Substituent Effects in Chemical Carcinogenesis: Methyl Derivatives of the Benzacridines

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An explanation for the different carcinogenic potencies observed among methyl derivatives of the angular benzacridines is given in terms of the tendencies of these compounds to undergo specific metabolic activating reactions analogous to those of polycyclic aromatic hydrocarbons. Theoretical reactivity indices representing these reactions correlate with the carcinogenic activities of these compounds.

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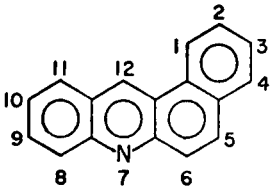
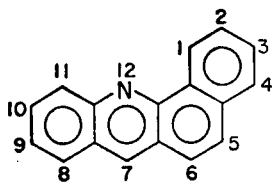
It has been known for many years that some methyl derivatives of the angular benzacridines are highly carcinogenic, whereas others are inactive (3-7). Furthermore, the methyl derivatives of benz[*c*]acridine tend to have higher carcinogenic activities than the methyl derivatives of benz[*a*]acridine (3). No convincing reason for these differing activities has yet been presented.



benz[a]acridine

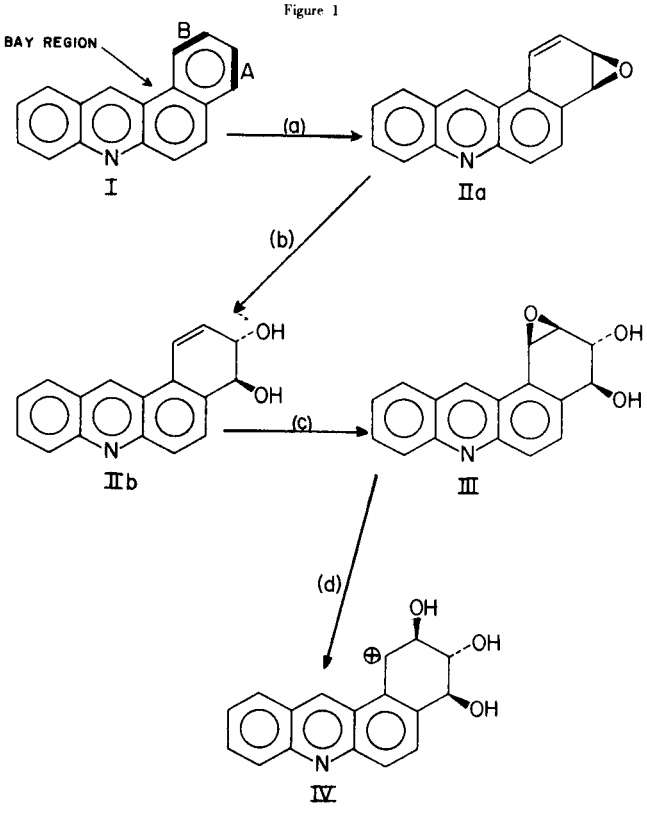


benz[c]acridine

Many chemical carcinogens are now known to be activated and transformed *in vivo* into highly active metabolites (8,9). Although the relevant metabolism for benzacridines has not received a great deal of recent attention, that of the homologous hydrocarbon benz[*a*]anthracene, as well as other polycyclic aromatic hydrocarbons, has been the subject of intensive scrutiny. From such experimental investigations, carcinogenic activity has been linked to the tendency of these latter compounds to undergo specific sequences of metabolic transformations. In particular, oxidation reactions on angular benzo rings, leading ultimately to so-called "bay region" (10) dihydrodiol epoxide and carbonium ion forms, appear to be central to carcinogenic activation in polycyclic aromatic hydrocarbons. The carbonium ions are presumably those forms which ultimately attack critical cellular components, possibly nucleic acids. Evidence for the importance of this reaction scheme has been summarized elsewhere (9,11,12). Interesting theoretical studies relevant to this problem have also been given (11,13,14).

We have previously presented an extensive theoretical examination of the putative activation steps for polycyclic aromatic hydrocrbons using reactivity indices taken from molecular orbital (MO) theory (12,15). In this, it was discovered that correlations exist between certain reactivity indices and the observed carcinogenic activities of the compounds, and it was inferred from the correlations that (a) the corresponding reactions maybe important to the carcinogenic process and (b) the reactions appear to be reasonably described in terms of the MO indices. This examination has been extended to the methyl derivatives of benz[*a*]anthracene (16) and chrysene (17), both cases in which well-established differences in carcinogenic potency result from substitution at different positions, and again correlations were observed. Methyl derivatives present attractive systems for examination since the physical properties of the derivatives (*e.g.* solubilities, diffusion coefficients, etc.) can be expected to be quite similar, and atten-

Figure 1



Possible metabolic transformations of benz[*a*]acridine discussed in the text, and locations of the molecular A, B, and bay regions. For convenience, only a single stereoisomeric form is illustrated.

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tion can be focused upon electronic (reactivity) differences without the potential intrusion of extraneous factors. Here we extend this analysis to the methyl derivatives of the angular benzacridines, assuming that the reactions of these compounds are analogous to those of benz[*a*]anthracene and other polycyclic aromatic hydrocarbons.

Methods of Calculation.

From the evidence for the polycyclic hydrocarbons, the analogous sequence of activating reactions which benz[*a*]acridine may undergo is illustrated in Figure 1. A corresponding sequence of reactions may be expected for benz[*c*]acridine. For convenience of description, the bond site of initial epoxidation on the benzo ring is termed the "A region," and the bond at which the second epoxidation takes place is termed the "B region" (12). The "K region" is as originally designated by the Pullmans (18).

Calculations were performed on the various intermediates in the reaction scheme of Figure 1 using Hückel molecular orbital theory, with parameters taken from Streitwieser (19). Within this π-electron framework, the A-region epoxide (IIa) and the A-region dihydrodiol (IIb) are equivalent. The methyl group was represented as a heteroatom ($h_x = 2.0$, $k_{cx} = 0.7$) with an auxiliary inductive parameter $\delta = -0.1$. From our previous work several indices were selected as representative for the reactions:

I_A, I_K: These represent the sums of the two atomic superdelocalizabilities (20) for the A and K region bonds, respectively, of the original compound. This type of index was first suggested by Mainster and Memory (21,22), and should represent tendency toward epoxidation at the indicated bond in the parent compound.

I_B': This is the sum of atomic superdelocalizabilities for the B region bond in the A-region dihydrodiol; its value provides a measure of the tendency for reaction c of Figure 1 to occur (15)

Q_b, S_b: These are, respectively, the net π-electron charge and atomic superdelocalizability at the benzylic carbon atom of the carbonium ion. Lower values of Q_b and higher values of S_b correspond to more stable carbonium ions (12).

Results and Discussion.

Available carcinogenicity data for the angular benzacridines and their methyl derivatives are summarized in Table 1. It is evident that although unsubstituted benz[*a*]acridine and benz[*c*]acridine are both noncarcinogens, methyl substitution at specific positions, especially in benz[*c*]acridine, can lead to highly active compounds.

Calculated results for the indices I_K and I_A are listed in Table 2, which includes calculated results for a number of untested compounds. These indices can be taken as measures of the tendencies for epoxidation to occur at the K and A regions, respectively, of the parent compounds. Examination of the results shows that both indices afford some degree of separation according to carcinogenic activity. All the known strong carcinogens show values $I_K > 2.10$ and all weak and noncarcinogens, values below 2.10. The weak and inactive compounds are not distinguished by I_K, although this may not be of major concern considering the crudity of the experimental data. (The unusually high I_K values for the 5- and 6- substituted benz[*c*]acridines are artifacts resulting from attachment of the methyl group directly to the K region. As in our previous studies (16,17), we assume that attachment of a methyl group inhibits reaction at the substituted position.) The index I_A does separate the known carcinogens ($I_A \geq 1.841$) from the noncarcinogens ($I_A \leq 1.840$), but does not distinguish between strong and weak carcinogens. This is consistent with earlier studies (12) which also showed little correlation with carcinogenicity for this index. The index I_K, as sometimes observed previously (13), gives a better correlation to carcinogenic activity than expected within the present theoretical framework, possibly because of some unrecognized relation to bay region properties (12,23).

Table 1.

Experimental Carcinogenicities of Benz[*a*]acridine, Benz[*a*]acridine and Some Methyl and Dimethyl Derivatives

Compound	Cardinogenicity Index	Reference
Benz[*a*]acridine	0	5
9-Methylbenz[*a*]acridine	0	5
10-Methylbenz[*a*]acridine	0	4
12-Methylbenz[*a*]acridine	0	4
8,12-Dimethylbenz[*a*]acridine	+	5
9,12-Dimethylbenz[*a*]acridine	+	5
10,12-Dimethylbenz[*a*]acridine	+	6
Benz[*c*]acridine	0	5
7-Methylbenz[*c*]acridine	+++	5
8-Methylbenz[*c*]acridine	0	5
9-Methylbenz[*c*]acridine	0	5
10-Methylbenz[*c*]acridine	0	5
5,6-Dimethylbenz[*c*]acridine	+++	7
7,9-Dimethylbenz[*c*]acridine	+++	5
7,10-Dimethylbenz[*c*]acridine	+++	5
7,11-Dimethylbenz[*c*]acridine	++	5

Table 3 shows results for the reactivity index I_B', a measure of the tendency of the A-region dihydrodiols to undergo epoxidation at their B regions. The correlation is fairly good, and about the same as that found for the parent-compound index I_K. The high values for the 1- and 2- substituted compounds are artifacts resulting from attachment of the methyl group directly at the 1- and 2- positions. Methyl substitution very likely blocks reaction at

Table 2.

Correlation Between Carcinogenicity and the Indices I_K and I_A for the Angular Benzacridines and Selected Derivatives

Compound	I_K	I_A	Cardinogenicity Index
5,6-Dimethylbenz[c]acridine	3.019*	1.960	++ +
5-Methylbenz[c]acridine	2.376*	1.822	
6-Methylbenz[c]acridine	2.354*	1.903	
6-Methylbenz[a]acridine	2.210*	1.890	
7,10-Dimethylbenz[c]acridine	2.135	1.849	+++
5-Methylbenz[a]acridine	2.133*	1.807	
7,11-Dimethylbenz[c]acridine	2.129	1.847	++
7,9-Dimethylbenz[c]acridine	2.127	1.848	+++
4-Methylbenz[c]acridine	2.113	1.967*	
7-Methylbenz[c]acridine	2.112	1.841	+++
2-Methylbenz[c]acridine	2.112	1.906	
10-Methylbenz[c]acridine	2.051	1.819	0
8-Methylbenz[c]acridine	2.050	1.818	0
1-Methylbenz[c]acridine	2.042	1.979	
3-Methylbenz[c]acridine	2.040	1.957*	
9-Methylbenz[c]acridine	2.032	1.817	0
11-Methylbenz[c]acridine	2.032	1.816	
Benz[c]acridine	2.025	1.810	0
2-Methylbenz[a]acridine	1.968	1.901	
4-Methylbenz[a]acridine	1.961	1.953*	
10,12-Dimethylbenz[a]acridine	1.930	1.846	+
8,12-Dimethylbenz[a]acridine	1.928	1.846	+
10-Methylbenz[a]acridine	1.926	1.815	0
8-Methylbenz[a]acridine	1.922	1.814	
3-Methylbenz[a]acridine	1.913	1.970*	
9,12-Dimethylbenz[a]acridine	1.909	1.847	+
1-Methylbenz[a]acridine	1.908	1.982	
9-Methylbenz[a]acridine	1.903	1.817	0
12-Methylbenz[a]acridine	1.903	1.840	0
11-Methylbenz[a]acridine	1.898	1.816	
Benz[a]acridine	1.898	1.808	0

*High values for these compounds result from direct attachment of methyl groups at the K or A region (see text).

Table 3.

Correlation Between the Index I'_B and Carcinogenicity for Angular Benzacridines and Selected Derivatives

Compound	I'_B	Cardinogenicity Index
2-Methylbenz[c]acridine	2.852*	
1-Methylbenz[c]acridine	2.833*	
1-Methylbenz[a]acridine	2.689*	
2-Methylbenz[a]acridine	2.617*	
5,6-Methylbenz[c]acridine	2.610	+++
6-Methylbenz[c]acridine	2.552	
6-Methylbenz[a]acridine	2.440	
7,10-Dimethylbenz[c]acridine	2.386	+++
7,11-Dimethylbenz[c]acridine	2.384	++
7,9-Dimethylbenz[a]acridine	2.382	+++
7-Methylbenz[c]acridine	2.373	+++
8-Methylbenz[c]acridine	2.334	0
10-Methylbenz[c]acridine	2.333	0
11-Methylbenz[c]acridine	2.320	
9-Methylbenz[c]acridine	2.319	0
3-Methylbenz[c]acridine	2.318	
4-Methylbenz[c]acridine	2.318	
5-Methylbenz[c]acridine	2.318	
Benz[c]acridine	2.318	0
10-Methylbenz[a]acridine	2.220	0
8-Methylbenz[a]acridine	2.217	
3-Methylbenz[a]acridine	2.200	
4-Methylbenz[a]acridine	2.200	
Benz[a]acridine	2.200	0
10,12-Dimethylbenz[a]acridine	2.198	+
9-Methylbenz[a]acridine	2.197	0
8,12-Dimethylbenz[a]acridine	2.195	+
11-Methylbenz[a]acridine	2.193	
5-Methylbenz[a]acridine	2.191	
9,12-Dimethylbenz[a]acridine	2.180	+
12-Methylbenz[a]acridine	2.180	0

*High values for these compounds result from direct attachment of the methyl group at the B region.

these positions, and we therefore expect these derivatives to be inactive.

Results for the carbonium ion indices Q_b and S_b are shown in Tables 4 and 5. The correlation of these indices with carcinogenic potency appears to be rather good, in agreement with results obtained for previous systems (12,16,17). Only the weak carcinogen 9,12-dimethylbenz[a]acridine is notably out of place. (We point out that this compound and the 8,12- and 10,12-derivatives of benz[a]acridine carry methyl substitution in their "L regions," classically considered to be sites of deactivating reactions (18). These compounds, as shown in Tables 2-5, also are generally more active than expected, possibly because their L regions are blocked by the methyl substitution.) The correlations of Tables 4 and 5 may indicate that "bay region" carbonium ion stability is an important factor influencing carcinogenicity in these compounds, as well as in the polycyclic aromatic hydrocarbons.

In summary, we conclude that the reactivity indices used previously in studies of the polycyclic aromatic hydrocarbons also correlate with carcinogenic potency for the methylbenzacridines. The results provide a reasonable rationale in terms of tendency to undergo specific metabolic transformations for the generally greater activity of benz[c]acridines relative to benz[a]acridines, and also for the differing activities observed among the methyl derivatives of these compounds. The results appear to imply that benzacridines are activiated to carcinogenic end products in a fashion similar to benz[a]anthracene and other aromatic hydrocarbons, and that epoxidation of the A-region dihydrodiols and the stability of the final carbonium ion may be important determinants of carcinogenicity. Predictions are presented regarding the potential carcinogenic activities of some still-untested methyl benzacridines.

Table 4.

Correlation Between Carcinogenicity and the Net Charge Density Q_b for the Benzylic Carbon of Selected Benzacridines

Compound	Q_b	Cardinogenicity Index
5,6-Dimethylbenz[*c*]acridine	0.3375	+++
6-Methylbenz[*a*]acridine	0.3642	
6-Methylbenz[*c*]acridine	0.3727	
7,11-Dimethylbenz[*c*]acridine	0.3993	++
7,9-Dimethylbenz[*c*]acridine	0.4035	+++
7,10-Dimethylbenz[*c*]acridine	0.4080	+++
7-Methylbenz[*c*]acridine	0.4126	+++
5-Methylbenz[*c*]acridine	0.4232	
8-Methylbenz[*c*]acridine	0.4268	0
11-Methylbenz[*c*]acridine	0.4278	
10,12-Dimethylbenz[*a*]acridine	0.4289	+
8,12-Dimethylbenz[*a*]acridine	0.4295	+
10-Methylbenz[*c*]acridine	0.4300	0
8-Methylbenz[*a*]acridine	0.4300	
10-Methylbenz[*a*]acridine	0.4307	0
9-Methylbenz[*c*]acridine	0.4320	0
2-Methylbenz[*c*]acridine	0.4365	
3-Methylbenz[*c*]acridine	0.4365	
4-Methylbenz[*c*]acridine	0.4365	
Benz[*c*]acridine	0.4365	0
5-Methylbenz[*a*]acridine	0.4416	
2-Methylbenz[*a*]acridine	0.4450	
3-Methylbenz[*a*]acridine	0.4450	
4-Methylbenz[*a*]acridine	0.4450	
Benz[*a*]acridine	0.4450	0
11-Methylbenz[*a*]acridine	0.4460	
9-Methylbenz[*a*]acridine	0.4472	0
12-Methylbenz[*a*]acridine	0.4472	0
9,12-Dimethylbenz[*a*]acridine	0.4498	+
1-Methylbenz[*c*]acridine	0.5416*	
1-Methylbenz[*a*]acridine	0.5518*	

*High values for these compounds result from direct attachment of the methyl group to the benzylic carbon.

Table 5.

Correlation Between Carcinogenicity and the Superdelocalizability S_b for the Benzylic Carbon of Angular Benzacridines and Selected Derivatives

Compound	Q_b	Cardinogenicity Index
5,6-Dimethylbenz[*c*]acridine	0.764	+++
6-Methylbenz[*a*]acridine	0.686	
7,11-Dimethylbenz[*c*]acridine	0.671	++
6-Methylbenz[*c*]acridine	0.657	
7,9-Dimethylbenz[*c*]acridine	0.653	+++
8,12-Dimethylbenz[*a*]acridine	0.642	+
10,12-Dimethylbenz[*a*]acridine	0.636	+
7,10-Dimethylbenz[*c*]acridine	0.629	+++
7-Methylbenz[*c*]acridine	0.616	+++
5-Methylbenz[*c*]acridine	0.599	
8-Methylbenz[*a*]acridine	0.596	
11-Methylbenz[*c*]acridine	0.590	
10-Methylbenz[*a*]acridine	0.587	0
8-Methylbenz[*c*]acridine	0.584	0
12-Methylbenz[*a*]acridine	0.581	0
9,12-Dimethylbenz[*a*]acridine	0.579	+
9-Methylbenz[*c*]acridine	0.573	0
5-Methylbenz[*a*]acridine	0.571	
10-Methylbenz[*c*]acridine	0.570	0
11-Methylbenz[*a*]acridine	0.562	
2-Methylbenz[*c*]acridine	0.553	
3-Methylbenz[*c*]acridine	0.553	
4-Methylbenz[*c*]acridine	0.553	
Benz[*c*]acridine	0.553	0
9-Methylbenz[*a*]acridine	0.550	0
2-Methylbenz[*a*]acridine	0.550	
3-Methylbenz[*a*]acridine	0.550	
4-Methylbenz[*a*]acridine	0.550	
Benz[*a*]acridine	0.550	0
1-Methylbenz[*c*]acridine	0.364*	
1-Methylbenz[*a*]acridine	0.352*	

*Low values result from direct attachment of the methyl group to the benzylic carbon.

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