Molecular Dynamic Study of Conformational Properties of Cyclopenta[*a*]phenanthren-17-ones. Comparison of Theoretical Structures to X-Ray Structures

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The conformational analysis of a group of carcinogenic cyclopenta[*a*]phenanthren-17-ones has been done using quenched molecular dynamics to simulate built models. Optimum energy conformers have been searched within 300 to 600 K. The results are presented and compared to structures derived from X-ray experiments. While the pattern of distortion is similar for the simulated molecules to the crystalline state, the conformers corresponding to minimum energy show more molecular distortions in the free state than the crystalline at the bay regions. From the results, it emerges that the observed out-of-plane distortions are an inherent feature of the bay region substituted compounds.

A great deal of effort has been expended in recent years on the study of the theoretical and experimental conformations of oligopeptides,[1—3] sugars,[4] and catecholamines.[5] The impetus for these studies arises from the intrinsic interest in understanding the factors which influence molecular conformation. These studies have been done with the firm conviction that biological activity is intimately related to the accessible, low energy conformations of these molecules.[1—6] Various techniques including spectroscopy, X-ray crystallography, and theoretical conformational analysis have been used.[1—5] Each of these methods has its limitations; the need for a crystal and the effect of crystal forces on the molecular conformation for X-ray crystallographic method, and the solvent effects, local minima, and the adequacy of the potential functions for theoretical analysis.[7] It would seem clear that a combination of various techniques, each contributing and providing feedback for the other, would be the desired approach in understanding conformational behavior of molecules in solution.[8] X-Ray crystallography is clearly the most powerful method for determining the conformations of molecules, however, the conformations of the molecules in the crystal may not correspond to the biologically relevant conformations in solution or in the biological medium.[7]

In the present study, the minimum energy conformations of four derivatives of cyclopenta[*a*]phenanthren-17-ones [**I** (11-methyl derivative), **II** (11-methoxy derivative), **III** (11-ethyl derivative), and **IV** (7,11-dimethyl derivative)] have been searched, and their conformational properties have been analyzed and compared to X-ray crystallographic structures.[9,10] The structural formulae, atomic numbering, and plane designation of the compounds, **I**—**IV** are shown in Fig. 1. The relationship between carcinogenicity of these compounds and the bay region distortion has previously been described in relation to the mechanism of carcinogenesis.[9] Compounds **I** and **IV** are selected because they have relatively high tumor inducing properties and a high distortion in the bay region. **II** is selected because it is the only exception in possessing a planar conformation and yet carcinogenic. **III** is chosen because it is carcinogenic and provides a case of dimorphic crystals of *Pnaa* form **III**(**a**) and *Pbca* form **III**(**b**) with distinguishable conformers.[9,10] These molecules serve as good subjects for study for the following reasons; they are carcinogenic, accurately determined X-ray diffraction results are available,[9,10] and besides they have rigid molecular skeletons, and thus, they are less prone to be trapped by local energy minima than the more flexible molecules. We have used dynamic simulation method because it gives a truly realistic view of the isolated molecules.[3] In the dynamic simulations, we have used the parameters of a new generic force field,

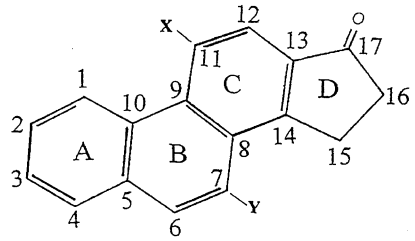

Fig. 1. Atomic numbering and plane designation of cyclopenta[*a*]phenanthren-17-ones. **I**. X=CH_3, Y=H; **II**. X=CH_3O, Y=H; **III**. X=$C_2H_5^{\bullet}$, Y=H; **IV**. X=CH_3, Y=CH_3.

DREIDING, because the accuracy of the force field has been tested with many accurately determined crystal structures of organic compounds.[12]

Method

Modeling, minimizations, and dynamic simulations were done by using the package of Biograf 3.22 on Silicon Graphics Indigo^2 R4000 computer.[11] The structures were built in Biograf from a library of standard phenanthrene base fragments. Molecular mechanics and dynamics have been used to investigate the conformations of the molecules that correspond to minimum energy. Prior to the dynamic simulations, sufficient minimization runs were done by molecular mechanics to remove any strain in the molecules. Energy minimization was carried out by conjugate-gradient method, at the end of which the value of the root-mean-square energy derivative of the atomic coordinates (rms gradient) was less than 0.1.

Molecular dynamic simulations were carried out to study the effect on the system at higher temperatures at 300, 400, 500, and 600 K. In the molecular dynamics simulations, the quenched dynamics option was used in order to find optimum geometry: In this option, the adiabatic dynamics was chosen. The temperature was checked every 0.1 ps to ensure that the temperature of the system does not significantly deviate from an input temperature, and energy minimization was performed at every interval of 0.1 ps. The run-time of 10 ps was chosen. The lowest energy conformers (best conformers) were obtained within 0.2 to 5.2 ps except for **IV** (Table 1). In the case of **IV**, a best conformer with the same energy as obtained under 10 ps run-time was reproduced within 10 ps under 15 ps run-time.

In all the simulations by using DREIDING force field, the potential energy for an arbitrary geometry of a molecule was assumed to be a superposition of valence interactions (E_{val}) and the non-bonded interactions (E_{nb}).[12] The E_{val} consists of body stretch (E_B, two-body), body-angle bend (E_A, three-body), dihedral torsion (E_T, four-body), and inversion terms (E_I, four-body), while E_{nb} includes van der Waals (E_{vdw}), electrostatic (E_Q), and hydrogen-bond terms.[12] The constituting atoms of the molecules were each converted to the appropriate DREIDING force atom types[12] before simulations, and the minimized structures were used as the starting conformation for each of the selected temperature run. A dielectric constant (ε=1) and a cut off radius of 9.00 Å was used. The best conformers were selected after each selected temperature run and analyzed. Dihedral angles between planes were calculated by MOLCON[13] using Cartesian coordinates generated by the simulations.

Results and Discussion

Figure 2 shows the best energy conformers of the title compounds. Table 1 shows the temperatures of simulation, corresponding best energies, and the obtained rms values. The geometric properties of the bay region for the calculated and the experimental are shown in Table 2. Table 3 lists the dihedral angles between the respective planes in the molecules.

The conformational energies from one simulated temperature to another for a given molecule may vary insignificantly as seen in Table 1. The energy differences between the highest and the lowest best energies for **I**, **II**, **III**, and **IV** are 3.53, 6.48, 7.74, and 5.61 kJ mol^{-1}. The simulated conformational geometries are in reasonable agreement with those of the experimental and molecular mechanics (MM) structures as seen in Tables 2 and 3 . The results indicate that the bond lengths and angles are well predicted by this simulation. The torsion angles of the bay region show some degree of variation with temperature (Table 2).

Table 1. Quenched Dynamics at Selected Temperatures

	T/K	Best time[a] t/ps	Best energy kJ mol^{-1}	rms Å
I				
	300	8.40	289.97	2.060
	400	5.10	289.48	1.812
	500	7.10	292.38	2.562
	600	0.30	293.01	2.648
MM			286.47	
II				
	300	2.50	268.53	1.521
	400	9.20	270.08	2.111
	500	2.20	272.92	2.819
	600	4.90	275.01	3.091
MM			264.73	
III				
	300	0.20	304.26	2.081
	400	1.90	305.60	1.729
	500	1.30	308.40	2.661
	600	6.10	312.00	3.547
MM			300.22	
IV				
	300	1.40	338.69	2.978
	400	10.00	336.65	1.836
	500	7.20	339.95	3.430
	600	8.30	341.96	3.347
MM			333.10	

a) Time along trajectory where the lowest energy conformer was obtained.

Molecule I. Angles 1–10–9 at 500 K and 10–9–11 at 600 K show some widening from the experimental as seen in Table 2. The torsion strain within the molecules indicated by the torsion angle 1–10–9–11 and the dihedral angles between planes show some variation from one simulated temperature to the other. It can be seen in Table 2 that the 300 to 500 K structures show greater distortion than the crystal structure. The variation in the calculated torsion angles is as much as 10 degrees. The calculation at 600 K for 10 ps run-time produced a structure whose bay region torsion angle was the closest to that determined by X-ray analysis as shown in Table 3.

The most energetically favorable conformer with the lowest rms occurred at 400 K [Fig. 2(a)]. This con-

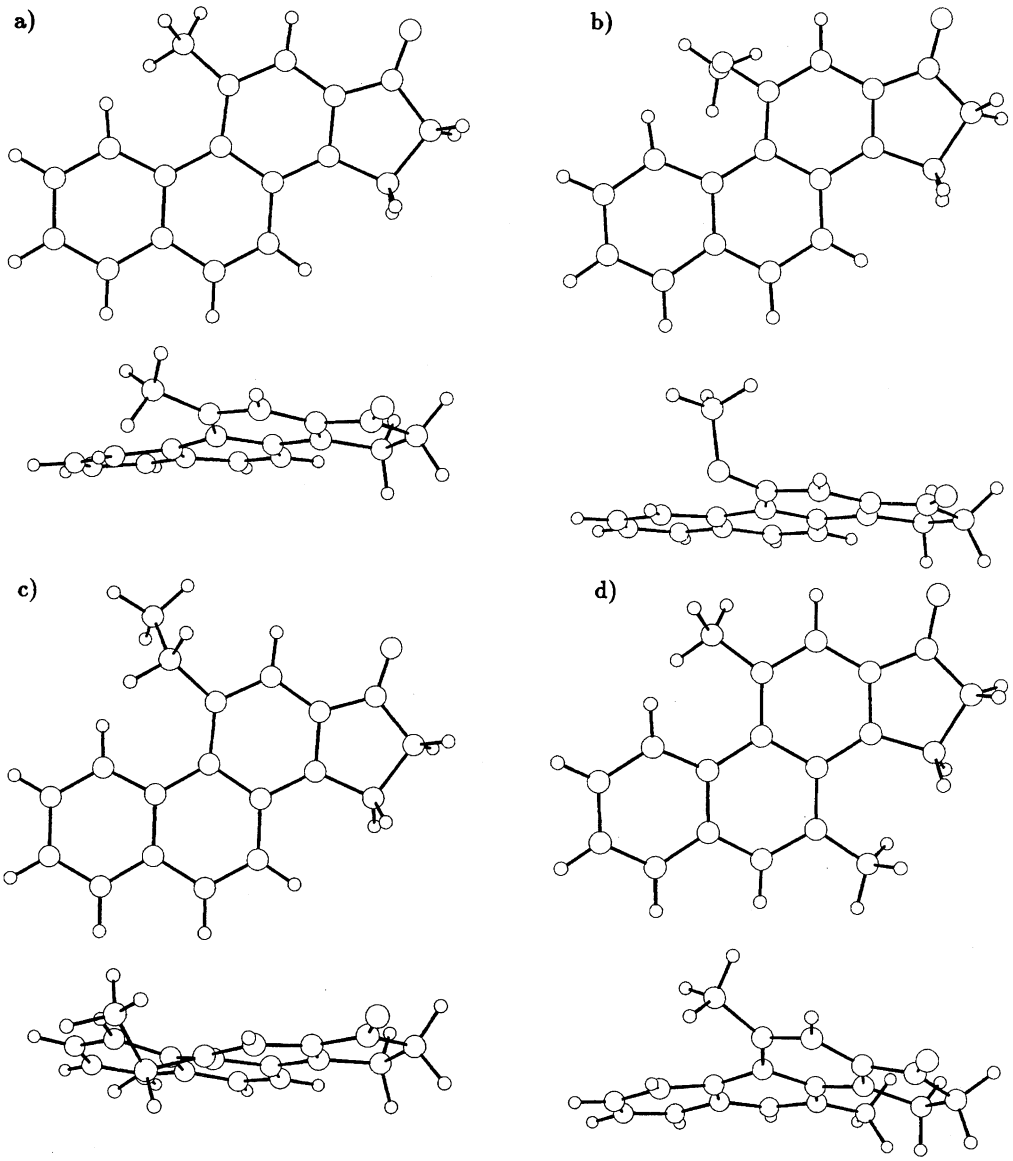

Fig. 2. Best conformers of a) **I** at 400 K, b) **II** at 300 K, c) **III** at 300 K, and d) **IV** at 400 K. The molecules have been oriented to show the bay region distortion.

former can be adopted as the best conformer that represents a simulated molecule of **I** in vacuo. A minimized molecule starting from the X-ray structure had a torsion angle of $-17.1°$, a value quite close to $-16.3°$ for the 400 K simulation. Possibility of the methyl group to flip from one side of the plane to the other in vacuo is seen from the reversed sign of the bay-region torsion-angle at 600 K in Table 2, although there was no evidence for a flip in the crystalline state.[9].

Molecule II. This molecule has the most planar bay region among the molecules [Fig. 2(b)]. This planarity is mainly ascribed to an attraction between methoxy O and H at C(1)[9]. The lowest energy conformer occurs at 300 K, and this is more stable than the least minimum energy conformer at 600 K by 6.48 kJ mol^{-1} as seen in Table 1. From Tables 2 and 3, this and the conformer at 500 K have the closest bay-region conformation to the experimental. Though the bay-region torsion-angle is close to 0° for the experimental structure, the simulated structure shows some level of distortion (Table 2). This is clearly reflected in the dihedral angles (A/C) between planes A and C in Table 3. This feature should be taken into account to explain the carcinogenicity of **II**. The distance between the methoxy O and H at C(1) is calculated to be 2.31 Å for the best model at 300 K. This is not as short as 1.98(2) Å for the X-ray structure. The torsion angle C(12)–C(11)–O–CH_3 is $-1.3(4)°$ for the experimental, while it is calculated to be 85.3° for the best conformer. The planarity of **II** observed in the crystalline state is considered to be a reflection of the extremely planar stacking of the molecules[10].

Molecule III. The dimorphic forms **a** and **b** provide an interesting case of study. The experimentally observed torsion angles at the bay regions observed for both forms are distinctly different from each other as shown in Table 2. The conformation observed for **b** is

Table 2. Conformational Properties of Bay Region

		Bond lengths l/Å			Bond angles ϕ/°		Torsion angles τ/°
	T/K	1–10	9–10	9–11	1–10–9	10–9–11	1–10–9–11
I							
	300	1.42	1.44	1.44	125.8	125.4	−18.4
	400[a)]	1.42	1.44	1.44	125.3	125.8	−16.3
	500	1.42	1.43	1.43	127.9	125.8	−27.6
	600	1.42	1.46	1.45	123.8	127.7	11.3
MM		1.42	1.44	1.44	124.5	125.7	−17.9
X-Ray		1.409	1.462	1.442	124.6	125.0	13.5
II							
	300[a)]	1.42	1.44	1.44	125.0	124.8	−7.7
	400	1.42	1.44	1.44	124.8	124.6	−11.6
	500	1.43	1.44	1.44	124.3	127.1	−5.7
	600	1.43	1.44	1.44	124.5	124.7	−13.9
MM		1.42	1.44	1.44	124.8	125.1	−7.6
X-Ray		1.407	1.470	1.435	124.4	124.8	0.7
III							
	300[a)]	1.42	1.44	1.45	124.5	125.7	17.4
	400	1.42	1.44	1.44	124.5	126.2	15.3
	500	1.43	1.45	1.44	126.3	126.5	13.5
	600	1.42	1.43	1.45	125.5	125.3	12.8
MM		1.42	1.44	1.45	124.5	126.3	18.5
X-Ray	a)	1.423	1.475	1.441	124.9	124.8	8.9
	b)	1.411	1.470	1.437	123.7	124.9	13.0
IV							
	300	1.43	1.42	1.43	124.2	122.1	−23.0
	400[a)]	1.42	1.44	1.44	123.3	123.5	−20.8
	500	1.43	1.44	1.44	124.3	123.1	−24.6
	600	1.42	1.44	1.44	127.0	122.7	−18.9
MM		1.42	1.43	1.44	124.1	123.0	−21.3
X-Ray		1.404	1.453	1.446	124.6	121.8	−20.5

a) The temperature at which the most energetically favorable conformer was obtained.

similar to that of molecule **I**.

Unlike **I** and **II**, the best conformers of the respective temperatures do not show much variation in the torsion angle at the bay region (Table 2). A consideration of both energy and rms values places the best conformer at 400 K as the most energetically favorable. The simulated values are similar and relatively closer to **b** than to **a** as seen in Tables 2 and 3, where the estimated dihedral angle (A/C) between planes A and C also simulates **b** rather than **a**. The torsion angle around the C(aromatic)–C(methylenic) bond of the ethyl group in the simulated structure is fairly large [Fig. 2(c)]. The value of 21.7° for this torsion is closer to the observed values of **b** [19.8(7)°] than for **a** [4.4(5)°].[10] The closeness of the simulated structure to **b** supports the existence of **b** in the crystalline state. It can be said that the planar conformation of the ethylenic side chain observed in **a** is an effect of the molecular stacking in the crystal from the following facts. The molecular arrangements are very similar in the crystals of **a** and **b**, and the molecules are stacked along a c axis in both crystals.[10] However, the intermolecular interactions between the stacking molecules are stronger in **a** than **b**, as seen from the smaller dimension of c for **a** than for **b** [c=7.584(1) Å for **a**; 7.6465(6) Å for **b**]. Such intermolecular interactions in **a** may allow a parallel stacking of the molecules with a planar conformation, even though the conformation may be energetically less favorable. Thus, the simulations are in agreement with the fact of dimorphism in the crystals of **III**.

Molecule IV. The effect of an extra methyl substitution at C(7) in increasing the distortion in the bay region is also observed in the simulation results as seen in Table 2. The average value of the torsion angles obtained at different temperatures is 21.5°, which is higher than 18.3° for **I**. The results in Table 1 show that the 400 K conformer [Fig. 2(d)] is of the lowest energy among the conformers simulated at different temperatures. In terms of the bay-region conformation, this conformer is the closest to the experimentally observed

Table 3. Dihedral Angles (φ/°) between Planes

	T/K	A/B	B/C	C/D	A/C	B/D	A/D
I							
	400[a]	7.9	6.4	1.5	14.3	5.8	13.6
	600[b]	5.8	6.4	1.4	12.1	5.1	10.9
MM		8.0	8.2	2.6	16.2	7.3	14.9
X-Ray		7.0	5.1	1.4	12.5	5.3	11.7
II							
	300[a]	3.8	2.9	3.5	6.5	4.6	6.3
	500[b]	4.1	3.6	1.5	7.5	2.2	6.3
MM		3.5	3.4	1.2	6.8	2.9	6.1
X-Ray		1.3	1.9	1.5	1.9	3.3	3.4
III							
	400[a]	5.8	8.2	5.6	12.7	8.5	10.2
	500[b]	7.4	6.5	4.5	13.9	8.6	15.4
MM		8.6	8.8	2.6	17.4	8.0	16.3
X-Ray							
	a	4.0	3.8	1.9	7.3	1.9	5.5
	b	6.2	7.2	3.0	13.3	6.9	13.1
IV							
	400[a,b]	9.9	13.7	5.9	23.5	16.2	25.3
MM		9.1	13.0	4.3	22.0	14.2	22.7
X-Ray		9.7	11.1	3.1	20.6	11.0	20.6

a) The temperature at which the most energetically favorable conformer was obtained. b) The temperature at which the most similar conformer to X-ray structure was obtained.

structure as seen in Table 2.

It is quite notable that, as observed experimentally,[9] the exception to the widening of the exocyclic bond angle 10–9–11 of **IV** is also true in these simulations. The lowest value 124.6° of the bond angle obtained from the simulation for **I**, **II**, and **III** is still higher than the highest value of 123.1° for **IV**. The shortest intramolecular distance between H(1)···H(methyl) in the bay region is 2.37 Å for the 400 K conformer. The corresponding distance lies near 1.95 Å for the observed structures of **I** and **IV**.[9] It is clearly seen from the dihedral angles of planes A/C in Table 3 that an additional methyl substitution enhances the bay region distortion.

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