Dimerization of Dexanabinol by Hydrogen Bonding Accounts for Its Hydrophobic Character

EMIL POP, MARCUS E. BREWSTER

Pharmos Corporation, 2 Innovation Drive, Alachua, Florida 32615

Received 1 March 1997; revised 22 March 1997; accepted 23 April 1997

ABSTRACT: Dexanabinol, a dihydroxylated synthetic cannabinoid, is a member of the nonpsychotropic (+) 3S, 4S enantiomeric series. Experimental evidence suggests that dexanabinol might form aggregates (e.g., dimers) in which the two OH (a phenol and an allylic alcohol) groups are involved in hydrogen bonding. The extremely low solubility of dexanabinol in water implies that this interaction may not involve solvent molecules. A theoretical study of this phenomenon in the framework of the PM3 molecular approximation is described. Simple molecular models (phenol and 6-cyclohexene-1-methanol) were initially examined followed by extension of the calculations to dexanabinol. The results indicate that dimers of dexanabinol resulting from hydrogen bonding are more stable than the isolated molecules with the differences attributed to hydrogen bonding energies. It is suggested that the phenolic hydroxy group of one molecule forms a hydrogen bond with the allylic OH group of the second molecule and vice versa, resulting in dimers which contain two hydrogen bonds. The hydrogen bonds are more stable (6.14 kcal/mol) and the complex formed is more favored energetically when the phenol groups act as hydrogen bond donors and the allylic OH groups as acceptors. These interactions are also energetically more favored than those between dexanabinol and water (3.70 kcal/mol). The dexanabinol dimer manifested a lower dipole moment as compared to the monomer (1.211 vs. 2.221 debye) as well as a much larger log P (11.16 vs. 5.90), indicating strong hydrophobic character. The optimized structure shows that the OH groups involved in hydrogen bonds are oriented to the interior of the dimers, while the lipophilic side chains are oriented toward the exterior. These properties of the dimer may explain the low water solubility of dexanabinol.
 Int J Quant Chem **65**: 1057–1064, 1997

Correspondence to: E. Pop.

CCC 0020-7608 / 97 / 061057-08

Introduction

Dexanabinol (HU-211), the (+) 3S, 4S-5′-(1′, 1′ - dimethylheptyl) - Δ^6-7-hydroxy-tetrahydrocannabinol is a nonpsychotropic, synthetic cannabinoid currently in clinical development as a neuroprotective agent [1,2]. The extremely low solubility of this compound in water complicates its formulation as an intravenous drug. While the bulky lipophilic 1′,1′-dimethylheptyl side chain should reduce water solubility, the two hydroxyl groups present in the molecule of dexanabinol would be expected to induce a moderating influence. The compound was, however, found to be practically insoluble in water.

A possible explanation for this behavior is that the OH groups of dexanabinol cannot form hydrogen bonds with the solvent since they are already involved in more favorable intramolecular or intermolecular (dexanabinol-dexanabinol) interactions. Both OH groups present in dexanabinol (allylic at C-7 and phenol at C-3′) can participate in hydrogen bonding. While intramolecular hydrogen bonding are less probable due to the large distance between the two OH groups, intermolecular bonding is predictable [3–6] and can occur in various ways (i.e., phenol–phenol and allylic OH–allylic OH, phenol–allylic OH, etc.). Experimental evidence for this assumption is supported by the infrared (IR) spectra of dexanabinol. The shift of IR frequencies of the hydroxyl groups from 3590 to 3650 cm^{-1}, typical for free groups to lower values (3226 and 3424 cm^{-1}) is indicative of hydrogen bonding [7,8]. The relatively high melting point of dexanabinol (140–143°C) as compared to related compounds (e.g., the 6-methyl analog, dexanabinol pivalate, etc.) which are oils, is also suggestive of stabilization due to hydrogen bonding. Furthermore, acylation of the phenolic position of dexanabinol to form the acetate or other esters, paradoxically results in increased water solubility. The observation is consistent with incipient disruption of hydrogen bonds.

A theoretical study of this phenomenon has been performed. The PM3 molecular orbital approximation [9,10] was used for this purpose. The paradigm of the study included a comparison of the thermodynamic stability, as reflected by the calculated heat of formation (ΔHf), of dexanabinol monomer to the stability of a dimer resulting by double hydrogen bond formation of two molecules of dexanabinol. If the energy of dimers were found to be lower than the sum of two isolated monomers, the dimerization should be energetically favored. Moreover, the difference in energy should be a measure of the energy of the hydrogen bonding. Since the computations are rather complex with over 300 orbitals to be calculated, simple models (phenol and 6-cyclohexene-1-methanol) were used for initial studies. Vibrational spectra were only calculated for these models. Other physical properties relevant to solubility (dipoles, log P) are also evaluated.

Methods

Theoretical studies were performed using PM3 molecular orbital approximation [9,10] which was included in the HyperChem (Hypercube, Inc., Waterloo, Ontario, Canada) version 5.0 software [11] run on a pentium Digital computer. PM3 uses a set of parameters derived from a larger number and variety of experimental versus calculated molecular properties, as compared to other semiempirical methods, including the AM1 procedure [12]. Typically, nonbonded interactions are less repulsive in the PM3 procedure [11]. Molecular models were constructed by the model builder of HyperChem. Geometry optimization was completed by using the Polak-Ribiere conjugate gradient algorithm method. The restricted Hartree–Fock (RHF) method was applied to the calculation of wave functions. Hydrogen bonds were displayed after molecule pairs were arranged so that the required conditions (hydrogen donor–acceptor distance less than 3.2 Å and the angle made by covalent bonds to the donor and acceptor atoms less than 120°) were fulfilled. Log P were calculated using a nonlinear regressional model in which all the descriptors used (molecular surface, volume, weight, etc.) are determined from the fully optimized structures [13], included in the QSAR package of the ChemPlus™ (version 1.5) extension for HyperChem.

Results and Discussion

The hydrogen bonding in the selected model systems, i.e., phenol (**1**) and 6-cyclohexene-1-methanol (**2**) (Fig. 1), was considered in the initial

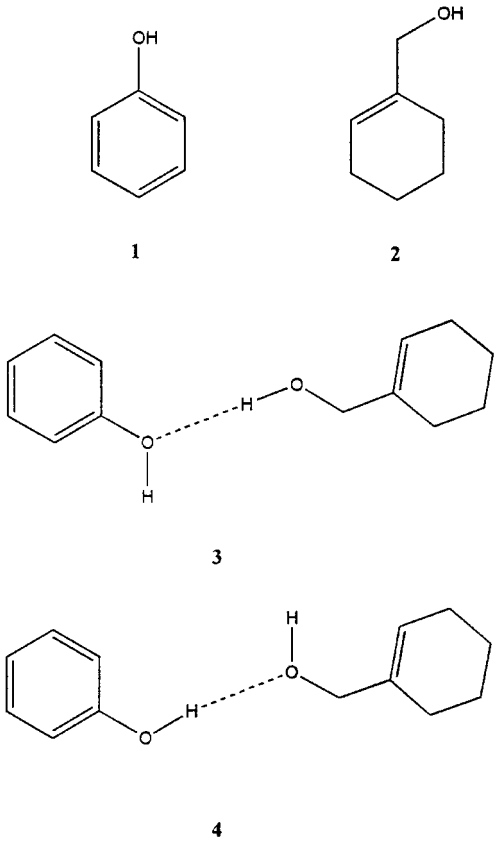

FIGURE 1. Structures of phenol (**1**), 1-cyclohexene-1-methanol (**2**), and two complexes (**3** and **4**) resulting by hydrogen bonding.

study, and heats of formation (ΔHf) determined for the optimized structures. Molecules **1** and **2** were then arranged so that the hydrogen bonding conditions were fulfilled. In model **3**, the allylic OH served as the hydrogen bond donor and the phenol as the acceptor, while in the model **4** the phenol is the hydrogen bond donor. Hydrogen bonds were displayed using the Hyperchem ''show hydrogen bonds'' and ''recompute hydrogen bond'' options. Both dimers were then reoptimized using the PM3 Hamiltonian. The calculated heats of formation of the complexes were compared to those of the monomers (Table I). In both cases, ΔHf of the complex resulting from hydrogen bonding was smaller than the sum of ΔHf's of **1** and **2**. It is reasonable to assume that these differences ($\Delta\Delta Hf$), calculated according to Eq. (1), represents the energies of the hydrogen bonding (the same results can be obtained by using the total binding energies of **1**, **2**, **3** and **4**, presented in Table I, instead of ΔHf's for these calculations). The results (Table I) indicate that the hydrogen bond energy was only 1.48 kcal/mol in the case of **3**, indicating the formation of a weak hydrogen bond, but 6.63 kcal/mol for **4** indicating a stronger hydrogen bond:

$$\Delta\Delta Hf = \Delta Hf_{(I)} + \Delta Hf_{(II)} - \Delta Hf_{(I+II)}, \qquad (1)$$

where $\Delta Hf_{(I)}$ is the heat of formation of the phenol, $\Delta Hf_{(II)}$ the heat of formation of the 1-cyclohexen-1-methanol, and $\Delta Hf_{(I+II)}$, the heat of formation of the dimers (**3** or **4**).

Net charges and atomic orbital populations are presented in Table II. A higher degree of polarization of the positive hydrogen and negatively charged oxygen atoms can be noticed in the case of hydrogen-bonded molecules **3** and **4**. In the case of **3**, a strong participation of the Pz orbital of the allylic alcohol oxygen (hydrogen donor) was noted, while in the case of **4**, of the Pz orbital of the phenol oxygen (hydrogen donor) can be seen.

A vibrational analysis was performed and the vibrational (IR) spectra were calculated for the models. No negative frequencies appeared in the

TABLE I
Calculated binding energies (E), heats of formations (ΔHf), and estimated hydrogen bond energies ($\Delta\Delta Hf$) (kcal/mol)

Compound	E (kcal/mol)	ΔHf (kcal/mol)	($\Delta\Delta Hf$) (kcal/mol)
1	−1419.36	−21.85	—
2	−1931.91	−50.90	—
3	−3352.76	−74.23	1.48
4	−3357.90	−79.38	6.63
5	−6584.86	−154.05	—
6	−13171.30	−309.69	0.80
7	−13180.23	−320.69	6.14
8	−7026.68	−268.36	3.70

TABLE II
Net charges and atomic orbital electron populations for atoms involved in hydrogen bonding

	Net charge and atomic orbital electron population			
	Phenol		Allylic alcohol	
Compound	O	H	O	H
Phenol (**1**)	−0.228 Px: 1.275 Py: 1.243 Pz: 1.916	0.196 *s*: 0.803	—	—
Cyclohexene-1-methanol (**2**)	—	—	−0.306 Px: 1.574 Py: 1.227 Pz: 1.645	0.181 *s*: 0.819
Complex **3**	−0.248 Px: 1.286 Py: 1.422 Pz: 1.751	—	−0.335 Px:1.300 Pz: 1.302 Pz: 1.921	0.209 *s*: 0.791
Complex **4**	−0.271 Px: 1.660 Py: 1.418 Pz: 1.891	0.232 *s*: 0.678	−0.335 Px: 1.392 Py: 1.830 Pz: 1.297	—
Dexanabinol (**5**)	−0.231 Px: 1.361 Py: 1.333 Pz: 1.743	0.194 *s*: 0.805	−0.308 Px: 1.349 Py: 1.377 Pz: 1.775	0.184 *s*: 0.816
Dimer **6**	*a*: −0.252 Px: 1.545 Py: 1.692 Pz: 1.222 *b*:− 0.250 Px: 1.379 Py: 1.318 Pz: 1.759	*a*: 0.208 *s*: 0.792 *b*: 0.203 *s*: 0.797	*a*: −0.330 Px: 1.250 Py: 1.754 Pz: 1.514 *b*: −0.335 Px: 1.464 Py: 1.406 Pz: 1.653	*a*: 0.200 *s*: 0.800 *b*: 0.202 *s*: 0.798
Dimer **7**	*a*: −0.267 Px: 1.285 Py: 1.872 Pz: 1.315 *b*: −0.268 Px: 1.287 Py: 1.837 Pz: 1.350	*a*: 0.205 *s*: 0.794 *b*: 0.211 *s*: 0.788	*a*: −0.333 Px: 1.741 Py: 1.251 Pz: 1.535 *b*: −0.333 Px: 1.583 Py: 1.345 Pz: 1.599	*a*: 0.197 *s*: 0.803 *b*: 0.194 *s*: 0.805
Dexanabinol-water complex (**8**)	−0.264 Px: 1.378 Py: 1.336 Pz: 1.754	0.215 *s*: 0.784	−0.350 Px: 1.209 Py: 1.387 Pz: 1.944	0.197 *s*: 0.803

Note: *a* and *b* represent the two hydrogen bonds and atoms involved, respectively.

calculated IR spectra, indicating that valid minimum energy structures were obtained [11]. Recent results [14] indicated that out of PM3, AM1 and MNDO methods used for calculating IR frequency, PM3 showed the closest correspondence (which is generally about 10% too high in value of stretches) to experimental values. Indeed, calculated values of the O–H stretching vibrations were 3891 cm^{-1} for phenol (**1**) and 3812 cm^{-1} for the hydrogen bond containing complex **4**, indicating a batochromic shift as that observed experimentally for hydroxyl groups involved in hydrogen bonding.

The study of dimers of dexanabinol formed by hydrogen bonding was performed using the same rationale: the thermodynamic stability of the dexanabinol monomer (**5**) (Fig. 2), as reflected by calculated PM3 heat of formation (ΔHf) was first determined. The optimized geometry of **5** was then examined to verify the possibility of formation of intramolecular hydrogen bonds. The distance between the two oxygen atoms of the OH functionalities was too large (5.939 Å) to form hydrogen bondings. Two dexanabinol molecules were then arranged so that intermolecular hydro-

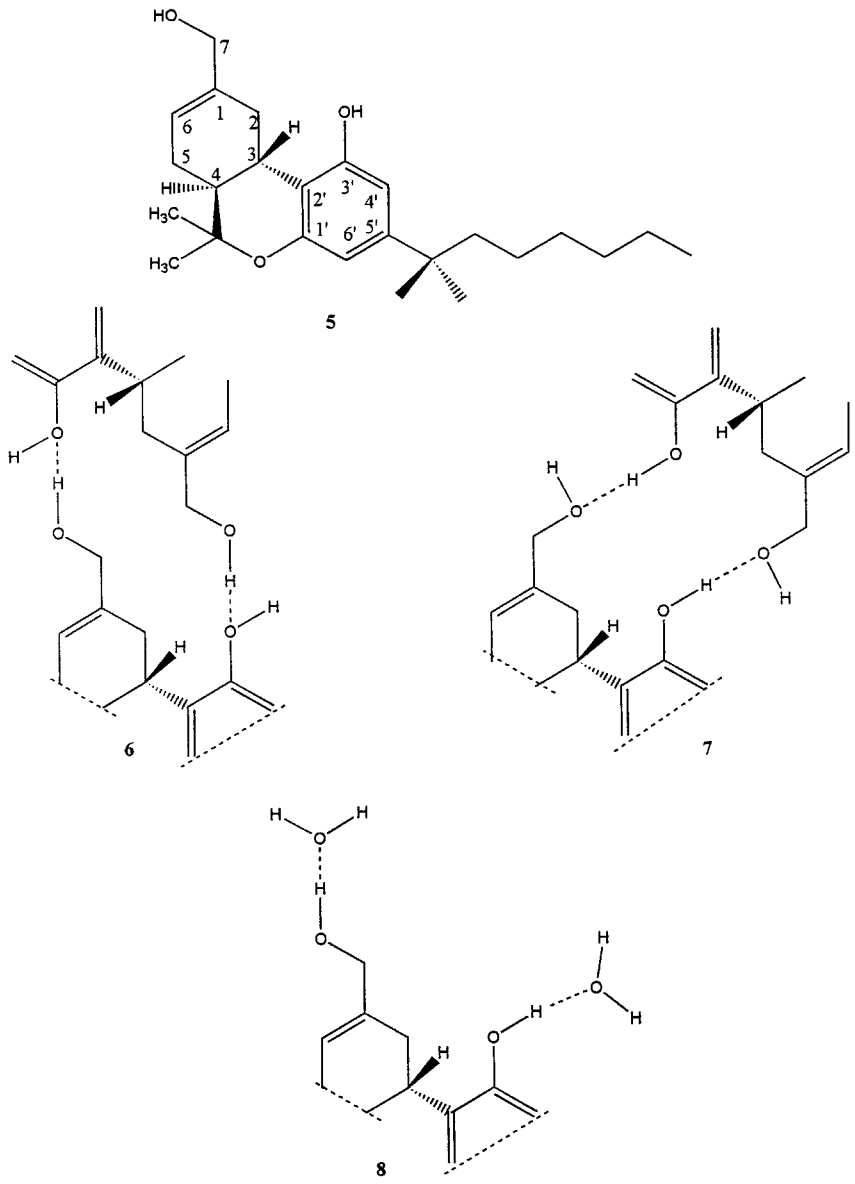

FIGURE 2. Structure of dexanabinol (**5**), two possible dimers (**6** and **7**), resulting by hydrogen bonding and the complex resulting by hydrogen bonding of **5** with water (**8**). Structures **6**–**8** are abbreviated.

gen bonding between OH groups could occur. Two models in which all four OH groups of the two dexanabinol molecules were involved in hydrogen bonding were built: one (models **6**) in which the allylic OH groups served as the hydrogen bond donors and the phenols as the acceptors, while in the other one (**7**) the phenols are the hydrogen donors and the allylic OH groups the acceptors. Due to sterical hindrance, models in which the phenol interacted with the juxtaposed phenol and allylic hydroxyl with the complementary allylic hydroxyl group could not be built. Also, models in which only one hydrogen bond was formed were not considered in this study. The geometries of the resulting dimers were then reoptimized using the PM3 procedure. Calculated heats of formations of dimers were compared with those of the monomers. The dimers had smaller ΔHf (-309.69 and -320.38 kcal/mol) than the sum of two monomers (-308.1 kcal/mol) (Table I), indicating that dimers were energetically favored. Equation (2) was used to calculate the hydrogen bond energies:

$$\Delta\Delta Hf = [2\Delta Hf_{(III)} - \Delta Hf_{(IV)}]/2 \qquad (2)$$

where $\Delta Hf_{(III)}$ is the heat of formation of dexanabinol and $\Delta Hf_{(IV)}$ is the heat of formation of the dimer **6** or **7**.

As in the case of the simpler systems discussed, the hydrogen bonds for the model in which the allylic OH was the hydrogen bond donor (dimer **6**) were less favored (0.795 kcal/mol) than those in which the phenol was the hydrogen donor (dimer **7**) (6.14 kcal/mol) (Table I). The polarization of the oxygen and hydrogen atoms involved in the bonding discussed above is also apparent in this case (Table II); i.e., the oxygen atoms have an increased negative charge, and the hydrogen atoms have an increased positive charge as compared to the monomer. In **6**, orbitals Py or the oxygen atoms have the larger contribution for one of the hydrogen bonds and the Px and Pz for the other, while in **7**, the Py orbitals were the major contributors to the highest occupied molecular orbitals (HOMO) for both oxygen atoms.

By following the same rationale, the hydrogen bonding of the dexanabinol monomer (**5**) with two molecules of water has been evaluated. The calculated (PM3) ΔHf for water is -53.46 kcal/mol. To both OH groups of optimized **5** a molecule of water was then added so that the hydrogen bond requirements were fulfilled. After the hydrogen bonds were built, the geometry of the trimolecular system, **8**, was reoptimized using the PM3 approximation. The calculated heat of formation of the supramolecular system was -268.36 kcal/mol. The energy of the hydrogen bonds ($\Delta\Delta Hf$) was calculated by using Eq. (3):

$$\Delta\Delta Hf = \left[(\Delta Hf_{(III)} + 2\Delta Hf_{H_2O}) - \Delta Hf_{(V)}\right]/2, \quad (3)$$

where ΔHf_{H_2O} is the heat of formation of water and $\Delta Hf_{(V)}$ the heat of formation of **8**. The energy of the hydrogen bondings between dexanabinol and water was found to be 3.70 kcal/mol.

Due to the large volume of computations required, no vibrational spectra were calculated for these molecules.

These data suggest that hydrogen bonding stabilizes dexanabinol but that dimer formation was more energetic than interaction with water molecules. While the data presented above refer to the gas phase, thermodynamic stabilities including solvent effects are currently being examined. Obviously, the presence of water may significantly alter energetics of the system. It is possible that in spite of stronger hydrogen bonding associated with the dimer, dilution with concomitant increase in water concentration and decrease of dexanabinol concentration may weaken the dimeric interaction or even lead to dissociation. On the other hand, the observed poor solubility of dexanabinol in water, even at very low concentration is consistent with the presence of stable dimers that do not readily dissociate.

In this context it is of interest to examine other molecular properties of dexanabinol related to solubility. Dipoles are importance for solvation, and polar compounds generally manifest better solubility in polar solvents, such as water. The calculated dipole moment of the dexanabinol monomer (**5**) is 2.221 debye, while dimer **7** is quite symmetrical, having an even lower dipole moment (1.211 debye) (Table III). The dipole moment of the complex of **5** with two water molecules is higher (3.499 debye). Dipole moments indicate that the solubility of dexanabinol in water, especially in the form of the dimer, should be low. Table III includes data about the geometries of the hydrogen bonds such as the distances between the heavy atoms (oxygen) participating in the hydrogen bonds and the angles formed by O—H—O atoms. These parameters were not modified significantly during computations since the conditions were imposed a priori. The hydrogen is intermediate between two

TABLE III
Calculated geometries of hydrogen bonds, dipole moments and log *P*

Compound	O — H — O Hydrogen bond: O — O Distance (Å)	O — H — O Hydrogen bond: Angle (O — H — O) (degrees)	Dipole (debye)	log *P*
3	2.783	170.66	2.671	1.37
4	2.767	170.98	2.774	4.27
6	2.776	159.44	2.325	10.83
	2.813	159.69		
7	2.769	173.18	1.211	11.52
	2.770	174.87		
8	3.159	165.11	3.499	1.34
	2.763	171.41		

participating oxygen atoms, but not equidistant. By examining the shape of the dimer (Figs. 3 and 4), it can be seen that its structure is symmetrical, having the polar OH groups engaged in hydrogen bonding in the interior and the highly lipophilic dimethylheptyl side chains projected toward the exterior. These types of compounds are not expected to be soluble in water.

Log *P* (Table III), which are reliable indices for the lipophilicity of various compounds, indicate that while dexanabinol itself is lipophilic (log *P*: 5.90), the lipophilicity of dimer **7** is extremely high (log *P*: 11.52). Furthermore, we have begun to look at explicit interactions between the hydroxyl functions and water. To this end, the dihydrate **8** was examined as described. Addition of water molecules to the structure affects log *P* as indicated by a calculated value of 1.34 for the trimolecular system.

In summary, a dimer of dexanabinol resulting from hydrogen bonding is thermodynamically more favored than the individual molecules or hydrates of dexanabinol. The dimer is symmetrical as reflected by a low dipole moment and a high lipophilicity. Dimers appear to be stable and viable in the solid state (as suggested by experimental evidence such as high melting points and batochromic shifts of the OH in IR frequencies) and

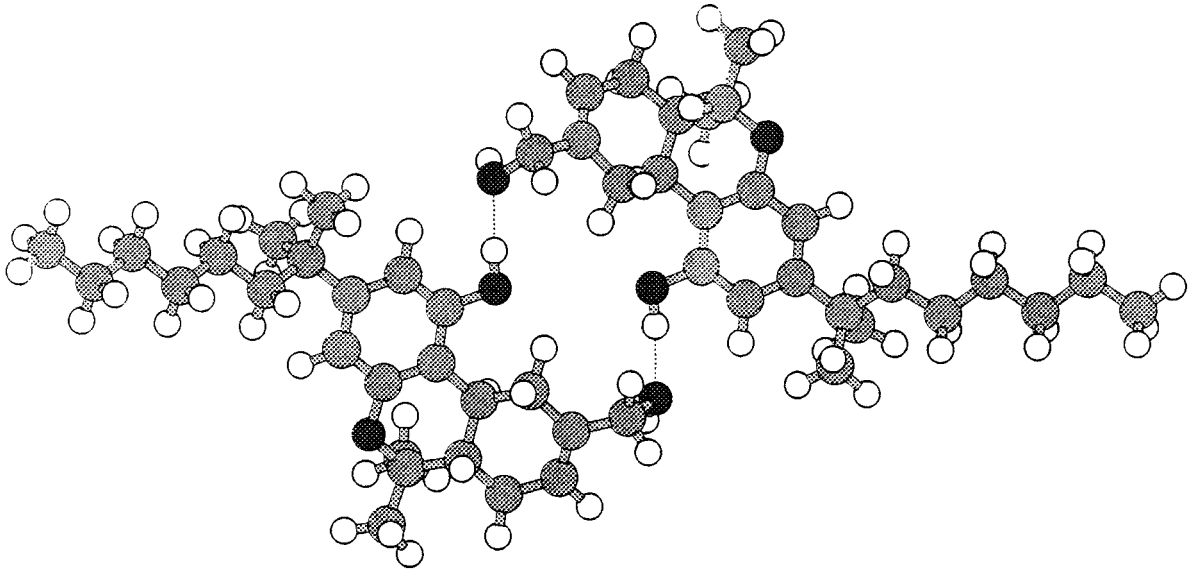

FIGURE 3. ''Balls and cylinders'' rendering of the optimized dimer **7**.

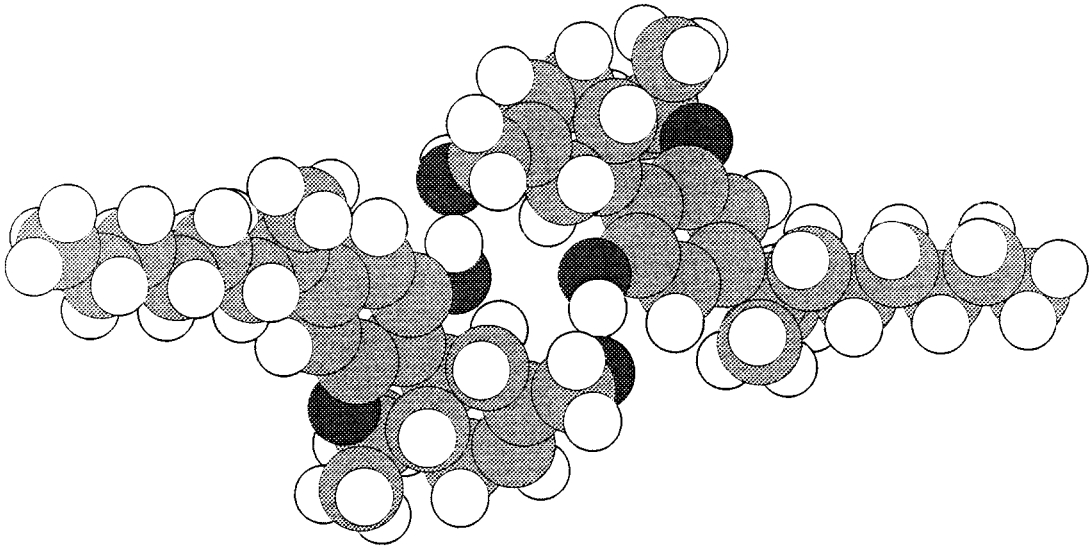

FIGURE 4. ''Balls'' representation of dimer **7**.

possible in gas phase as well. The poor solubility of dexanabinol in water indicate that dimers may not dissociate even when present at very low concentration. The theoretical findings presented above are supported by experimental evidence indicating poor aqueous solubility of this important drug candidate.

References

1. R. Mechoulam, N. Lander, A. Breuer, and Z. Zahalka, Tetrahedron-Asymmetry **1**, 315 (1990).
2. R. Mechoulam, W. A. Devane, and R. Glaser, in *Marijuana/Cannabinoids*: *Neurobiology and Neurophysiology*, L. Murphy and A. Batke, Eds. (CRC, Boca Raton, FL, 1992), pp. 1–33.
3. M. C. Etter, Acc. Chem. Res. **23**, 120 (1990).
4. Y. Ducharme and J. D. Wuest, J. Org. Chem. **53**, 5789 (1988).
5. S. K. Chang and A. D. Hamilton, J. Am. Chem. Soc. **110**, 1318 (1988).
6. R. Stadler, Prog. Colloid. Polym. Sci. **75**, 140 (1987).
7. M. Tichy, Adv. Org. Chem. **5**, 112 (1965).
8. M. R. C. Symons, Chem. Soc. Rev. **12**, 1 (1983).
9. J. J. P. Stewart, J. Comput. Chem. **10**, 209 (1989).
10. J. J. P. Stewart, J. Comput. Chem. **10**, 221 (1989).
11. HyperChem 5.01. Hypercube, Inc. Waterloo, Ont., Canada, 1996.
12. M. J. S. Dewar and D. M. Storch, J. Am. Chem. Soc. **107**, 3893 (1985).
13. N. Bodor, Z. Gabanyi, and C.-K. Wong, J. Am. Chem. Soc. **111**, 3783 (1989).
14. D. M. Seeger, C. Korzeniewski, and W. Kowalchyk, J. Phys. Chem. **95**, 68 (1991).