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Thermal Isomerization of Cannabinoid Analogues

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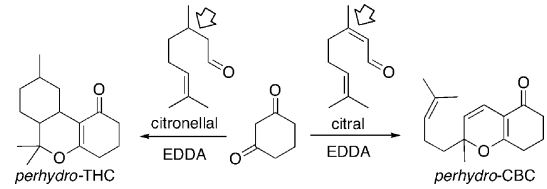
Most pharmacotherapeutic and psychoactive effects of marijuana (*Cannabis sativa*) are attributed to a small subset of the ~60 known plant cannabinoids, namely Δ^1-tetrahydrocannabinol (THC) and cannabidiol (CBD); nonpsychoactive cannabinoids such as cannabichromene (CBC; a focus of this paper) have garnered less interest.[1] As exogenous CB_1 and/or CB_2 cannabinoid receptor ligands, THC and CBD are believed to mediate central nervous system (CNS) disorders, pain, inflammation, digestive disorders, and immune response.[2] 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_{an} and THC_{an} (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.

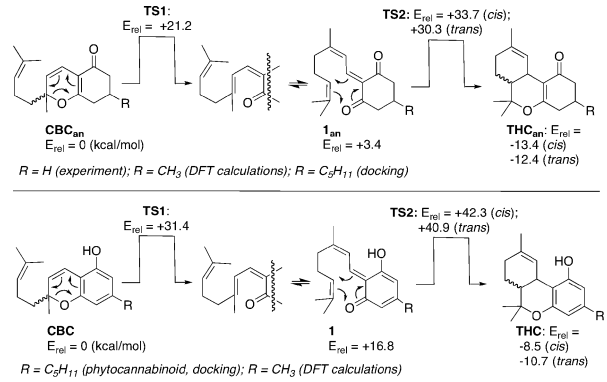
Synthetically, olivetol is often employed to establish the 1,3-dioxo-5-alkylbenzene counterpart moiety of THC.[3−6] An alternate approach utilizes a Knoevenagel/Diels−Alder reaction sequence between citronellal and 1,3-cyclohexadione to yield *perhydro*-THC, a nonaromatic THC analogue lacking the Δ^1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

We propose that controlling the competition between the hetero-Diels−Alder and oxo 6π electrocyclization 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_5H_{11}) to in silico studies. Furthermore, compounds CBC_{an}, $\mathbf{1_{an}}$, and THC_{an} 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_{an} is appended with a pentyl side chain (in silico), it is predicted to have CB_1 binding affinity comparable to THC (see below).

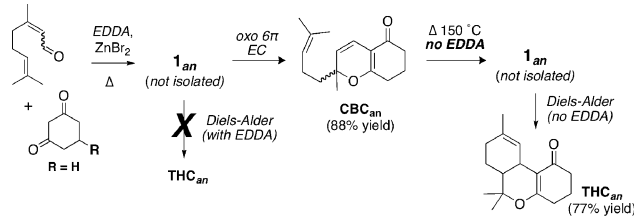
Scheme 1



Scheme 2



Scheme 3



The energies associated with the conversions of CBC/CBC_{an} to $\mathbf{1/1_{an}}$ and $\mathbf{1/1_{an}}$ to THC/THC_{an} 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_3. Calculated energies relative to the compounds CBC and CBC_{an} are reported in Scheme 2. In brief, $\mathbf{1/1_{an}}$ → CBC/CBC_{an} are kinetic pathways ($E_{TS1} < E_{TS2}$), while $\mathbf{1/1_{an}}$ → THC/THC_{an} are thermodynamic pathways. Overall, CBC/CBC_{an} → THC/THC_{an} 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_{an} and THC_{an} are shown in Scheme 3. The EDDA-catalyzed Knoevenagel condensation of citral and 1,3-cyclohexadione affords intermediate $\mathbf{1_{an}}$ (not isolated), which rapidly undergoes oxa 6π electrocyclization to provide CBC_{an} in 88% isolated yield (the Diels−Alder product, corresponding to THC_{an}, was not observed).[9] In our hands, *EDDA promotes exclusive formation of* CBC_{an}, the kinetic reaction product.

10.1021/ja907062v CCC: $40.75

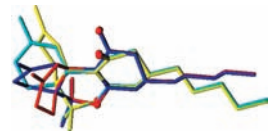


Figure 1. Superposition of THC_{an} stereoisomers: blue, *trans*-(*R*,*R*); cyan, *trans*-(*S*,*S*); yellow, *cis*-(*R*,*S*); red, *cis*-(*S*,*R*). Although each stereoisomer generates a slightly different ring conformation, the pentyl group remains in an extended conformation in all cases.

In a second series of experiments, CBC_{an} was prepared as described above, isolated, purified, adsorbed onto silica, and heated at 150 °C *in the absence of EDDA*. Under these conditions, CBC_{an} was cleanly converted to THC_{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 CBC_{an} to THC_{an} was observed (see the Supporting Information). Isomerization of CBC_{an} to THC_{an} is likely influenced by temperature and catalysis: silica promotes and EDDA retards isomerization.

The synthesis of THC_{an} via CBC_{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 CBC_{an} to 1_{an} (Scheme 2).

Aromatization of THC_{an} to yield THC has precedent in the perhydrocannabinoid literature.[7] However, we suggest that aromatization of THC_{an} is *not* a prerequisite for 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 THC_{an} contained a pentyl side chain ($R = C_5H_{11}$). Figure 1 reports the superposition of the global minimum-energy conformers of the four THC_{an} stereoisomers.

The minimum-energy conformations of the THC and THC_{an} stereoisomers were docked to a modeled CB_1 receptor to establish ligand−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 CB_1 was used in this study.[10] It should be recalled that (*R*,*R*)-THC is the naturally occurring isomer.

Docking studies indicate that (*R*,*R*)-THC_{an} can adopt different conformations within the 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)-THC_{an} does not form stable hydrogen bonds, (R,R)-THC and (R,R)-THC_{an} have similar interaction energies* ($\Delta E \approx -34$ kcal/mol). Notably, the reported ΔE 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 THC_{an} suggest similar entropic and desolvation terms, thereby justifying our comparison of *relative* binding energies.

Similar to previous studies,[11] 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 ∼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*-THC_{an} enantiomers also demonstrate strong interactions with the 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*-THC_{an} possess rings with nonsuperimposible poses. This variation suggests that with proper design, ligands adopting significantly different ring conformations may display similar CB_1 binding affinities.

In summary, both in silico and experimental evidence have revealed a mechanism for thermal isomerization of CBC_{an} to THC_{an} via tandem pericyclic reactions. This observation has led to a concise synthesis of CBC_{an}, a nonaromatic CBC analogue that readily isomerizes to THC_{an} in high conversion. Docking studies suggest that although it is nonaromatic, (*R*,*R*)-THC_{an} has 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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