **1**<sub>an</sub>, and THC<sub>an</sub> were designed to mimic the *chemical reactivity* of plant cannabinoids while ensuring CNS *inactivity* through substitution of the pentyl side chains with hydrogen atoms (R = H; see Scheme 2). Interestingly, when THC<sub>an</sub> is appended with a pentyl side chain (in silico), it is predicted to have CB<sub>1</sub> binding affinity comparable to THC (see below).

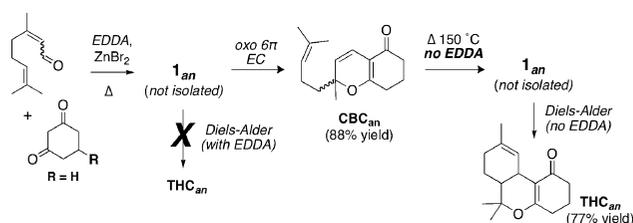
### Scheme 1



### Scheme 2



### Scheme 3



The energies associated with the conversions of CBC/CBC<sub>an</sub> to **1**/**1**<sub>an</sub> and **1**/**1**<sub>an</sub> to THC/THC<sub>an</sub> were calculated using density functional theory (DFT) at the B3LYP/6-31G\* level. To reduce computational cost, side chains in all of the compounds were truncated to R = CH<sub>3</sub>. Calculated energies relative to the compounds CBC and CBC<sub>an</sub> are reported in Scheme 2. In brief, **1**/**1**<sub>an</sub> → CBC/CBC<sub>an</sub> are kinetic pathways ( $E_{TS1} < E_{TS2}$ ), while **1**/**1**<sub>an</sub> → THC/THC<sub>an</sub> are thermodynamic pathways. Overall, CBC/CBC<sub>an</sub> → THC/THC<sub>an</sub> is favored thermodynamically by 8.5/10.7 (cis/trans) and 13.4/12.4 (cis/trans) kcal/mol, respectively.

The syntheses of the phytocannabinoid analogues CBC<sub>an</sub> and THC<sub>an</sub> are shown in Scheme 3. The EDDA-catalyzed Knoevenagel condensation of citral and 1,3-cyclohexadione affords intermediate **1**<sub>an</sub> (not isolated), which rapidly undergoes oxo  $6\pi$  electrocyclicization to provide CBC<sub>an</sub> in 88% isolated yield (the Diels–Alder product, corresponding to THC<sub>an</sub>, was not observed).<sup>9</sup> In our hands, EDDA promotes exclusive formation of CBC<sub>an</sub>, the kinetic reaction product.



**Figure 1.** Superposition of  $\text{THC}_{\text{an}}$  stereoisomers: blue, *trans*-(*R,R*); cyan, *trans*-(*S,S*); yellow, *cis*-(*R,S*); red, *cis*-(*S,R*). Although each stereoisomer generates a slightly different ring conformation, the pentyl group remains in an extended conformation in all cases.

In a second series of experiments,  $\text{CBC}_{\text{an}}$  was prepared as described above, isolated, purified, adsorbed onto silica, and heated at 150 °C in the absence of EDDA. Under these conditions,  $\text{CBC}_{\text{an}}$  was cleanly converted to  $\text{THC}_{\text{an}}$  as a mixture of *cis* and *trans* diastereoisomers (1:1.2; 77% isolated yield). When the reaction was repeated using an admixture of EDDA and silica, only incomplete isomerization of  $\text{CBC}_{\text{an}}$  to  $\text{THC}_{\text{an}}$  was observed (see the Supporting Information). Isomerization of  $\text{CBC}_{\text{an}}$  to  $\text{THC}_{\text{an}}$  is likely influenced by temperature and catalysis: silica promotes and EDDA retards isomerization.

The synthesis of  $\text{THC}_{\text{an}}$  via  $\text{CBC}_{\text{an}}$  (Scheme 3) agrees with our *in silico* predictions, thereby providing additional support for thermal conversion of CBC to THC. Notably, the penalty associated with dearomatization of CBC to yield compound **1** is reflected by a 10.2 kcal/mol increase in the transition-state energy relative to that for the isomerization of  $\text{CBC}_{\text{an}}$  to  $1_{\text{an}}$  (Scheme 2).

Aromatization of  $\text{THC}_{\text{an}}$  to yield THC has precedent in the perhydrocannabinoid literature.<sup>7</sup> However, we suggest that aromatization of  $\text{THC}_{\text{an}}$  is *not* a prerequisite for  $\text{CB}_1$  receptor affinity. We reached this conclusion on the basis of results from ligand–receptor docking studies. For these studies, all of the stereoisomers of THC and  $\text{THC}_{\text{an}}$  contained a pentyl side chain ( $\text{R} = \text{C}_5\text{H}_{11}$ ). Figure 1 reports the superposition of the global minimum-energy conformers of the four  $\text{THC}_{\text{an}}$  stereoisomers.

The minimum-energy conformations of the THC and  $\text{THC}_{\text{an}}$  stereoisomers were docked to a modeled  $\text{CB}_1$  receptor to establish ligand– $\text{CB}_1$  binding poses and interaction energies. It is believed that agonists (e.g., THC) have higher affinities for the activated form of G-protein-coupled-receptors; therefore, an active model of  $\text{CB}_1$  was used in this study.<sup>10</sup> It should be recalled that (*R,R*)-THC is the naturally occurring isomer.

Docking studies indicate that (*R,R*)- $\text{THC}_{\text{an}}$  can adopt different conformations within the  $\text{CB}_1$  binding pocket, and the best ranked conformation is shown in Figure S2 in the Supporting Information. A set of aromatic and hydrophobic residues interacts with the ligand, and the binding is driven primarily by attractive van der Waals interactions. No hydrogen bonds or salt bridges between oxygen atoms of the ligand and the receptor were observed. Interestingly, although (*R,R*)- $\text{THC}_{\text{an}}$  does not form stable hydrogen bonds, (*R,R*)-THC and (*R,R*)- $\text{THC}_{\text{an}}$  have similar interaction energies ( $\Delta E \approx -34$  kcal/mol). Notably, the reported  $\Delta E$  values are more negative than experimental binding affinities, as our calculations did not include entropy losses and the electrostatic desolvation penalty,

which can largely oppose binding. Fortunately, the similar structures of THC and  $\text{THC}_{\text{an}}$  suggest similar entropic and desolvation terms, thereby justifying our comparison of *relative* binding energies.

Similar to previous studies,<sup>11</sup> docking results for (*R,R*)-THC predicted a hydrogen bond between its phenolic hydrogen and residue K3.28 (192), with an N–O distance of  $\sim 2.78$  Å (Figure S3). The ring moieties of both compounds interact with a cluster of residues, T3.33 (197), Y5.39 (275), W5.43 (279), and M6.55 (363), while the pentyl side chain points to different positions in the most stable docked conformation (Figure S4; see the Supporting Information).

Both *cis*- $\text{THC}_{\text{an}}$  enantiomers also demonstrate strong interactions with the  $\text{CB}_1$  receptor ( $\Delta E \approx -33$  kcal/mol; see Figure S4 and the Supporting Information). Notably, both the (*R,R*) and (*R,S*) isomers of *cis*- $\text{THC}_{\text{an}}$  possess rings with nonsuperimposable poses. This variation suggests that with proper design, ligands adopting significantly different ring conformations may display similar  $\text{CB}_1$  binding affinities.

In summary, both *in silico* and experimental evidence have revealed a mechanism for thermal isomerization of  $\text{CBC}_{\text{an}}$  to  $\text{THC}_{\text{an}}$  via tandem pericyclic reactions. This observation has led to a concise synthesis of  $\text{CBC}_{\text{an}}$ , a nonaromatic CBC analogue that readily isomerizes to  $\text{THC}_{\text{an}}$  in high conversion. Docking studies suggest that although it is nonaromatic, (*R,R*)- $\text{THC}_{\text{an}}$  has  $\text{CB}_1$  receptor affinity similar to that of naturally occurring THC. Our calculation predicting thermal isomerization of CBC to THC (via formation of **1**, a transient *o*-quinone methide) awaits experimental confirmation (e.g., by detection of a distribution of THC stereoisomers in marijuana smoke) and will be reported in due course.

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**Supporting Information Available:** Synthesis, characterization, coordinates, and Figures S2–S4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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