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MOLECULAR ORBITAL THEORETICAL PREDICTION OF THE ISOMERIC PRODUCTS FORMED FROM REACTIONS OF ARENE OXIDES AND RELATED METABOLITES OF POLYCYCLIC AROMATIC HYDROCARBONS

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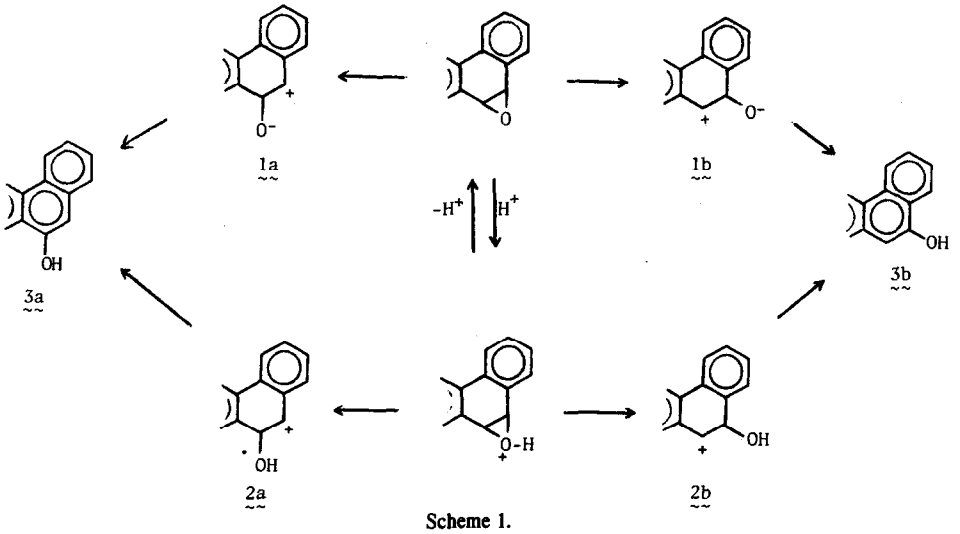
Abstract—MO theoretical calculations based on the perturbational method of Dewar provide good correlation between predicted and observed structures of products formed during: (1) isomerization of arene oxides to phenols; (2) hydration and nucleophilic addition to arene oxides; and (3) dehydration of arene dihydrodiols. The method is equally applicable to the arene oxides, dihydrodiols, etc. derived from carcinogenic and noncarcinogenic polycyclic hydrocarbons. Extension to the related enzymatic reactions occurring during metabolism of carcinogenic hydrocarbons and to the reactions of the biologically active arene diolepoxides and aryloxiranes suggests the potential utility of this approach in predicting (a) metabolite structure and (b) the structural requirements for carcinogenic and mutagenic activity.

Arene oxides are the primary metabolites of polycyclic hydrocarbons,[1,2] both carcinogenic and non-carcinogenic, in mammalian cells. They exhibit significant mutagenic,[1,3] carcinogenic,[1,4] anti-viral,[5] and cellular transformation[1,6] activity coupled with the ability to bind covalently to nucleic acids.[1,7] In a previous paper[8] it was shown that reactions of K-region oxides with the model nucleophile t-butylthiolate take place regioselectively in accord with MO theoretical prediction. It is now proposed that isomerization and hydration of arene oxides, both K-region and non-K-region, dehydration of arene dihydrodiols, and related reactions of other hydrocarbon metabolites are generally predictable by simple MO theory (i.e. Dewar reactivity numbers, N_t).[9]

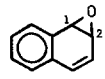
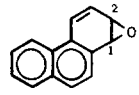
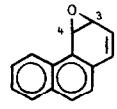
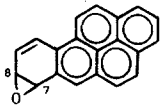
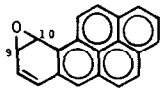
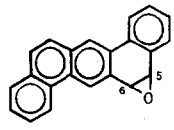
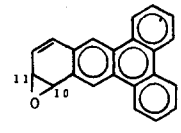
Isomerization of arene oxides. Isomerization of asymmetric arene oxides can in principle afford two isomeric phenols (**3a, b**) arising through ring-opening in either direction via zwitterionic intermediates (**1a, b**) in neutral or basic solution, or via carbocations (**2a, b**) in acidic media (Scheme 1). Generally one of the two possible phenols is formed preferentially or exclusively. Although such preferences have been qualitatively explained in individual cases in terms of intermediate ion stability,[10-12] no general theoretical treatment has been proposed.

We now report that the phenolic products of isomerization of arene oxides are conveniently predictable by application of the simplified MO methods of Dewar.[9] In all cases, the predominant isomer is the one for which the calculated value of N_t for the corresponding zwitterion or carbocation intermediate is minimum.



Scheme 1.

Table 1. Isomerization of arene oxides to the corresponding phenols

Arene Oxide	N_t (position)[a]	Phenol Isomers (%)	Reference
	1.81 (1) 2.12 (2)	1-HO (90-100) 2-HO (0-10)	13
	1.86 (1) 2.18 (2)	1-HO (69-82) 2-HO (18-31)	11
	1.96 (4) 2.04 (3)	4-HO (76-97) 3-HO (3-23)	11
	1.55 (7) 2.12 (8)	7-HO (~100) 8-HO (~0)	14, 15
	1.73 (9) 1.81 (10)	9-HO (~100) 10-HO (~0)	14, 15
	1.66 (5) 1.71 (6)	5-HO (85) 6-HO (15)	10
	1.70 (10) 2.00.(11)	10-HO (major) 11-HO (minor)	16

[a]The values of N_t are calculated as described in the text. For example, the N_t for the 7-position of benzo[a]pyrene 7,8-oxide (N_t = 1.55) is calculated for structures 4a,b in which ring opening occurs to leave oxygen bonded to the 7-position.

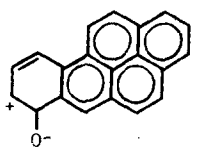
N_t is derived from the non-bonding MO coefficients (NBMO) on the carbon atoms adjacent to that bearing the O atom. Consider, for example, isomerization of benzo[a]pyrene-7,8-oxide. Two sets of ionic intermediates **4a**, **b** and **5a**, **b**, must be considered. In the approximation employed, the C atom bearing oxygen is omitted since it is tetrahedral and N_t is calculated from the formula

$$N_t = 2(a_r + a_s)$$

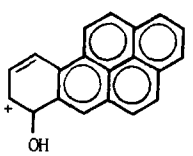
where a_r and a_s are the NBMO coefficients for the adjacent positions (i.e. C-6a and C-8 in **4a**, **b** and C-7 and C-9 in **5a**, **b**). In the case of BP-7,8-oxide, the N_t value for structure **4** is 1.55, while that for **5** is 2.12. Since the former N_t is lower, the isomeric intermediate **4** is more stable, and ring-opening in this direction to furnish the 7-phenol is predicted to be favored. This agrees with experimental observation.[14,15] Furthermore, as shown in Table 1, the distribution of the phenols formed from the isomerization of arene oxides is in accord with similar prediction in every case for which reliable experimental data is available.

The magnitude of the difference between the two reactivity numbers may be expected to provide an approximate index of the ratio of the isomers anticipated to be formed. A relatively large difference (e.g. 0.57 in the case of BP-7,8-oxide) predicts a high probability of formation of a single isomer, while the nearly equal values found for the K-oxide of dibenz[a,h]anthracene predict correctly a more equivalent ratio of both isomers. However, no simple quantitative relationship of this type is evident in the remainder of the cases in Table 1. The number of examples for which reliable data is available is still quite small, and the experiments were not conducted under comparable conditions. Other factors such as steric crowding in the bay regions, are undoubtedly also involved. However, in all instances N_t predicts reliably the predominant isomeric product, if not the precise ratio of isomers.

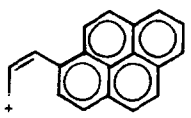
Hydration of arene oxides. Hydration of arene oxides to afford dihydrodiols competes with isomerization in aqueous solution. Since water is a relatively poor nucleophile, phenolic products generally predominate. In the absence of epoxide hydratase, the ratio of the phenolic to dihydrodiol products is determined by the



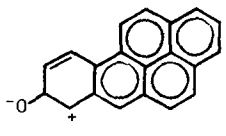
4a



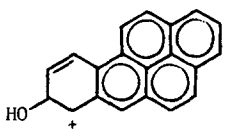
4b



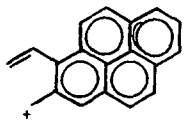
$N_t = 1.55$



5a



5b



$N_t = 2.12$

relative rates of hydride shift (k_1) and direct proton loss (k_2) to that of hydration (k_3) of the carbocation (or zwitterion) intermediate. The relative rates of these processes may be expected to be a function of the stability of the intermediate as measured by N_t. A lower N_t implies a more stable intermediate which will have a longer lifetime, favoring hydration and a greater extent of diol formation. Where the value of N_t is large, it is likely that the carbocation is only partially formed as hydride shift (or proton loss) begins. Benzene oxide and phenanthrene 1,2- and 3,4-oxides have large N_t values (Table 2) and undergo exclusive isomerization to the corresponding phenols,[11a,c] while the K-oxides of phenanthrene, benz[a]anthracene, dibenz[a,h]anthracene, and 3-methylcholanthrene which have lower values of N_t (Table 2) afford substantial amounts (20–30%) of the dihydrodiols.[10] While these results accord with prediction, it should be kept in mind that the mechanistic pathways, and consequently the phenol to dihydrodiol ratios, are likely to be dependent upon the pH and other conditions.

Enzymatic hydration of arene oxides affords efficiently the corresponding dihydrodiols. It is pertinent to inquire to what extent the site specificity of the enzymatic process obeys purely chemical theoretical prediction. The direction of ring opening has been shown for several arene oxides (Table 3) by means of isotopic labeling to involve regiospecific addition of water at one position. In the case of naphthalene 1,2-oxide and benzo[a]pyrene 7,8-oxide,[19] hydration occurs at the site favoring the more stable ring-open form of the intermediate (e.g. **4b** rather than **5b**) in agreement with MO theoretical prediction. In the case of benzo[a]pyrene-9,10-oxide, hydration occurs at C-9,[19] contrary to prediction. In the case of benzo[a]pyrene 4,5-oxide, although the calculated values of N_t are equivalent at the 4- and 5-positions, attack apparently takes place exclusively at the 4-position.[19] A tentative explanation of this selectivity on the 4,5- and 9,10-oxides may be that the relatively bulky dimensions of the molecule direct attack on the less crowded side of the oxide ring. Oesch *et al.*[17] have demonstrated the sensitivity of epoxide hydratase to steric effects. With aryloxiranes, such as styrene oxide and naphthyloxirane (Table 3), hydration appears to occur on the position remote from the large arene ring system and contrary to prediction. Thus, while enzymatic hydration of the arene oxides examined to date appears to conform to prediction on electronic grounds, steric effects are likely to play an important role in other cases.

Reactions of arene oxides with nucleophiles. Reactions of arene oxides with nucleophiles other than water are of great potential biological significance, since interaction with nucleic acids and other cellular macromolecules is thought to be a key step in the mechanism of carcinogen action. In a previous paper[8] it was shown that reactions of a series of K-oxides with t-butylthiolate afford products arising from addition of the nucleophile at the position of the incipient carbocation in the ring-open form of the epoxide having the minimum value of N_t. Reactions of several non-K-oxides derived from naphthalene and phenanthrene with oxygen, nitrogen, and sulfur nucleophiles were investigated by Bruice *et al.*,[23] and only the latter were found sufficiently reactive for nucleophilic displacement to compete with aromatization to phenolic products. Unfortunately, product structures were not determined. The only non-K-oxide to be studied and products characterized is naphthalene 1,2-oxide.[24] Reaction of the latter with ethylthiolate, azide, and

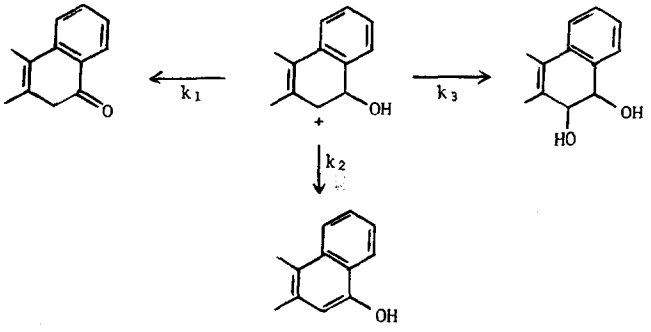
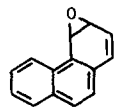
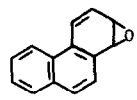
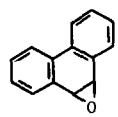
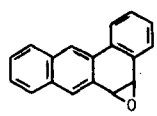
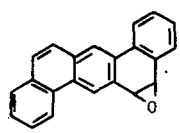
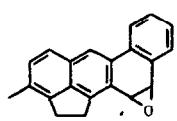


Table 2. Hydration of arene oxides

Arene Oxide	N_t (position)	Products (%) Phenol	Dihydrodiol	Reference
	2.31	100	0	11c
	1.96 (4) 2.04 (3)	100	0	11a
	1.86 (1) 2.18 (2)	100	0	11a
	1.80 (9) 1.80 (10)	81	19	10
	1.66 (5) 1.66 (6)	67	33	10
	1.66 (5) 1.71 (6)	78	22	10
	1.66 (11)[a] 1.66 (12)	74	26	10.

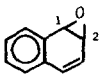
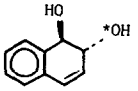
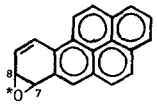
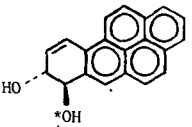
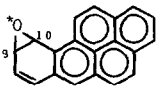
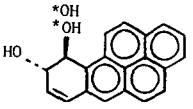
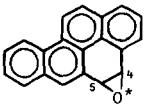
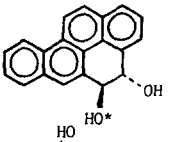
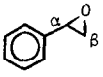
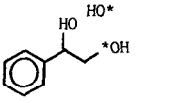
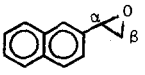
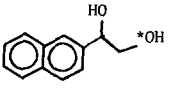
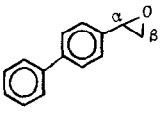
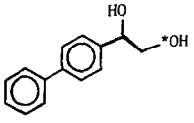
[a]The values cited are for benz[a]anthracene, since the effect of alkyl substitution cannot be determined by these calculations. It is reasonable to assume, however, that ring opening at C-11 should be favored.

methyllithium furnished the products of attack at the 2-position. This result is also in agreement with MO theoretical prediction. Thus the available experimental information, though still somewhat limited, supports the hypothesis that reactions of both K- and non-K-region arene oxides with nucleophiles occur preferentially at the C atom having the lowest Dewar reactivity number.

Dehydration of arene dihydrodiols. Dewar reactivity numbers can also be utilized to predict the structure of the isomeric product formed from dehydration of arene dihydrodiols (*cis* or *trans*) or elimination of carboxylic acid from the corresponding diesters. It is assumed that the product determining step is loss of a hydroxyl (or acyloxy) group to furnish intermediates (e.g. **2a**, **2b**) identical or analogous to those obtained from acid-catalyzed opening of the oxide ring. A relatively large number of such reactions have been reported, and all the available experimental results (Table 4), with one exception, are in accord with the molecular orbital theoretical prediction. The *cis*- and *trans*-3,4-dihydrodiols of phenanthrene furnish principally 3-phenol, apparently as a consequence of steric acceleration of loss of the 4-HO group due to interaction between this group and the H atom at C-5. This interaction is apparently greater in the *cis* dihydrodiol, leading to formation of a higher percentage of the 3-phenol from this isomer. Similar bay region steric interaction also explains why only 9-HO-BP is obtained from dehydration of BP-9,10-dihydrodiol. Theoretical calculations of charge density and the index of free valence were employed some years ago by Badger[22] for a similar purpose. While these older correlations made on a much smaller number of compounds are in approximate agreement with those reported herein, the present method is considerably simpler and more convenient for general use.

Reactions of arene diolepoxides. In light of the recent evidence implicating a diolepoxide derivative (**6**) as the biologically active metabolite of the carcinogen benzo[a]pyrene,[31] it is pertinent to inquire whether reactions of diolepoxides are predictable theoretically. Reactions on the epoxide ring are expected to occur preferentially at the benzylic position, since reactions of aryloxiranes, such as styrene oxide, are well established to take place at this site in the absence of steric and other effects.[32] Ring-opening in this direction is favored by stabilization of the carbonium ion intermediate by conjugation with the aromatic system (**7**). Reaction of **6** with t-butylthiolate was shown by Beland and Harvey[33]

Table 3. Enzymatic hydration of arene oxides and aryloxiranes

Arene Oxide[a]	N_t for reaction at (position)	Dihydrodiol[a]	Reference
	1.81 (2) 2.12 (1)		18
	1.55 (8) 2.12 (7)		19
	1.73 (10) 1.81 (9)		19
	1.55 (4) 1.55 (5)		19
	1.51 (α)[b] 2.00 (β)		20
	1.46 (α)[b] 2.00 (β)		21
	1.44 (α)[b] 2.00 (β)		21

[a]Asterisk indicates ^{18}O isotopic label employed in the arene oxide or water.
[b]Dewar reactivity numbers were derived as described in the text for calculation of N_t for structures 9 and 10.

Table 4. Dehydration of arene dihydrodiols and their diesters

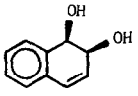
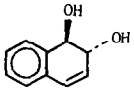
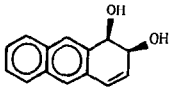
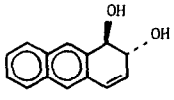
Arene Dihydrodiol (or diester)	N_t (position)	Phenol Isomers (%)	Reference
	1.81 (1) 2.12 (2)	1-HO (>95) 2-HO (<5)	25
	1.81 (1) 2.12 (2)	1-HO (>95) 2-HO (<5)	25
	1.57 (1) 1.89 (2)	1-HO (90) 2-HO (10)	26
	1.57 (1) 1.89 (2)	1-HO (86) 1-HO (14)	26

Table 4. *(Contd.)*

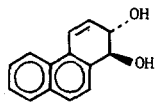
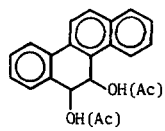
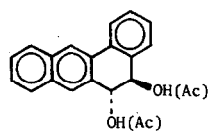
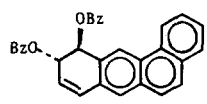
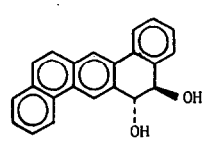
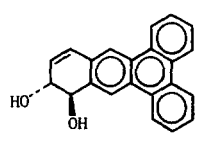
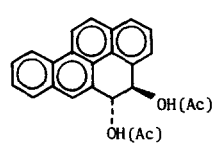
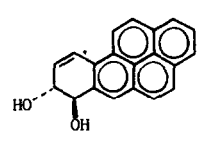
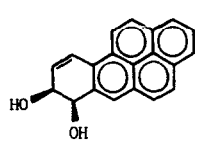
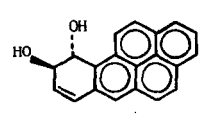
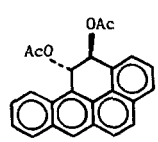
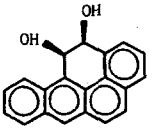
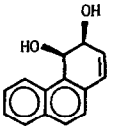
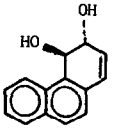
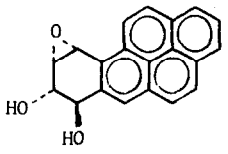
Arene Dihydrodiol (or diester)	N_t (position)	Phenol Isomers (%)	Reference
	1.86 (1) 2.18 (2)	1-HO (66) 2-HO (34)	26
	1.67 (6) 1.90 (5)	6-HO (100) 5-HO (0)	27, 28
	1.66 (5) 1.66 (6)	5-HO (75) 6-HO (25)	28
	1.66 (11) 1.92 (10)	11-HO (65) 10-HO (35)	29
	1.66 (5) 1.71 (6)	5-HO (major) 6-HO (minor)	29, 30
	1.70 (10) 2.00 (11)	10-HO (major) 11-HO (minor)	16
	1.55 (4) 1.55 (5)	4-HO (40) 5-HO (60)	19[a], 27, 29
	1.55 (7) 2.12 (8)	7-HO (97) 8-HO (3)	19
	1.55 (7) 2.12 (8)	7-HO (~100) 8-HO (~0)	29
	1.73 (9) 1.81 (10)	9-HO (99) 10-HO (1)	19
	1.50 (12) 1.81 (11)	12-HO (~100) 11-HO (~0)	29

Table 4. (*Contd.*)

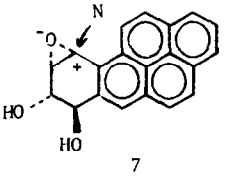
Arene Dihydrodiol (or diester)	N_t (position)	Phenol Isomers (%)	Reference
	1.50 (12) 1.81 (11)	12-HO (~100) 11-HO (~0)	26
	2.04 (3) 1.96 (4)	3-HO (>98) 4-HO (<2)	26
	2.04 (3) 1.96 (4)	3-HO (59) 4-HO (41)	26

[a]Yang *et al.*[19] report detection of only the 5-phenol on dehydration of the diol.

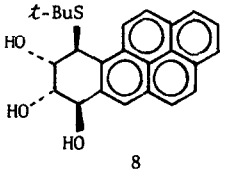
to afford the product of exclusive reaction at the 10-position (**8**). Subsequently, reactions of **6** on the 2-NH_2 group of guanosine in nucleic acids and reactions of **6** with other nucleophiles have also been shown to occur at the same position.[31–34] It is reasonable to predict that analogous reactions of other diolepoxides should also take place preferentially in the benzylic position.



6

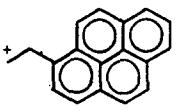


7

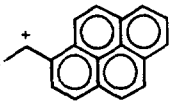


8

Prediction based on Dewar reactivity numbers supports this expectation. Calculations were performed on the two carbocations, *e.g.* **9** and **10**, which represent the essential structural components of the two ring-opened forms of the diolepoxide derivatives. The N_t for **9** (which represents attack at C-9) is the product of interaction between an isolated methine at C-9, which by definition has an NBMO a_0 of 1, and pyrene, which being an even alternate hydrocarbon does not have NBMO's. This gives an N_t for this and all like species of 2. The N_t for epoxide ring opening via nucleophilic attack at C-10



9



10

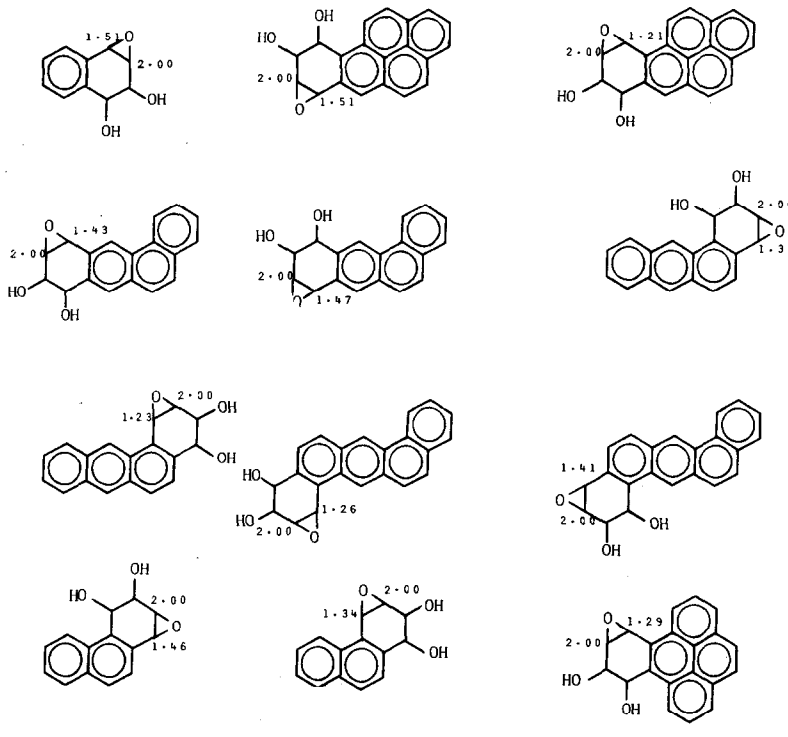
is based simply on the NBMO a_0 at this position of the pyrenyl carbocation of **10**. The calculated values of N_t for a series of diolepoxides (Table 5) predict, in accord with expectation, that nucleophilic attack will occur preferentially on the benzylic carbon atom of the epoxide ring. Of course, steric and other factors may conceivably dictate attack on the alternative ring position in special cases.

It is tempting to inquire whether N_t which provides an index of diolepoxide reactivity may also furnish some insight into the relationship between reactivity and carcinogenic activity. Recently, Jerina *et al.*[35] estimated the relative reactivity of the diolepoxide derivatives of various polycyclic hydrocarbons through calculations of the difference in delocalization energy (ΔE_{deloc}) between the epoxide structure and its ring-opened ionized form. They predicted from comparison of the calculated values of (ΔE_{deloc})† that arene diolepoxides having the oxide ring in a bay region should exhibit exceptional reactivity and proposed that this structural feature is characteristic of the active metabolites of carcinogenic hydrocarbons.‡

†ΔE_{deloc} is related to N_t calculated as described herein by the relationship $N_t = (2\text{-}\Delta E_{deloc})\beta$, since $\Delta E_{deloc} = 2(1 - a_0)\beta$ and $Nt = 2a_0\beta$.

‡A referee has correctly pointed out that there are actually two factors to be considered, formation of a zwitterion and its subsequent reaction. If formation of the zwitterion is favorable as measured by ΔE_{deloc}, it might be anticipated to be less, rather than more, reactive as assumed in the Jerina theory. Therefore, it may be the stability of the carbocation which ensures its survival sufficiently long to react with DNA which is the unique feature of the carcinogenic intermediates.

Table 5. Dewar reactivity numbers (N_t)[a] of arene diolepoxides



[a]The calculated values of N_t in benzylic positions are twice the coefficient of the NBMO a_o, i.e. $N_t = 2(a_o + o)\beta$.

The relationship was not clearcut, however, and a number of exceptions were noted. Comparison of the calculated values of N_t in Table 5, while confirming a tendency towards smaller values in bay regions, reveals a relatively narrow overall range in magnitude between the predicted least reactive ($N_t = 1.51$) and most reactive ($N_t = 1.21$) diolepoxides. Comparison of the calculated values of N_t with the biological activity of the parent hydrocarbons reveals no simple relationship. Thus, the values for the derivatives of the potent carcinogens benzo[a]pyrene ($N_t = 1.21$) and dibenz[a,h]anthracene ($N_t = 1.26$) are close to those for the inactive or borderline hydrocarbons benzo[e]pyrene ($N_t = 1.29$) and benz[a]anthracene ($N_t = 1.23$). Unfortunately, experimental data on the biological activity of the diolepoxides themselves is still largely unavailable. Preliminary results on the mutagenic activity of the diol epoxides of benz[a] anthracene indicate that the 3,4-diol-1,2-epoxide is the most mutagenic,[36] in agreement with theoretical prediction. On the other hand, the *anti*-isomer of the 8,9-diol-10,11-epoxide of benz[a]anthracene has been shown to interact moderately effectively with viral DNA,[5] contrary to what might be expected if the capability of reaction with DNA is the distinguishing feature of active carcinogen metabolites. Indeed, the assumption that reactivity is the principal factor determining the extent of the reaction with DNA is open to question. A highly reactive metabolite is also likely to be rapidly destroyed through indiscriminate reactions with water, protein and other cellular nucleophiles. Therefore, there may be an optimum range of reactivity. Clearly, current knowledge is inadequate to reach any meaningful conclusion in this regard which must await the results of more complete biological studies with a wider range of synthetic diolepoxide derivatives.

DISCUSSION

The foregoing results indicate that the direction of isomerization of arene oxides, the site of hydration of nucleophilic addition to arene oxides, and the products of dehydration of arene dihydrodiols, both K-region and non-K-region, are all predictable by the simple perturbational MO method of Dewar.[9] A rather good correlation between product structure and the calculated values of the corresponding Dewar reactivity numbers, N_t, is evident in all cases. Since N_t is readily calculable for any even alternate hydrocarbon by simple arithmetic methods, N_t provides a convenient predictive tool for reactions of this type. The method appears to provide a sufficiently good account of these reactions that apparent discrepancies between experiment and theory can be used to elucidate steric and other effects not considered in the theory. A case in point is the preferential dehydration of the 3,4-dihydrodiol of phenanthrene principally to the 3-phenol isomer. Another type of example involves reaction of arene oxides with glutathione. Several such reactions have been reported to occur regioselectively to afford the same isomeric addition products when conducted in the presence or in the absence of glutathione-S-transferase.[1] The isomer structures assigned do not correspond in several cases to those predicted theoretically or to those found from

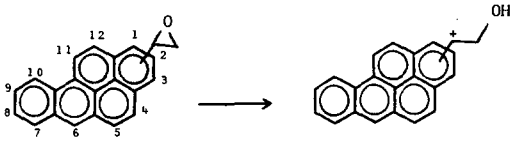
analogous reactions with another sulfur nucleophile t-butylmercaptan.[8] Since the structures of the glutathione adducts have been generally assumed without rigorous chemical proof, these earlier structural assignments must now be considered questionable.

An understanding of the basic laws which govern the purely chemical aspects of carcinogen metabolism is the first step towards understanding the more complex enzymatic processes involved in hydrocarbon activation and detoxification. Extension of the theoretical concepts developed herein to interpretation of the factors governing related enzyme catalyzed processes is hampered by the relative deficiency of relevant experimental data. The regiospecificity of enzymatic hydration of arene oxides accords with MO theoretical prediction (Table 3) in only two of four examples. The steric factor appears to dominate in the other cases. Hydration of the related aryloxiranes catalyzed by epoxide hydratase occurs contrary to theoretical prediction (Table 3); it appears that the steric requirements of substituent groups may contribute importantly to determining the orientation of the substrate within the enzyme cavity, thereby influencing the site of hydration. Steric effects are probably responsible for the inactivity of epoxide hydratase in the hydration of benzo[a]pyrene diolepoxide, **6**, and other sterically crowded epoxides.[17,39] Further experiments with a wider range of epoxide substrates will be required to provide greater insight into the relative contributions of the steric and electronic factors.

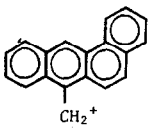
One of the principal values of any new hypothesis lies in its ability to suggest new experiments and predict results which otherwise might not have been anticipated. Consider, for example, extension of the perturbational MO theory of Dewar to the epoxide derivatives of polycyclic hydrocarbons, i.e. aryloxiranes, such as 1-oxiranylpyrene (**11**) and 6- and 1-oxiranylbenzo[a]pyrene (**12**, **13**). The calculated value of N_t for **11** ($N_t = 1.21$) is identical with that for **6**, since it is calculated on the same structure, **10**. Similar calculations on all possible oxiranyl derivatives of benzo[a]pyrene (Table 6) reveal the minimum value to reside at the 6-position ($N_t = 1.00$) followed by that at the 1-position ($N_t = 1.13$). On this basis it may be predicted that **12** should be more reactive than **13** or even the related bay region diolepoxide structure **14**. In general, minimum values of N_t calculated in this manner appear to fall in the meso regions of many

Table 6. Calculated values of N_t for arylmethyl carbocations†

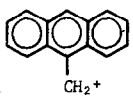
Benzo[a]pyrene



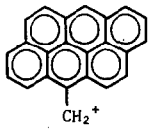
Position	N_t	Position	N_t
1	1.13	7	1.22
2	1.50	8	1.46
3	1.15	9	1.31
4	1.22	10	1.34
5	1.22	11	1.34
6	1.00	12	1.20



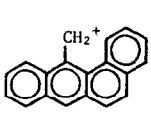
$N_t = 1.12$



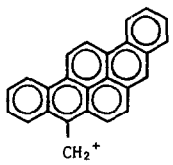
$N_t = 1.07$



$N_t = 0.91$

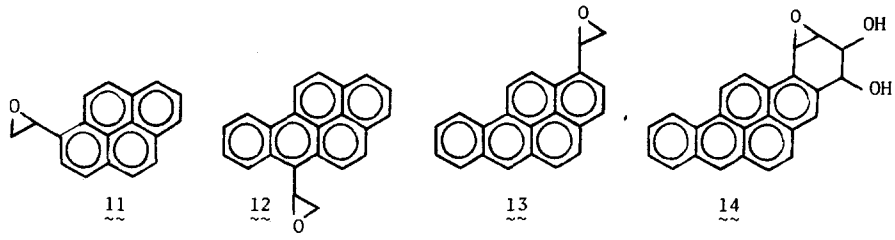


$N_t = 1.17$



$N_t = 0.97$

†Values of N_t are calculated as in Table 5.



11 12 13 14

hydrocarbons. Examples of predicted highly reactive meso substituted carbonium ions are presented in Table 6. On this basis it would be predicted that the corresponding aryloxiranes (or other derivatives capable of formation of a carbonium ion in this region) should be highly reactive. While it does not follow that reactivity will correlate with biological activity, since this depends on survival of the compound long enough to reach the critical target and other factors, these findings suggest that compounds such as **12** or potential procarcinogens such as 6-vinylbenzo[a] pyrene (**15**) deserve serious attention as potential carcinogens and mutagens.[37]

In summary, the simplified perturbational MO theory of Dewar provides a good correlation between predicted and observed structures of products formed during: (1) isomerization of arene oxides to phenols; (2) hydration and nucleophilic addition to arene oxides; and (3) dehydration of arene dihydrodiols. The method is equally applicable to the arene oxides, and dihydrodiols derived from carcinogenic and non carcinogenic polycyclic aromatic hydrocarbons. Extension to the related enzymatic reactions occurring during metabolism of carcinogenic hydrocarbons and to the reactions of the biologically active arene diolepoxides and aryloxiranes suggests the potential utility of this approach in predicting (a) metabolite structure and (b) the structural requirements for carcinogenic and mutagenic activity.

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