

**Theoretical Study of the Metacyclophanes
anti-Benzo[9,10-*a*][2.2]metacyclophan-1-ene,
trans-12c,12d-Dihydrobenzo[*e*]pyrene, and Benzo[*e*]pyrene**

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The MM2, MNDO, and AM1 methods are used to carry out a theoretical study of the relative stabilities of the two isomers of *anti*-benzo[9,10-*a*][2.2]metacyclophan-1-ene and *trans*-12c,12d-dihydrobenzo[*e*]pyrene and ultimately benzo[*e*]pyrene.

Introduction

The isomerization of certain metacyclophanes into dihydropyrenes and the dehydrogenation of these to form pyrene¹ is a reaction that plays a crucial role in biological processes.²

The benzo[*e*]pyrene and benzo[*a*]pyrene that appear as products of the combustion of certain fossil fuels, and that are the final product of the transformation of some metacyclophanes, exhibit broadly different biological activities.³ Whereas benzo[*a*]pyrene has strong carcinogenic effects, all the tests performed with benzo[*e*]pyrene show that it does not.⁴ It is possible that the carcinogenic effects of the former polycyclic aromatic hydrocarbon derive from its being too sterically hindered to undergo epoxide formation, an important step in this compound's metabolic oxidation. Accordingly, knowledge of the primary structure of these metacyclophanes and their derivatives is important.

In a series of previous studies, we investigated the conformational characteristics of *anti*-[2.2]metacyclophan-1,9-diene⁵ and [2]metacyclo[2](1,3)naphthalenophane-1,11-diene⁶ using a semiempirical quantum mechanics method, namely the AM1 method. This procedure affords a uniform and coherent explanation of the conformational behavior and interconversion of this type of compound, that is consistent with the experimental results.

The aim of the present work was to investigate the basic conformational characteristics of *anti*-benzo[9,10-*a*][2.2]metacyclophan-1-ene and of its derivatives. The molecules studied and their numbering are shown in Figure 1. In addition to the above-cited method, another semiempirical method, MNDO, and one based on molecular mechanics, MM2, were used, in order to make a comparative study of the results that can be obtained with the three methods. The optimum geometries of the three molecules and their relative stabilities were calculated. Additionally, we established the most important differences in the geometric and energy parameters shown by these molecules and compared them with the results of previous studies.

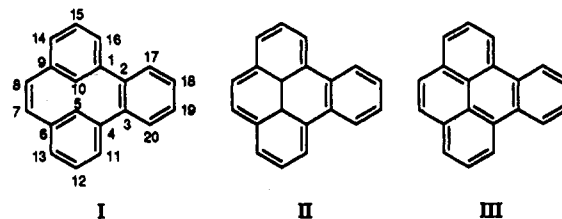


Figure 1.

Methodological Aspects

Calculations were performed at three levels. Semiempirical studies were conducted with the AM1⁷ and MNDO⁸ methods of Dewar, included within the MOPAC⁹ program. And, molecular mechanics calculations using MM2 by Allinger¹⁰ were performed. There were two goals in this: first, to compare the data already reported and thereby to evaluate the appropriateness of these methods for this type of molecule and, second, to facilitate data entry for future calculations on the formation of epoxides and dihydro alcohols that act as intermediate products in the biological reactions in which this kind of aromatic compound participates. A final aim was to obtain bonding orders more readily since these govern the values of different parameters such as stretching constants, rotational barriers, and the natural lengths of the bonds.

The geometries of all the compounds were optimized with no constraints, which ensured the existence of C_{2h} symmetry for I and II, since the optimization results with and without symmetry constraints were the same.

Results and Discussion

The differences between geometries I-III lie in the molecular organization of these compounds. In moving from I to II, carbon atoms C5-C10, which bear the Csp^2 hybridization in I, become Csp^3 in II, with the formation of a new bond and, as a result, the C-C distance in some of the six-membered rings, that were similar in I, cease to be so in II.

The most important differences occur in the molecular zone of the ring formed by atoms 1 through 10. All three methods produced longer C5-C10 distances in I and II, and in II than in III, allowing one to conclude that there is a stronger degree of bonding in II than in III and that

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Table 1. Bond Lengths (Å) for Compounds I-III

bond	MNDO			AM1			MM2			I ^a	III ^b
	I	II	III	I	II	III	I	II	III		
3-2	1.442	1.435	1.433	1.418	1.415	1.416	1.420	1.416	1.455	1.341	1.37
4-3	1.492	1.481	1.477	1.468	1.458	1.455	1.492	1.475	1.410	1.483	1.45
5-4	1.416	1.526	1.439	1.401	1.498	1.421	1.402	1.511	1.469	1.404	1.39
6-5	1.423	1.533	1.434	1.406	1.504	1.417	1.404	1.511	1.421	1.404	1.39
7-6	1.479	1.365	1.454	1.460	1.356	1.437	1.479	1.358	1.411	1.483	1.45
8-7	1.359	1.459	1.363	1.347	1.440	1.356	1.341	1.454	1.356	1.361	1.37
19-18	1.401	1.402	1.406	1.393	1.394	1.398	1.393	1.393	1.400	1.399	-
20-19	1.405	1.403	1.397	1.392	1.390	1.386	1.396	1.393	1.390	1.390	-
11-4	1.421	1.366	1.412	1.406	1.356	1.398	1.403	1.360	1.401	1.396	1.42
12-11	1.404	1.458	1.409	1.393	1.441	1.397	1.397	1.453	1.402	1.383	1.39
13-12	1.406	1.357	1.394	1.395	1.350	1.385	1.395	1.353	1.387	1.383	1.39
3-20	1.415	1.418	1.425	1.403	1.405	1.409	1.403	1.407	1.412	1.412	-
6-13	1.414	1.465	1.419	1.395	1.445	1.385	1.401	1.456	1.408	1.396	1.42
5-10	2.682	1.560	1.459	2.459	1.533	1.437	2.616	1.533	1.442	2.567	1.45

^a Reference 11. ^b Reference 14.

Table 2. Bond Angles (deg) for Compounds I-III

bond angles	MNDO			AM1			MM2			I ^a
	I	II	III	I	II	III	I	II	III	
4-3-2	122.75	120.70	120.25	122.79	120.82	120.31	124.52	119.79	119.51	126.6
5-4-3	122.44	116.56	119.24	121.72	116.49	119.11	122.34	117.72	119.53	121.1
6-5-4	120.35	115.11	120.00	119.63	114.43	119.86	118.08	114.15	120.86	119.2
7-6-5	121.52	119.01	119.25	120.95	119.50	119.47	122.55	119.45	120.32	121.5
8-7-6	126.03	121.29	121.26	124.98	120.64	120.98	125.03	120.16	120.73	125.3
20-19-18	119.55	119.55	119.49	119.73	119.78	119.79	119.58	119.36	119.97	-
11-4-3	119.87	123.84	122.89	119.27	122.86	122.25	119.48	123.07	122.98	119.9
12-11-4	120.66	122.57	121.95	120.17	121.77	121.19	120.84	123.02	121.83	120.2
13-12-11	120.15	121.27	120.28	120.15	120.91	120.49	119.15	121.09	120.32	120.7
6-13-12	119.80	121.28	121.26	119.73	121.02	120.69	118.55	119.45	119.84	119.8

there is no bond in I. The C5-C10 distance can be compared with the results obtained in similar systems by consulting Table 1. Thus, for *anti*-[2.2]metacyclophane-1,9-diene, Hanson¹¹ obtained a value of 2.57 Å, which is intermediate to that obtained in this work by MM2, AM1, and MNDO. The distance obtained in the present study for *anti*-benzo[9,10-*a*][2.2]metacyclophane-1-ene (I) varies, depending on the method applied, between 2.459 and 2.682 Å. The most important difference among the three methods is found for the zone of atoms C5-C10. The MNDO method derives C5-C10 distances that are longer in compounds I and II (2.682 Å in I and 1.561 Å in II, compared to 2.459 and 1.533 Å by AM1 and 2.616 and 1.533 Å by MM2), whereas the discrepancies in III with the three methods are less pronounced. Additionally, in compound I, the 3-4 bond has the same length by MNDO and MM2; the difference obtained for the 2-3 bond is 0.022 Å. The same is the case for bonds 6-7 and 7-8. The explanation of these observations should be sought in the greater importance given to the delocalization of bonds by the MNDO method.

Other distances of interest are also shown in Table 1. By all three methods, the 2-3 bond appears to be quite long for being part of a phenyl group. For compound I, it was logical that the value obtained for this 2-3 bond would be similar to that observed for 4-5 or 5-6. Furthermore, on comparing the value of this bond with that obtained for other members of this family, it is surprising that its value is higher than 1.40 Å and especially so, since the 3-4 bond has a similar value. This lengthening must, at least in part, be due to the adoption by the phenyl group (joined to the 2-3 bond) of a position perpendicular to the other two rings. The rest of the bond lengths are in good agreement with those of the other aforementioned members of the family.

In general, the same is the case for the bond angles, which appear in Table 2. One observes an opening of angles 6-7-8 and, to a lesser extent, of 2-3-4 and 3-4-5 for compound I, and of 4-5-6 in compound II. This widening must be partially due to the interactions between C5 and C10 and be more pronounced in 6-7-8 owing to the lesser degree of hindrance. In compound I, deviations occur relative to the normal 120° that are less than 6°. It should be stressed that the MNDO method affords the most pronounced deviations.

The dihedral angles provide information concerning the planarity (Table 3). In general, the results obtained predict fairly unimportant losses of planarity in compound II, and only the value observed for 2-3-4-5 and 2-3-4-11 is significant. Compound III is completely flat. However, in compound I, the deviations from planarity in the inside 10-membered ring are great. The deviations calculated for 2-3-4-5, to a large extent different from those of 5-6-7-8, are due to the existence of a phenyl group at C2-C3, which significantly impacts the molecular geometry.

Table 4 shows the steric energies, $E(s)$, calculated by MM2 for the compounds studied. Table 4 also shows the different contributions to $E(s)$: bond stretching, deformation energy of bond angles, energy of interaction between nonbonded atoms, twisting energy, energy corresponding to crossed atoms. These data show that, for all the compounds, the only important contributions are the twisting energies and van der Waals energies. The values of $E(s)$ indicate that the order of stability is I < II < III. The greater relative stability of molecule III is attributable to its low relative twisting energy, which is consistent with its relatively short C5-C10 bond distance and hence the greater planarity of the molecule. The van der Waals interaction energies increase in the same order, but more slowly. In them, the compression and bending interactions are less important than the 1-4 van der Waals

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Table 3. Dihedral Angles (deg) for Compounds I and II

dihedral angles	MNDO		AM1		MM2	
	I	II	I	II	I	II
5-4-3-2	310.76	339.35	41.51	343.14	40.29	345.85
6-5-4-3	148.47	169.49	208.41	168.34	213.55	166.48
7-6-5-4	215.18	197.77	149.09	198.01	145.76	197.80
8-7-6-5	41.39	4.64	322.72	4.84	323.86	3.31
20-19-18-17	4.55	2.72	357.57	1.20	358.28	1.05
19-20-3-4	166.23	174.23	188.95	177.96	-173.84	179.96
11-4-3-2	120.81	160.03	230.99	165.47	228.97	167.72
12-11-4-3	195.50	178.58	165.27	179.19	165.66	179.88
12-13-6-7	233.29	184.10	198.01	167.81	138.167	-179.72
13-12-11-4	7.71	6.06	353.02	5.64	350.30	7.89

Table 4. Steric Energies, $E(s)$, Calculated by MM2 and Its Different Contributions in kcal/mol

	I	II	III
$E(s)$	10.8973	-0.0406	-23.0921
compression	1.2213	0.9859	0.6488
bending	2.3243	2.2432	0.8252
stretch-bending	0.0658	0.0937	0.0389
van der Waals 1,4	13.3749	13.9210	13.9487
van der Waals other	3.3492	-0.9454	-1.3738
torsion	-9.4381	-16.6286	-37.1800

Table 5. Parameters of Energies of I-III at 298.15 K Calculated Using the AM1 and MNDO Methods

	MNDO			AM1		
	I	II	III	I	II	III
heat of formation (kcal mol ⁻¹)	126.392	110.301	80.175	120.233	114.665	83.990
μ (D)	0.128	0.059	0.043	0.044	0.316	0.033
HOMO (eV)	-8.576	-8.004	-8.108	-8.542	-7.837	-8.219
LUMO (eV)	-0.332	-0.844	-0.889	-0.325	-0.840	-0.855

interaction energy, which is almost the same in all three cases. For the nonbonding interactions between the benzene groups in the molecule to be minimal, these groups will tend to become oriented in parallel, in agreement with the geometric results obtained in Table 4. In molecule I, it is seen that the benzene group has much greater rotational freedom.

Table 5 offers the heats of formation calculated by the MNDO and AM1 methods for the three compounds. By both methods, the relative stabilities of these compounds are consistent with those obtained by the molecular mechanics method.

Another aspect of the results to be considered is the difference between the HOMO and LUMO shown by the AM1 and MNDO methods. The AM1 method predicts that the reactivity shown by I will be greater than that of II, and that of II greater than that of III; these values are less marked for the MNDO method. Regarding the dipolar moment, the values given by AM1 are higher than those

obtained by MNDO, although they follow the same order, compound II being the most soluble in polar solvents.

Owing to the existence of other, similar AM1 studies and the fact that the AM1 method seems to afford data that are more consistent with experimental data, it seemed appropriate to include in the present work the interconversion between I and II by AM1. The barriers obtained are 44.03 and 43.932 kcal/mol for the forward and reverse processes of I and II, respectively. This value is lower than that obtained by Hernando et al.¹² It establishes the existence of an inverse barrier of small magnitude, compared to the activation energy derived in this work.

The results obtained, together with others previously reported, indicate that these methods are valid for describing the transformation of I and II and, finally, into III, since the data obtained are in good agreement with the known experimental results¹⁵ regarding certain similar compounds. The differences in energy calculated by the AM1 method for I and II are not large and, in fact, are smaller than those calculated for *anti*-[2.2]metacyclophane-1,9-diene⁵ by the same method. This situation is confirmed for other molecules containing the same number of atoms. This can be interpreted to mean that the transformation of I into II entails less hindrance than the transformation of [2]metacyclo[2](1,3)naphthalenophane-1,11-diene into dihydrobenzo[*e*]pyrene, which agrees with the experimental data obtained by Mitchell et al.¹³ The greater stability of benzo[*e*]pyrene relative to benzo[*a*]pyrene could explain the former's lower reactivity in metabolic processes and, possibly, its lack of carcinogenicity.

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