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Semiempirical Study of Geometries and Valence Isomerization of Pyrene-4,5-oxide and Pyrene-2,3-oxide, Their Oxepines and Related Compounds

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A conformational study of the energies and geometries of the stable compounds obtained from pyrene *via* enzymatic treatment with oxygen has been carried out using two semiempirical quantum mechanical methods: AM1 and MNDO. The energies of the two possible isomers are strongly dependent upon the spatial position of the oxygen of the pyrene molecule. The valence isomerization of pyrene-4,5-oxide and pyrene-2,3-oxide and their oxepine is discused and related to AM1 and MNDO calculations.

Key words: annulenes, pyrene, oxepines, valence isomerization, AM1 and MNDO methods.

INTRODUCTION

As is well known, some metacyclophanes readily transform upon irradiation with light into pyrene[1] and, in so doing, become much more planar.[2–4]

The pyrene molecule has been studied for purposes of both characterizing its biological activity[5–8] and fully understanding its chemical reactivity. In this regard, the biological activity of pyrene,[9] in contrast to the non-biological activity of benzo[*e*]pyrene, is striking.[10–13]

Among the experimentally important processes in which this type of compound participates is enzymatic oxygenation, studied with benzo[*e*]pyrene by

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Agarwal *et al.*[14] In this reaction, this compound gives rise to two different epoxides, as dictated by the position adopted by the oxygen atom on the periphery of the benzo[*e*]pyrene molecule. These epoxides[15] are later hydrolyzed to two *trans*-dihydrodiols which appear in unequal proportion.

In the present work, we report a theoretical study of the conversion of pyrene into *trans*-dihydrodiol in order to predict which of the two possible epoxides is more stable and, thereby, to determine which of the two dihydrodiols will preferentially be formed. We used two quantum mechanical methods to determine the molecular structure of the compounds participating in the process and to determine their relative stabilities. Figure 1 shows the molecules studied. We also aim to establish the differences between the *trans*-dihydrodiols obtained from benzo[*e*]pyrene and from pyrene because this might shed light on their disparate biological activities.

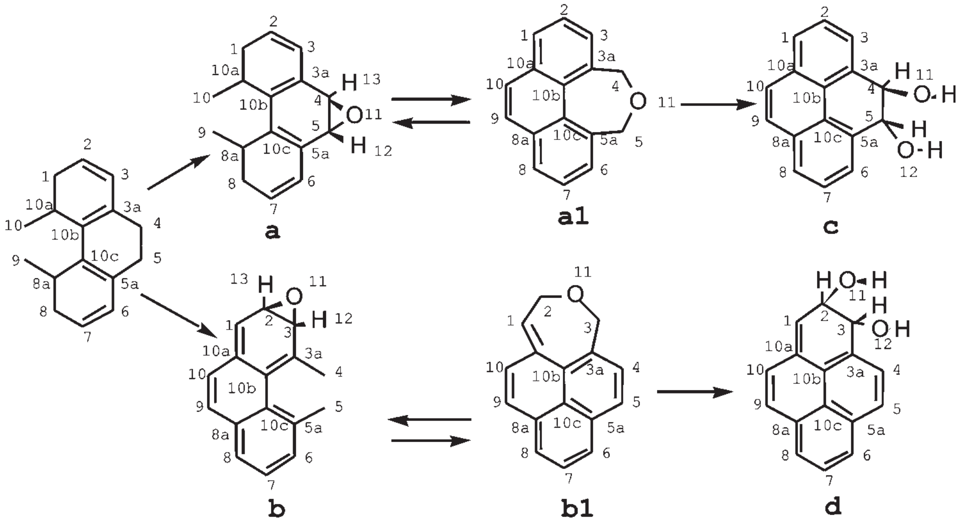

Figure 1. Pyrene-4,5-oxide (**a**), pyrene-2,3-oxide (**b**), their oxepines (**a1**, **b1**) and dihidrodiols (**c**, **d**).

Calculation Method

The AM1[16] and MNDO[17] semiempirical methods were used; these are included in the MOPAC[18] package. Both methods are parametrized to reproduce certain experimental magnitudes as well as possible. The MNDO and AM1 methods permit to calculate the heats of formation, molecular geometries, dipole moments and force constants satisfactorily.

Energy minimization was carried out by the method described by Broyden,[19] Fletcher,[20] Goldfarb,[21] and Shanno.[22] The energy convergence criteria for each of the self-consistent calculations was fixed to be 1×10^{-5} eV. In all cases, the starting point was completely flat structures, assuming distances and bond angles typical of aromatic hydrocarbons. In the optimizations carried out by both methods, initially no constraints were accepted. The optimum geometry was calculated for the isolated molecules.

RESULTS AND DISCUSSION

Pyrene

The initial starting point in pyrene was 1.40 Å for all C–C bonds, with all angles at 120°. Both methods revealed the flatness of the structure, in agreement with the experimental data available for this molecule.[23–26] A clear alternation of bond lengths can be seen.[27–28] In the case of the MNDO method, an alternation occurs in the bonds 3a–4, 4–5, 5–5a, 8a–9, 9–10 and 10–10a; these bond lengths vary between 1.457 Å and 1.365 Å. Likewise with the AM1 method, these bond lengths vary between 1.440 Å and 1.357 Å. The remaining C–C bonds, with both methods, show deviations from the 1.400 Å value of less than 0.008 Å. With respect to the bond angles, the deviations from a 120° angle by both methods are less than 1.4°. The molecule displays C_{2h} symmetry and is flat. The heats of formation are 67.344 kcal mol^{-1} and 60.699 kcal mol^{-1} according to the AM1 and MNDO methods, respectively.

*Pyrene-4,5-oxide (Compound **a**) and Pyrene-2,3-oxide (Compound **b**)*

Upon treatment with oxygen, pyrene gives rise to two different epoxides, depending on whether the epoxide is formed at position 2–3 or 4–5. The C–C bond lengths are very similar to the pyrene ones, with the exception of the C4–C5 bond length of **a** and that of C2–C3 of **b**, which are longer than those obtained for pyrene. The C4–C5 distance of **a** is 0.150 Å or 0.170 Å longer, depending on whether the AM1 or MNDO method is used. However, the difference is less pronounced for the C2–C3 bond of **b** (0.104 Å longer with the AM1 method, and 0.113 Å with the MNDO method).

Special mention should be made of the angle formed between the C–O–C atoms. While with the AM1 method one obtains an angle of 62.60° and 63.12°, the MNDO method yields values of 65.00° and 67.48° for molecules **a** and **b**, respectively, indicating a greater tension along these atoms. Both methods predict a smaller angle for the more stable molecule.

Both the AM1 and the MNDO methods yield a nearly flat structure, in which all of the carbon atoms deviate from the plane by less than 3°. The hydrogen atoms on the carbon atoms joined to the oxygen atom, and the

TABLE I

Geometrical parameters of pyrene-4,5-oxide (**a**) and pyrene-2,3-oxide (**b**) obtained using MNDO and AM1 calculations

	MNDO		AM1	
	a	**b**	**a**	**b**
Bond lengths/Å				
2–3	1.417	1.537	1.405	1.507
3–3a	1.397	1.499	1.387	1.471
3a–4	1.499	1.434	1.474	1.419
4–5	1.527	1.379	1.497	1.370
5–5a	1.499	1.439	1.474	1.424
4–11	1.421	–	1.440	–
2–11	–	1.441	–	1.421
Bond angles/°				
2–3–3a	120.7	117.9	120.3	117.8
3–3a–4	120.6	119.8	120.0	119.3
3a–4–5	119.0	120.9	118.0	120.6
4–5–5a	119.0	118.7	118.9	119.2
4–5–11	57.5	–	58.7	–
2–3–11	–	57.3	–	59.5
Torsion angles/°				
5–4–3a–3	–179.7	179.3	179.5	178.2
4–3a–3–11	–	244.3	–	242.9
3a–3–2–11	–	253.1	–	252.3
2–3–3a–10b	–	359.9	–	1.3
4–5–5a–6	179.6	–179.5	181.2	179.7
5a–5–4–11	106.3	–	105.4	–
6–5a–5–11	113.3	–	113.9	–
4–5–5a–10c	1.7	359.2	0.4	358.4
3a–4–5–5a	0.0	0.5	359.8	0.7
8a–9–10–10a	0.0	–0.5	0.1	–0.8
12–5–5a–6	153.0	–	155.6	–
12–3–3a–4	–	25.6	–	20.8
13–2–1–10	–	154.3	–	158.3

Atom numbering as in Figure 1.

oxygen atom, deviate most from the plane, as may be seen in Table I. The oxygen atom forms a semienvelope with a pseudo-axial pseudo-equatorial orientation.

As regards the charge on the oxygen atom, both methods, MNDO and AM1, yield similar values (approximately 0.03 electronic charge units difference between the two methods). For isomer **a**, both methods provide the same charge distribution for the carbon atoms bound to the oxygen, while in the case of isomer **b**, the charge on these carbon atoms differs. This latter observation may be attributed to the asymmetry of **b.** The values obtained for the oxygen atom are 0.24 times the electronic charge with AM1, and 0.25 times the electronic charge with MNDO for molecule **a**, slightly higher than those calculated for molecule **b** (0.23 and 0.25 times the electronic charge with the AM1 and MNDO methods, respectively). Additionally, the AM1 method does not give rise to so pronounced a polarization of the carbon atoms bound to the oxygen like the MNDO method does. It is more dispersed among all the carbon atoms and therefore expected that the AM1 values should be lower than the obtained by the MNDO method ones.

Calculated values were obtained for the heat of formation and electronic energies. Isomer **b** was more energetic, its energy value being 83.225 eV and 82.278 eV by the MNDO and AM1 methods, respectively. Both methods confirm the greater stability of **a** relative to **b** (Table II). Molecule **a** is more stable than **b** by 12.716 and 11.169 kcal mol^{-1} according to the AM1 and MNDO methods, respectively, in agreement with published experimental results for benzo[*e*]pyrene.[14]

The dipolar moment of the more stable isomer is lower than that of the other isomer by both methods.

Finally, published experimental results concerning epoxides joined to aromatic rings confirm the existence of an equilibrium between the epoxide and the oxepine[10] due to the effect of heat or radiation. However, the experi-

TABLE II

The heats of formation of pyrene-4,5-oxide (**a**) and pyrene-2,3-oxide (**b**) and the oxepines **a1** and **b1** obtained using MNDO and AM1 calculations

Isomer	E / kcal mol^{-1}	
	MNDO	AMI
a	44.131	59.868
b	55.300	72.584
a1	75.611	92.806
b1	50.268	64.600

mental reaction proposed by Wood *et al.*[10] and Agarwal *et al.*[14] only shows that the transformation occurs through an epoxide. In the present study, the oxepine has also been included in case it could give an idea about some of the possible intermediate processes of the reaction. The most interesting dihedral angles for the oxepines **a1** and **b1** are shown in Table III. Both oxepines **a1** and **b1** acquire planarity as the seven-membered ring is formed. However, their greater flatness is not sufficient to have greater stability than that of the epoxide **a**. Study of the heats of formation for these oxepines are shown in Table II. The oxepine **a1** is less stable than their corresponding epoxide **a**, whereas the oxepine **b1**, is more stable than their corresponding epoxide according to the AM1 and MNDO methods (see Table II). The difference in heats of formation between the oxepine and the epoxide is less than 33 kcal mol^{-1}. The enthalpy changes that occur during a valence isomerization of pyrene-oxide to a oxepines deserve some comment. During the isomerization of pyrene-oxide to a oxepine, a sp^3–sp^3 bond is lost. The energy changes which accompany the isomerization of **a–a1** and **b–b1** are thus not obvious, they are not even equal, although **a** and **b** are isomeric pyrene-oxide, and **a1** and **b1** are isomeric oxepine. From the heat of formation it can be seen that in the pyrene-oxide, the type **a** is more stable than the type **b** by 11.169 kcal mol^{-1} and 12.716 kcal mol^{-1}, whereas in the oxepine, the type **a (a1)** is less stable than the type **b** by 25.343 kcal mol^{-1} and 28.208 kcal mol^{-1} according to the MNDO and AM1 methods. The difference between the pyrene-oxide **a** and oxepine **a1** is a difference in strain energy, where the oxepine **a1** is more strained, presumably due to the increased strain C–C between three benzene rings in **a**. In addition, the most stable of

TABLE III

Geometrical parameters of oxepines (**a1** and **b1**) obtained using MNDO and AM1 calculations

	MNDO		AM1	
	a1	**b1**	**a1**	**b1**
	Torsion angles/°			
3–3a–4–5	190.3	–159.8	188.5	–161.7
2–3–3a–4	–2.0	–148.6	–1.8	–151.2
3a–4–5–5a	13.9	2.8	12.35	2.7
1–10a–10–9	0.0	–178.5	0.3	–177.8
3a–4–11–5	351.3	–	352.0	–
3a–3–11–2	–	49.3	–	335.2
3–11–2–1	–	308.4	–	308.7

Atom numbering as in Figure 1.

the two isomers **a** and **b**, is the isomer which has the more resonance energy. So we consider that the strong strain of **a1** is not enough to compensate for the differences in resonance energy between **a1** and **b1** isomers. The study of transition state confirms that the interconversion of **b–b1** is easier than the interconversion of **a–a1**. Additionally, when the reaction way is **b,** the oxepine would be the intermediate compound between the epoxides and the dihydroalcohols. Accordingly, this compound is an intermediate state through which the reaction takes place.

To sum up, studing the transition state and the difference in energy of the oxepine and the epoxide, can be concluded that the calculations performed with the AMI and MNDO methods confirm the existence of the interconversion of oxepine into epoxide both in types **a** and **b**. These results confirm the experimental observation of the interconversion between the oxepine and the corresponding epoxide. The energy difference between the type **a** compounds is significantly larger that the value obtained for the energy difference between the type **b** compounds. The higher energy of the oxepine **a1** explains why heat or light radiation is required in order to the equilibrium between the two compounds to exist, and the experimental fact that hydrolysis always occurs through the epoxide.

trans-*4,5-Dihydroxy-4,5-pyrene-4,5-oxide (Compounds Type* ***c****)* *and* trans-*2,3-Dihydroxy-2,3-pyrene-2,3-oxide (Compounds Type* ***d****)*

Hydrolysis of each of the epoxides, **a** and **b**, gives rise to two dihydrodiols: **c**1, **c**2 and **d**1 and **d**2. The conformers of **c** (**c**1 and **c**2) and the conformers of **d** (**d**1 and **d**2) differ in the orientation of the OH group. Theoretical studies of these compounds were carried out by both methods. Although the results were similar, only those obtained with the AM1 method are reported. The method AM1 is more appropriate for these compounds.[29] The carbon skeleton of these structures is almost flat. The deviations from flatness are shown in Table IV. The two conformers of **c** are more stable than the conformers of **d**. Additionally, the difference in the heats of formation of the conformers of **c** is greater than the conformers of **d** one.

According to the AM1 study of the conformers of **c,** the most stable is **c**2 which has a pseudoequatorial orientation, while **c**1 with a pseudoaxial orientation is less stable by 2.666 kcal mol^{-1}. In the case of the **d** conformers, the pseudoequatorial one is also the more stable (Table V).

In our previously-reported work on benzo[*e*]pyrene,[30] it was found that the most stable dihydrodiol was pseudoaxial. This orientation was consistent with that reported in the experimental work of Wood *et al.,*[10] in which the dihydroalcohols essentially adopt the pseudoaxial conformation for ste-

TABLE IV

Geometrical parameters of *trans*-pyrene-4,5-dihydroxy-4,5-oxide (**c1, c2**) and *trans*-pyrene-2,3-dihydroxy-2,3-oxide (**d1, d2**) obtained using AM1 calculation

	c1	**c2**	**d1**	**d2**
	Torsion angles/°			
5–4–3a– 3	182.9	180.9	172.0	–175.9
4–3a–3–11	–	–	330.1	70.0
3a–3–2–12	–	–	193.0	113.8
4–5–5a–6	196.7	209.1	–175.7	–179.6
6–5a– 5–12	236.5	332.7	–	–
4–5–5a–5b	15.3	34.9	0.6	0.5
3a–4–5–5a	336.8	313.4	1.2	0.3
8a–9–10–10a	–1.3	–2.3	–1.3	–0.4
5a–5–4–11	235.3	191.6	–	–
11–4–5–12	226.4	65.4	–	–
11–2–3–12	–	–	237.2	71.1

Atom numbering as in Figure 1.

TABLE V

The heats of formation of *trans*-pyrene-4,5-dihydroxy-4,5-oxide (**c1, c2**) and *trans*-pyrene-2,3-dihydroxy-2,3-oxide (**d1, d2**) obtained using AM1 calculation

Isomer	E/ kcal mol^{-1}
c1	35.395
c2	38.061
d1	–22.824
d2	–24.394

ric reasons, as well as work of Lamm *et al.*[31] However, the disparity between the present work and the AM1 benzo[*e*]pyrene study of the stability of the conformers in the pseudoequatorial orientation suggests that the metabolic activation that gives rise to a carcinogenic effect might occur through the equatorial conformer.

CONCLUSION

All of the compounds studied are nearly flat. As a consequence of the results obtained, it can be stated that the most likely reaction route is *via* **a** and **c**. Furthermore, whereas the epoxide prefers a pseudoequatorial orientation, when hydrolyzed it has two distinct conformations: pseudoaxial and pseudoequatorial. The different biological activities shown by pyrene and benzo[*e*]pyrene could be related to the different stabilities of the quasiequatorial conformations of their dihydrodiols.

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SAŽETAK

Poluiskustveno proučavanje geometrije i valencijske izomerizacije piren-4,5-oksida i piren-2,3-oksida, njihovih oksepina i srodnih spojeva

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Konformacijsko proučavanje energija i geometrija stabilnih spojeva dobivenih enzimskom oksidacijom pirena provedeno je uporabom dviju kvantno-mehaničkih metoda: AM1 i MNDO. Energije dvaju mogućih izomera jako su ovisne o prostornoj usmjerenosti kisika pirenske molekule. Valencijska izomerija piren-4,5-oksida i piren-2,3-oksida te njihovih oksepina razmatrana je i uspoređena s rezultatima računa AM1 i MNDO.