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An *ab initio* theoretical study of the stereoisomers of tetrahydrocannabinols

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Summary

An extensive theoretical study of the stereoisomers of tetrahydrocannabinols has been performed at the ab initio HF/6-31G* and B3LYP/6-31G* levels. Effects of solvation were calculated with the Onsager model (with full geometry optimization), SCRF with Tomasi's PCM, and isodensity polarization continuum models. Single-point MP2//HF/6-31G* calculations were carried out. Frequency calculations for all the isomers at the HF/6-31G* level and for two natural isomers Δ^1-THC-RR and Δ^6-THC-RR at the B3LYP/6-31G* level were performed. Our results support the findings of the previous AM1 studies that the orientation of the carbocyclic ring and its C1 substituent with respect to the phenyl group hydroxyl oxygen play the major role in the activity. The calculated values of the LUMO energy (lowest unoccupied molecular orbital) and the hardness of the stereoisomers show that for the trans isomers it is easier to remove one electron from its HOMO (highest occupied molecular orbital) to the LUMO and easier to accept an electron from the receptor binding site than for the cis isomers. Combining geometric features (the orientation of the carbocyclic ring and its C1 substituent with respect to the phenyl group hydroxyl oxygen) with electronic features (LUMO and hardness), we explain the activity differences among the stereoisomers.

Introduction

Cannabinoids have been the subject of much research since the mid-1960s when Mechoulam and his colleagues first isolated (−)-trans-delta-1-tetrahydrocannabinol (Δ^1-THC) [1–2], the major psychopharmacologically active component of cannabis. More than 300 cannabinoids have been synthesized and tested. Before the cannabinoid receptor was found, cannabinoid structure-activity relationships were based on the assumption that the effects produced by cannabinoids may be receptor mediated [3–4]. SAR studies at Pfizer led to the development of the non-classical cannabinoids such as CP 55,940 [5–7], 10-100 times more potent than THC, that could be radiolabelled and used as a probe for the characterization of a selective, high-affinity cannabinoid binding site. This discovery was the key to the cannabinoid receptor breakthrough. The search for a cannabinoid receptor depended on the use of a potent synthetic that would allow observation of the binding. CP 55,940 provided this potency, and it allowed Howlett, Devane and their associates to perform a successful resource with tissue of a rat brain [8], which would be not possible using Δ^1-THC. To date, two subtypes of the cannabinoid receptors, CB_1 [9] and CB_2[10], have been identified. CB_1 receptor is largely found in the brain and CB_2 is in the periphery, both are G-protein-coupled receptors.

Since each of Δ^1-THC and Δ^6-THC has two chiral centers, there are four possible stereoisomers for each of them. The structures of these eight stereoisomers are shown in Figure 1. The numbering of each non-hydrogen atom is described in Figure 2. Stereospecificity accounts for the fact that natural (−)-trans-Δ^1-THC (Δ^1-THC-RR) and (−)-trans- Δ^6-THC (Δ^6-THC-RR) are many times more potent than the corresponding synthetic (+)-isomer in a variety of tests

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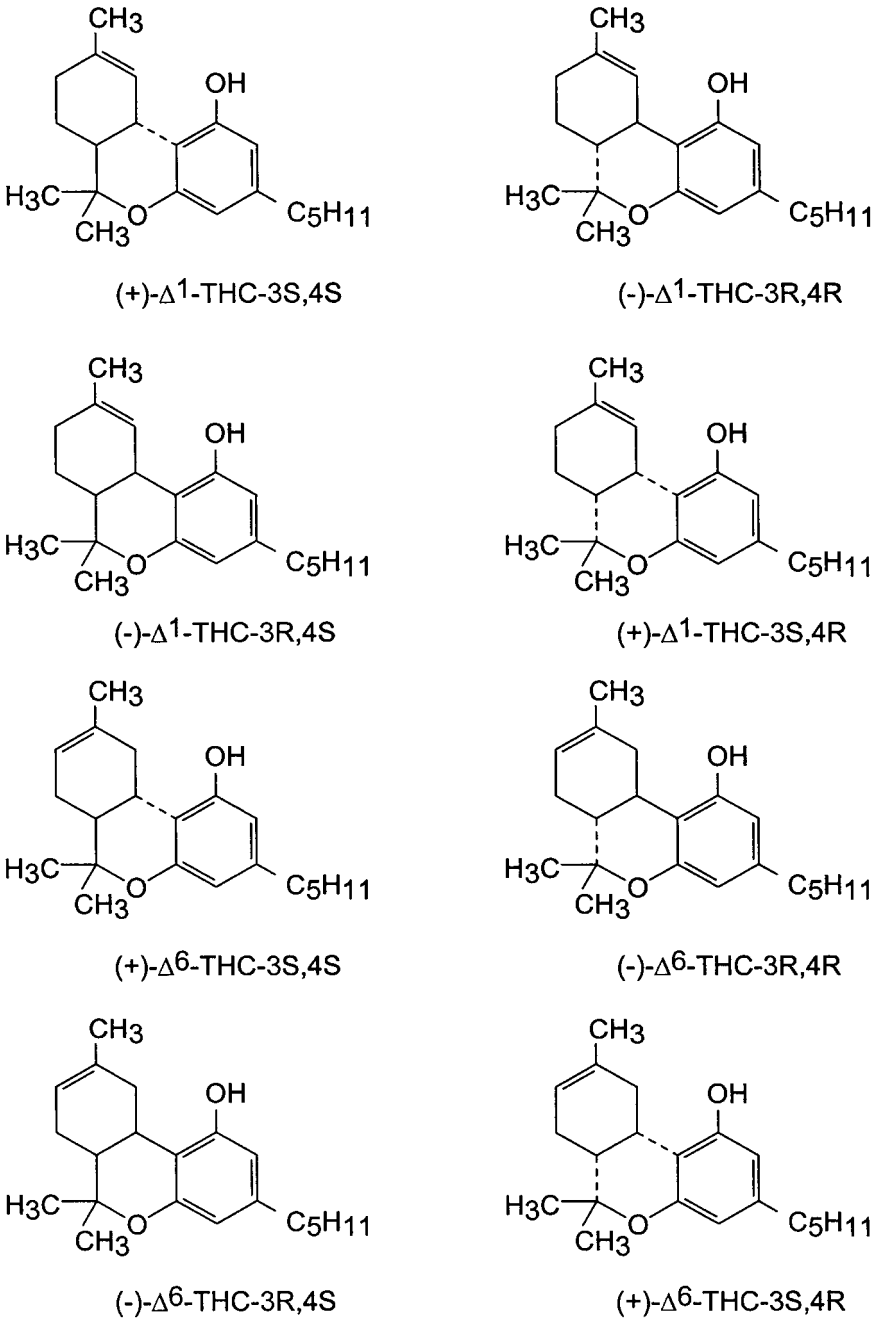

Figure 1. The structures of the stereoisomers of Δ^1-THC and Δ^6-THC.

[11–13]. The hypothermia in mice produced by natural (−)-trans- Δ^1-THC (Δ^1-THC-RR) and (−)-trans- Δ^6-THC (Δ^6-THC-RR) were 9.1 and 30.4 times greater than that produced by their respective synthetic (+)-isomers [13]. For the depression of spontaneous activity in mice, the ED_{50} (95% confidence limits) for (−)-trans- Δ^1-THC (Δ^1-THC-RR) was 2.6 mg/kg (1.3-5.1) and 14.6 mg/kg (9.1-23.5) for (+)-trans-Δ^1-THC (Δ^1-THC-SS). The potency ratio of the ED_{50}'s was 5.6. A greater potency is found in cannabinoids with the trans ring junction than with the cis junction [13]. The relative potency of (−)-trans- Δ^1-THC (Δ^1-THC-RR), (+)-trans- Δ^1-THC (Δ^1-THC-SS), and (+)-cis-Δ^1-THC (Δ^1-THC-SR) in the dog static ataxia test

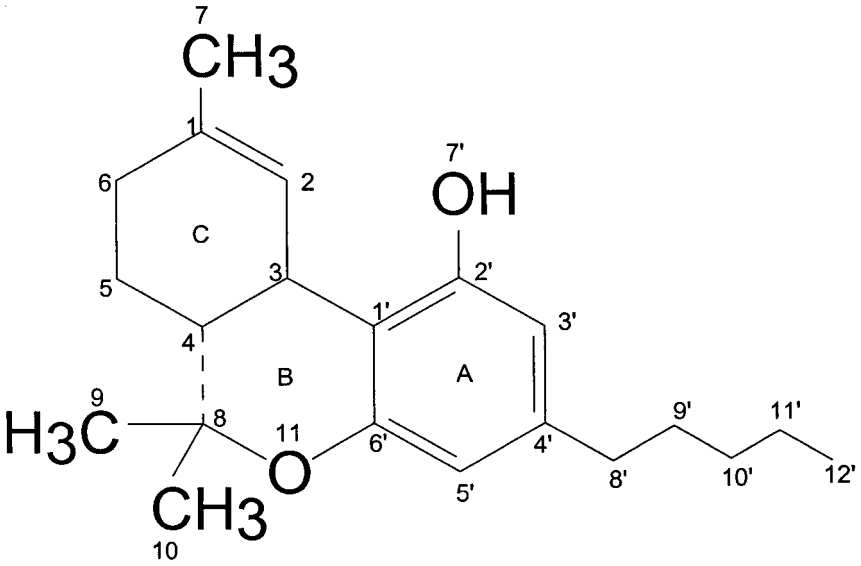

Figure 2. The structure and numbering of Δ^1-THC.

Table 1. The absolute (in a.u.), relative energies (ΔE, in kcal mol^{-1}), and dipole moments (in Debyes) of stereoisomers of Δ^1-THC and Δ^6-THC at HF/6-31G* and B3LYP/6-31G* level

	HF/6-31G*	ΔE	Dipole moments	B3LYP/6-31G*	ΔE	Dipole moments
Δ^1-THC-RR	−962.42988	0.98	1.05	−968.75914	1.21	0.95
Δ^1-THC-SS	−962.42999	0.91	0.93	−968.75925	1.14	0.87
Δ^1-THC-SR	−962.42546	3.76	1.11	−968.75556	3.46	1.13
Δ^1-THC-RS	−962.42544	3.76	1.06	−968.75546	3.52	1.09
Δ^6-THC-RR	−962.43144	0.00	2.31	−968.76107	0.00	2.40
Δ^6-THC-SS	−962.43044	0.63	2.38	−968.76035	0.45	2.50
Δ^6-THC-SR	−962.42707	2.74	1.27	−968.75733	2.34	1.19
Δ^6-THC-RS	−962.42938	1.29	1.13	−968.75925	1.14	1.09

Table 2. The absolute (in a.u.) and relative energies (ΔE, in kcal mol^{-1}) of stereoisomers of Δ^1-THC and Δ^6-THC at IPCM, PCM and optimized Onsager models

	IPCM	ΔE	PCM	ΔE	Onsager	ΔE
Δ^1-THC-RR	−962.44606	4.04	−962.40713	−5.14	−962.42997	1.17
Δ^1-THC-SS	−962.44748	3.16	−962.39765	0.81	−962.43007	1.11
Δ^1-THC-SR	−962.43931	8.28	−962.40370	−2.99	−962.42556	3.94
Δ^1-THC-RS	−962.44232	6.39	−962.39344	3.44	−962.42553	3.96
Δ^6-THC-RR	−962.45251	0.00	−962.39893	0.00	−962.43183	0.00
Δ^6-THC-SS	−962.44473	4.88	−962.42409	−15.79	−962.43087	0.60
Δ^6-THC-SR	−962.43844	8.82	−962.40520	−3.94	−962.42719	2.91
Δ^6-THC-RS	−962.44065	7.44	−962.39716	1.11	−962.42948	1.47

Figure 3. Orientation of the C1 substituent with respect to phenol hydroxyl oxygen of Δ^1-THC-RR from B3LYP/6-31G*.

Table 3. The relative free energies of hydration estimated by IPCM, PCM models, and optimized Onsager level with respect to Δ^6-THC-RR (in kcal mol^{-1})

	IPCM	PCM	Onsager
Δ^1-THC-RR	3.07	−6.12	0.20
Δ^1-THC-SS	2.25	−0.11	0.20
Δ^1-THC-SR	4.53	−6.75	0.19
Δ^1-THC-RS	2.63	−0.32	0.19
Δ^6-THC-RR	0.00	0.00	0.00
Δ^6-THC-SS	4.25	−16.41	−0.02
Δ^6-THC-SR	6.08	−6.68	0.17
Δ^6-THC-RS	6.15	−0.18	0.19

Figure 4. Orientation of the C1 substituent with respect to phenyl hydroxyl oxygen of Δ^1-THC-SS from B3LYP/6-31G*.

is 1: < 0.1: < 0.04 [11]. Unfortunately, the (−)-cis-Δ^1-THC (Δ^1-THC-RS), (−)-cis- Δ^6-THC (Δ^6-THC-RS), and (+)-cis- Δ^6-THC (Δ^6-THC-SR) species have not been synthesized.

Structure-activity relationship studies of classical cannabinoids have indicated that a number of regions are important in determining receptor affinity and pharmacological potency, including the phenolic hydroxyl at C2′, the C1 position of the cyclohexene ring, and the nonpolar alkyl side chain at the C4′ position. This approach assumes that modification of one group does not affect the reactivity, geometric, and stereometric factors of another. In fact, the molecular properties are encoded in the entire molecular structure and are responsible for the interactions of the ligand with the receptor. The existence of two out of three regions, the phenolic hydroxyl at C2′ and the nonpolar alkyl side chain at the C4′ position, can not explain the activity differences between the stereoisomers.

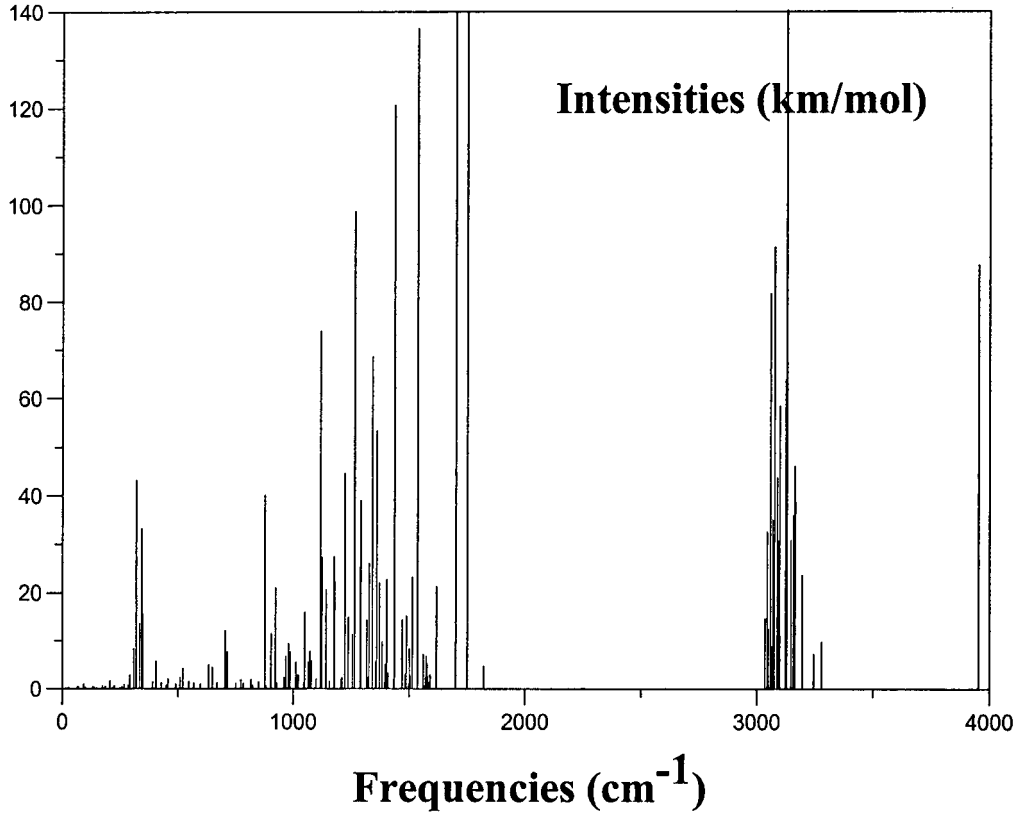

Figure 5. HF vibrational frequencies for Δ^1-THC-RR.

There are several previous theoretical studies of cannabinoids. These include studies with the extended Hückel molecular orbital theory [14], perturbative configuration interaction with localized orbitals (PCILO) [15], molecular mechanics method [16–22], and the AM1 semiempirical quantum chemical method [23]. There have not been any attempts to distinguish the different activities of the stereoisomers of the tetrahydrocannabinols based on the properties of optimized conformers obtained by reliable ab initio methods. Ab initio is the most advanced method, while molecular mechanics involves a parameterized classical 'balls and springs' model. AM1 takes account of the electronic structure of the system, but AM1 parameters were derived from geometries and heats of formation of the reference systems. The aim of this work is to obtain structural information and the electronic features of the stereoisomers of tetrahydrocannabinols and provide a better understanding of their activity.

Methods

For each of the eight stereoisomers, the MM2 [24] optimized geometry was used as the starting point for semiempirical AM1 calculations [25]. The AM1 optimized geometry was then used as the starting point for ab initio Hartree-Fock (HF) level geometry optimizations with the 6-31G* basis set. The ab initio calculations were performed by either the Gaussian 94 or Gaussian 98 software packages [26].

Even though the Δ^1-THC and Δ^6-THCs are all extremely hydrophobic compounds that partition into the membrane immediately, for completeness the relative free energies of hydration of these compounds were also calculated. Effects of solvation were calculated at the HF level using the 6-31G* basis set and the self-consistent reaction field (SCRF) method. The Onsager model [27] (with full geometry optimization), Tomasi's polarized continuum model (PCM) [28] and the isodensity polarized continuum model (IPCM) [29] were used.

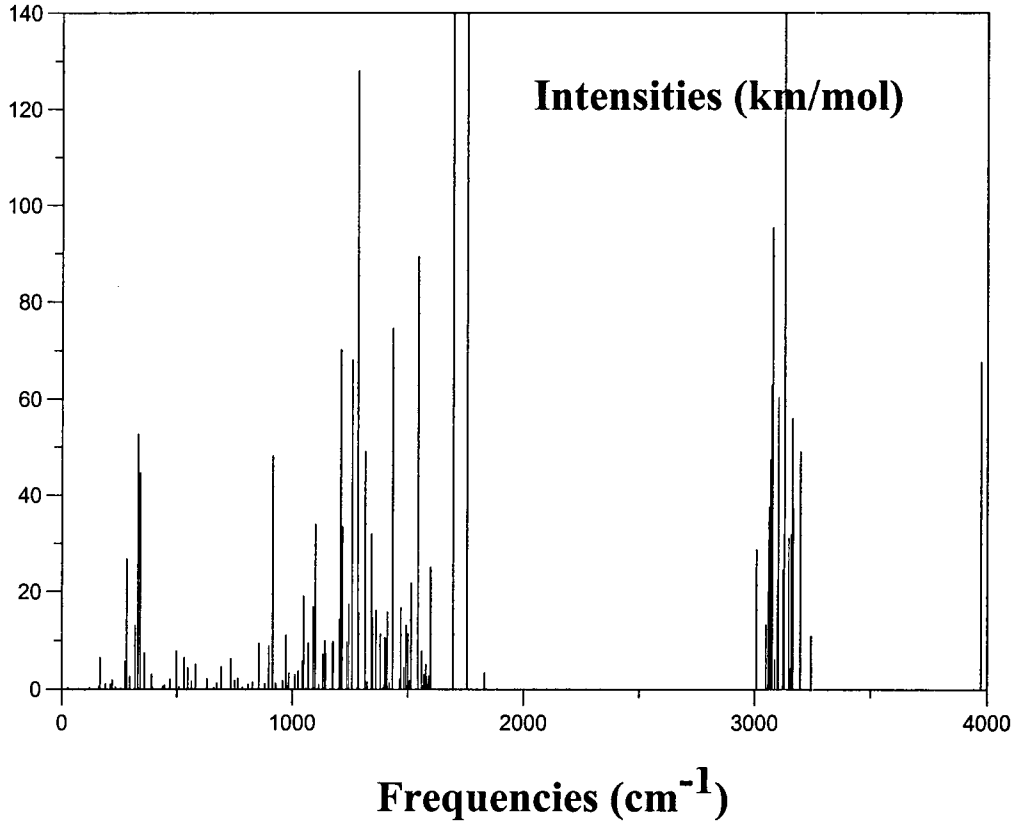

Figure 6. HF vibrational frequencies for Δ^6-THC-RR.

Single-point second-order Møller-Plessett perturbation theory (MP2) calculations were carried out using the optimized SCF level geometries. Geometry optimizations with density-functional theory using the B3LYP approximation, where the Becke exchange functional [30] is coupled with the Lee-Yang-Parr correlation functional [31], were also performed. Harmonic vibrational frequency calculations were performed for all the isomers at the HF/6-31G* level. In addition, for two natural isomers, (−)-trans- Δ^1-THC and (−)-trans-Δ^6-THC harmonic vibrational frequencies were also calculated at the B3LYP/6-31G* level.

Results and Discussion

Table 1 shows the calculated absolute energy (in a.u.), relative energy (in kcal mol^{-1}), and dipole moments (in Debyes) of stereoisomers of Δ^1-THC and Δ^6-THC at the HF/6-31G* and B3LYP/6-31G* levels. Both HF/6-31G* and B3LYP/6-31G* results show similar trends. The Δ^6-THC series is slightly more stable than the corresponding Δ^1-THC isomers which corresponds with the experimental findings that the Δ^1-THC isomers are easily isomerized to Δ^6-THC on treatment with acids [32]. The trans isomers (RR and SS) of Δ^1-THC and Δ^6-THC are slightly more stable than the cis isomers (RS and SR). This is due to the steric interaction between H_3 and H_4. Among all of the eight stereoisomers, the natural Δ^6-THC-RR has the lowest energy.

Both HF/6-31G* and B3LYP/6-31G* calculations show that trans isomers of Δ^1-THC have smaller dipole moments than its cis isomers, but the trans isomers of Δ^6-THC have larger dipole moments than its cis isomers.

Table 2 displays the results of solvation effects for the studied systems. With the IPCM model and optimized Onsager model, the free energies of hydration of Δ^1-THC and Δ^6-THC are lower than the corresponding energies evaluated with the HF/6-31G* geometry. However, with the PCM model, the free energies of hydration of Δ^1-THC and Δ^6-THC

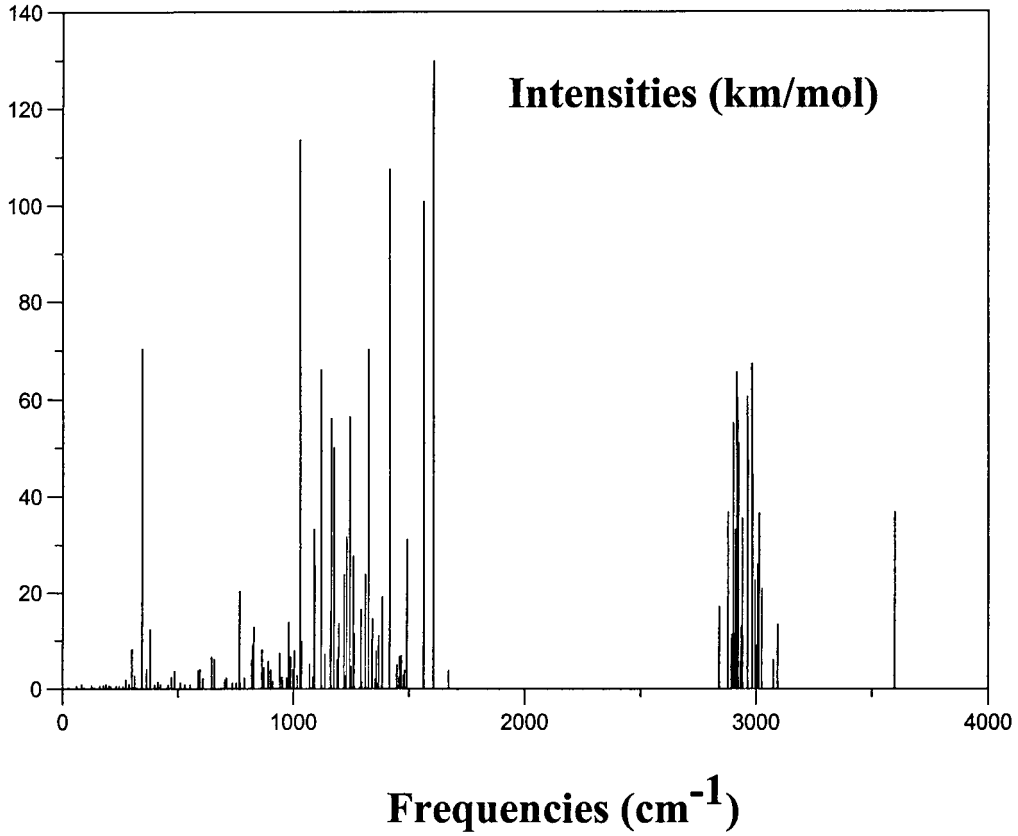

Figure 7. B3LYP/6-31G* vibrational frequencies for Δ^1-THC-RR.

are higher than the corresponding energies evaluated with the HF/6-31G* geometry. The relative free energies of hydration estimated by the IPCM, PCM, and optimized Onsager models with respect to the natural Δ^6-THC-RR (in kcal mol^{-1}) are shown in Table 3. The IPCM model shows that Δ^6-THC-RS is the most hydrated species, with a $\Delta\Delta G_{hyd}$ value of 6.15 kcal mol^{-1}which is very close in energy to the Δ^6-THC-SR (only 0.07 kcal mol^{-1} less). The natural Δ^6-THC-RR is the least hydrated species. The PCM model shows that natural Δ^6-THC-RR, Δ^6-THC-RS, Δ^1-THC-SS, Δ^1-THC-RS are comparably easier-hydrated species than the other four stereoisomers. The optimized Onsager model can not differentiate the relative free energies of hydration among all the four stereoisomers of Δ^1-THC and the two cis stereoisomers of Δ^6-THC. The two trans stereoisomers of Δ^6-THC (Δ^6-THC-RR and Δ^6-THC-SS) are the least hydrated species. In particular, Δ^6-THC-SS is the least hydrated isomer among eight stereoisomers from either PCM or Onsager models. The natural Δ^6-THC-RR is highly lipophilic. As mentioned by Thomas et al. [33], whether the double bond is in position 1 or 6 has no effect on the partition coefficients. These workers used the shake-flask method to determine the octanol-water partition coefficient for Δ^1-THC. From 12 measurements, they obtained an average value of 12 091 $\pm$ 3941 (log $P = 4.08$).

From the structure-activity relationship studies, we conclude that two out of three important regions, the phenolic hydroxyl at C2′ and the nonpolar alkyl side chain at the C4′ position, can not explain the activity differences between these stereoisomers. The C1 position of the cyclohexane ring plays an important role in determining receptor affinity [19–21, 23]. The C7-C1$\cdots$C2′-O7′ dihedral angle for all the stereoisomers from HF/6-31G*, B3LYP/6-31G*, and optimized Onsager geometries are shown in Table 4. We found the dihedral angles C7-C1$\cdots$C2′-O7′ for all the stereoisomers display similar trends in these three different level optimizations. The dihedral angles C7-C1$\cdots$C2′-O7′ for Δ^1-THC-RR and Δ^6-THC-RR are in the ranges of (-46.76 to -47.17) and (-38.50 to -38.88) respectively, which are closer to molecular mechanics

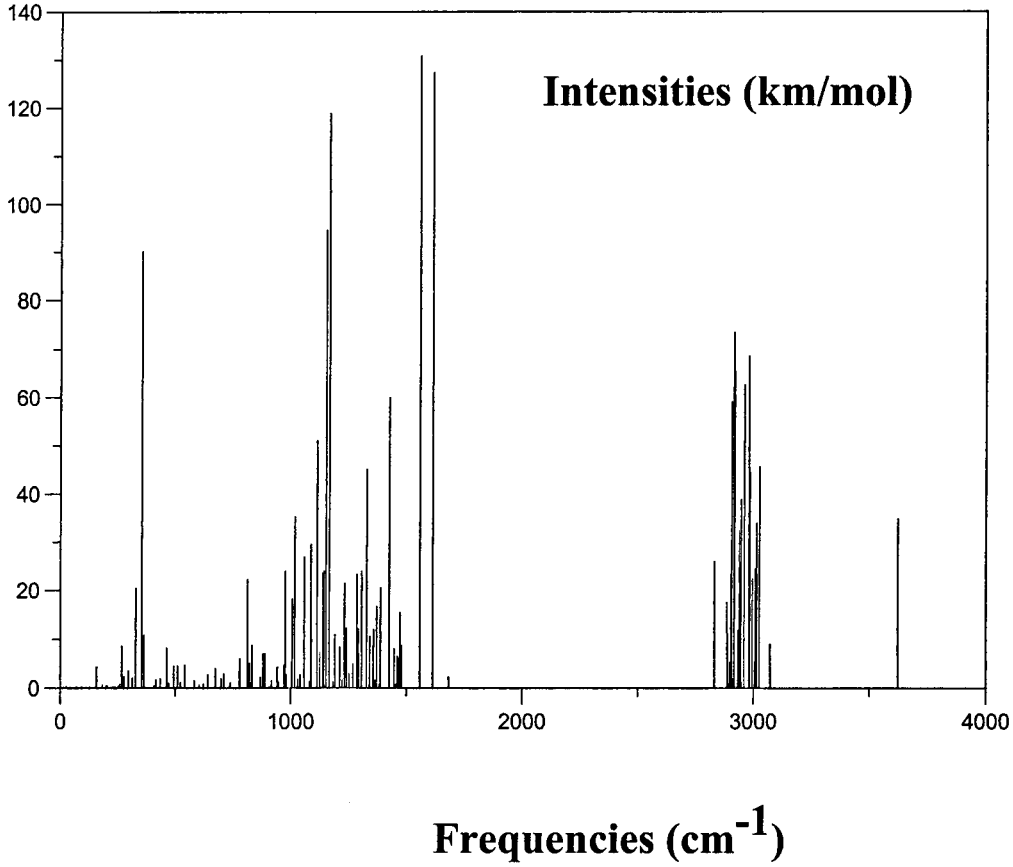

Figure 8. B3LYP/6-31G* vibrational frequencies for Δ^6-THC-RR.

Table 4. The dihedral angles C7-C1···C2′-O7′ of stereoisomers of Δ^1-THC and Δ^6-THC in HF/6-31G*, B3LYP/6-31G*, and optimized Onsager model

	C7-C1···C2′-O7′ at HF/6-31G*	C7-C1···C2′-O7′ at B3LYP/6-31G*	C7-C1···C2′-O7′ at optimized Onsager
Δ^1-THC-RR	−47.16	−46.76	−47.12
Δ^1-THC-SS	47.40	47.53	47.40
Δ^1-THC-SR	57.91	58.18	57.86
Δ^1-THC-RS	−57.69	−57.40	−57.62
Δ^6-THC-RR	−38.59	−38.88	−38.50
Δ^6-THC-SS	38.59	38.74	38.55
Δ^6-THC-SR	43.14	44.52	43.33
Δ^6-THC-RS	−54.65	−55.02	−54.58

Table 5. The zero point corrected HF/6-31G* and MP2//HF-6-31G* absolute (in a.u.), relative energies (ΔE, in kcal mol $^{-1}$) of stereoisomers of Δ^1-THC and Δ^6-THC at HF/6-31G*

	HF/6-31G*+ZPE	ΔE	MP2//HF-6-31G*	ΔE
Δ^1-THC-RR	−961.92689	0.95	−965.50470	1.27
Δ^1-THC-SS	−961.92699	0.89	−965.50481	1.20
Δ^1-THC-SR	−961.92246	3.73	−965.50206	2.92
Δ^1-THC-RS	−961.92245	3.74	−965.50203	2.94
Δ^6-THC-RR	−961.92841	0.00	−965.50672	0.00
Δ^6-THC-SS	−961.92721	0.76	−965.50719	−0.29
Δ^6-THC-SR	−961.92370	2.95	−965.50383	1.82
Δ^6-THC-RS	−961.92620	1.38	−965.50355	1.99

values [20–21] (−49 and −38) than the AM1 values [23] (−45.67 and −34.21). The negative dihedral angle in Δ^1-THC-RR, Δ^1-THC-RS, Δ^6-THC-RR, and Δ^6-THC-RS is in agreement with the AM1 results and coincides with the sign of the rotation of plane-polarized light. The negative value of this dihedral angle means that the C1 substituent points toward the top or to the left of the phenyl hydroxyl oxygen when the molecule is viewed in a sideways perspective with the sidechain closest to the viewer and induces a more favorable interaction [34] for the binding of the drug with the active site. Orientation of the C1 substituent with respect to phenyl hydroxyl oxygen of Δ^1-THC-RR and Δ^1-THC-SS from B3LYP/6-31G* are shown in Figures 3 and 4. The negative value of this dihedral angle also allows us to predict the activity for the compounds which have not been synthesized, Δ^1-THC-RS, Δ^6-THC-RS, and Δ^6-THC-SR. Since the dihedral angles in Δ^1-THC-RS and Δ^6-THC-RS are negative, they are expected to be more active than Δ^1-THC-SR and Δ^6-THC-SR, which is in agreement with the AM1 finding.

The zero-point corrected energies at the HF/6-31G* and MP2//HF/6-31G* levels are shown in Table 5. We found that the energies at the MP2//HF/6-31G* level, the most accurate method applied in this study, follow the general trend such as Δ^6-THC is more stable than its corresponding Δ^1-THC and trans isomers are more stable than its cis isomers, except that Δ^6-THC-SS has the lowest energy. The energy differences between Δ^6-THC-RR and Δ^6-THC-SS are very small; they are 0.63, 0.45, and −0.29 kcal mol^{-1}at the HF/6-31G*, B3LYP/6-31G*, and MP2//HF/6-31G* levels respectively.

The HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of all the stereoisomers of Δ^1-THC and Δ^6-THC from the HF/6-31G*, B3LYP/6-31G*, and optimized Onsager model are shown in Table 6. The consideration of HOMO energies of all the stereoisomers from three different optimized geometries does not reveal any clear trends. The comparison of LUMO energies of all the stereoisomers shows that the trans isomers have less positive LUMO energies than the cis isomers and that the (+)-trans isomers have less positive LUMO energies than the (−)-trans isomers. This may imply that the trans isomers accept an electron from the binding receptor site more easily than the cis-isomers, especially the (+)-trans could more easily accept an electron from the binding receptor site than the (−)-trans isomer. The hardness values [35], one half of the LUMO-HOMO energy difference, of the stereoisomers are shown in Table 7. From the hardness, we found that the trans isomers have less hardness (more softness) than the cis isomers and the (+)-trans has the least hardness (most softness) in Δ^1-THC and Δ^6-THC. The increasing softness, corresponds to lower energy necessary to promote an electron from the HOMO to the LUMO. This implies that removing one electron to the binding receptor site from the trans isomers is easier than from the cis isomers and it is easier for the (+)-trans than for the (−)-trans form.

Frequency calculations for all the stereoisomers from HF/6-31G* and Δ^1-THC-RR and Δ^6-THC-RR from the B3LYP/6-31G* prove that all stereoisomers are at minimum energy configurations. The vibrational frequencies for normal modes vs infrared intensities from the HF/6-31G* and B3LYP/6-31G* for Δ^1-THC-RR and Δ^6-THC-RR are depicted in Figures

Table 6. The HOMO and LUMO energies (in a.u.) of stereoisomers of Δ^1-THC and Δ^6-THC at HF/6-31G*, B3LYP/6-31G*, optimized Onsager model

	HOMO HF/6-31G*	LUMO HF/6-31G*	HOMO B3LYP/6-31G*	LUMO B3LYP/6-31G*	HOMO Onsager	LUMO Onsager
Δ^1-THC-RR	−0.29448	0.15546	−0.20091	0.01248	−0.29451	0.15550
Δ^1-THC-SS	−0.29458	0.15495	−0.20108	0.01196	−0.29435	0.15523
Δ^1-THC-SR	−0.29465	0.15763	−0.20094	0.01492	−0.29468	0.15766
Δ^1-THC-RS	−0.29468	0.15756	−0.20102	0.01480	−0.29454	0.15772
Δ^6-THC-RR	−0.29344	0.15407	−0.20074	0.01157	−0.29335	0.15363
Δ^6-THC-SS	−0.29381	0.15287	−0.20124	0.01068	−0.29412	0.15194
Δ^6-THC-SR	−0.29391	0.15521	−0.20136	0.01235	−0.29389	0.15531
Δ^6-THC-RS	−0.29352	0.15866	−0.20035	0.01523	−0.29339	0.15892

Table 7. The hardness energies (in a.u.) of stereoisomers of Δ^1-THC and Δ^6-THC at HF/6-31G*, B3LYP/6-31G*, optimized Onsager model

	Hardness HF/6-31G*	Harness B3LYP/6-31G*	Harness Onsager
Δ^1-THC-RR	0.22497	0.10670	0.22500
Δ^1-THC-SS	0.22476	0.10652	0.22479
Δ^1-THC-SR	0.22614	0.10794	0.22617
Δ^1-THC-RS	0.22612	0.10791	0.22613
Δ^6-THC-RR	0.22376	0.10616	0.22349
Δ^6-THC-SS	0.22334	0.10596	0.22303
Δ^6-THC-SR	0.22456	0.10686	0.22460
Δ^6-THC-RS	0.22609	0.10779	0.22616

5–8. Computed vibrational frequencies are usually somewhat larger than experiment due to the use of harmonic approximation and incomplete inclusion of electron correlation. Different scaling factors have been proposed to correct the calculated frequencies [36]. We applied the scaling factor of 0.96 in our case and show the results in the Figures 5–8. As expected from the similarity of their structures, the predicted infrared spectra are similar. The B3LYP spectra show an O-H stretching band at about 3750 cm^{-1}, a series of C-H stretching bands around 3000 cm^{-1}, C-C stretches and bends in the 1000–1500 cm^{-1} range, and some out-of-plane bends in the 300–500 cm^{-1} range. The HF and B3LYP results are in general agreement, with some differences in the details. The HF frequencies tend to be somewhat higher than the B3LYP results, as commonly found. For the most part, the HF intensities are greater than B3LYP intensities, with the exception of some of the low-frequency modes. The most significant differences between the DFT spectra for the two isomers are in the 1000–1500 cm^{-1} range. For the Δ^1 isomer the most intense bands of this range are at the low and high ends of the range. For the Δ^6 isomer on the other hand, the most intense band is in the middle (1167cm^{-1}). Also, the Δ^1 isomer has in general more intense bands in the 1000–1500 cm^{-1} range than the Δ^6 isomer.

In conclusion, we predicted that all considered forms are local minimum energy species, Δ^6-THC is more stable than its corresponding Δ^1-THC, and trans isomers are more stable than its cis isomers in HF/6-31G*, B3LYP/6-31G*, and MP2//HF/6-31G* calculations. Δ^6-THC-RR has the lowest energy in HF/6-31G* and B3LYP/6-31G*. Δ^6-THC-SS has the lowest energy in MP2//HF/6-31G*. However, the energy differences between Δ^6-THC-RR and Δ^6-THC-SS are very small at these three levels. The C7-C1$\cdots$C2′-O7′ dihedral angle plays the major role in the activity. The negative value of this dihedral angle means the C1 substituent points toward the top or to the left of the phenyl hydroxyl oxygen is viewed in a sideways perspective with the sidechain closest to the viewer and induces a more favorable interaction for binding of the drug with the active site. This also allows us to predict the activity for the stereoisomers which have not been synthesized. The electronic features such as LUMO and hardness of the stereoisomers indicate that for the trans isomers it is easier to remove one electron from its HOMO to LUMO and easier to accept an electron from the receptor binding site than for the cis isomers. Combining these two factors, we can differentiate the activity between the stereoisomers.

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