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The possible correlation of carcinogenic activity with electronic structure of benz(a)anthracene

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THE POSSIBLE CORRELATION OF CARCINOGENIC ACTIVITY WITH ELECTRONIC STRUCTURE OF BENZ(A)ANTHRACENE

BY

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Approved by

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C. H. Ho

This work is dedicated to

several very special people

MY MOTHER

Mr. & Mrs. T. McGill

and my second family

The T. McCabes

and to the goal

of a carefully coordinated and

comprehensive investigation

into the basic nature of

carcingensis

ABSTRACT

The electronic structure of benz(a)anthracene based on the sigma and pi electrons was predicted by the modified intermediate neglect of differential overlap (MINDO) molecular orbital method and compared with the pi electronic structure determined by the Pople method. The crystalline molecular structure was used for both methods. The Pople calculation was also done on the aromatic molecular structure and a combination structure which assumed the bond lengths of the crystal structure and the bond angles of the aromatic structure.

Chemical properties predicted by the MINDO and POPLE electronic structures were compared; the MINDO results provided the best agreement with experimental results.

Based on the MINDO results, a bonding model for benz(a)anthracene was proposed and was found to be consistent with the known chemical reactivity of benz(a)anthracene.

The carcinogenic activity of benz(a)anthracene was considered and possible general types of interactions between the molecule and cellular proteins or nucleic acids was suggested.

Several suggestions for additional study were made.

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I. INTRODUCTION

The two-fold purpose of this investigation was to select the best theoretical approach to the study of the electronic structure of the carcinogenic (i.e., cancer producing) derivatives of benz(a)anthracene and to present a detailed consideration of the electronic structure of benz(a)anthracene.

The benz(a)anthracene molecule is extremely interesting because it serves as the basic ring structure for numerous carcinogens. The degree of carcinogenic activity depends upon the type of chemical substitutent introduced into the benz(a)anthracene ring system and upon its position.[1,2,3] Table A-1 and Figure A-1 of the Appendix summarize the various benz(a)anthracene derivatives and their carcinogenic potency.

The electronic theory of organic chemistry[4] indicates that a molecule's chemical reactivity is related to its electronic structure. Accurate knowledge of the electronic structure of a molecule will allow the prediction of plausible reaction intermediates and realistic reaction mechanisms. Such insight into the nature of the reaction(s) of carcinogenic molecules might be most helpful in elucidating the basic nature of cancer.

II. REVIEW OF THE LITERATURE

A review of the literature was conducted for two reasons: (1) to determine the state of knowledge of the correlation of electronic structure and carcinogenic activity and (2) to obtain information on the available molecular orbital methods for determining the electronic structure of molecules.

A. Correlation between carcinogenic activity and electronic structure

The correlation between carcinogenic activity and the electronic structure of aromatic hydrocarbons has been a subject of great interest in both chemistry and biology for over 30 years. In 1939, Otto Schmidt[5] proposed that carcinogens might possess a common region of high reactivity capable of binding to tissue components and producing cancer. He suggested that this region, which he called the K-region (i.e., Krebs or cancer region), was located in a position corresponding to the 9,10-double bond of phenanthracene. The K-region of phenanthracene is shown in Figure 1. The correlation between the electronic structure and carcinogenic activity was widely investigated in the decade following Schmidt's suggestion.[6,7,8,9,10]

The most significant development was Pullman's quantum mechanical description of the electronic structure of the aromatic hydrocarbons using valence bond theory[11] and subsequently the demonstration that the K-region was indeed a region of high electron density which corresponded to a region of high chemical reactivity. In a later study,[12] Alberte and Bernard Pullman achieved a more detailed picture of the electronic structure of aromatic hydrocarbons by using the Hückel molecule orbital (HMO) method.[13] Wheland[14] suggested that it should be

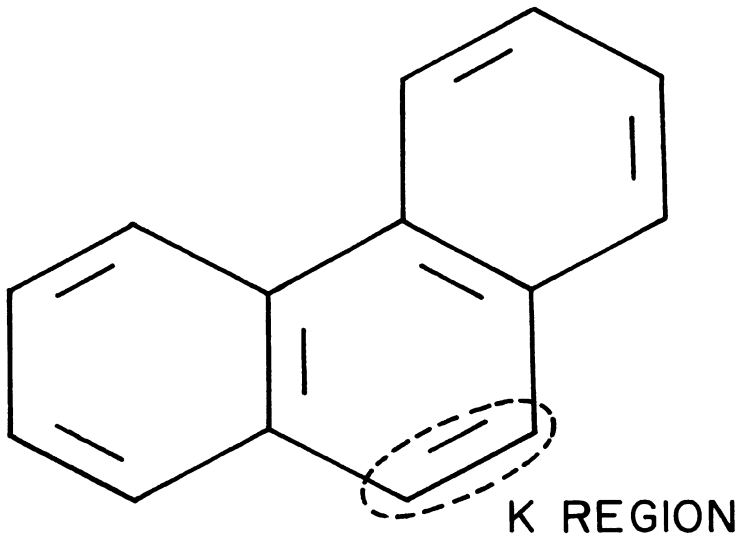

Figure 1. K-Region of Phenanthracene

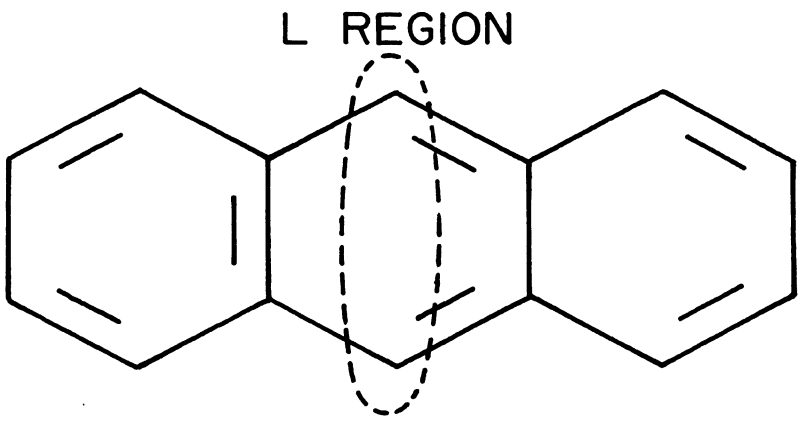

Figure 2. L-Region of Anthracene

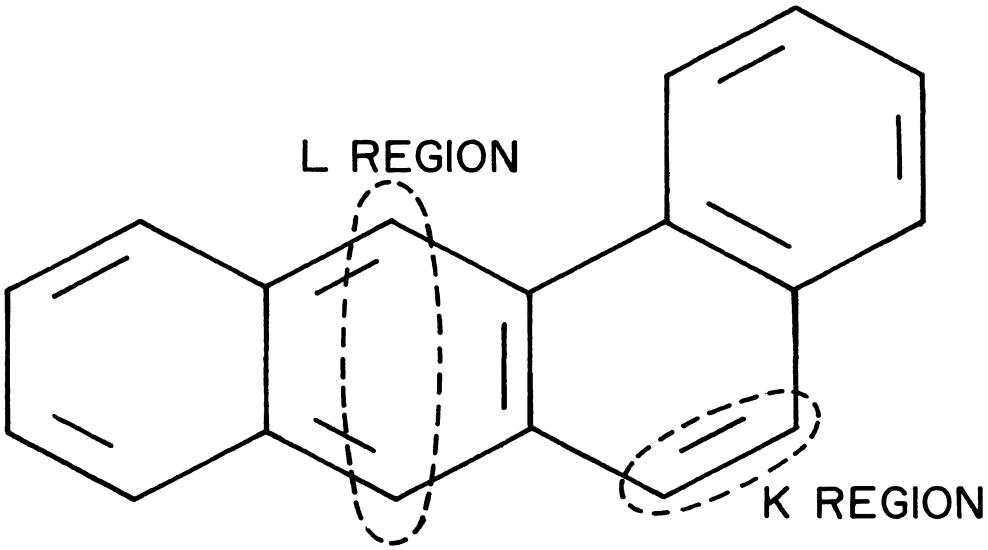

Figure 3. K and L-Regions of Benz(a)anthracene

possible to correlate the magnitude of the bond order with the chemical reactivity of that bond. The Pullmans' study did not obtain this correlation. However, their study did verify the existence of the reactive K-region in carcinogenic hydrocarbons by using a combination of calculated indices. The carbon localization energy (C.L.E.), bond localization (B.L.E.) and para localization energy (P.L.E.) were the indices used. The best correlation with carcinogenic activity was obtained by describing the K-region with the quantity $C.L.E._{min} + B.L.E.$ This same study suggested that a second region, the L-region was present in many carcinogens and corresponded to the meso or 9,10-bond of anthracene shown in Figure 2. The reactivity of the L-region was described by the quantity $C.L.E._{min} + P.L.E.$ The K and L-regions were shown to be the principal reactive centers which govern the addition and substitution reactions respectively.[15] This led the Pullmans to suggest that these same two regions were also of importance for carcinogenic activity. Figure 3 illustrates the K and L-regions of benz(a)anthracene.

The Pullmans' study[16] produced two postulates for predicting carcinogenic activity:

1. ..."The appearance of carcinogenic activity in aromatic hydrocarbons is determined by the existence of an active K-region." That is, the theoretical index governing the activity must be below a certain threshold value which the Pullmans suggest is 3.31β.

2. ..."If the molecule contains an L-region, a supplementary condition requires that the L-region be rather inactive." That is the theoretical index governing the activity must be above a threshold value of 5.66β.

β is the resonance integral which the Pullmans used as 20 k cal/mole.

Based on these postulates, the carcinogenicity of 32 out of 37 unsubstituted hydrocarbons was predicted correctly.

In attempting to correlate electronic structure, chemical reactivity and carcinogenic activity the Pullmans considered the rate of substitution reactions in both carcinogenic and noncarcinogenic hydrocarbons. They observed that the carcinogenic molecules underwent substitution with difficulty. An unsuccessful attempt was made to correlate the ease of substitution with the index of the L-region. They concluded that it was unlikely that substitution reaction played a part in carcinogensis.

The addition reactions were also studied for a possible correlation to carcinogenic activity. Badger;[17] Berither, Coulson, Greenwood and Pullman[18] and Fieser[19] each studied the experimental rates of addition to a bond in carcinogenic and noncarcinogenic molecules. The most complete set of experimental data on bond reactions has been given by Badger using Griegee's reagent (i.e., osmium tetraoxide in the presence of pyridine). Figure A-2 of the appendix illustrates the reaction of osmium tetraoxide and a carcinogen. Badger reported a correlation between the rate of addition of osmium tetraoxide and the strength of the carcinogen. These results including the Pullman indices for the K-region of each molecule, are given in Table 1. At the time of Badger's study, both chrysene and benz(a)anthracene were thought to be noncarcinogenic. Later testing[20] revealed that these were each weak carcinogens. This would appear to detract from the "very satisfactory correlation" which Badger reported.

TABLE I. CORRELATION BETWEEN RATE OF OSMIUM TETRAOXIDE ADDITION AND CARCINOGENIC POTENCY

Compound	Relative reactivity to OsO_4	Pullman index of K-region
Benz(o)pyrene	2.0	3.23
1,2;5 6-dibenzanthracene	1.3	3.30
Benz(a)anthracene	1.0	3.29
Pyrene	0.66	3.33
Phenanthracene	0.10	3.36
1 2;5 6-dibenzphenanthracene	S	3.41
Chrysene	S	3.38

S = slow

It was concluded that the carcinogenicity of a molecule roughly parallels the activity of the molecule toward an electrophilic reagent.[21] This electrophilic reagent was assumed to be a tissue component perhaps a protein or nucleic acid.

Intrigued by Schmidt's suggestion of a protein-carcinogen interaction Miller[22] sought after and isolated such compounds which were derived from 3,4-benz(o)pyrene combined with cellular protein. Following this study, Wiest and Heidelberger,[23] Bharagava et. al.[24] and other investigators attempted to determine the precise structure of the proteinbound complexes. In 1956, Heidelberger and Moldenhauser[25] attempted to correlate the degree of carcinogenic activity with activity toward skin-protein binding. This work was extended by Oliverio and Heidelberger,[26] Daudel et. al.[27] and Chalvet et. al.[28]. Their studies suggested that binding between skin-protein and carcinogens could occur

in two possible ways: one way involves addition to the K-region and the other involves addition to an L-region. Only the K addition appears to induce tumor production.[29]

Many compounds reacting via the K-region do exhibit a correlation between carcinogenic activity and protein binding; however, exceptions do exist such as the carcinogen tricycloquiazoling[30] which does not exhibit protein binding. In addition, it is noted that many noncarcinogens also exhibit strong affinity for protein binding.[31] Hueper and Conway suggest that the rough qualitative correlation of the K and L-regions with the carcinogenic activity of a molecule requires refinement.[32] "This improved theory using complex theoretical indices still fails to explain the effect of methyl substitution in the angular ring of benz(a)-anthracene. It is also difficult to explain the increase in potency observed in the 10 positions of benz(a)anthracene. It is also difficult to explain these effects on steric grounds since the 2 and 3 methyl benz(a)anthracenes which correspond to the 7 and 8 methylbenz(a)anthracenes are carcinogenic."[32]

Clayson states the major objection which most cancer research raise with the Pullmans' K and L theory, "The major criticism of the Pullmans' theory is their insistence that very small variation in the activation energies of the order of .01 (about .2kcals) are sufficient to decide whether or not a compound is carcinogenic. Thus, for example, 1,2;5,6-dibenzanthracene has an electronic index for its K-region of 3.30β and pyrene has an index of 3.33β. The former is active and the latter is inactive."[33]

These objections to the K and L theory most probably result from the

use of the HMO method. The HMO consist of three basic assumptions:

1. All overlap integrals, S_{ij}, are assumed equal and all atomic orbitals are normalized ($S_{ij} = 1$).

2. The matrix element H_{jj} is assumed to be the same for all atoms and is set equal to the coulomb integral, α.

3. The matrix element H_{ij} is assumed to have the constant value β if i and j are adjacent atoms. All other H_{ij}'s are set equal to zero.

These assumptions of the HMO method restrict its application to conjugated hydrocarbons because this is the one class of compounds where the assumptions are valid.[34] However, even for the conjugated hydrocarbons the complete neglect of interelectronic repulsion of the HMO becomes a serious error. In the case of benzene, this amounts to 4-5% of the pi electronic energy. Benz(a)anthracene and the other condensed ring hydrocarbons have pi-systems four to five times the size of the benzene pi-system. Consequently, the interelectronic repulsion can not be disregarded. The inadequacies of the HMO have been discussed by various authors.[35, 36]

In summary, it is suggested that a thorough consideration of the electronic structure of benz(a)anthracene and its various carcinogenic derivatives requires a molecular orbital method which (1) considers all the valence shell electrons, (2) includes interelectronic repulsion and (3) evaluates the overlap integrals in a realistic manner.

B. State of the art

It would seem that the semiempirical molecular orbital method best capable of determining the electronic structure of benz(a)anthracene derivatives should include the sigma electrons in its calculation. The modified intermediate neglect of differential overlap (MINDO) developed by Dewar and Baird[37] is one such method specifically designed to calculate the ground state properties of molecules. Essentially, MINDO is an extension of the Pople self-consistent field (SCF) treatment of pi electrons in conjugated systems.[38] The problems involved in extending the Pople method to include all the valence electrons have been discussed in detail by Parr[39] and Lykos.[40]

The basic criterion for an effective method is that the calculations be invariant to the choice of coordinate axes. In other words, the resulting molecular wave functions and all the properties which may be derived from them as expectation values must be invariant with respect to a unitary transformation of the occupied molecular orbitals between atomic orbital basis functions. This requirement forms a restraint on the neglect of differential overlap. When differential overlap is indiscrimately neglected (as in the complete neglect of differential overlap-CNDO-),[41] the results are not invariant to the choice of coordinate axes.

The most rigorous approximation is by the neglect of diatomic differential overlap (NDDO) method.[42] This method retains integrals involving one-center differential overlap but neglects two-center differential overlap. For example, (ij, kl) is negelected when φ_i and φ_j are atomic orbitals (AO's) of

different atoms. While NDDO is the most desirable method theoretically, its use requires an extremely large computer storage area and extremely long periods for calculations. Consequently, no NDDO calculations have been reported in the literature. It is highly improbable that such calculations would be feasible for the large basis set (i.e., many valence electrons) that need be considered when dealing with carcinogens.

The MINDO method is a compromise between the simplicity of the CNDO method and the desired rigor of the NDDO method. It consists of three main modifications to Pople's intermediate neglect of differential overlap (INDO) method.[43]

1. Selection of parameters is controlled by the goal of calculating ground state properties rather than the INDO goal of reproducing the results of an exact Hartree-Fock calculation. Consequently, the MINDO method choses parameters by fitting them to the observed properties of appropriate reference molecules, while INDO attempts to use results of a priori calculations.
2. The one-center integrals used in the molecular calculations are derived from an analysis of the atomic spectra of the first row atoms. All the one-center core-electron attraction integrals are denoted U_{ss} and U_{pp} and the one-center electron repulsion integrals are written in terms of the Shortley and Condon F^k and G^k parameters:[44]

   $(ss, ss) = (ss, pp) = F^0$ $\qquad$ $(sp, sp) = G^1/3$

$$(pp,\ pp) = F^{o} + 4/25\ F^{2} \qquad (pp,\ p'p) = F^{o}/25\ F^{2}$$

$$(pp',\ pp') = 3/25\ F^{2}$$

3. The various two-center integrals were estimated by a procedure similar to Pople's treatment of pi electron systems.[45] The two center repulsion integrals between AO's of a given pair of atoms A and B are assumed to have a common value α_{AB}. Consequently, the attraction $\int \varphi_u v_B \varphi_u d\tau$ between an electron in an AO φ_u of atom A, and the core of atom B was assumed to be:

$$\int \varphi_u v_B \varphi_u d\tau = -C_B \alpha_{AB}$$

here C_B is the core charge of atom B (i.e., the atomic number less the number of inner shell electrons). Using the preceding approximation, the Hartree-Fock F matrix for a closed shell of electrons is:

$$H_{uu}^{AA} = U_{uu} - \sum_{B=A} C_B \alpha_{AB} \qquad H_{uv}^{AA} = 0$$

$$H_{uv}^{AB} = \beta_{uv}\ C_{uv} \qquad F_{uu}^{AA} = U_{uu} + \tfrac{1}{2} q_u (uu,\ uu) + \sum_{u=v}^{A} qn$$

$$F_{uu}^{AA} = U_{uu} + \tfrac{1}{2} q_u (uu,\ uu) + \sum_{u \neq v}^{A} q_v ((uu,\ vv) - \tfrac{1}{2}(uv,\ uv)) + \sum_{B \neq A} (Q_B - C_B)\alpha$$

$$F_{uv}^{A,A} = P_{uv}\ (3/2\,(uv,\ uv) - \tfrac{1}{4}(uu, vv))$$

$$F_{uv}^{A,B} = \overset{c}{\beta}_{uv} - \tfrac{1}{2} P_{uv} \alpha_{AB}$$

In the preceding equations

q is the electron density of the AO's,

Q is the total valence shell electron density of an atom

and

P is the bond order matrix.

The one-center integrals and derived quantities used in the MINDO method are summarized in Table A-2 of the appendix.

III. COMPUTATIONAL PROCEDURE

All calculations reported in this thesis were conducted at the UMR computer laboratory on an IBM 360-model 50 computer. The four programs used were POPLE and MINDO molecular orbital methods discussed in the preceding sections and Dewar's program for calculating cartesian coordinates (COORD)[46] and Baur's program for calculating bond angles Searches for Atomic DIstances and ANgles (SADIAN).[47] These latter two programs will be discussed in the next section. Each of these programs were written in the Fortran language. After the programs were converted to the Fortran IV language and adapted to run under the UMR operating system, each of them was compiled in H-level object decks. Table 2 lists the time a core storage requirements for typical calculations.

It should be noted that there are two reasons for the difference in the run time of the object and source decks. First, the object deck is in machine language, hence, the time required to compile the program is saved. Essentially, this is the reason for the time difference in the first three programs of Table 2. Secondly, the object decks compiled in H-level allows an optimization of the program.[48] This is evident in the MINDO program which has a compile time of 2 minutes and 32 seconds. Here the object deck cuts down on each iteration by 2-3 minutes.

The time-consuming portion of the MINDO program is the diagonalization routine. The Jacobi method of matrix diagonalization is used and the diagonalization time is observed to vary as the cube of the size of the basis set.

TABLE II. COMPUTER PROGRAM TIME AND CORE STORAGE REQUIREMENTS

PROGRAM		TIME	CORE REQUIRED	TYPE OF CALCULATION
COORD	Source deck	65 seconds for 30 atoms	100K	Cartesian coordinates are calculated from input of structural data.
	H-level object deck	31 seconds for 30 atoms		
SADIAN	Source deck	250 seconds for 30 atoms	140K	Bond angles and other structural data are calculated from input of crystal graphic data.
	H-level object deck	190 seconds for 30 atoms		
POPLE	Source deck	180 seconds 25 sec/iteration for basis set of 18 atoms	140K	Electronic structure based on the pi electrons is calculated from input data consisting of the molecular structure, number of pi electrons and the resonance integral.
	H-level object deck	100 seconds		
MINDO	Source deck	11 minutes/ iteration basis set of 84	280K	Electronic structure based on both the sigma and pi valence electrons is calculated from input data consisting of molecular structure.
	H-level	8-9 minutes/ iteration basis set of 84 5 hours 22 minutes required for convergence of benz(a)anthracene calculation (i.e., basis set of 84).		

IV. RESULTS

A. Bond angles and cartesian coordinates of benz(a)anthracene

The crystallographic investigation of the structure of benz(a)anthracene was begun in 1939 with the identification of the space group (C_2^2) to which it belongs.[49, 50] In 1956 Friedlander and Sayre[51] reported the structure of benz(a)anthracene citing the experimental error as .03A. Their published results included the atomic positions in terms of unit cell coordinates and the bond lengths in angstroms, however, the bond angles were not reported.

Unit cell coordinates give the atomic positions relative to a set of oblique axes rather than relative to the orthogonal axes of the cartesian coordinates. While such coordinates are useful to the crystallographer, they can not be used in conventional molecular orbital calculations which assume cartesian coordinates. Consequently, it is necessary to obtain the cartesian coordinates in order to do the molecular orbital calculations. However, the cartesian coordinates require the knowledge of both the bond lengths and bond angles.

Previous MO calculations on benz(a)anthracene lacked the correct cartesian coordinates of the crystal structure, hence, these calculations were based on one of two assumptions:

1. benz(a)anthracene was assumed to be an aromatic hydrocarbon with equal carbon-carbon bond lengths and all angles equal to 120^o.[52, 53]

2. benz(a)anthracene was assumed to have the bond lengths reported by Friedlander and Sayre and all bond angles were assumed to be equal to 120^o.[54]

The molecular structure based on these two assumptions will be referred to as structures 1 and 2 in the remainder of this thesis.

Baur has written the computer program SADIAN which among other things, is capable of calculating bond angles of a molecule from the unit cell coordinates, the space group, the lengths of the unit cell edges and the three angles between the edges. The accepted numbering for benz(a)anthracene is shown in Figure 4. For the sake of clarity in the discussion of this work, the numbering system has been revised to correspond to Figure 5. The remainder of this thesis will use the numbering scheme of Figure 5 exclusively. When it is necessary to cite literature references, the numbering in the literature will also be transposed to correspond to that of Figure 5. Figure 6 shows the bond lengths reported by Friedlander and Sayre. Table 3 shows the carbon bond angles of benz(a)anthracene as calculated by SADIAN. Identification of the angles of Table 3 corresponds to Figure 7. Figure 7 shows the bond angles of the hydrogens.

X-ray data does not allow the location of the hydrogens and electron diffraction data which would locate the hydrogens has not been reported on benz(a)-anthracene. Consequently, the positions of the hydrogens were assumed to bisect the angle formed by the atoms adjacent to the carbon to which the hydrogen is bonded. The distance of the C-H bond was taken as 1.08A.[55]

It is now possible to calculate the cartesian coordinates of benz(a)anthracene based on the crystallographic data. Dewar's COORD computer program was used to calculate the coordinates based on the molecular structure of the molecule. The structure represented by these coordinates will be referred to as structure 3. Table 4 compares the bond lengths of structures 1, 2, and 3 with the crystallographic data.

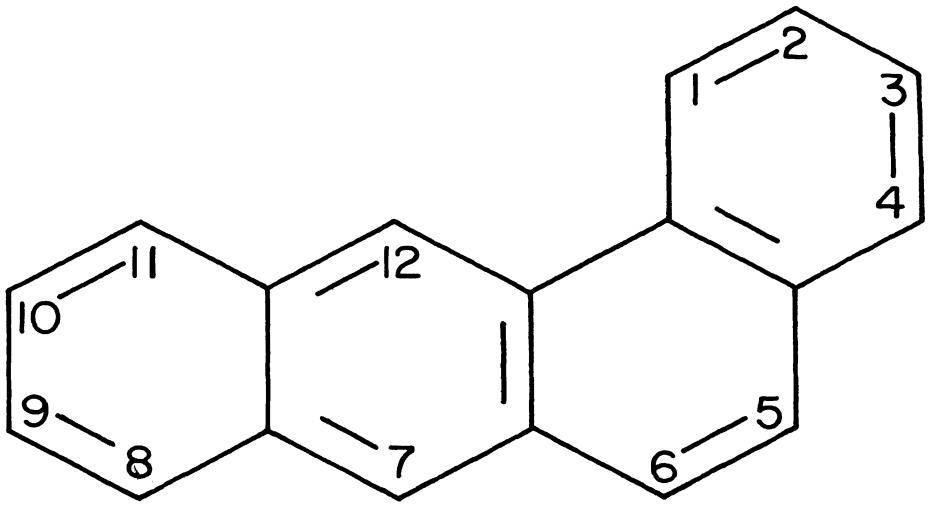

Figure 4. Conventional Numbering for Benz(a)anthracene

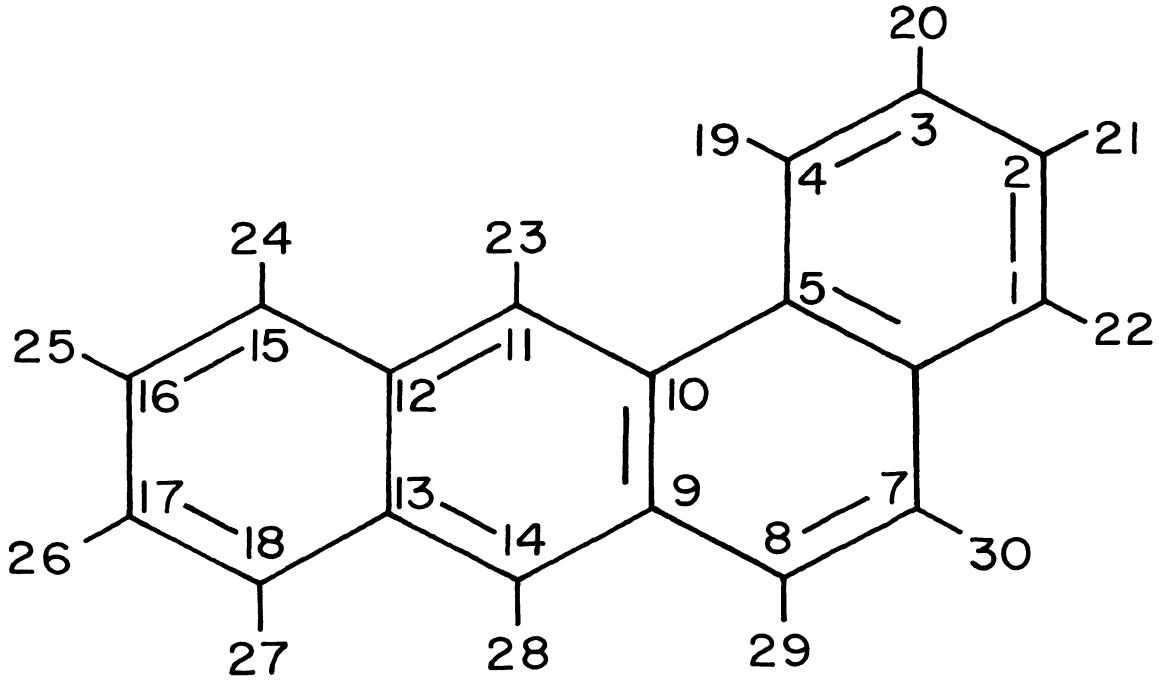

Figure 5. Revised Numbering for Benz(a)anthracene

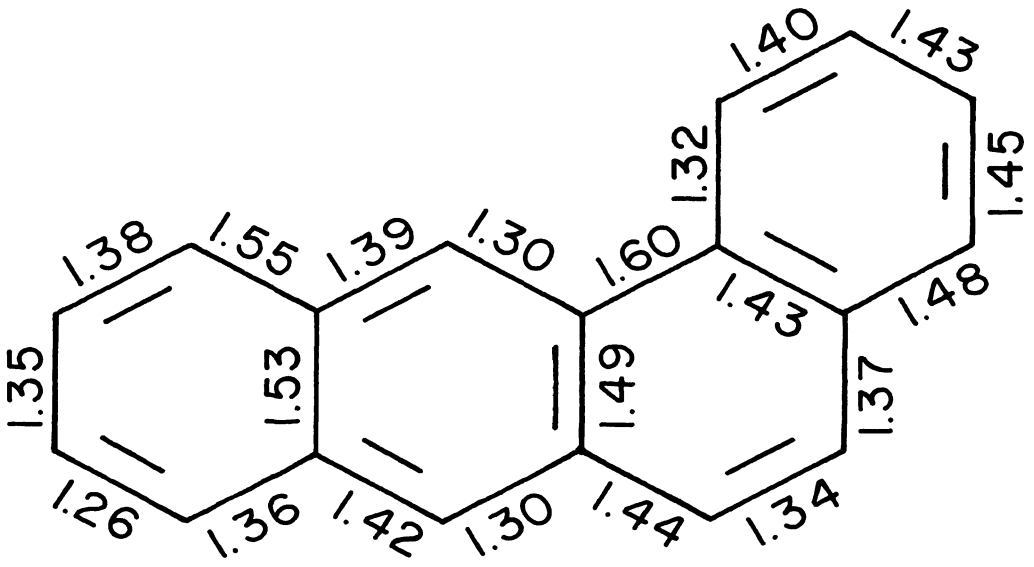

Figure 6. Bond Lengths in Angstroms of Benz(a)anthracene

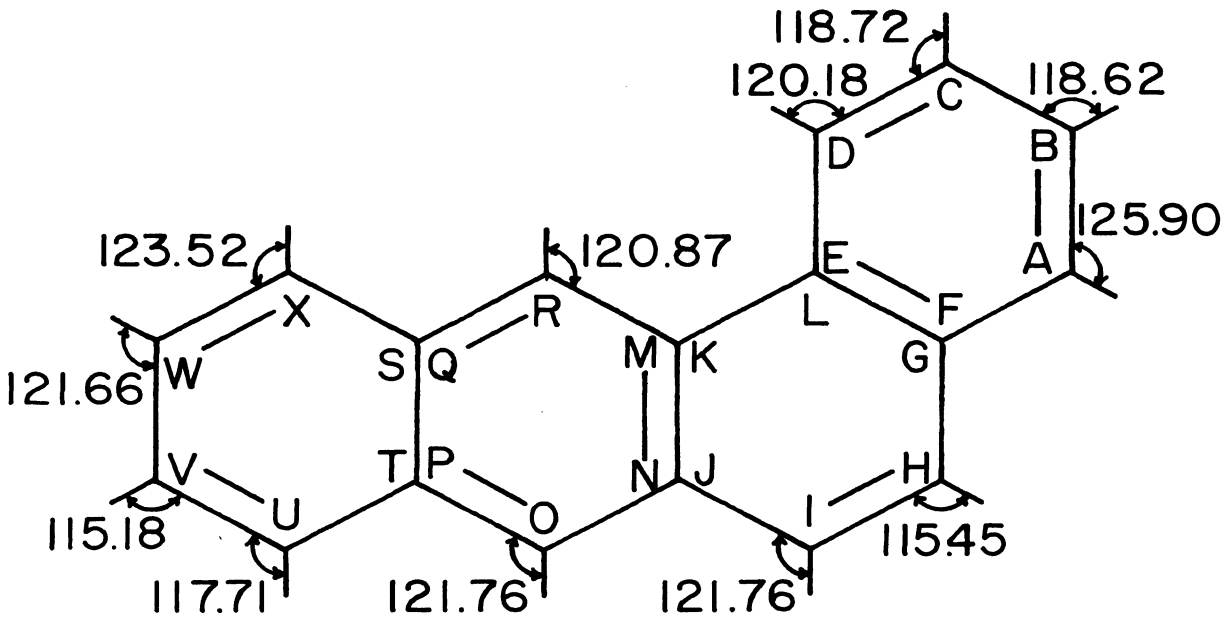

Figure 7. Bond Angles for the Hydrogens of Benz(a)anthracene

TABLE III. CARBON BOND ANGLES IN BENZ(A)ANTHRACENE

Angle	Degrees	Angle	Degrees
A	108.20	M	124.75
B	122.76	N	119.50
C	122.56	O	116.59
D	119.60	P	116.07
E	119.18	Q	124.74
F	127.42	R	118.06
G	119.42	S	121.35
H	129.08	T	114.80
I	116.52	U	124.59
J	123.01	V	129.63
K	113.71	W	116.62
L	118.12	X	112.92

Table 4 shows the comparision of the experimentally observed bond lengths and the bond lengths calculated in each of the three structures previously discussed.

TABLE IV. BOND LENGTHS OF BENZ(A)ANTHRACENE

Bond	Experimental	Structure 1	Δ	Structure 2	Δ	Structure 3	Δ
1-2	1.45	1.397	+0.053	1.3859	+0.0641	1.45	0.0
2-3	1.43	1.397	.033	1.4006	.0294	1.43	0.0
3-4	1.40	1.397	.003	1.3856	.0144	1.40	0.0
4-5	1.32	1.397	-.007	1.4102	.0227	1.32	0.0
5-6	1.43	1.397	.033	1.4073	.0815	1.43	0.0
6-7	1.37	1.397	-.020	1.4515	.0166	1.37	0.0
7-8	1.34	1.397	-.057	1.3566	-.0126	1.34	0.0
8-9	1.44	1.397	.043	1.4526	.0691	1.44	0.0
9-10	1.49	1.397	.093	1.4209	-.0894	1.49	0.0
10-11	1.30	1.397	-.097	1.3894	.0238	1.30	0.0
11-12	1.39	1.397	-.007	1.4138	-.0238	1.39	0.0
12-13	1.53	1.397	.133	1.4094	.1206	1.53	0.0
13-14	1.42	1.397	.023	1.4135	.0065	1.42	0.0
14-9	1.50	1.397	.103	1.3899	.1101	1.5002	-0.0002
15-16	1.38	1.397	-.017	1.3686	.0114	1.38	0.0
16-17	1.35	1.397	-.027	1.4289	-.0789	1.35	0.0
13-18	1.36	1.397	-.037	1.4343	-.0743	1.36	0.0
5-1	1.60	1.397	.203	1.4549	.1151	1.5771	0.0229
17-18	1.26	1.397	-.137	1.3686	-.1086	1.2607	-.0007
1-6	1.48	1.397	.083	1.4108	-.0692	1.4815	-.0015
12-15	1.55	1.397	.153	1.4342	.0158	1.55	0.0

B. Electronic Structure of Benz(a)anthracene

1. The POPLE Method

The Pople SCF-MO method invokes the principle of sigma-pi separability[56] and calculates the pi electronic structure of a molecule. The theoretical basis of this method has been thoroughly discussed in the literature[57] and has proven very useful in application to conjugated systems.[58,59] It is used in this work for two purposes: (1) to compare the predicted results of the three sets of cartesian coordinates discussed in section A, and (2) to compare the predicted results of the pi-electronic structure with the electronic structure based on both the sigma and pi valence electrons.

Figures 8, 9 and 10 present the bond orders which are determined by the Pople method using each of the three structures. The resonance integral used was 2.05 ev. Table 5 compares the ionization potential, electron affinity and pi energy predicted by each of the three structures with the experimental quantities. The ionization potential is equal to the energy of the highest filled (HFO) molecular orbital with its sign changed.[60] In a similar manner the electron affinity is assumed equal to the lowest empty orbital (LEO). Table 5 also contains the results of applying the Pople-Pariser-Parr (PPP)[61] MO method to the benz(a)anthracene molecule using structure 2.[62]

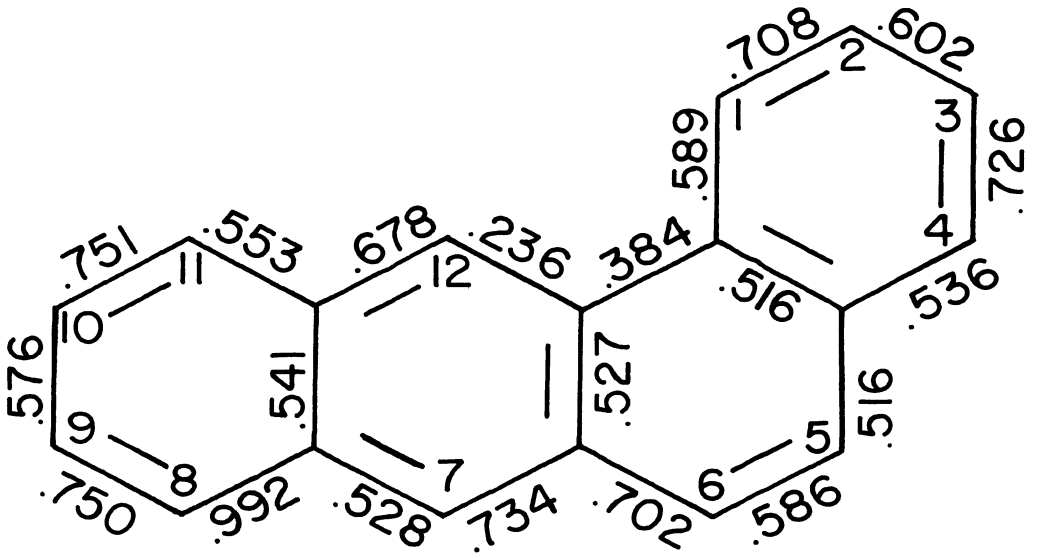

Figure 8. Bond Orders of Benz(a)anthracene Based on Structure 1

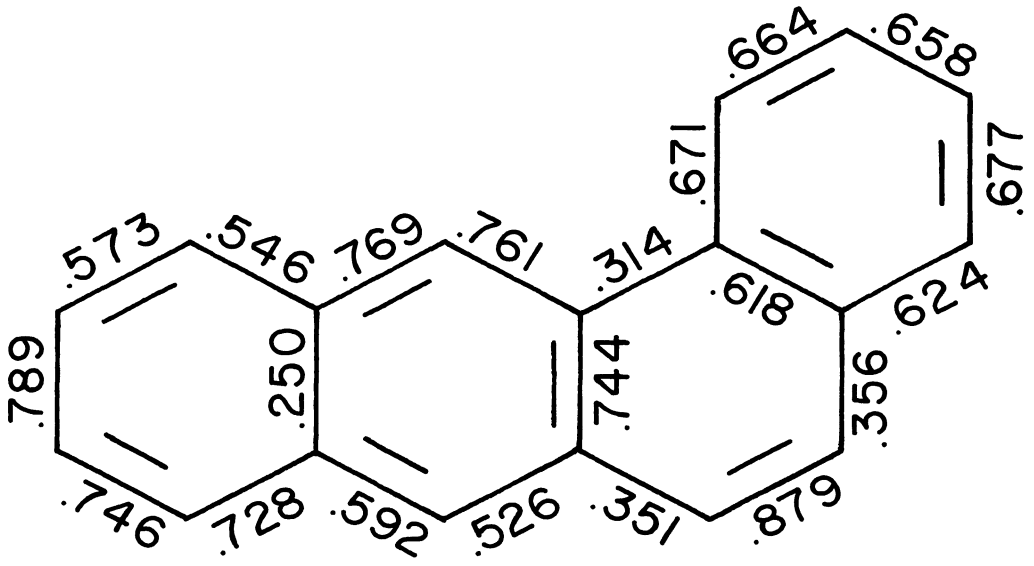

Figure 9. Bond Orders of Benz(a)anthracene Based on Structure 2

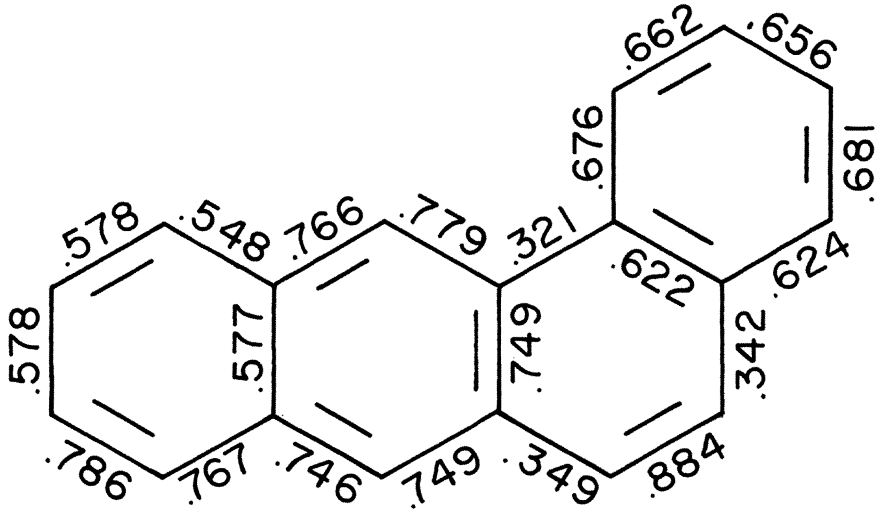

Figure 10. Bond Orders of Benz(a)anthracene Based on Structure 3

TABLE V. MOLECULAR QUANTITIES PREDICTED BY THE POPLE AND PPP ELECTRONIC STRUCTURE OF BENZ(A)ANTHRACENE

	Ionization Potential	Ionization Potential Times β	Electron Affinity	Pi Energy
Structure 1 Pople	2.67	5.66	8.74	-29.62
Structure 2 Pople	3.12	6.49	7.34	-27.89
Structure 2 PPP	9.34	--	1.78	-26.36
Structure 3 Pople	3.12	6.38	7.32	-27.91
Experimental	7.35[63]		3.04[65]	
	7.54[64]			

2. The MINDO Method

Table 6 summarizes the molecular quantities calculated by the MINDO method. Figure 11 represents the electron density based on the sigma and pi electrons, Figure 12 represents the electron densities based on only the pi electrons, and Figure 13 represents the electron densities based on only the sigma electrons. Figure 14 represents the polarizability of the molecule. Figure 15 represents the bond orders based on the sigma and pi electrons. Figure 16 represents the pi contribution to the bond orders and Figure 17 represents the sigma contribution to the bond orders.

TABLE VI. CALCULATED AND EXPERIMENTAL PROPERTIES OF BENZ(A)ANTHRACENE

Properties	Calculated Value	Experimental Value	Difference
Valence shell energy	-127.954 ev	--	--
Heat of Formation	160.60 ev	157.74 ev[66,67]	2.86 ev
Ionization Potential	8.20	7.35[68] 7.54[69]	0.85 0.66
Electron Affinity	2.65	3.04[70]	0.39
Dipole Moment	0.35 Debye	--	--

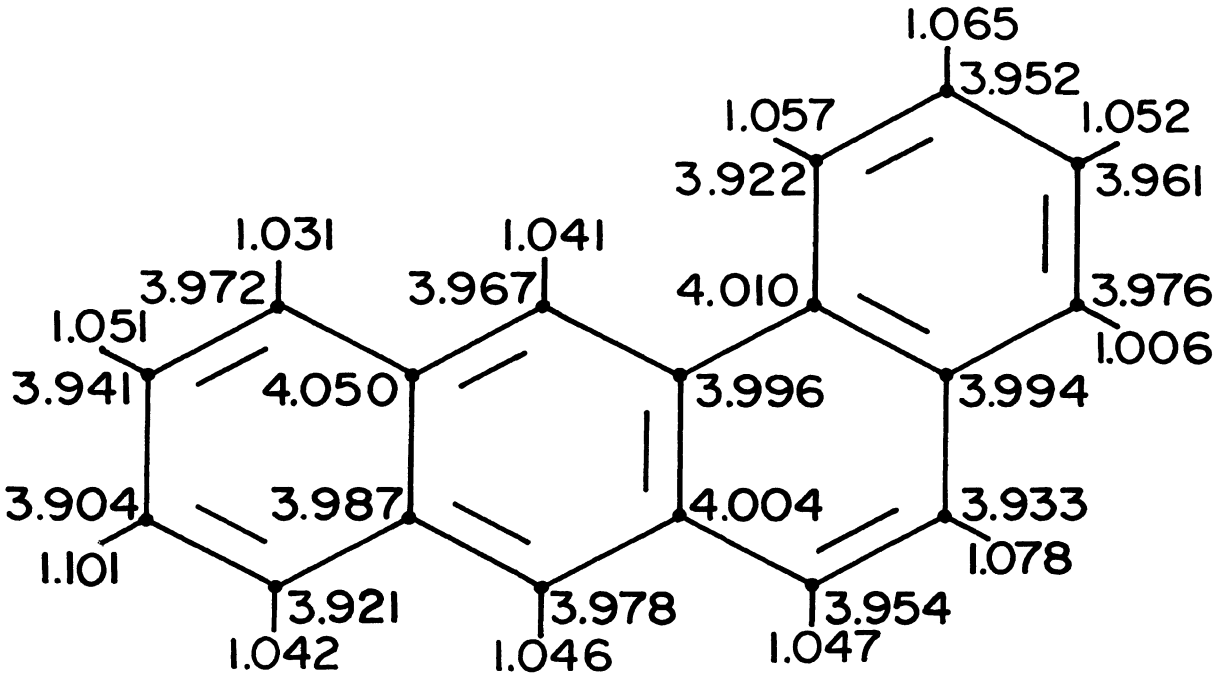

Figure 11. Electron Densities Based on Sigma and Pi Electrons

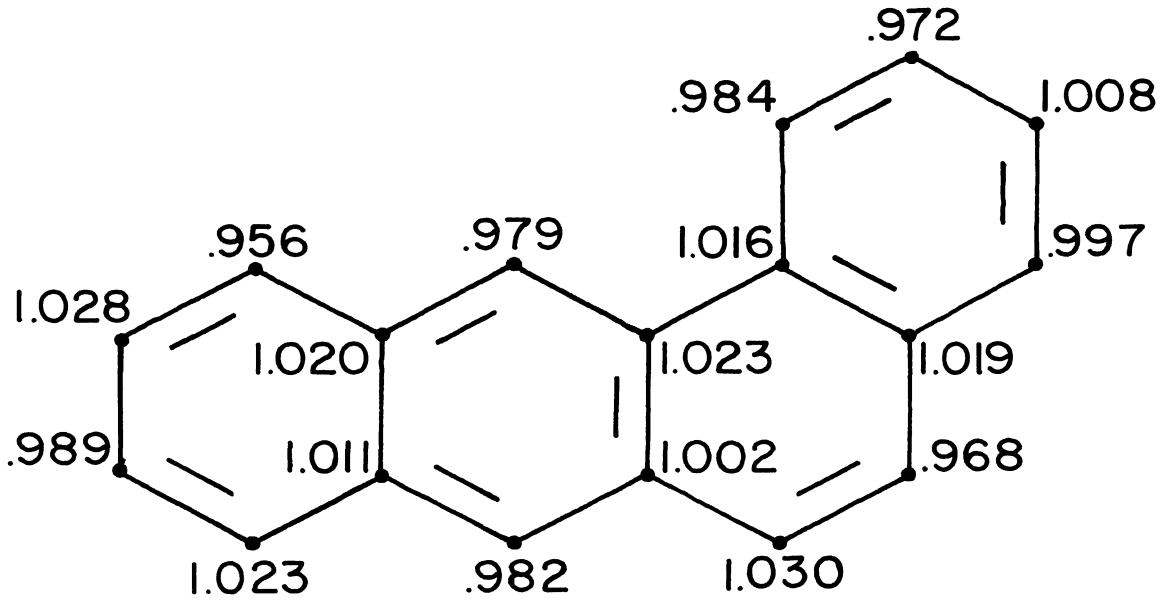

Figure 12. Electron Densities Based on Pi Electrons Only

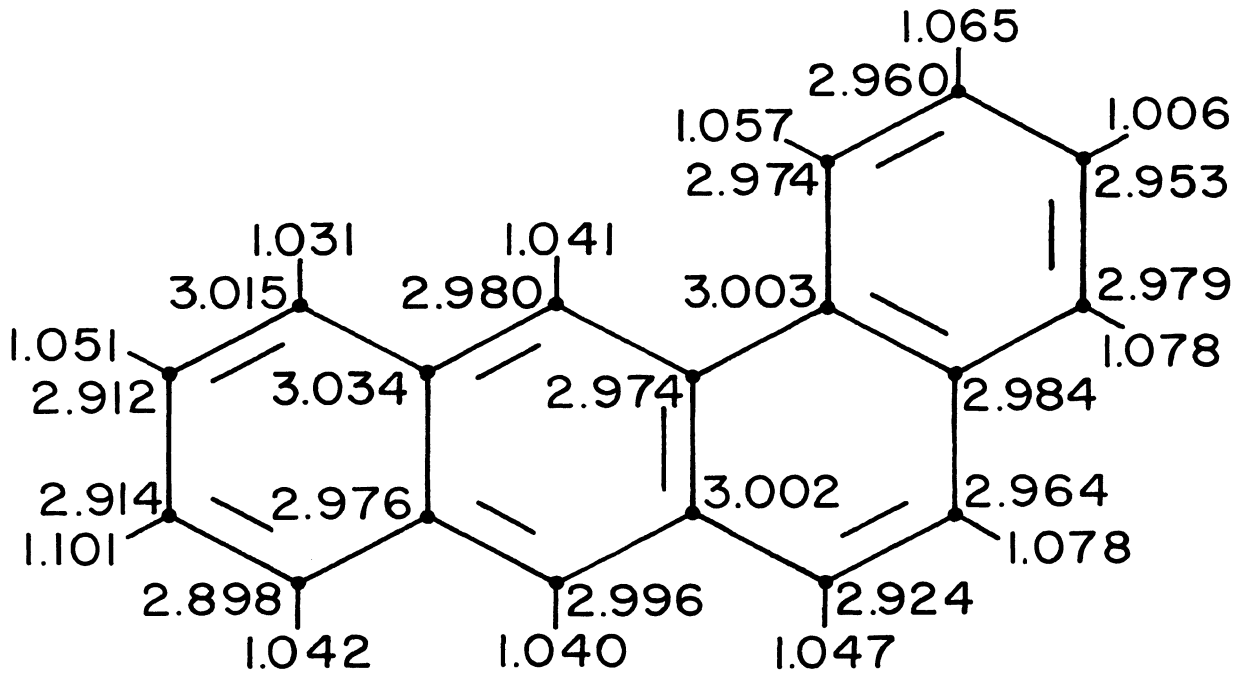

Figure 13. Electron Densities Based on Sigma Electrons Only

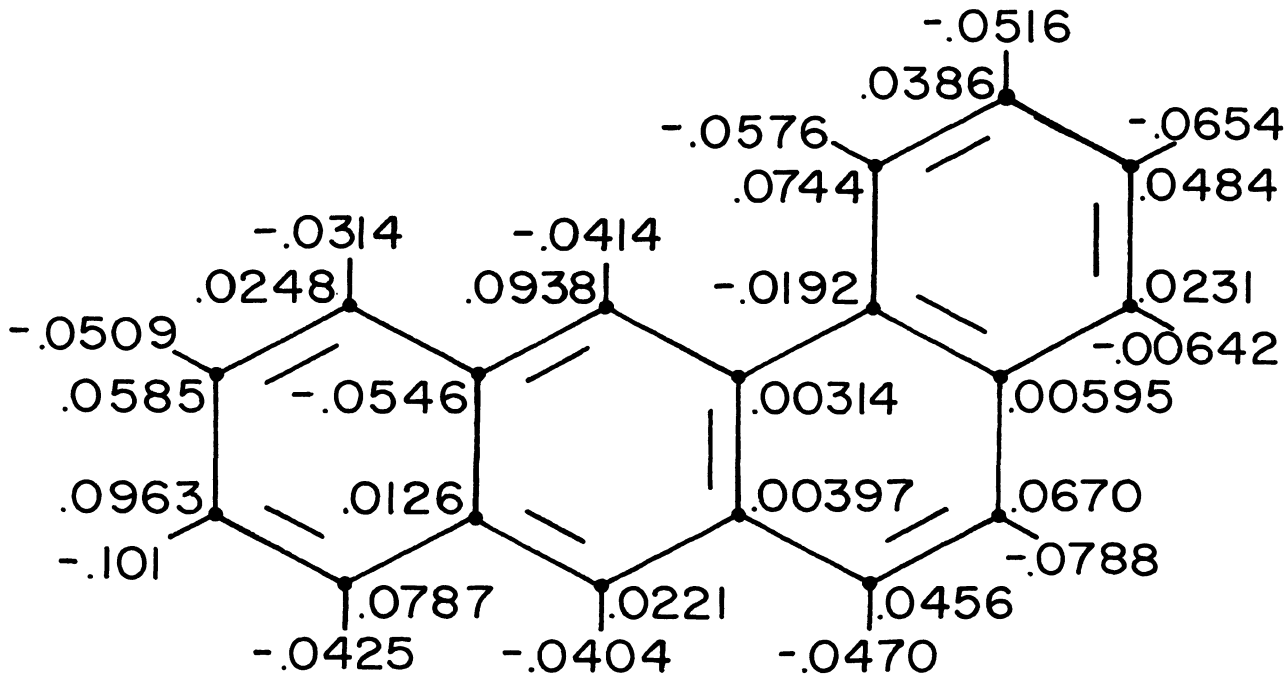

Figure 14. Polarizability of Benz(a)anthracene

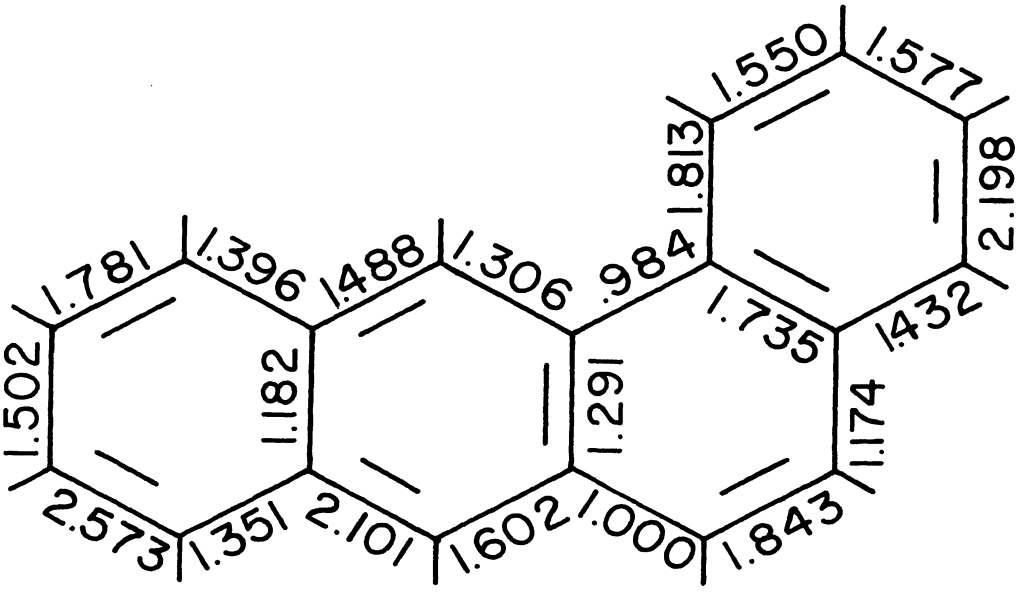

Figure 15. Bond Orders of Benz(a)anthracene Based on Sigma and Pi Electrons

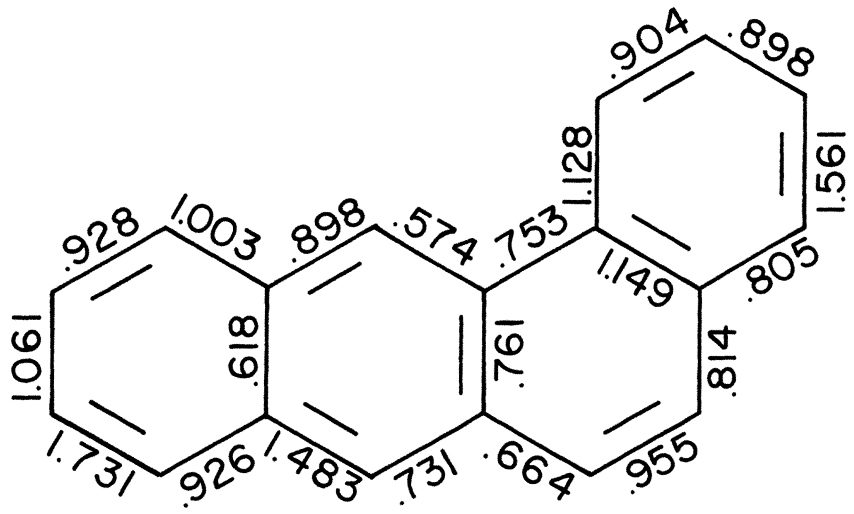

Figure 16. Sigma Electron Contribution to the Bond Orders of Benz(a)anthracene

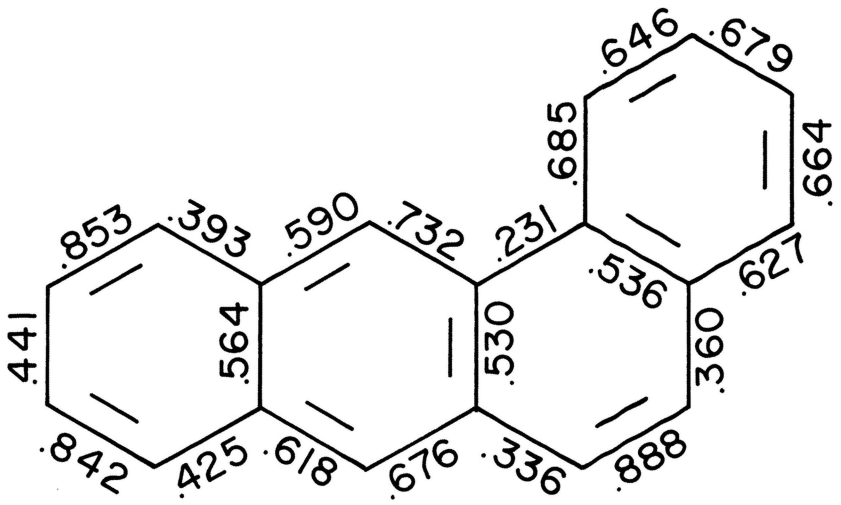

Figure 17. Pi Electron Contribution to Bond Orders of Benz(a)anthracene

A MINDO calculation was attempted on 17-methylbenz(a)anthracene but the calculation did not converge. Instead, it became trapped in an energy well. Table A-3 of the appendix shows the energy and bond order changes after each iteration. This is always a possibility when the SCF iterative technique is used; however, normally the convergence is obtained.

V. DISCUSSION

A. Bond Lengths and bond angles

Reference to the bond lengths and bond angles of structure 3 given in section IV-A reveals considerable molecular distortion. Distortion is also observed in the crystal structure of other large ring hydrocarbons (e.g., phenanthracene[71] -1.46A -; chrysene[72] -1.47A -; 3,4-benz(o)phenanthracene[73] -1.55A -). Certainly part of this distortion can be attributed to the packing of the molecule into a crystalline lattice structure. This constitutes an environment which is different than that of a molecule in solution. Craig, et. al.[74], have discussed in detail the problem of molecular packing in crystals of aromatic hydrocarbons. Their conclusion is, "The conclusion that the H-H interactions are of prime importance is supported by their calculated magnitude which are of the correct order to account for the frequencies of torsional motion in the lattice." Applied to the distorted benz(a)anthracene system, this means that part of the distortion may be due to the physical presence of adjacent molecules in the crystal lattice. However, part of this distortion may also be intrinsic in the molecule and this part would remain in the structure of the molecule in solution. Consequently, the treatment of this thesis is based on the crystal structure of benz(a)anthracene as this is the only structure for which experimental data is available. This structure may be considered as the first - order approximation to the structure of benz(a)anthracene in solution.

Considering the abnormally long bonds in benz(a)anthracene one notes that eight of the eighteen carbon-carbon bonds fall outside the "aromatic range" of bond length. The normal "aromatic range" is 1.38-1.44A; recalling the accuracy

of the structure determination (.03A) this range may be extended to 1.35-1.48A. Table 7 lists the 8 bonds outside this range. The accuracy of the structure determination (.03A) this range may be extended to 1.35-1.48A. Table 7 lists the 8 bonds outside this range.

TABLE VII. ABNORMAL LONG BENZ(A)ANTHRACENE BOND LENGTHS

Bond	Length in Angstroms
17-18	1.26
9-14	1.30
10-11	1.30
7-8	1.34
5-10	1.60
9-10	1.49
12-13	1.53
12-15	1.55

It has been observed that the bonds in perylene are longer than the usual carbon-carbon aromatic bond length.[75,76,77] Coulson and Skanckee[78] attempted to explain this anomaly by using the steric repulsion between hydrogens which are located ortho to the peri or long bond. Such an idea is applicable to the long 5-10 bond of benz(a)anthracene where the hydrogens numbered 19 and 23 may be considered as located ortho to the 5-10 bond. Geometric calculation show that if the 5-10 bond were aromatic in length (i.e., 1.397 $\mathring{A}$), then the distance between the 19 and 23 hydrogens would be 1.7A. The van der Waals radius of hydrogen is 1.04A. Consequently, the minimum noninteraction distance is 2.08A. The calculated hydrogen-hydrogen distance assuming an aromatic structure is less than this, thus, creating steric repulsion between the hydrogens. Herreaz and Arranz[79]

suggest that the stretching of the peri bond is a great help to the relief of steric strain. They are a bit uncertain as to the magnitude of angular deformation and suggest that .02 ev in the case of perylene and 1.02 ev in the case of triphenylene be attributed to the energy of deformation. Their calculations show that molecular deformation requires less energy than bending of the hydrogens outside the plane. It would seem that the lengthening of the 5-10 bond of benz(a)anthracene would cause additional distortion in other bonds. It would seem that the 7-8, 9-10, and 9-14 would be most affected by such distortion.

There is experimental evidence for the lack of double bond character in the peri-bond in perylene. Magnetic susceptibility measurements[80] show that the susceptibility of perylene is equal to the sum of the values of two naphthalene molecules minus the value of two hydrogen atoms. It would be most interesting to have the magnetic susceptibility data on benz(a)anthracene.

B. The POPLE method

As previously mentioned the 7-8 bond of benz(a)anthracene is experimentally the most reactive bond toward electrophilic reagents. The bond orders calculated by the POPLE method using structures 2 and 3 correctly predicted this bond as the most reactive. The bond orders calculated using structure 1 incorrectly predicted the 18-13 bond as the most reactive. There are additional differences between the bond orders predicted by structures 2 and 3, however, they will not be considered. The purpose of using the POPLE method was to determine which of the structure correctly predicted the most reactive bond and to compare the bond orders with those predicted by the MINDO method.

None of the three structures correctly predict the ioniazation potential or the electron affinity. It is noted that the proper magnitudes of each could be obtained by correlating the ionization potential with the LUO and the electron affinity with the HFO. However, there is no theoretical reason for doing so. It is also noted that the ionization potential times the resonance integrals comes to the correct magnitude of the experimental ionization potential. Again, there is no theoretical justification for doing so.

C. The MINDO method

1. Calculated and experimental properties

There is better agreement between the ionization potential and electron affinity calculated by the MINDO method and the experimental results than was achieved by either the POPLE or PPP methods.

Part one of this discussion pointed out the need for correcting the calculated heat of formation for steric strain. Estimating this correction to be .02 ev on the basis of the work of Herreaz and Arranz, the remaining discrepancy between the calculated and experimental results is 2.87 ev. This is disturbing when one considers that Dewar reports heats of formation calculated by the MINDO method to agree with the experimental results to within 2-3 kcal/mole.[81] Several items must be taken into account. First, Dewar's calculations are on small molecules for which the heat of formation has been accurately determined. This makes the comparison of experimental and calculated heats of formation valid. Difficulties arise in the experimental determination of the heat of formation of large aromatic molecules. Strickler and Pitzer[82] discuss this problem. Second, the experimental heat of formation of benz(a)anthracene is based on heat of atomization and the number of "supposedly" single and double bond present in the molecule. If in fact the benz(a)anthracene molecule is distorted, then this method of calculation would tend to make the molecule more stable than is actually the case, thus, accounting for the higher heat of formation predicted by MINDO. Finally, the problem of electron correlation has not been explicitly considered in the MINDO method.

Perhaps the best validity check on the comparison of the electronic structure of the crystal and solution forms of benz(a)anthracene would be the comparison of the calculated and experimental dipole moments. Unfortunately, the dipole moment of benz(a)anthracene has not been determined.

2. Electronic Structure

Table 8 lists the reactivity of the various carbon atoms and carbon-carbon bonds as predicted by the MINDO data given in section IV-2. The sigma and pi electron density data indicate that each carbon atom effectively has 4 electrons - the slight discrepancy is attributed to the carbon-hydrogen bonding. Looking at the individual contributions of the sigma and pi electrons, it seems apparent from the quite different ordering pattern that the two are dependent on different factors. It would seem reasonable to assume that different types of reactions may be determined by the sigma and the pi electrons.

The bond orders predict different reactivity for the various bonds depending on which set of bond orders one considers. However, it is noted that both the bond orders predicted by the sigma electrons only and the pi electrons only predicted that the 7-8 and the 17-18 bonds will be among the first four most reactive bonds of the molecule. As previously mentioned, the 7-8 bond of benz(a)anthracene has been shown experimentally to be the most reactive bond toward an electrophilic reagent. On the basis of the MINDO detailed electronic structure of benz(a)anthracene, it would seem that this reactivity is primarily determined by the pi electrons of the 7-8 bond region. This is the K region of the Pullmans' theory.

a. Comparison with electronic structure of anthracene, phenanthracene and benz(o)pyrene

It will be interesting to compare the bond orders of benz(a)anthracene with appropriate model systems. Benz(a)anthracene may be considered as a three ring system to which a benzene ring is added to form the final four-ring

TABLE VIII. PREDICTED REACTIVITY OF THE CARBON ATOMS AND CARBON-CARBON BONDS IN DECREASING ORDER

REACTIVITY	ELECTRON DENSITY			BOND ORDER			POLARIZABILITY
	$\sigma+\pi$	σ	π	$\sigma+\pi$	σ	π	
1	5	15	8	17-18	17-18	7-8	12
2	9	12	16	1-2	1-2	15-16	5
3	10	5	18	13-14	13-14	17-18	10
4	6	9	10	7-8	5-6	10-11	9
5	13	14	12	5-14	4-5	4-5	6
6	14	6	6	15-16	16-17	2-3	13
7	1	11	5	5-6	12-15	1-2	14
8	15	1	13	9-14	7-8	3-4	1
9	11	13	2	2-3	15-16	9-14	15
10	12	4	9	3-4	13-18	1-6	11
11	2	10	1	16-17	3-4	13-14	3
12	8	7	17	11-12	2-3	11-12	8
13	3	3	11	1-6	11-12	12-13	2
14	16	2	4	12-15	6-7	5-6	16
15	7	8	14	13-18	1-6	9-10	18
16	18	17	3	10-11	5-10	13-18	7
17	4	16	7	9-10	9-14	12-15	12
18	17	18	15	12-13	9-8	16-17	17
19				6-7	9-10	8-9	
20				8-9	12-13	6-7	
21				5-10	10-11	5-10	

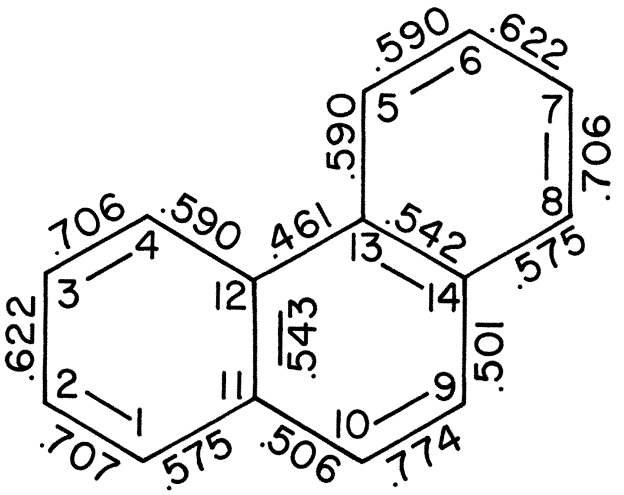

Figure 18. Bond Orders of Phenanthracene

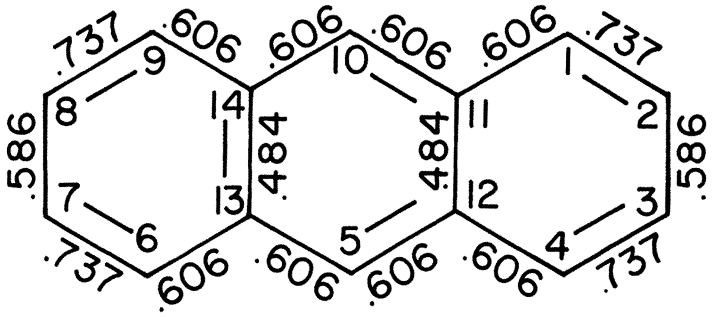

Figure 19. Bond Orders of Anthracene

structure. This may be accomplished in two different ways:

1. The three rings may be linearly arranged (i.e., as in the anthracene structure) and the fourth ring located at the 2-3 bond.

or

2. The three rings may be arranged in an phenanthracene type structure with the fourth ring located at the 13-14 bond.

Figures 17 and 18 show the bond orders for anthracene and phenanthracene as predicted by the HMO method.[83] SCF calculations have been conducted on these molecules,[84] however, the bond orders were not reported. Hence, the comparison between the HMO bond orders and the MINDO bond orders for benz(a)anthracene are only qualitative at best.

The most reactive bonds in phenathracene are the 9-10 followed by the 3-4 and 7-8 bonds. The 12-13 bond is predicted to be the least reactive. The first three rings of benz(a)anthracene may be compared to the phenanthracene structure. The benz(a)anthracene 7-8 bond which corresponds to the 9-10 bond of phenanthracene is predicted as the most reactive bond and the 5-10 bond which corresponds to the 12-13 bond of phenanthracene is predicted to be the least reactive. The 1-2 bond of benz(a)anthracene which corresponds to the 7-8 bond of phenanthracene is not predicted as especially reactive on the basis of the pi electronic structure.

Next, considering the anthracene molecule, it is noted that the 1-2, 3-4, 7-6 and 8-9 bonds are predicted to have equal bond orders and to be the most reactive bonds in the molecule. The three linear rings of benz(a)anthracene may be considered as similar to the anthracene molecule. The benz(a)anthracene

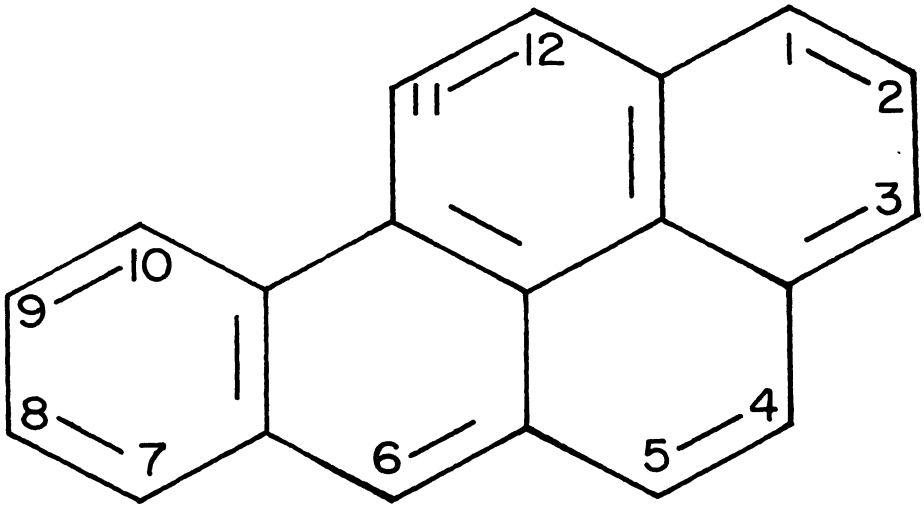

Figure 20. Conventional Numbering of Benz(o)pyrene

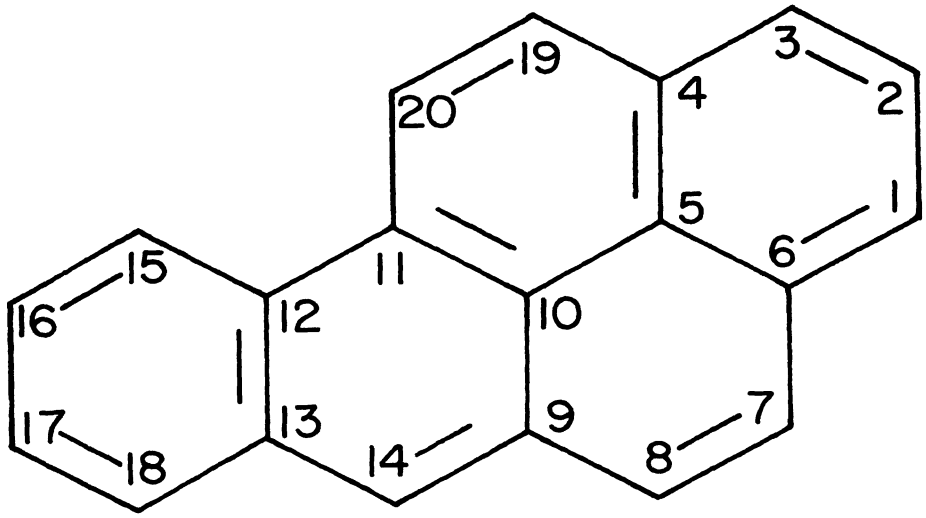

Figure 21. Revised Numbering of Benz(o)pyrene

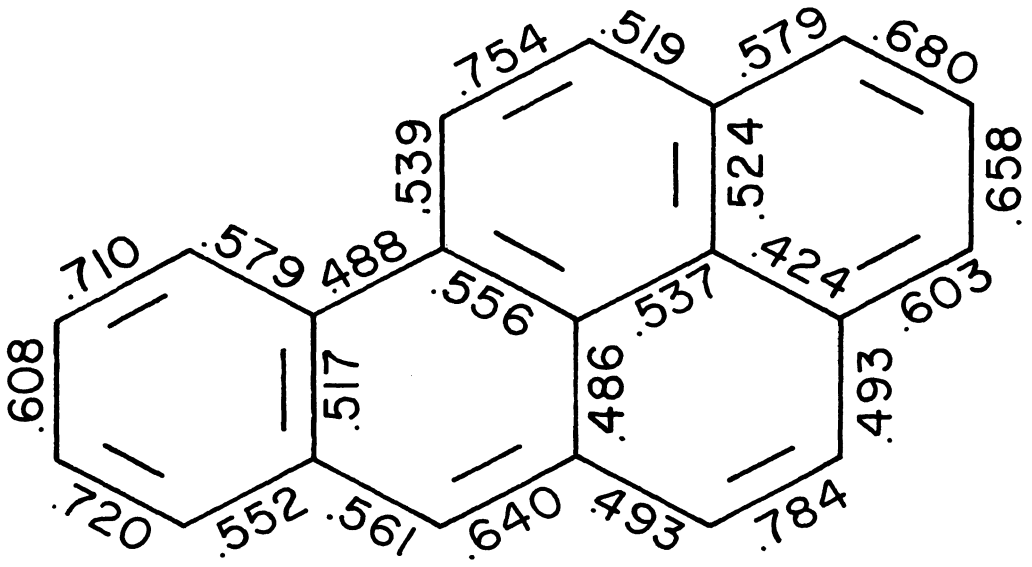

Figure 22. Bond Orders of Benz(o)pyrene

bonds corresponding to the active bonds in anthracene would be the 15-16, 17-18, 5-6 and 7-8 bonds. The 5-6 bond can not be used in this comparison as it serves as a common bond with the angular ring of benz(a)anthracene. The other bonds are predicted to be the three most reactive of the benz(a)anthracene bonds based on the pi electronic structure.

If the benz(a)anthracene structure is considered as a composite of these two structures, the three most reactive bonds in the molecule are correctly predicted. The 7-8 bond of phenanthracene which is predicted as quite reactive does not appear in the pi electronic structure of benz(a)anthracene.

Another comparison of value concerns the benz(o)pyrene molecule which may be considered as the benz(a)anthracene structure with an additional benzene ring located at the 5-6 and 5-10 sites. Figure 20 shows the conventional benz(o)-pyrene numbering scheme and Figure 21 shows the numbering similar to that used in this thesis for benz(a)anthracene. The bond orders for benz(o)pyrene based on a SCF calculation,[85] are given in Figure 22. The site of prime reactivity is the 7-8 bond, with the 19-20 bond possessing secondary activity. The 15-16 and 17-18 are predicted to have slightly lower magnitude but significantly greater than the other bond orders. There is not a bond of benz(a)anthracene corresponding to the 19-20 benz(o)pyrene bond. However, the remaining three reactive bonds of benz(o)pyrene have corresponding reactive bonds in benz(a)anthracene. If the electronic structure of benz(o)pyrene where available as calculated by the MINDO method, it might be possible to distinguish between strong and weak carcinogens (i.e., benz(o)pyrene and benz(a)anthracene) on the basis of quantitative differences

in bond orders of one or more of the reactive bonds. The Pullmans attempted such a correlation based on the HMO method. As previously pointed out, their "correlation" has been critized mainly on the basis of the small increments serving to differentiate carcinogens from noncarcinogens.

b. Polarizability

The concept of polarizability was first studied by Coulson and Longuet-Higgens.[86] The atom self-polarizability serves as an indicator of chemical reactivity for the molecule. This is based on the assumption that the atom with the self-polarizability of the greatest magnitude can most easily adjust its charge in response to an attacking species, hence, it is the most reactive atom. In the butadiene molecule, this approach correctly predicts that the terminal carbons with a polarizability of -0.071 will be more reactive than the two internal carbons with a polarizability of 0.071.[87]

The MINDO method calculates the polarizability of the hydrogens as well as the carbons, hence, the carbons are all internal atoms having less polarizability than the external hydrogens. The reactive of the hydrogens is 26>30>21>19>20>25>29>27>23>28>24>22. The polarizability of the carbons will be considered relative to one another in order to establish a relative order of reactivity. The majority of the carbons have positive polarizability but as previously mentioned, this is a result of their position internal to the hydrogens. The ordering of reactivity among the carbons is 10>1>15>3>7>2>16>4>7>11>17. The 5, 6, 9, 10, 13 and 14 carbons have been omitted from consideration as they can not undergo further reaction without disrupting the benz(a)anthracene structure. It is noted that the bond with the lowest polarizability is the 1-2 bond.

Bereblum and Schoental[88] found that the metabolite of benz(a)anthracene was 1-hydroxy-benz(a)anthracene. The Pullmans noted[89] that their indices predicted that the 9 or 10 hydroxybenz(a)anthracene would be the preferred product. Boyland and Sims[90] indicate that benz(a)anthracene actually forms an epoxide which is oxidized to form the 1, 2 diol which in turn forms the 1-phenol observed by Bereblum and Schoental.

c. Free valence

The concept of free valence was proposed by Coulson.[91] It is calculated by assuming that the total bond order (sigma plus pi) of all the bonds that terminate on atom r. This quantity is called N_r and measures the extent to which atom r is engaged in bonding. Moffitt[92] showed that the carbon atoms have a maximum possible value of N: $N_{max} = 3 + \sqrt{3} = 4.732$. The difference between N_{max} and N_r represents the amount by which the actual bonding falls below the maximum. This difference is the free valence.

Using the sigma and pi bond orders calculated by the MINDO method, the free valences were calculated for benz(a)anthracene and are given in Table 9 along with the free valences calculated by the Pullmans[93] using the bond orders from the HMO method and a modified $N_{max} = 1.732$.

The advocates of the free valence theory claim that the free valence number can be considered as the residual bonding power of an atom, Coulson points out that the free valence number also appears to indicate the relative reactivities of two comparable atoms in different molecules. Such information would be interesting in comparison of similar bond in carcinogenic compounds of varying activity.

TABLE IX. FREE VALENCE OF CARBON ATOMS

OF BENZ(A)ANTHRACENE

Carbon Number	Free Valence HMO(Pullman)	Order of Reactivity	MINDO (this thesis)	Order of Reactivity
1	.451	14	.756	17
2	.404	11	.776	18
3	.409	18	.780	4
4	.440	7	.809	7
5	.142	15	.722	16
6	.112	8	.738	3
7	.456	1	.799	8
8	.455	4	.778	2
9	.110	3	.728	11
10	.139	16	.736	15
11	.502	17	.775	1
12	.108	2	.682	14
13	.195	13	.745	13
14	.514	5	.754	6
15	.456	6	.760	10
16	.408	10	.791	9
17	.407	9	.831	5
18	.458	12	.811	12

Burkitt, Coulson and Longuet-Higgens[94] have compared the polarization energy required to localize one pi electron at the position of attack with the free valence at the same position. It was also suggested that free valence may indicate the susceptibility of an atom or bond to homolytic (i.e., free radical) attack. Assuming that the free valence of a bond is the sum of the free valence of adjacent atoms, the bond most susceptible to free radical reactions are the 17-18, 7-8 and 3-4.

d. Sigma complexes

Regions of high sigma electron bond orders are predicted for the 17-18, 13-14, 1-2, 4-5 and 5-6 bonds. The 5-6 bond can not undergo reaction, but the other bonds might possibly undergo reaction forming sigma complexes. Fieser has described the formation of such complexes as follows, "The conversion of a carbon atom having planar, aromatic bonds to one having four tetrahderally aliphatic bonds is a transition from sp^2 to sp^3 hybridized electronic orbitals. The hybridization is described as an aronium ion; the complex resulting from the combination of this aronium ion with an anion is called a sigma complex. Zollinger[95] in a review emphasized the point that this sigma-complex is an intermediate and not a transition state."[96]

Benz(a)anthracene is a weak carcinogen while most of its methyl derivatives are potent carcinogens. It is the opinion of this author that benz(a)-anthracene has a highly reactive region which is not involved in the carcinogenic mechanism. Substitution of various groups might destroy this reactive region, thereby, making the most probably reaction the one involving the carcinogenic

reaction. In order to prove this hypothesis, it would be necessary to have the electronic structure available for various benz(a)anthracene derivatives and to observe the differences in the reactivity of the various bonds toward different types of reagents.

e. Proposed bonding model

In summary, the electronic structure of benz(a)anthracene predicted by the MINDO method suggests a bonding model which is present in Table 10 and compared to the available experimental results.

TABLE X. COMPARISON OF MODEL WITH EXPERIMENTAL RESULTS

Bonding Model	Experimental Results
1. The 7-8 bond is predicted to be the most reactive bond toward electrophilic reagents; the 15-16 and 17-18 bonds have secondary reactivity.	1. Reaction with osmium tetraoxide, tetra-acetate and oxidation with peroxybenzoic acid occur at the 7-8 bond.
2. The 17-18 bond is predicted to be most reactive to free radical attack; the 3-4 and 7-8 bonds have secondary activity.	2. The reactivity towards free radicals has not been studied in detail. Fieser studies the reaction rates for various hydrocarbons.
3. The 1-2 bond is predicted to be the most easily polarized bond. The 10 carbon is the most easily polarized atom.	3. The metabolite of benz(a)anthracene is the 1-phenol, which is formed from the 1-2 epoxide.
4. The electrons within the angular ring of benz(a)anthracene tend to remain within that ring, the 7-8 electrons remain within that bond, and the remaining electrons tend to distribute themselves in the last two rings of the benz(a)anthracene structure. This is concluded from the bond order matrix, which indicates the bonding is localized within the angular ring and the latter two linear rings.	4. Methyl substitution[97] in the angular ring does not increase the carcinogenic activity of benz(a)anthracene, but methyl substitution in the anthracene moiety does increase the carcinogenic activity. Hydrogenation of th 14-methylbenz(a)-anthracene proceeds only at the 15, 16, 17 and 11 positions.[98]

VI. CONCLUSION

The bonding model of benz(a)anthracene predicts various sites of reactivity. Precisely which of these sites are necessary for the induction of cancer by benz(a)anthracene and which sites are necessary and sufficient sites for induction of cancer by aromatic hydrocarbons in general, can not be determined from the electronic structure of just one molecule.

The conclusions which result from this study are:

1. The MINDO MO method predicts a useful detailed electronic structure for benz(a)anthracene based on the sigma and pi electrons. In this regard, the MINDO method is superior to the Pople, PPP or Hückel methods which only predict the pi electronic structure.
2. The bonding model of benz(a)anthracene derived from the MINDO electronic structure is consistent with the known chemical reactivity of the molecule.
3. The bonding model predicts several reactive sites most reactive of which is the K-region of the Pullmans' theory. Assuming that the K-region is the reaction associated with carcinogensis, it is possible that reaction at any or all of the remaining positions rends the molecule noncarcinogenic as it would change the reactivity of the K-region. Comparison of the methylbenz(a)-anthracenes would be helpful in establishing which reactive bond(s) were noncarcinogenic.

4. The bonding model suggests that sigma-complex formation may be of importance in the reactions of benz(a)anthracene, though not necessarily those reactions which produce cancer.
   In this regard, a re-examination of the studies by Fieser on addition reactions would be of interest.

VII. SUGGESTIONS FOR ADDITIONAL STUDY

1. The dipole moment of benz(a)anthracene should be measured and compared to the results reported in this thesis.
2. The magnetic anisotropy of benz(a)anthracene should be determined and the ring currents of each of the four rings determined, perhaps using a method similar to Memory's[99] study of ring currents in pentacyclic compounds.
3. The nuclear magnetic resonance spectra should be calculated and chemical shifts predicted on the basis of suggestion 2 and then compared with the experimental results.

These three suggestions would help in establishing whether the benz(a)anthracene molecule in solution is distorted in a fashion similar to the distortion in the crystal.

4. Electron diffraction studies should be conducted and the precise crystal structure determined as compared with the X-ray data. This experiment would also accurately locate the hydrogens of benz(a)anthracene.
5. The methylbenz(a)anthracenes should be studied by NMR and using Clar's approach, the double bond character of various bonds determined and the results compared with the results in suggestions 2 and 4.
6. The MINDO method should be used to obtain the detailed electronic structure of the nucleic acids.
7. The results from suggestion 6 and the bonding model of benz(a)anthracene proposed herein should be studied for possible binding between benz(a)anthracene and nucleic acids. Figure 23 demonstrates this possibility in a schematic manner.[100,101]

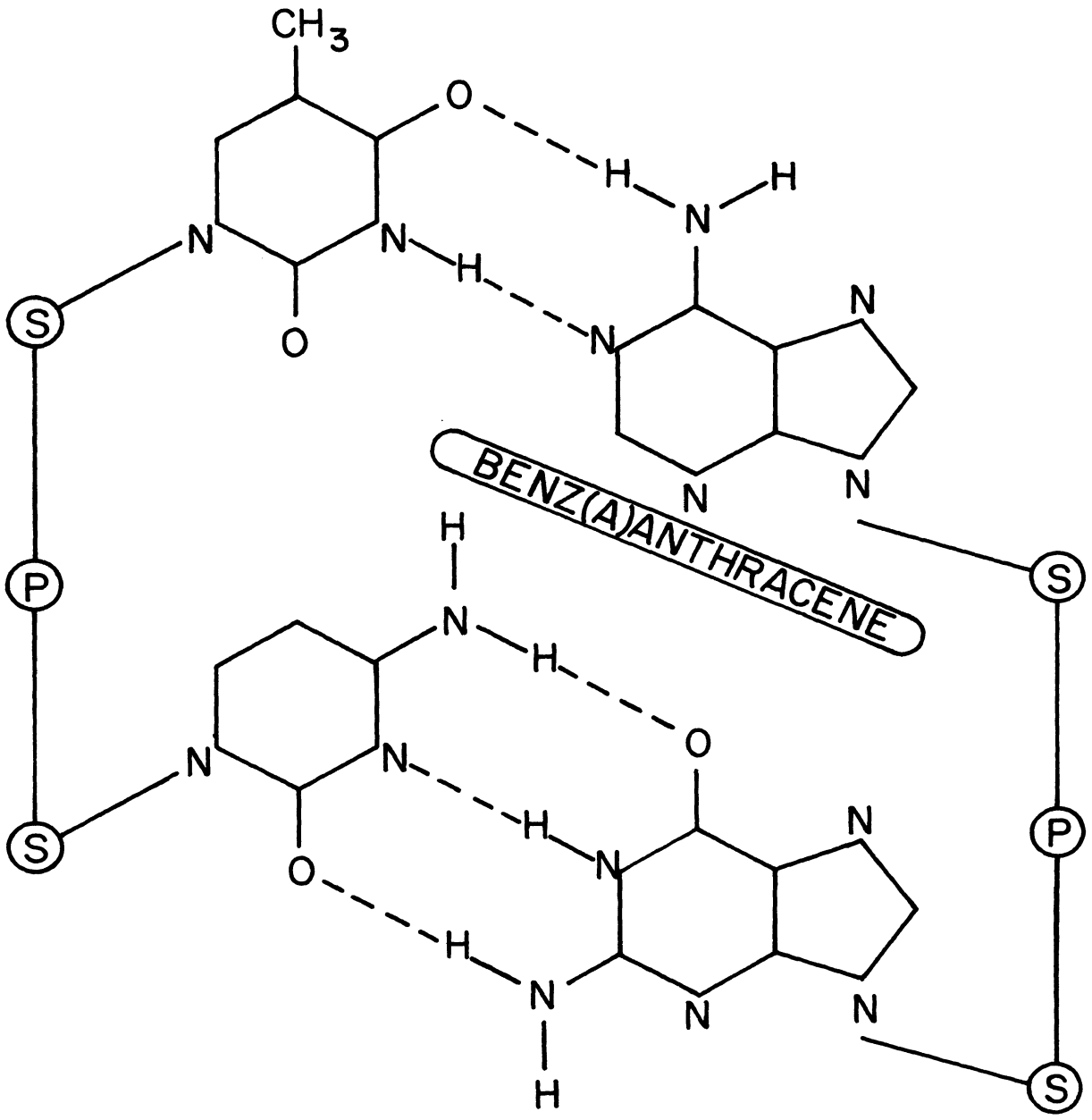

Figure 23. Schematic Representation of Benz(a)anthracene-Nucleic Acid Interaction

8. Calculation of the electronic structure of benz(o)pyrene by the MINDO method should be compared with that of benz(a)anthracene to observe quantitative differences in the reactivity of the various bonds toward different types of reagents.
9. The monomethyl derivatives of benz(a)anthracene should be studied by the MINDO method and the reactivity of various bonds compared to those of benz(a)anthracene.
10. Other derivatives of benz(a)anthracene (i.e., dimethyl and benzaridens) should be studied by the MINDO MO method and a correlation sought between carcinogenic potency and electronic structure.

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IX. VITA

Patricia Joan Blair was born in Kearns, Utah on June 19, 1945. She received her secondary education in Magna, Utah, Colorado Springs, Colorado, Cheyenne, Wyoming, and Rolla, Missouri. Her undergraduate training was received from the University of Missouri - Rolla, Rolla, Missouri and the University of California, Los Angeles, Los Angeles, California. During this period she received a curator's scholarship and a March of Dimes scholarship. In August of 1969 she received her Bachelor of Science degree in Chemistry from the University of Missouri - Rolla. In September of 1969 she began graduate studies at the University of Missouri - Rolla. She has been admitted to Medical School at the University of Missouri - Columbia School of Medicine to pursue additional study.

She is a member of the American Chemical Society, the Chemical Society of London and the Society of Women Engineers and Scientists.

X. APPENDIX A. SUPPLEMENTAL DATA

TABLE A-1. CARCINOGENIC POTENCY OF BENZ(A)ANTHRACENE DERIVATIVES

Compound	CARCINOGENIC POTENCY determined by Subcutaneous Injection	Skin Painting	Synthesis	Structure Determination	CARCINOGEN BINDING with Cellular Protein	Nucleic Acid
Benz(a)anthracene	1,2,3	VW		10	25	
and monomethyl	VW		103	51,104		26
derivatives						
1-methyl-		I				
2-methyl-		I				
3-methyl-	I					
4-methyl-	I					
5-methyl-	G					
6-methyl-	G					
7-methyl-	VS					
8-methyl-	VS					
9-methyl-	VS					
10-methyl-	G					
11-methyl-	G					
12-methyl-	G					
Dimethyl-derivatives			103		25	
7,12-dimethyl-		VVS		33,34		26
7,8-dimethyl-		VS				
8,9-dimethyl-		VS				
Trimethyl-derivatives					25	
7,9,12-tri-methyl-		G	103	33,34		
7,8,12-tri-methyl-		VS				26

TABLE A-1 continued

Compound	CARCINOGENIC POTENCY determined by Subcutaneous Injection	Skin Painting	Synthesis	Structure Determination	CARCINOGEN BINDING with Cellular Protein	Nucleic Acid
Tetramethyl-derivative					25	
7,8,9,12-tetramethyl-		G	103	33,34		26
Fluoro-derivatives						
7-methylbenz(a) anthracene	105					
3-fluoro-	G					
4-fluoro-	toxic	toxic				
5-fluoro-	I					
6-fluoro-	G					
9-fluoro-	G					
10-fluoro-	G					
Dibenz(a,h) anthracene mono-methyl-derivatives				104	25	26
2-methyl-		W				
3-methyl-		G				
6-methyl-	G					
7-methyl-	VS					
Dimethyl-	VS	VS				
7,1--dimethyl-						

LEGEND
VVS = extremely strong carcinogen
VS = strong carcinogen
G = greater potency than parent hydrocarbon
W = weaker potency than parent hydrocarbon
VW = extremely weak carcinogen

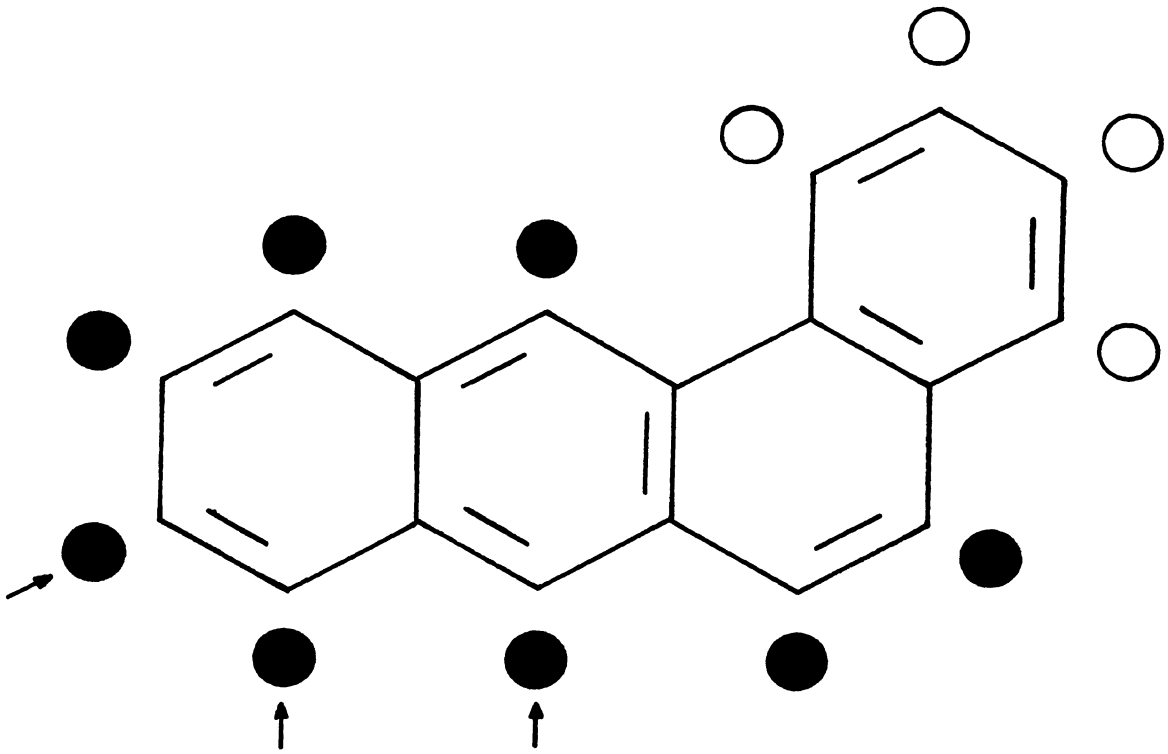
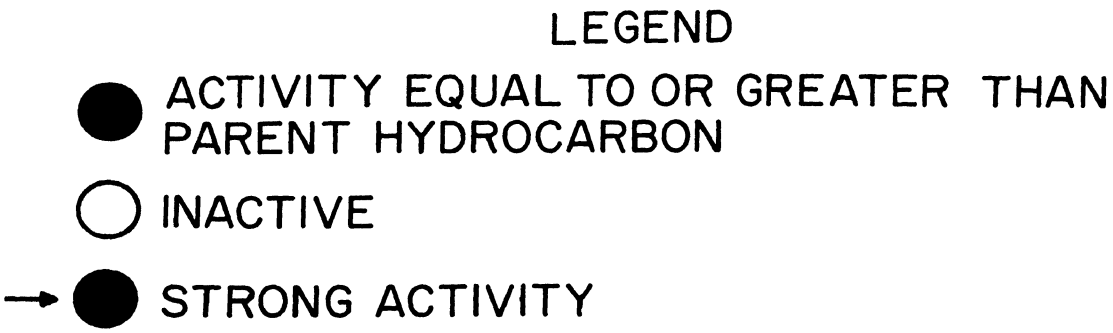


Figure A-1. Carcinogenicity of Monomethylbenz(a)anthracene Derivatives



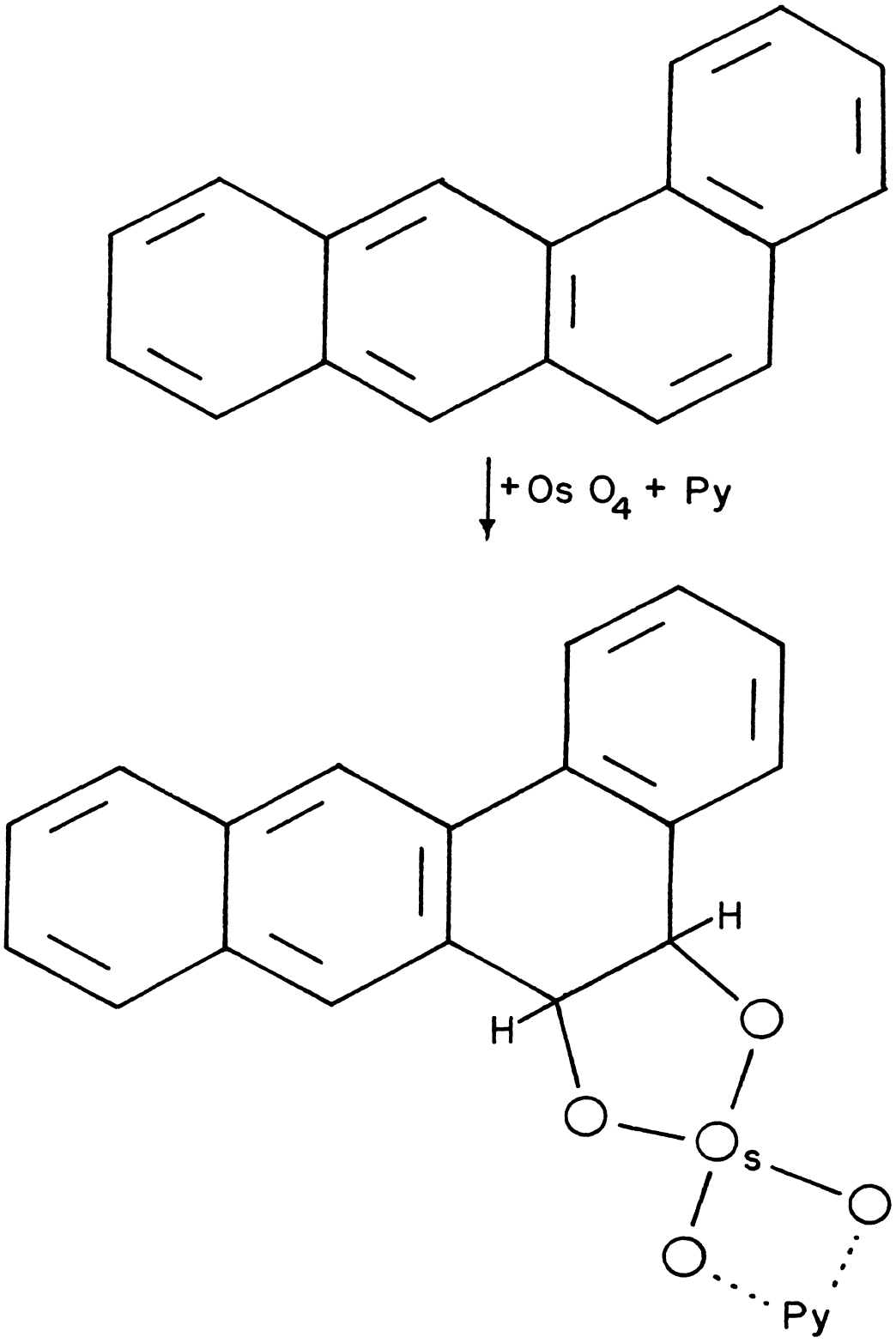


Figure A-2. Reaction of Osmium Tetraoxide and Benz(a)anthracene

TABLE A-2. ONE-CENTER INTEGRALS AND DERIVED QUANTITIES

Quantity	H	C
U_{ss}	-13.595	-49.659
U_{pp}	...	-41.159
F^0	12.845	11.089
F^2	...	4.727
G^1	...	7.285
I_s	-13.595	-20.035
I_p	...	-10.430
Neutral atom energy	-13.595	-120.904
ΔH_f^b for free atom	52.102	170.890
Slater exponent	1.00	1.62

TABLE A-3. CONVERGENCE INFORMATION ON

17-METHYLBENZ(A)ANTHRACENE

Iteration	Energy Change	Maximum P(I, I) Change
1	-16270.30078	1.00000
2	- 1179.75000	2.00000
3	1750.53516	2.00000
4	- 3798.43359	3.42578
5	55.35156	2.00000
6	- 2143.53516	2.00001
7	1209.74219	3.03809
8	- 1219.53125	2.00000
9	990.60156	2.00000
10	- 770.93359	3.00372
11	770.88281	2.00001
12	- 984.04297	2.00001
13	1205.00391	3.00116
14	- 1210.08203	2.00001
15	988.42188	2.00000
16	- 770.91406	3.00308
17	771.74219	2.00000
18	- 984.12891	2.00001
19	1204.68750	3.00128
20	- 1209.62891	2.00001
21	987.85547	2.00001
22	- 770.22266	3.00301
23	771.64844	2.00000
24	- 984.46875	2.00000
25	1205.10156	3.00121
26	- 1210.06250	2.00001
27	988.37109	2.00000
28	- 770.91406	3.00307
29	771.75000	2.00000
30	- 984.12500	2.00001
31	1204.68750	3.00128
32	- 1209.61328	2.00001
33	987.85156	2.00001
34	- 770.21875	3.00302
35	771.60547	2.00001

XI. APPENDIX B. OBSERVATIONS CONCERNING CARCINOGENSIS

The cancer literature abounds with reports of thousands of experiments of various natures, none of which have allowed scientists to gain any real insight into the fundamental nature of cancer. The importance of basic research into the nature of cancer has been summarized by Haddow,

> "The carcinogens are notable among chemical agents in producing a permanent transformation in the growth properties of cells. The chief feature of the new cell type is an increased automony, which shows itself by growth and invasiveness, independently alike from the further presence of the carcinogen or of the needs of the body as a whole. How is the change produced? From present evidence the essential influence of the carcinogen is to restrict normal cellular growth. The interferences is characteristic in that no escape or easy acclimatization seems possible. At length, however, the biological response does occur, not as a continuous adaption, but rather as a comparatively sudden break which permits the cell to achieve independence in an environment still umpropitious for the normal form. Once emerged, growth of the new cell strain proceeds indefinitely both in the same host and when carried through a series of healthy animals by transplantation - where it develops according to its new constitution and continues to exhibit an astonishing degree of constancy and specificity. As to the genetic nature of the change, many questions remain to be answered. Whatever the outcome, there can be no doubt of the fundamental character of these problems transcending even their interest for medicine. There is, however, a need for more effectively integrating the subject with biology as a whole. When this is accomplished, the greatest contribution of such studies may yet be seen in the light they shed on cellular growth and variation in general of which the problem of tumor induction is only a special part."[102]

Very little is known about the role of chemical carcinogen inside the cell despite the fact that aromatic hydrocarbons have been known as carcinogens for about 200 years. Indeed, comparatively little is known about the nature of cellular growth under normal conditions. Recent years have seen great strides in terms of elucidation of the structure of deoxyribonucleic acid (DNA), synthesis of DNA and recognition of the dynamic effect ribosomes have on protein

synthesis. However, this is merely a trifle compared to the future work which must be done in areas of cellular metabolism, protein synthesis, structure and function of the mitochrodia, membrane transport and a vast number of other complex subjects. Cancer research may provide tremendous insight into each of these fields. The cancer cells represent a low energy version of a normal cell. With the loss of organization which is characteristic of a cancer cell, the cell must adapt to a less energetic life pattern. Hence, the cancer cell represents a simplified model of the normal cell. Effort directed towards understanding the function of the cancer cell may also provide the benefit of "explaining" the growth and ageing process in general.

Certainly such a goal is worthy of the best efforts of quantum chemists in particular and scientists in general.

"I like the dreams of the future better than the history of the past."
-T. Jefferson