Theoretical Reaction Indices for Dibenz[a,h]acridine

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Dedicated to Professor Norman H. Cromwell upon his retirement

Huckel molecular orbital calculations and application of Seybold-Smith reactivity theory suggest that the Bay-Region diol epoxide derived from the 8,9,10,11-benzo ring of dibenz[a,h]acridine (**1**) is the same in reactivity as that of the 1,2,3,4-ring in agreement with experimental findings. The calculations dispute an earlier claim of regioselective reactivity at the 8,9,10,11-benzo ring.

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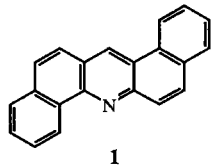
During the past decade, the sum of experimental investigations have indicated that "Bay-Region" diol epoxides are the major ultimate carcinogenic metabolites of a large number of polycyclic aromatic hydrocarbons [1,2,3]. Indeed, in recent years, the focus of polycyclic aromatic hydrocarbons has transferred from the parent hydrocarbon to closer examination of various metabolites associated with the parent PAH [4]. These experimental findings are consistent with perturbational molecular orbital predictions of the much greater reactivity of the Bay-Region epoxides relative to epoxides at other positions on the tetrahydrobenzo rings of PAH, which was responsible for the introduction of the Bay-Region theory of carcinogenesis [5].

Jerina and Lehr [6] have calculated the ease of carbonium ion formation from various dihydrodiol epoxides in which an estimate of the increase in delocalization energy on going from an epoxide to a cation, $\Delta E_{delocal}$, can be approximated to $2(1\text{-}a_o r)\ \beta$ where β is the resonance integral. Seybold and Smith have examined several indices describing polycyclic hydrocarbons in relation to their carcinogenicity and have concluded that an index, Q_B, describing the net π electron charge at the benzylic carbon of an ionized Bay-Region dihydrodiol epoxide represents the best correlation with Jerina's $\Delta E_{delocal}/\beta$ index [7,8].

Very little is currently known about the properties of analogous epoxides derived from aza-PAH [9] although numerous aza-PAH are carcinogens [10] and aza-PAH are known to be environmental contaminants produced *via* combustion [11]. Kumar [12] has suggested that Bay-Region theory may be extended to certain aza-PAH of the acridine series. Benz[c]acridine and selected methylated benz[c]acridines have been shown to be metabolized to those dihydrodiols which are the direct precursors of the respective Bay-Region diol epoxides [13,14].

In contrast to the weak carcinogenicity of benz[c]acridine and benz[a]acridine, dibenz[a,h]acridine (**1**) has been reported as a weak carcinogen by Dipple [11] but was considered more potent than benzo[a]pyrene (**2**) in inducing pulmonary adenomas [15]. We wish to report herein Huckel molecular orbital calculations and application of Seybold-Smith reactivity theory on the title system **1** in order to ascertain whether the position of nitrogen substitution can exert a marked influence on the reactivity of regioisomeric epoxides.



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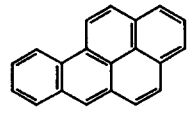

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From the evidence obtained from the PAH, the analogous sequence of activating reactions which **1** may undergo is outlined in Figure 1. For convenience of description, the bond site of initial epoxidation, for the two benzo rings, is termed the "A" region, and the bond site for the second epoxidation in the sequence is termed the "B" region [16]. The "K" and "L" regions are as originally described by the Pullmans [17]. Calculations were performed on the various intermediates shown in Figure 1 using Huckel molecular orbital theory with parameters previously reported [18]. Several indices were selected from Seybold-Smith theory [19] as representative for the reactions: I_A, I_K, I_L. These represent the sums of the two atomic superdelocalizabilities [20] for the A, K, and L regions, respectively, for parent compound **1**. The parameters have previously been shown to represent the tendency toward epoxidation at the indicated bond in the parent compound [21].

I_B'.

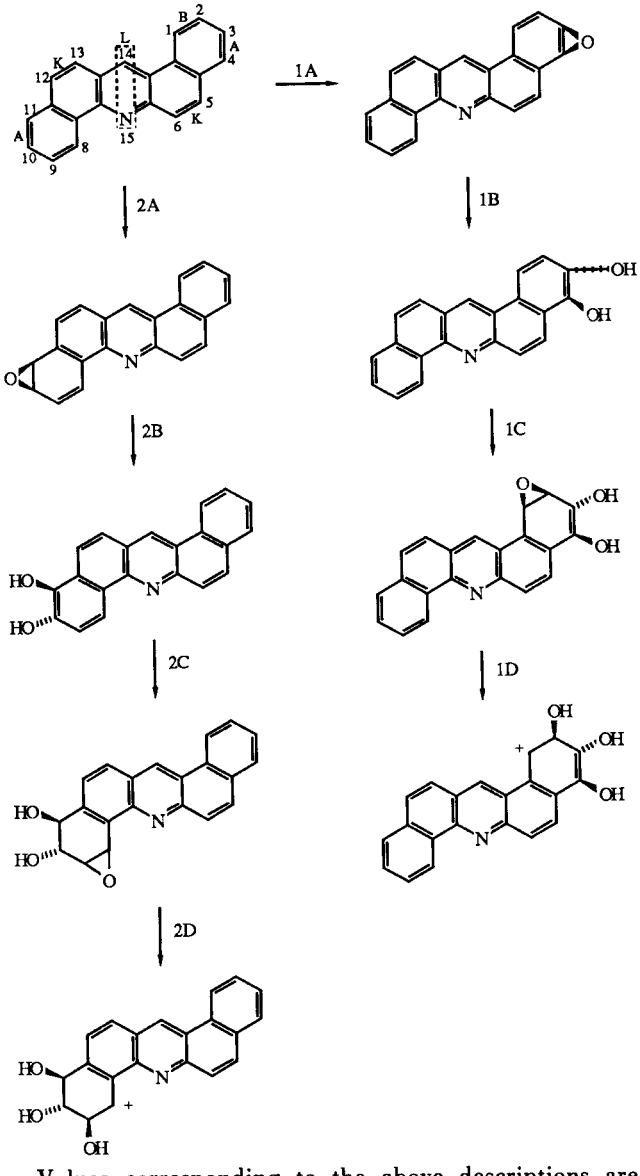
This is the sum of atomic superdelocalizabilities for the B region bond in the A region dihydrodiol. Its value provides quantitative measure of the tendency for reaction C of Figure 1 to occur.

Q_B.

This is the net π electron charge at the benzylic carbon

atom of the carbonium ion. Lower values of Q_B correspond to a more stable carbonium ion [19].

Figure 1



Values corresponding to the above descriptions are listed in the following table.

Table

Index	Value	Index	Value
I_K (5,6)	1.9129	Q_B (1)	0.4550
I_L (14,15)	1.9183	$I_{B'}$ (1,2)	2.2113
I_K (12,13)	2.0063	$I_{B'}$ (8,9)	2.3101
I_A (3,4)	1.8124	S_B (8)	0.5030
I_A (10,11)	1.8140	S_B (1)	0.5160
Q_B (8)	0.4480		

The K and L region values agree with those given previously by Mainster and Memory [16] who suggest that a compound is expected to be a mild carcinogen if $I_K \leq 2.05$ and $I_L \leq 2.30$. For the dibenz[*a*,*h*]acridine system the I_A values, for both angular rings, are less than the corresponding I_K values. We interpret this to mean that the reactions 1A, 2A of Figure 1 represent a minor chemical pathway compared to reactions at the two K regions, consistent with experimental evidence. Differences in I_A indices for the two Bay-Regions of **1** can, however, be taken as evidence of the greater tendency toward initial epoxidation of the 10,11-Bay-Region. The values for I_B', epoxidation of the A region dihydrodiol forms, further substantiates the tendency of the 8,9,10,11-benzo ring system to undergo oxidation. It has previously been demonstrated that a strong correlation exists between this index for the B region and carcinogenicity of the parent compound [19]. The values of I_B', 2.3101 and 2.2113, are about the same in value as the mild carcinogens dibenz[*a*,*h*]anthracene and benzo[*c*]chrysene. In the case of both Bay-Regions, formation of the A region dihydrodiol significantly activates the B region bond, toward subsequent oxidation, as shown by the higher values of I'_B. The I_A and I'_B values for the 3,4- and 10,11-bonds are similar in magnitude which indicates low probability of selective epoxidation at either of the two Bay-Region A and B bonds. This is in agreement with the experimental findings of Kumar [24] who found that **1** is metabolized on both angular benzo rings to form dibenz[*a*,*h*]acridine 3,4- and 10,11-dihydrodiols during rat liver microsomal incubation.

According to current Bay-Region theory, the trihydrotriol carbonium ions act as the ultimate metabolic species that presumably attack critical cellular nucleophiles such as DNA. [22,23] The next index in the table is the net π electron charge ($Q_B = 1\text{-}q\beta$, where $q\beta$ is the π electron density at the benzylic carbon of the trihydrotriol carbonium ion). The Q_B values for atoms 1 and 8 indicate stability of generated carbonium ions and the values are similar in magnitude which indicates no noticeable influence of the nitrogen atom toward stabilization of the 8,9,10,11-Bay-Region.

The last entry in the table is S_B which is the atomic superdelocalizability at the indicated benzylic carbon atom of the benzylic carbonium ion. This parameter has previously been shown to correlate strongly with carbonium ion stability/carcinogenicity for related systems [8]. Again, the similarity of values for atoms 1 and 8 leads us to disagree with the observation of Kumar [6] that the 8,9,10,11-benzo ring of **1** will be more reactive than that derived from the 1,2,3,4-benzo ring size. Huckel molecular orbital studies of methylated dibenzacridine environmental contaminants are in progress and will be reported at a later time.

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