sample of **12b**, 1.14 g (6.7 mmol) of benzyltrimethylammonium fluoride, 1.69 g (6.1 mmol) of 1-(trimethylsilyl)-2-methyl-1-propenyl triflate (**4**), and 100 mL of glyme was reacted for 8 h according to the general procedure. Column chromatography on 150 g of silica gel with 50:1 hexanes/THF gave 0.22 g (10%) of **14b**. Recrystallization from 20:1 hexanes/THF gave a very pure product. Physical properties and spectral data are listed in Table II. Anal. Calcd for $C_{32}H_{22}F_{12}N_4$: C, 55.66; H, 3.21; N, 8.11; F, 33.02. Found, C, 55.48; H, 3.29; N, 8.08; F, 33.09.

Preparation of 1-Methyl-2-phenyl-3-isopropylindazolium Triflate (15a). To a solution of 30 mg (0.15 mmol) of 2-phenyl-3-isopropoylindazole (**6a**) in 5 mL of diethyl ether was added 25 mg (0.15 mmol) of methyl trifluormethanesulfonate, and the reaction mixture was stirred for 1 h at room temperature. Gas chromatography revealed the absence of starting indazole, and a white product was formed. The solution was filtered, and the product was washed with ether to yield 50 mg (86%) of indazolium triflate **15a**: mp 154–156 °C; IR (KBr) 1623, 1516, 1470, 1372, 1275, 1229, 1152, 1038, 912, 806, 780, 760, 705, 644 cm^{-1}; ^1H NMR (C_3D_6O) δ 1.61 (d, 6 H, J = 7.4 Hz), 3.35 (sept, 1 H, J = 7.4 Hz), 4.12 (s, 3 H), 7.7–8.8 (m, 9 H); ^{19}F NMR (C_3D_6O) δ 79.3 (s); UV (C_2H_5OH) λ (log ϵ) 217 nm (4.2), 261 (3.9), 268 (4.0), 307 (3.9); mass spectrum, m/z (relative intensity) 252 (20.7), 251 (M^+, 100.0), 250 (42.7), 249 (17.0), 235 (24.7), 209 (23.5), 173 (22.3), 77 (16.5).

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Carcinogenesis by Polycyclic Aromatic Hydrocarbons: A Multilinear Regression on New Type PMO Indices†

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Abstract: A new MCS model of chemical carcinogenicity of polycyclic aromatic hydrocarbons is presented. M stands for metabolism at the M region, C for carbocation formation, and S for size and solubility. Two perturbational MO indices are introduced and discussed together with a size criterion. Thereby, PMO is extended similar to the ω-method in order to differentiate between carbocations and radicals. A three-variable linear regression on carcinogenic potency yields a multiple correlation coefficient $r = 0.961$ for a representative sample of 26 polycyclic aromatic hydrocarbons. The deviations are within the confidence limits of the experimental Iball index. Predictions are given for some hydrocarbons whose carcinogenic potencies are yet unknown.

1. Introduction

Because of the complexity of chemical carcinogenesis, linear correlations of carcinogenic potency with a single theoretical variable[1–7] are a very crude first step. In the case of polycyclic aromatic hydrocarbons (PAHs), the influence of distinct molecular regions is well established. The experimental evidence[8–13] for the metabolism via epoxide, dihydro diol, and dihydrodiol epoxide to a bay-region carbocation reacting with DNA (Figure 1) clearly points to the pertinent reactivity centers. In addition, molecules containing reactive L regions,[14–16] such as polyacenes, are known for not being carcinogenic. A competition between different regions has been predicted by the Pullmans[14,15] and constitutes a lasting success of the early MO theory of chemical carcinogenesis.

During the last ten years, the theoretical interest has concentrated on the bay-region carbocations[2–7,16–18] that have been assumed to be the ultimate carcinogens. However, the rank correlations between the MO theoretical stability of such carbocations and carcinogenicity[2–5,7] give rise to a serious number of "false positives".[6,13,16]

It will be shown that one main reason for the exceptions is that the indices used so far are inadequate to characterize the formation of the bay-region carbocation. They are unable to distinguish between the formation of a radical and that of carbocation. Such a distinction is necessary for an improved correlation with experimental facts. It is possible to account for the differences between radicals and ions, e.g., by the Pariser–Parr–Pople approximation[19–21] and—as shown below—even by an improved and extended[22] perturbational MO (PMO) method. In this article, I present a linear correlation with three independent variables yielding a good correlation with experimental Iball indices of carcinogenicity.[23] The exceptions mentioned in earlier papers[6,13,24,33] disappear.

† This article is dedicated to the 430 former assistant professors dismissed in Hessen State (FRG) between 1978 and 1980 and cum grano salis to Hans Krollman (Wiesbaden) who signed responsibility for this deed.

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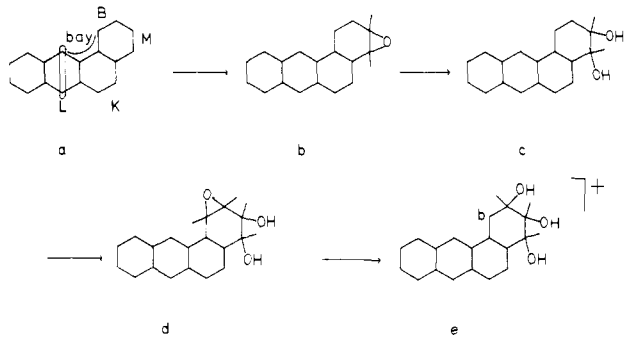

Figure 1. Reactivity centers and metabolic activation leading to ultimate carcinogens.

2. PAH Metabolism and the MCS Model of Carcinogenesis

The present theoretical calculations on PAH molecules and their metabolites are based on a model of chemical carcinogenesis incorporating experimental facts. The experimental knowledge regarding the oxidative metabolism[8-13] of a PAH molecule is outlined in Figure 2. The first step is an oxidation by P-448,[25] an isoenzyme of cytochrome P-450, yielding epoxides, phenols, and quinones. The M-region epoxide is then transformed to a *trans*-diol by epoxide hydrolase whose mechanism of action is yet unknown.[26,27] It is believed that the hydration occurs through a cationic or radicalic intermediate. The third step involves a second epoxidation through the P-448 enzyme system, oxidizing the bond proximal to the bay and forming a dihydro diol epoxide.[8,13,28] The last step is an opening of this oxirane ring and a reaction with DNA according to an S_N1 or S_N2 mechanism in a hydrophilic medium.[29-32]

The chemical picture behind the choice of the independent variables may be termed the MCS model. Three important influences on carcinogenic potency are taken into account: M, the initial epoxidation of the M region in competition with reactions on other centers of the PAH moleule; C, carbocation intermediate(s) in the reaction of the B-region diol epoxide with DNA and/or in the M-region epoxide hydration; S, a size and solubility dependence, since the enzymatic epoxidation by cytochrome P-448 takes place in the microsomal[13,27,28] endomembrane system, from where the metabolites have to reach the cell nucleus in order to react with DNA.

The constituents of this model have been discussed before[1-7,16-18,24,32-34] but (a) they have not been condensed into a synoptic theoretical treatment, (b) the formation of the carbocations has not been calculated correctly, except in a paper by Loew et al.,[32] (c) the competition to the first epoxidation has not received enough attention, and (d) the negative correlation between the ability of the PAH to reach the site of epoxidation and that of the metabolites to reach the DNA has not been connected with carcinogenic potency, except intuitively by Herndon.[24]

In order to solve the problem according to Ockham's razor, i.e., using the simplest theoretically sufficient concept, let us proceed in terms of the PMO method.[35-37] PMO has the advantage to require only a pencil and the back of an envelope; nevertheless, it is firmly based on wave mechanics and gives reliable reactivity indices.[37,22] In this paper, the PMO method will be implemented by an ω-type electron repulsion, in order to differentiate between radicals and carbocations.

2.1. Initial Epoxidation and Competing Processes. For a fast screening of carcinogenic PAH molecules, we need a simple, but nonetheless effective, index describing the probability of metabolism into ultimate carcinogens as compared to detoxification pathways.

Caution is required in applying MO reactivity indices to enzymatic reactions. However, as a specific reaction at a given region in a group of related compounds is investigated, the effects of differing reactivities should predominate over differences in binding to the enzyme. Some account of the optimal fit into the enzymatic receptor site is taken in section 2.3.

A positive correlation between M-region reactivity indices and carcinogenity has been published in earlier work.[32,33] Concerning the second run through the P-448 system, a further epoxidation in vicinal position, i.e., in the B region, is generally greatly enhanced by the M-region dihydro diol formation.[4,5,32,33] However, carcinogenic and noncarcinogenic M-region dihydro diols were calculated to be equally reactive to B-region epoxidation. Therefore this reaction needs *not* to be considered by an independent variable in a regression analysis. The role played by cationic and/or radicalic reaction intermediates is treated in section 2.2 and discussed in section 3. Thus, the metabolic variable M has to deal with the probabilities for the initial epoxidation and its competing reactions.

In choosing a proper reactivity index, one has to be accept a biomimetic model for enzymatic epoxidation. Two mechanisms have been recently under discussion: a concerted oxidation across a C=C bond and nonconcerted addition beginning at the more reactive carbon atom.[38-48] In the former case, a PMO approach should use the M-region ortholocalization energy index $\delta E_o(M)$;[37] in the latter case, the smaller of the two Dewar reactivity numbers N[37] of the region under attack. There has been increasing evidence, both experimental[41-45] and theoretical[46-48] that epoxidation is nonconcerted. Therefore, the ease of epoxidation at the region will be negatively correlated to N_m, the smaller of the Dewar numbers in this region, defined as

$$N_m = 2(c_{o,m-1} + c_{o,m+1}) \quad (1)$$

$c_{o,m-1}$ and $c_{o,m+1}$ are the nonbonding MO coefficients at atoms $m - 1$ and $m + 1$ of the odd PAH which results if we interrupt the π-system at atom m. These coefficients are obtained by pencil and paper,[35-37] as illustrated for two positions of benzo(g)chrysene in Figure 3.

There are different centers and regions where deactivating reactions can occur.[13-16,28,34,49] For the sake of simplicity, the

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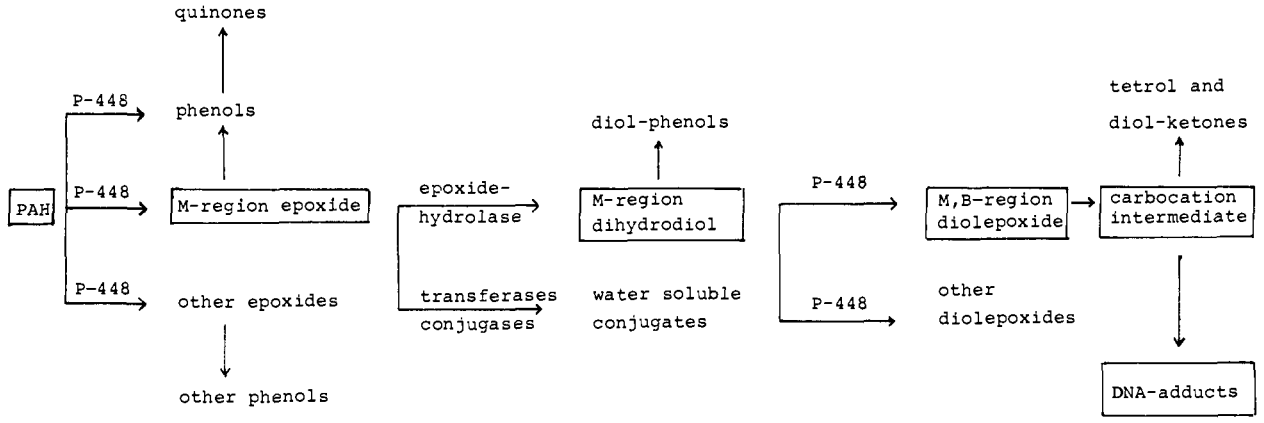

Figure 2. Pathways for the metabolism of polycyclic aromatic hydrocarbons.

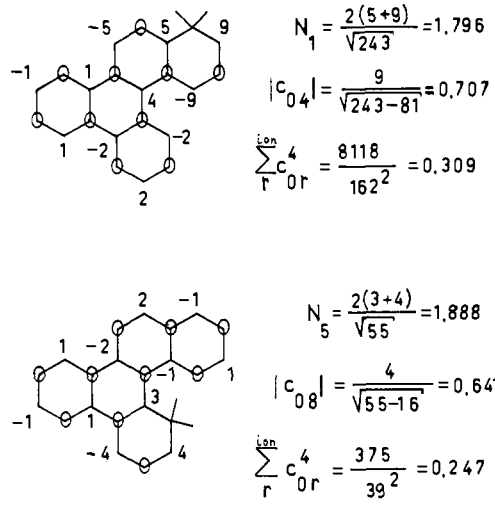

Figure 3. Pencil and paper calculation of Dewar numbers N_m (eq 1), nonbonding MO coefficients $|c_{ob}|$ of carbocations (eq 4), and charge dispersal energies E_C (eq 7 and 11) illustrated on benzo(*g*)chrysene.

center *c* with the smallest Dewar number, N_c, will be considered only; i.e., it is assumed that the fastest reaction predominates and the other competitions are unimportant. In fact, the Dewar numbers of the molecules under consideration support such a picture. Usually, the smallest N_c is found on an anthracene-9 or meso-type position. The assumption of nonconcerted reactions described by N_m is advantageous in comparing epoxidations and one-center detoxification reactions yielding, e.g., phenols and quinones. N_m and N_c are combined into a single metabolic index M describing which of the competing reactions is favored

$$M = (N_m - N_c)^2 \tag{2}$$

Several exponents and combinations of N_m and N_c have been tested. They do not greatly influence the correlation with Iball indices, but the form given in eq 2 is both simple and satisfactory. Within the limited range, it mimics an exponential relation which would be appropriate, if we knew more details of the transition structures. Without such a knowledge, exponential relations would additionally require some hidden parameters.

2.2. Carbocation Formation. Within the bay model[2-7,16-18,32-34] the ease of the carbocation formation has been negatively correlated with either the charge $q_b e$ that remains at the atom *b* of the ion[4,5] or $|c_{ob}| = (q_b)^{1/2}$, the nonbonding MO coefficient at the exocyclic atom *b*[1-3,33,34] (Figure 1e). Osborne[6] has pointed out the "false positives" due to such indices: noncarcinogenic polyacenes and phenes have lower q_b values than those of the most dangerous dibenzopyrenes. Instead, Osborne[6] proposes a new index $\sum_r |c_{or}|$, the sum of all the NBMO coefficients, expressing the evenness of the charge distribution. However, Osborne's $\sum_r |c_{or}|$ index shows false positives as well and increases too fast with molecular size. Further, Osborne was arguing on wrong grounds with "the energy *needed* to solvate the ion".

The above indices are based on the Hückel approximation. The Hückel (HMO) model does not differentiate between the formation of an odd PAH radical and that of the corresponding carbocation. This difference is very relevant, however, and can be calculated approximately by unsophisticated methods. In order to improve the theoretical foundation of the calculations, let us consider a simplified self-consistent method with Hückel orbitals as a base.[19-21]

In this approximation, the reaction of a dihydro diol epoxide to a carbocation (Figure 1) is associated with a resonance energy E_R of the "arylmethyl ion" additional to that of the aromatic

$$E_R = E_D + E_C + E_B \tag{3}$$

system of the dihydro diol epoxide. E_D is the delocalization energy arising without explicit electron interaction; it is equivalent to the

$$E_D = (1.50 - 1.03|c_{ob}|)\beta \tag{4}$$

Hückel delocalization energy and is well approximated by the PMO model[36,37,50] (Figure 3). The second term, E_C, has been

$$E_C = -\tfrac{1}{2}\sum_r\sum_s c_{or}^2 c_{os}^2(\gamma_{11} - \gamma_{rs}) < 0 \tag{5}$$

called charge dispersa[1] energy.[21,50] The probability to find two π-electrons on the same atom in the aromatic ion is lower than that in one of the classical structures. For the radical, there is an increase in the corresponding probability. The resonance energy of the ion exceeds that of the radical by $2|E_C|$.[21] γ_{rs} is the Coulomb interaction energy of an electron on atom *r* with one on atom *s*. According to Pariser and Parr,[19] the values γ_{rs} = 10.53, 7.30, 5.46, and 4.90 eV are chosen for interatomic distances 0, 1, $(3)^{1/2}$, and 2 times the C–C distance in benzene. For larger separations, a point-charge approximation is used.[20,21]

In some early applications of the simplified self-consistent method to reactivities of arylmethyl chlorides, Mason[50,51] has found a rather close linear correlation between E_C and the solvation energy due to Born charging[52]

$$G_s = -\sum_r q_r^2 e^2(1 - (1/D)/2R_r \tag{6}$$

where *D* is dielectric constant of the solvent and R_r is the effective radius of the atom *r* in the carbocation. For odd alternating PAH cations, we have $q_r = c_{or}^2$ according to Longuet-Higgins.[35] With R_r taken as a constant for a given solvent, E_C of eq 5 and $\sum_r c_{or}^4$ are correlated. For 20 odd alternant cations investigated in ref 50 and in this paper

$$E_C = -41.71 + 56.64\sum_r c_{or}^4 \tag{7}$$

is obtained in units of kilocalories per mole with a correlation coefficient $r = 0.980$. The calculation of $\sum_r c_{or}^4$ is indicated on Figure 3.

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Equation 7 can be rationalized in terms of the ω-method.[53-55] According to it, each Hückel parameter α_r is changed by an amount $\omega\beta q_r$, ω being a parameter. To the first order, the extra stabilization energy of a carbocation is given by

$$E_{C,\omega} = \omega\beta\sum_r(1 - q_r)q_r = \omega\beta(1 - \sum_r c_{or}^4) \quad (8)$$

because of $\sum_r q_r = 1$ and $q_r^2 = c_{or}^4$. In the ω-method, E_R is approximated to the first order as

$$E_R \approx E_{R,\omega} = E_D + \omega\beta(1 - \sum_r c_{or}^4) \quad (9)$$

Equations 7 and 8 allow us to calculate E_C in a much simpler way than using eq 5. The first-order ω-type perturbation in eq 8 generally permits inclusion of electron repulsion in PMO.

According to Mason,[50] carbocation reaction rates are dominated by E_C, but this influence is somewhat offset by G_s. Although Mason has discussed the negative correlation between E_C and G_s, some misunderstandings have arisen in literature.[6,55] Thus, the rate dependence is *not* "following from the ω-technique as well as from the solvation energy approach".[56] A similar wrong reasoning has led Osborne[6] to argue with "the energy *needed* for solvating the ion". Nevertheless, I owe the hint to $\sum_r q_r^2$ to Osborne's paper.

The last term in eq 3 is called bond–bond interaction energy[21,50]

$$E_B = \tfrac{1}{2}[\sum_{r>s}^{ArMe^+} P_{rs}^2(\gamma_{12} - \gamma_{rs}) - \sum_{r>s}^{ArH} P_{rs}^2(\gamma_{12} - \gamma_{rs})] \quad (10)$$

It is a smaller stabilizing quantity depending mainly on the number of rings or carbon atoms in the PAH and not its particular topography.[50] E_B will be taken into account together with solubility considerations in the size criterion, i.e., the third independent variable, see 2.3.

Thus, the ease of the carbocation formation will be described by combining eq 4 and 7 as an approximation of the Pariser–Parr–Pople method by PMO data. With $\beta = -20.0$ kcal/mol, the second independent variable is obtained in kcal/mol as

$$E_D + E_C = -20.0(1.50 - 1.03|c_{ob}|) - 41.71 + 56.64\sum_r c_{or}^4 \quad (11)$$

2.3. Size Criterion. Two reasons seem important for the assumption of an optimum size for carcinogenicity:

(1) Generally, there is a size dependence including an optimum on any receptor, be it an enzyme or another receptor. The enzyme systems involved in the metabolism of PAHs show, however, broad and undiscriminating substrate specificities.[27,49] This has been rationalized teleologically by the need to metabolize a broad class of xenobiotic compounds.[27,49] (Ironically enough, it is at the same time responsible for the activation of inert compounds into ultimate carcinogens.) Nevertheless, there must be increasing steric hindrance from some substrate size on. There exists also an optimum size for intercalation of PAHs[57,58] and ultimate carcinogens into the DNA, but its influence on carcinogenic potency is unclear yet.

(2) The ability of the PAH to reach the cytochrome P-448 receptor situated in the microsomal endomembrane system[13,27,28] and that of its metabolites to reach the cell nucleus are negatively correlated. Before epoxidation, the PAH has to enter into the membrane's lipid phase. A more lipophilic substance gets into the membrane easier, but it is more difficult for its diol epoxide to return into the hydrophilic medium surrounding the cell nucleus. The inverse is true for less lipophilic PAHs. This indicates an optimum solubility but not yet an optimum size. The connection between size and solubility is shown in the following argument.

Molecular partitioning across polar–nonpolar interfaces is described by the partition coefficient P. According to Rogers and Cammarata,[59] the lipophilicity of aromatic molecules is linearly proportional to $\sum_r S_r$, the sum of electrophilic superdelocalizabilities,[60] whereas hydrophilicity is proportional to $\sum_r|q_r|$, the sum of the absolute charges on the atoms.

$$\ln P(\text{calcd}) = 0.667\sum_r S_r - 2.540\sum_r|q_r| + 0.478 \quad (12)$$

In view of eq 6 describing solvation energy, it would be advisable to correlate hydrophilicity with $\sum_r q_r^2$. For neutral PAHs, i.e., $q_r = 0$, Smith et al.[4] have found a poor correlation between carcinogenic potency and $\sum_r S_r$–no surprise in view of a single variable. Their data disclose, however, a strong correlation between $\sum_r S_r$ and the size, i.e., the number of carbon atoms. This is the rationale behind Herndon's[24] statement, that an entropy term can be defined by either solubility or molecular size.

Such an optimum molecular size for carcinogenic potency of PAHs will be influenced also by the bond–bond interaction energy E_B (eq 10), which increases with size. Indeed, the size criterion must be regarded as a composite index of carcinogenicity.

The optimum molecular size is taken as an empirical parameter and seems to be between 20 and 24 carbon atoms. The size criterion is chosen as

$$\Delta = |n - 20|^3 \quad (13)$$

This is a modification of Herndon's size criterion.[24] Δ cannot be a dominating parameter, since there are many PAH molecules with $n \cong 20$ that are definitely noncarcinogenic, e.g., pentacene. Prior to quantitative discussion, this is an evidence that the intrinsic activity, i.e., the activity once the carcinogen has reached its site(s) of action, will be governed by the molecular electronic structure. Furthermore, Δ should not contain a strong bias toward large carcinogenic potency with $n = 20$. Therefore, it is reasonable to choose the exponent 3. It will be seen in the discussion that the exponent and to some extent the whole Δ parameter are of conceptional rather than numerical importance for the molecules studied.

3. Results, Discussion, and Predictions

The MCS model is tested on the carcinogenic potencies of 26 PAH molecles (Figure 4, Table I). Similar samples of molecules have been considered to be representative of this class of compounds.[4,6,24,32,33] The sample has not been restricted to molecules with bay regions. It would be theoretically unsatisfactory to limit the analysis to bay-region containing molecules, i.e., to the existence of a particular topological form. Besides, naphtho(2,3-*a*)pyrene is heavily carcinogenic without having a proper bay region. Nonalternant PAHs can be treated according to a proposal by Herndon.[61] Fluoranthene is included as a first example. Other nonalternants will be discussed in forthcoming papers. Special care is given to discuss the unexplained "false positives"[6,13,24,33] of earlier theoretical work and to give some predictions for carcinogenic PAHs.

The unambiguous determination of any carcinogenity index by animal tests is hampered by the different response due to differences in e.g., age and nutrient state of the animals, dose, purity, and route of administration of the carcinogens. Nevertheless, there is an excellent rank correlation[4] between experimental indices, such as the crude Badger index[62] ((–) to (++++)) and the Iball index I.[23] The latter is defined as the percentage of papilloma-bearing mice (among those who survived beyond the shortest time of latent period) divided by the average length of the latent period in animals affected by cancer. Thus, I is proportional to the fraction of subject animals that show a carcinogenic response divided by the mean latent period. Iball indices can be trusted within a range of ± 10.[63]

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Table I. Metabolic Indices M (eq 2), Delocalization Energies $|E_D|$ (kcal/mol) (eq 4), Charge Dispersal Energies $|E_C|$ (kcal/mol) (eq 7), Size Factors Δ (eq 13), and Observed[a] as well as Calculated Iball Indices I of Polycyclic Aromatic Hydrocarbons

hydrocarbon	M	$\|E_D\|$	$\|E_C\|$	$\|E_D + E_C\|$	Δ	I_{obsd}[a]	I(PMO-ω), eq 14	I(PMO), eq 15
benzo(*e*)pyrene (**1**)	0.125	16.7	25.7[b]	42.4	0	2	8	17
benzo(*a*)pyrene (**2**)	0.155	17.6	32.0[b]	49.6	0	72	65	48
dibenzo(*e,l*)pyrene (**3**)	0.040	16.5	25.6	42.1	64	0/+	7	18
naphtho(2,3-*a*)pyrene (**4**)	0.151	16.5	28.2	44.7	64	27	20	2
dibenzo(*a,e*)pyrene (**5**)	0.106	17.0	29.8[b]	46.8	64	50	41	28
dibenzo(*a,h*)pyrene (**6**)	0.186	18.1	32.0	50.1	64	68	62	59
dibenzo(*a,i*)pyrene (**7**)	0.176	18.3	33.9[b]	52.2	64	74	80	68
tribenzo(*a,e,h*)pyrene (**8**)	0.111	17.3	30.7	48.0	512	~20	17	13
tribenzo(*a,e,i*)pyrene (**9**)	0.121	17.5	31.3[b]	48.8	512	17	23	20
tetracene (**10**)	0.151	15.9	24.2	40.1	8	0	−14	−18
pentacene (**11**)	0.252	16.7	26.2	42.9	8	0	1	−2
hexacene (**12**)	0.294	17.5	28.0	45.5	216	0?	4	11
phenanthrene (**13**)	0.004	16.2	24.9[b]	41.1	216	0	−9	3
benzo(*a*)anthracene (**14**)	0.235	17.3	26.5[b]	43.8	8	7	10	24
benzo(*a*)tetracene (**15**)	0.500	18.1	27.8[b]	45.9	8	0	5	16
benzo(*a*)pentacene (**16**)	0.771	18.8	30.5	49.3	216	0	−4	−8
triphenylene (**17**)	0.000	16.2	24.6[b]	40.8	8	0	4	16
chrysene (**18**)	0.017	16.0	25.7[b]	41.7	8	5	10	5
benzo(*c*)chrysene (**19**)	0.012	16.0	25.7	41.7	8	~10	10	6
benzo(*g*)chrysene (**20**)	0.021[c]	16.1[c]	26.1[c]	42.2[c]	8	18	14	9
benzo(*c*)phenanthrene (**21**)	0.002	15.6	24.2[b]	39.8	8	4	−4	−8
dibenzo(*a,c*)anthracene (**22**)	0.246	16.8	26.1[b]	42.9	8	3	2	3
dibenzo(*a,j*)anthracene (**23**)	0.167	16.8	26.9	43.7	8	4?	15	15
dibenzo(*a,h*)anthracene (**24**)	0.101	17.0	27.6	44.6	8	26	27	32
tribenzo(*a,c,h*)anthracene (**25**)	0.069	16.7	26.7	43.4	216	0?	5	13
fluoranthene (**26**)	0.027	16.2	25.3	41.5	8	0	8	12
pentaphene (**27**)	0.077	15.6	25.2	40.8	8	*d*	*d*	
benzo(*c*)pentaphene (**28**)	0.226	17.0	27.7	44.7	216	*d*	*d*	
hexaphene (**29**)	0.274	15.9	26.3	42.2	216	*d*	*d*	
picene (**30**)	0.019	16.2	26.3	42.5	8	*d*	*d*	
dibenzo(*c,g*)phenanthrene (**31**)	0.008	16.0	25.4	41.4	8	*d*	*d*	
naphtho(2,3-*e*)pyrene (**32**)	0.041	15.2	23.6	38.8	64	*d*	*d*	
benzocoronene (**33**)	0.046	16.2	26.9	43.1	512	*d*	*d*	
dibenzo(*a,l*)pyrene (**34**)	0.128	16.7	29.4	46.1	64	*e*	33	
dibenzo(*g,p*)chrysene (**35**)	0.000	16.7	27.7	44.4	216	*f*	18	
dibenzo(*a,j*)tetracene (**36**)	0.321	17.8	28.9	46.8	216	*f*	12	

[a] Experimental values taken from: Arcos, J. C.; Argus, M. F. *Adv. Cancer Res.* **1968**, *11*, 305–471. And from ref 4, 6, 24, 33, and 34. [b] Calculated according to eq 5. [c] Mean values, as explained in text. [d] See discussion Table IV. [e] See text. [f] Unknown.

The three independent variables defined in section 2 are assumed to be linearly related to the experimental Iball indices. The partial regression coefficients in eq 14 and their standard errors

$$I(\text{PMO} - \omega) = -(80.47 \pm 9.46)M + (8.244 \pm 0.510) \times |E_D + E_C| - (0.0739 \pm 0.0107)\Delta - (331.7 \pm 21.6) \quad (14)$$

are obtained by a multilinear regression analysis on the sample listed in Table I. The quality of the fit is characterized by the multiple correlation coefficient $r = 0.961$ (i.e., $r^2 = 0.923$ of the variation about the mean) and the standard error SE = ±6.8. The accuracy obtained could and should not be any better, considering that the confidence limit of the Iball index is of the same size (Figure 5).

Partial F tests[64] were used as a criterion for the importance of the individual variables. Such a test is made for every regression coefficient, as if the corresponding variable were added to the model last—to see the relative effects of each variable in excess of the others. The method breaks down the regression sumof squares into two parts: one due to the variable under investigations, the other due to all other variables together. The variable $|E_D + E_C|$ (eq 11), expressing the carbocation formation, is by far the most important, followed by M, the metabolic index. The size criterion Δ is the least important; this is fortunate with respect to its largely empirical character (Table II).

With $|E_D + E_C|$ as the prime variable, it is of interest to test the influence of E_C (eq 7) within this variable. Let us neglect E_C, i.e., restrict ourselves to a Hückel level of calculation $E_R = E_D$, while leaving the other indices unchanged. Once more assuming linear relations between the variables and the Iball index, we obtain

$$I(\text{PMO}) = -(146.33 \pm 26.44)M + (38.91 \pm 5.72)|E_D| - (0.0569 \pm 0.0213)\Delta - (614.17 \pm 92.88) \quad (15)$$

The quality of the correlation drops drastically. As shown in Table I and Figure 6, there are very serious discrepancies between experimental Iball indices and those calculated at the Hückel level.

Table II. Analysis of Variances Including Partial F Tests for M, $|E_D + E_C|$, and Δ

source of variatn	deg of freedom	sq sum	mean sq	F
total (cor)	25	563.533		
regressn	3	519.936	173.312	87.455
partial F tests		adjusted		
due to M	1	143.496		72.410
due to $\|E_D + E_C\|$	1	517.400		261.086
due to Δ	1	94.930		47.903
residual	22	43.598	1.9817	

Table III. Analysis of Variances Including Partial F tests for M, $|E_D|$, and Δ

source of variatn	deg of freedom	sq sum	mean sq	F
total (cor)	25	563.533		
regressn	3	382.746	127.582	15.525
partial F tests		adjusted		
due to M	1	251.729		30.633
due to $\|E_D\|$	1	380.210		46.268
due to Δ	1	58.397		7.106
residual	22	180.787	8.2176	

(63) Herndon, W. C., private communication.
(64) Draper, N. R.; Smith, H. "Applied Regression Analysis"; Wiley: New York, 1981.

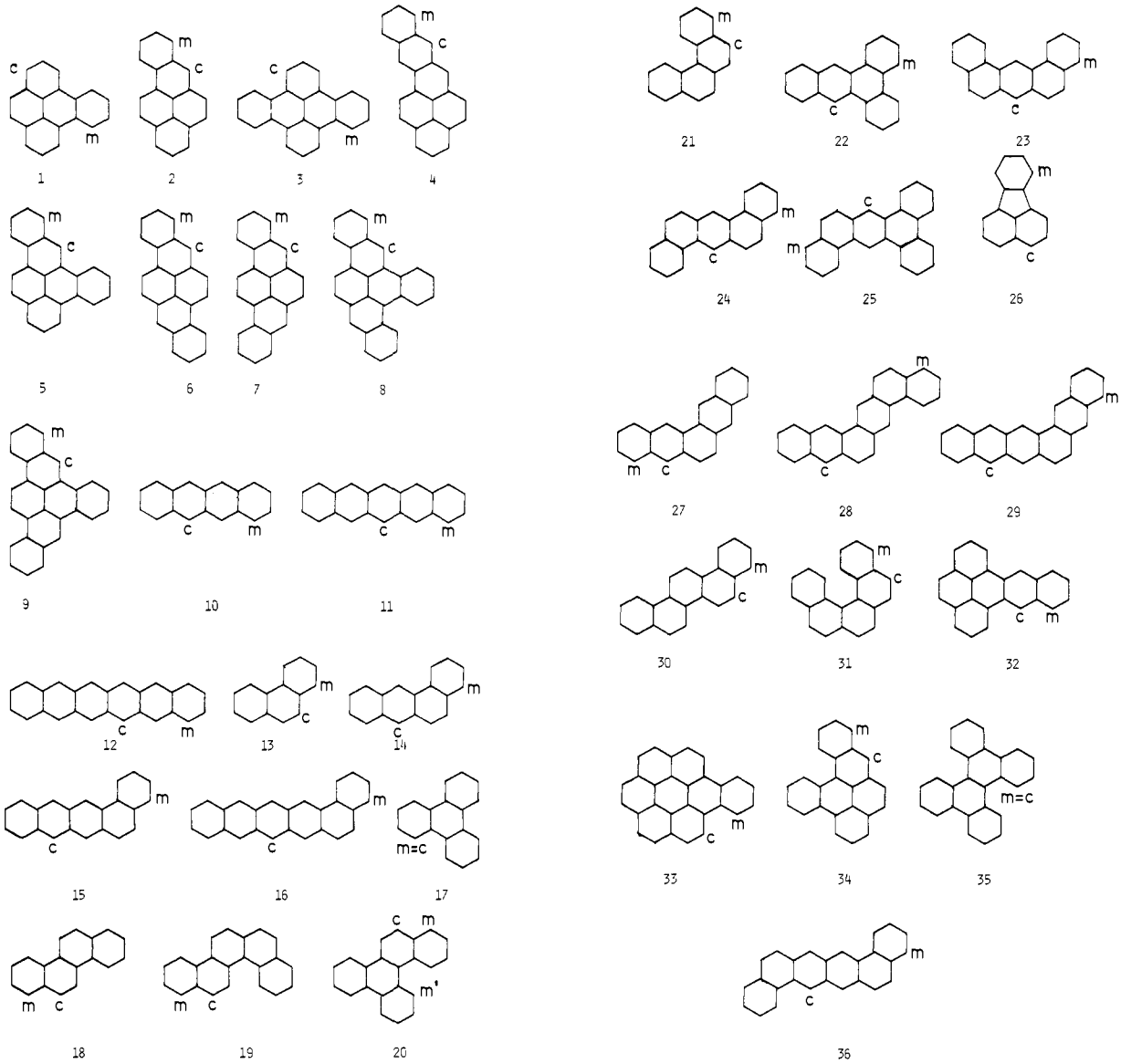

Figure 4. Structures for compounds in Table I. Unsaturation is not depicted. Epoxidation starting on position *m* is competed by reactions on position *c*.

The multiple correlation coefficient has dropped to $r = 0.824$, and the standard error has increased to SE = ±14.1. The partial F value of $|E_D|$ is much smaller than that of $|E_D + E_C|$ (Table III). Compared to M and Δ, $|E_D|$ is still the most important variable but by a lesser margin than $|E_D + E_C|$. The linear correlation in (15) is about the limit obtainable by either the HMO model or the usual PMO method without explicit inclusion of an ω-type electron repulsion.

This analysis of variances (Tables II and III) represents a strong argument for the role played by carbocations as intermediates either in the ultimate reaction with DNA, in the M-region epoxide hydration, or in both. Topological considerations, easily rationalized by the PMO model, show that corresponding bay-region and M-region carbocations have strongly related charge distributions (Figure 7). With cationic intermediates, the ring opening at a given M-region epoxide closely parallels the rate of ring opening of the corresponding B-region diol epoxide. Therefore, one has to bear in mind that the good correlation with B-region carbocation formation does not necessarily indicate a mechanism involving such a cation, since the carcinogenic potency could as well depend on the ease of the first diol formation via carbocation intermediate.

At the moment, it cannot be decided whether the first or the second oxirane ring opening is more important for the carcinogenesis, and this renders the bay-region hypothesis somewhat nebulous. On the other hand, it is sufficient to calculate one of the carbocations, otherwise we would introduce linearly dependent variables.[65] If it turned out that the second ring opening did *not* occur via carbocation,[31,32] the correlation presented here would support an ionic mechanism of the M-region epoxide hydration. In any case, the importance of E_C is a strong argument for carbocation intermediates.

Apart from the general improvement of the correlation with experimental Iball coefficients, the importance of E_C can be convincingly demonstrated on some molecules. Benzo(*a*)tetracene ($I = 0$) and dibenzo(a,*h*)pyrene ($I = 68$) have identical $|E_D|$ = 18.1 kcal/mol, i.e., $q_b = 0.333$, according to both HMO and PMO. The corresponding $|E_C|$'s are quite different, however: 27.8 kcal/mol for the former and 32.0 kcal/mol for the latter. According to HMO, triphenylene, $|E_D|$ = 16.2 kcal/mol, would be more dangerous than chrysene, $|E_D|$ = 16.0 kcal/mol; this contradiction to experiment disappears, if we include E_C.

In addition to the prime importance of E_C in a quantitative correlation, the metabolic index M is essential in explaining the noncarcinogenicity of polyacenes and phenes. Both $|E_D|$ and $|E_C|$ increase with longer linear annelation in these series. This would inevitably lead to heavily carcinogenic polyacenes and phenes, were

(65) Such linear dependencies have been found between K-region and bay-region indices.[16-18]

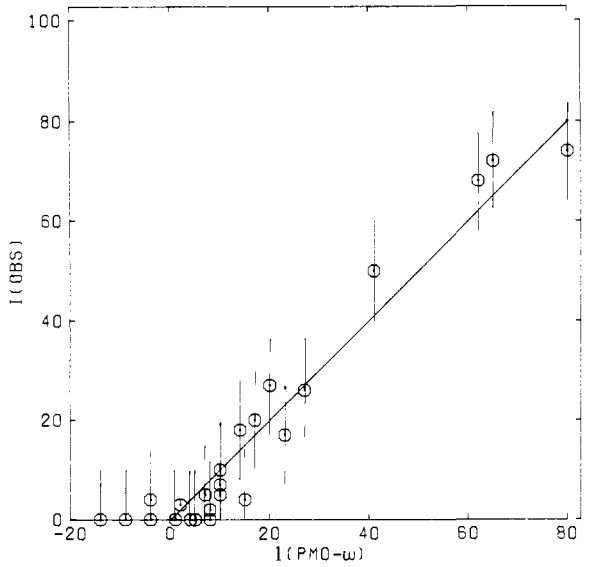

Figure 5. Observed Iball indices of carcinogenicity vs. MCS model calculations using eq 14. The bars attached to the points refer to experimental uncertainties ±10.

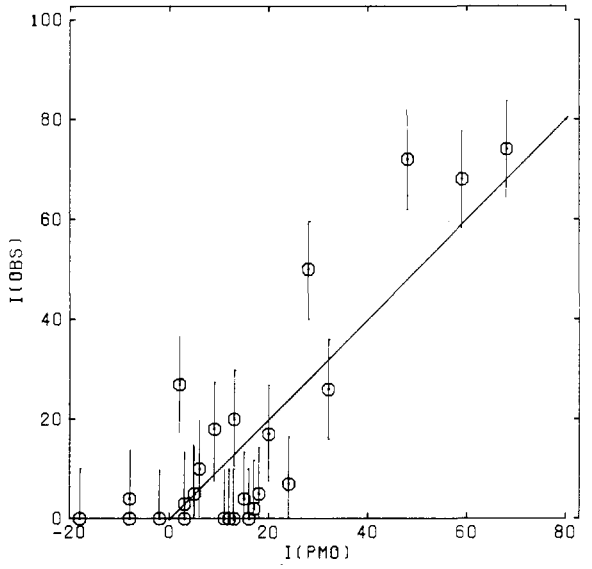

Figure 6. Observed Iball indices of carcinogenicity vs. calculated ones using eq 15. The bars attached to the points refer to experimental uncertainties ±10.

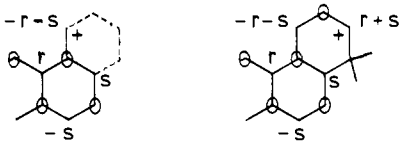

Figure 7. Topological relations between unnormalized nonbonding MO coefficients of bay- and M-region carbocations with identical nondepicted molecular structures.

it not for the detoxification at the centers belonging to the L region. The Dewar number N_c at the competitive center decreases much more rapidly than N_m at the M region. Consequently, the first epoxidation becomes less probable with the increasing length of the linearly annelated part of the PAH.

Benzo(*g*)chrysene, Figure 3,is an interesting example for a breakdown of the limitation to two competing reactions only. The lowest $N_m = 1.796$ ($m = 1$) is associated with $|E_D + E_C| = 39.6$ kcal/mol only, whereas the highest $|E_D + E_C| = 44.8$ kcal/mol belongs to an initial epoxidation characterized by $N_m = 1.888$ ($m' = 5$). The usual detoxification is described by $N_c = 1.698$ ($c = 14$). Thus, two initial epoxidations are competing with each other, and the theoretically faster one leads to a less carcinogenic carbocation intermediate than the slower one. Admittedly, such a situation is difficult to handle with simple reactivity indices. Note, that even an inclusion of an ω-correction to N_m, with $\omega = 1.4$ as usual, would favor the initial epoxidation at atom $m = 1$.

Table IV. MCS Results for Hydrocarbons Known as False Positives or False Negatives in Earlier Calculations

hydrocarbon	I_{obsd}	I(PMO-ω), eq 14	ref 24	ref 33
pentaphene	0	−3	47	
benzo(*c*)pentaphene	0	4	38	10
hexaphene	0	−22	32	
picene	0?	17	45	16
dibenzo(*c*,*g*)phenanthrene	0	8	45	12
dibenzo(*a*,*h*)anthracene	26	27	38	9
tribenzo(*a*,*c*,*h*)anthracene	0?	5	46	8
naphto(2,3-*e*)pyrene	0	−20	41	
benzocoronene	0	−18	32	

$$N_m^{\omega} = N_m - \omega(1 - \sum_r q_r^2) \qquad (16)$$

$$N_1^{\omega} = 1.796 - 1.4(0.751) = 0.744$$

$$N_5^{\omega} = 1.888 - 1.4(0.791) = 0.781$$

As a compromise, we may use averaged $\bar{N}_m$ and $|\bar{E}_D + \bar{E}_C|$ values. Then, the calculated Iball index agrees with the experimental one.

In view of the limited accuracy of experimental Iball indices and the secondary importance of the M index, it seems neither worthwhile to elaborate a more sophisticated M-type index nor to insist on detailed mechanisms of epoxidation. This has to be postponed until more accurate experimental data will be available.

The size criterion becomes effective for $n \leqslant 14$ and $n \geqslant 26$, between 16 and 24 it almost does not discriminate between the different molecules. Its small partial F value indicates (a) the low size specificity of the enzymatic processes involved and (b) the importance of the electronic structure, i.e., of pure theoretical indices, for the intrinsic activity, once the carcinogen has reached its site(s) of action.

After this general discussion of the multilinear correlation, let me now turn to some specific molecules, especially the former false positives.[6,13,24,33] An interesting list was given by Herndon,[24] who was the first to publish a three-variable linear correlation with carcinogenic potency based on Pullman's K,L hypothesis[14-16] and an optimum molecular size. In view of the linear dependence between the K- and bay-region indices,[16-18] Herndon's analysis is essentially confirming the importance of the bay and L regions. However, a good deal of false positives remained with calculated $I \approx 40$, for which no explanation could be given, cf. Table III in ref 24 and Table IV, this paper. The list of exceptions given by Umans et al.[33] is similar, though less complete. The type of false positives pointed out by Osborne[6] has been discussed in connection with E_C and M. As shown in Table IV, the false positives disappear with the sole exception of picene.

By its electronic structure, ($M = 0.019$, $|E_D + E_C| = 42.5$ kcal/mol), picene is at least as dangerous as chrysene ($I = 5$). This is concluded from INDO calculations[32] as well, where it was found to be more dangerous than dibenzo(*a*,*h*)anthracene. As picene is a carcinogen by theoretical standards, it is suggested to repeat and reevaluate the experiments. State-of-the-art experimental results should help to improve or confirm the theoretical model proposed here.

Dibenzo(*c*,*g*)phenanthrene (pentahelicene) is not believed to be carcinogenic, because it is known from H/T-isotope-exchange reactions that Dewar numbers and HMO localization energies do not describe its positional reactivity order correctly.[66] These indices give a relative overestimate of the reactivity at position m in the M region. Thus the molecule may appear too carcinogenic in the MCS model using Dewar numbers. This should be different in a free-electron-MO version of the MCS model[67] since

(66) Le Guen, M. M. J.; El-Din Shafig, Y.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1979**, 803–807.

the PMO:F reactivity numbers[68] give the correct positional reactivity order.

Hexaphene, naphtho(2,3-*e*)pyrene, and benzocoronene are calculated with negative Iball indices considerably exceeding the standard error SE = ±6.8. They are not false negatives, however, this expression being reserved for truly carcinogenic molecules that are calculated as noncarcinogens. These molecules, together with tetracene in Table I, just reflect the limits of the quasilinear relationship imposed upon the regression. Exponential relations would seem more appropriate than linearized ones,[24] but they would require some hidden parameters, because of our lack in detailed knowledge of the transition structures of the metabolites and their connection to Iball indices.

Besides the former false positives, an important molecule is not included in the regression: dibenzo(*a*,*l*)pyrene. It has been repeatedly quoted as the most dangerous of all PAH carcinogens: $I_{obsd} = 82$,[6,24,33] whereas, in other sources,[4,69] it is labeled with $I_{obsd} = 33$ only. According to the MCS model, cf. Table I, dibenzo(*a*,*l*)pyrene is calculated to have $I(\text{PMO-}\omega) = 33 \pm 15$[70] and is somewhat less potent than the related dibenzo(*a*,*e*)pyrene with $I(\text{PMO-}\omega) = 41 \pm 15$ and $I_{obsd} = 50 \pm 10$. With respect to $I_{obsd} = 82$, dibenzo(*a*,*l*)pyrene seemed to be a false negative due to the MCS model. To make it worse, some calculations[24,33] yielded $I_{calcd} \simeq 70$. Nevertheless, I predicted to colleagues that there was something wrong with the extremely high potency attributed to this molecule.

Later, a thorough checking of the references revealed that both experimental values need reinterpretation. Lavit-Lamy and Buu-Hoï[71] have disclosed that the supposed "dibenzo(*a*,*l*)pyrene" in ref 69 was really dibenzo(*a*,*e*)fluoranthene, and $I_{obsd} = 33$ was probably obtained with the latter compound. On the other hand, the $I_{obsd} = 82$ is not referring to the usual Iball papilloma index but to the sarcoma index obtained by subcutaneous injections.[72] This index cannot be treated on the same scale with the Iball papilloma index. Within the scale of the sarcoma index, 82 is by no means the highest potency obtained, e.g., the sarcoma index of dibenzo(*a*,*i*)pyrene is 124.[73] Assuming an approximate linear relation between the sarcoma index and the usual Iball index, we obtain an estimated $I_{est} = 82(74/124) = 49$ for dibenzo(*a*,*l*)pyrene, similar to $I_{obsd} = 50 \pm 10$ found for dibenzo(*a*,*e*)pyrene. This would be in good agreement with the MCS model that predicts similar potencies for the two compounds. The resolution of this potentially prominent discrepancy between experiment and the MCS model is very encouraging indeed, as it represents the first qualitatively confirmed prediction of this model. Most probably, there has been no unequivocal experimental determination of the Iball papilloma index of dibenzo(*a*,*l*)pyrene. Dibenzo(*a*,*e*)fluoranthene will be discussed together with other fluoranthene derivatives in a forthcoming paper.

Besides for picene and dibenzo(*a*,*l*)pyrene, positive Iball indices are predicted by the MCS model for dibenzo(*g*,*p*)chrysene $I(\text{PMO-}\omega) = 18 \pm 15$ and dibenzo(*a*,*j*)tetracene $I(\text{PMO-}\omega) = 12 \pm 15$. It may be noticed here that the diol epoxide formed during the metabolism of dibenzo(*g*,*p*)chrysene probably would not intercalate in DNA.[57,58] Thus, the role played by intercalation could be tested with this molecule.

4. Concluding Remarks

It has been shown that the carcinogenic potency of polycyclic aromatic hydrocarbons (PAH) is successfully described by a new MCS model, with M standing for M-region metabolism, C for carbocation formation, and S for size and solubility. The experimental Iball carcinogenicity indices I are correlated with Perturbational MO (PMO) reactivity indices and a size criterion. A metabolic index M is related to the probability of the initial epoxidation step at the M region. In order to describe the formation of carbocations, it is necessary to extend the PMO method by including an ω-type perturbation accounting for electron repulsion. Solubility and optimal fit into receptor sites are described by an empirical size factor, which becomes effective for PAHs containing either <15 or >25 carbon atoms.

The bay-region hypothesis is both substantiated and called into question. Comparison of benzo(*a*)polyacenes and polyacenes of the same size in Table I shows that the angular annelation favors the formation of carbocations on the terminal ring. On the other hand, it cannot be decided whether the first diol formation via carbocation intermediate or the bay-region carbocation formation is more important for chemical carcinogenesis. The indices describing these two carbocations are linearly dependent due to the topology of the molecules. To avoid linear dependencies, it is sufficient and necessary to calculate one of the carbocations only.

Future work will discuss the influence of methylations and the carcinogenicity of fluoranthene derivatives.

Note Added in Proof: Corrections for fluoranthene (**26**), $\Delta = 64$, $I(\text{PMO-}\omega) = 4$, and $I(\text{PMO}) = 9$. The results of the regression analysis are only marginally improved.

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Registry No. **1**, 192-97-2; **2**, 50-32-8; **3**, 192-51-8; **4**, 196-42-9; **5**, 192-65-4; **6**, 189-64-0; **7**, 189-55-9; **8**, 60032-75-9; **9**, 192-47-2; **10**, 92-24-0; **11**, 135-48-8; **12**, 258-31-1; **13**, 85-01-8; **14**, 56-55-3; **15**, 226-88-0; **16**, 239-98-5; **17**, 217-59-4; **18**, 218-01-9; **19**, 194-69-4; **20**, 196-78-1; **21**, 195-19-7; **22**, 215-58-7; **23**, 224-41-9; **24**, 53-70-3; **25**, 215-26-9; **26**, 206-44-0; **27**, 222-93-5; **28**, 222-54-8; **29**, 222-78-6; **30**, 213-46-7; **31**, 188-52-3; **32**, 193-09-9; **33**, 190-70-5; **34**, 191-30-0; **35**, 191-68-4; **36**, 227-04-3.

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(69) Arcos, J. C.; Argus, M. F. *Adv. Cancer Res.* **1968**, *11*, 305–471.
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