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Molecular Mechanics Explanation for the Stereochemical and Shape Selectivity of B-DNA for "Bay-Region" Carcinogens

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SUMMARY

The equilibrium structures of 20 intercalated physical complexes of "bay-region" triol carbocations of polycyclic aromatic hydrocarbons (PAHs) with B-DNA are obtained by AMBER molecular modeling. The complexes with highly potent carcinogens are found (i) to undergo only minor conformational changes upon complexation, (ii) to be stabilized by hydrogen bonds between two hydroxyl groups of the triol carbocations and N3 atoms of the adjacent guanine residues, and (iii) to be "preorganized" for covalent bonding. A new explanation for the absolute stereochemical and shape dependence of carcinogenesis by PAHs is presented. The biologically active conformers of both carcinogenic stereoisomers (*anti* and *syn*) of triol carbocations are characterized by a quasi-diaxial orientation of the neighboring hydroxyl groups and fulfill the spatial requirements for hydrogen bonding to the adjacent guanine residues of B-DNA. The striking dependence of potency on the shape of the PAHs is largely caused by repulsion from the C2′-methylene groups of the deoxyribose residues of DNA. This interaction may shift the intercalated triol carbocation, thereby enhancing or reducing the preorganization for covalent bonding. The molecular modeling study is augmented by benchmark *ab initio* calculations on the bay-region triol carbocation of phenanthrene.

The covalent bonding of ultimate carcinogens to DNA is considered to be the most significant irreversible step in the chemical initiation of cancer (1–4). The "bay-region" diol epoxides of PAHs have been shown to bind almost exclusively to the N2-amino group of guanine (2). Transformation of diol epoxides into triol carbocations is followed by their covalent bonding to this binding site (4). As would be expected, more potent PAHs usually form more stable triol carbocations (3, 5). However, the structure-carcinogenicity relationships of PAHs display two challenging phenomena that cannot be explained by the stability of the free triol carbocations. First, the carcinogenicity of bay-region diol epoxides is determined by their absolute configuration (4, 6–9). Second, carcinogenicity is highly dependent on the shape of the aromatic system of PAHs (3–5, 9–11).

The covalent bonding of carcinogens to DNA is preceded by their intercalation (4), and this physical complex is believed to be responsible for the absolute stereochemical and shape dependence of PAH carcinogenesis (4, 12). The aim of this work is to explain the enantiomeric stereoselectivity and shape dependence of PAH carcinogenicity in terms of the geometric compatibility of PAH triol carbocations with B-DNA in forming the reaction intermediate.

Model and Computational Procedures

The DNA is represented by the fragment dGG/dCC. No phosphate groups are placed at the ends of the strands, which have terminal O3′ and O5′ hydroxyl groups.

The geometry of the dinucleotide and its complexes with ultimate carcinogens is obtained by all-atom AMBER force-field calculations (13). The equilibrium geometry of molecular systems under study is calculated by potential energy minimization in the space of the independent bond and torsional angles, whereas the covalent bond lengths are fixed at their standard values. Following the method of Ref. 13, the potential energy function is represented by bond angle bending, torsional distortion, van der Waals and electrostatic interactions, and hydrogen bonding. Atomic point-charges of the dinucleotide are taken from Ref. 13. Because our model does not explicitly include solvent molecules, a dielectric function of $\epsilon(R) = R/1$ Å is applied (13). The geometry of nucleic bases is fixed and corresponds to the X-ray structure (14). The hydrogen atoms of hydroxyl and methyl groups are allowed to rotate around the C—O and C—C bonds, respectively, whereas the other hydrogens are attached unequivocally to the nonhydrogen backbone.

Bond lengths and atomic point-charges of PAH triol carbocations are obtained from fully optimized AM1 calculations (15). The charge of hydrogen atoms attached to sp^2 carbons is incorporated into the charge of the latter, whereas the other hydrogens are explicitly treated.

The B-DNA structure given by Arnott and Hukins (14) is taken as the initial conformation for the DNA fragment, because this structure is close to the native DNA under physiological conditions. According to electric linear dichroism measurements (16), there are several possibilities for the mutual geometric arrangement of the components of the physical complex. Hence, different initial orientations and conformations of PAH metabolites are considered, with the aim of finding the most stable structure for the intercalated complex.

The conformational energies of the half-chair conformers of the

ABBREVIATION: PAH, polycyclic aromatic hydrocarbon.

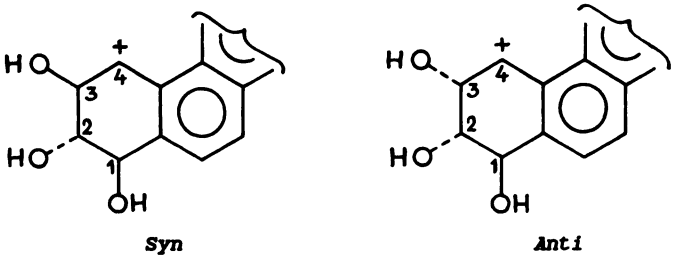

Fig. 1. Diastereoisomeric forms of PAH triol carbocations.

metabolically allowed diastereoisomers of phenanthrene triol carbocation are obtained by semiempirical and *ab initio* calculations at the fully optimized Hartree-Fock HF/6–31G and HF/6–31G* levels and are checked by single-point, full second-order Moller-Plesset MP2/6–31G* calculations for the HF/6–31G* geometry. All calculations are performed by the Gaussian 90 program (17) on the CONVEX C3440 minisupercomputer of the University of the West Indies. The full geometry optimization of each conformer of phenanthrene triol carbocation at the direct HF/6–31G* level requires approximately 3 weeks of CPU time, and each single-point correlated calculation by the direct MP2/6–31G* method takes 24 hr of CPU time. These are indeed benchmark calculations on a highly asymmetric molecule of biological interest. A detailed comparative discussion of high-level, *ab initio* calculations on the triol carbocations of benzene, naphthalene, methylnaphthalene, and methylphenanthrene will be presented in a later publication.

Results and Discussion

There are two metabolically possible diastereoisomeric forms of PAH triol carbocations, *syn* and *anti* (Fig. 1), each with two conformers differing by the geometry of the half-saturated ring. The energy difference between the two conformers is expected to be rather small (18); hence, correlated *ab initio* calculations should be performed to obtain reliable results. However, it is still prohibitive to fully optimize the geometry of triol carbocations of carcinogenic PAHs at a high

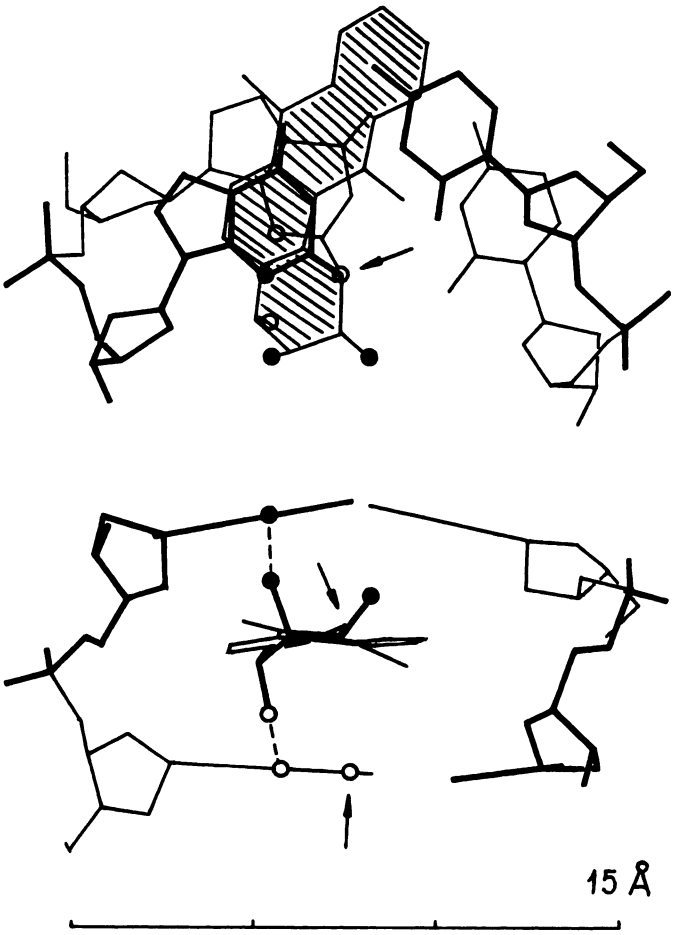

Fig. 2. Predicted structure of the physical complex of the *anti*-triol carbocation of 7,12-dimethylbenz[*a*]anthracene with the $dG_2 \cdot dC_2$ fragment of B-DNA. *Circles*, key heteroatoms, at the top (●) and at the bottom (○). *Arrows*, reactive centers to be chemically bonded. Hydrogen atoms are not shown.

TABLE 1

Conformational energies of different forms of the phenanthrene triol carbocation

Conformer[a]	Conformational energy[b]				
	AM1[c]	MNDO[d]	HF/6–31G*[e]	HF/6–31G**[e]	MP2/6–31G**//6–31G**[f]
	kJ/mol				
Syn					
eee	0.0	3.1	0.1	0.0	0.0
aaa	20.8	0.0	0.0	9.6	7.3
Anti					
eea	0.0	9.4	6.5	3.5	0.0
aae	2.0	0.0	0.0	0.0	0.6

[a] The orientation of the 1-, 2-, and 3-OH groups is shown; *a*, quasi-axial; *e*, quasi-equatorial.

[b] Total *ab initio* energies of the *aaa* conformation of the *syn*-triol carbocation at the HF/6–31G, HF/6–31G*, and MP2/6–31G* levels are −761.775153, −762.064022, and −764.427099 atomic units, respectively. Those of the *aae* conformation of the *anti*-isomer are −761.777162, −762.067611, and −764.430184 atomic units, respectively. 1 atomic unit of energy is equivalent to 2625.5 kJ/mol.

[c] Relative energy of the fully optimized structure by the AM1 semiempirical method (15).

[d] Relative energy of the fully optimized structure by the MNDO semiempirical method (19).

[e] Relative *ab initio* energy of the fully optimized structure with the Hartree-Fock approximation.

[f] Relative *ab initio* energy by single-point, full second-order Moller-Plesset perturbation theory calculations.

level of *ab initio* theory, and no such calculation has been published to date. Phenanthrene, although not carcinogenic, is the smallest bay-region PAH (3). The conformational equilibrium of its triol carbocation is expected to be similar to that of the carcinogenic bay-region PAH metabolites, because the geometry of the saturated part is likely to be determined by its near environment.

Table 1 presents the relative energies of the conformers of phenanthrene triol carbocation isomers obtained from AM1, MNDO, and *ab initio* calculations. According to our *ab initio* results, the conformational energy differences for the *syn*- and *anti*-structures are sufficiently small to allow for the coexistence of the two conformers at room temperature. At the correlated MP2/6–31G*//HF/6–31G* level of theory, the *eee* and *eea* conformers of phenanthrene triol carbocation are predicted to correspond to the global energy minima *in vacuo* for the *syn*- and *anti*-configurations, respectively. These conformations have two intramolecular hydrogen bonds, whereas the diaxial forms, namely *aaa* and *aae*, have only one. In the latter forms one of the three hydroxyl groups (2-OH in the *syn*-diastereoisomer and 1-OH in the *anti*-diastereoisomer) is separated from the others. The energetics of hydrogen bonds are known to be very sensitive to the level of approximation used (20) and, remarkably, those that do

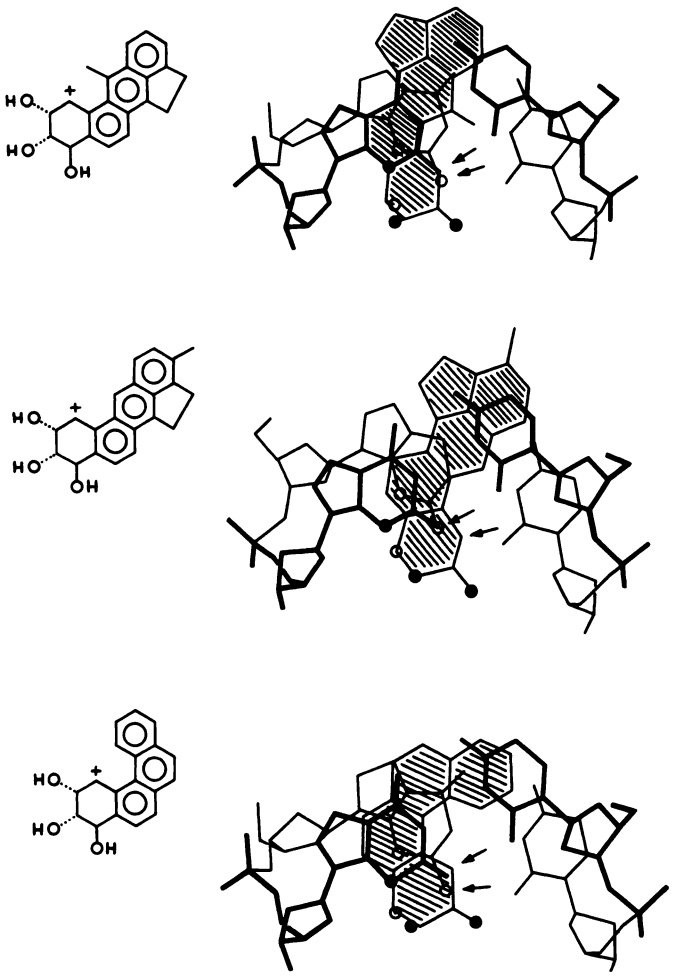

Fig. 3. Equilibrium structures of the intercalated complexes of various potent PAH triol carbocations with the $dG_2 \cdot dC_2$ fragment of DNA. *Arrows*, reactive centers to be chemically bonded. The bay-region methyl group preorganizes the geometry for bonding.

not describe hydrogen bonding sufficiently well, namely, MNDO and HF/6–31G, predict the greater stability of the diaxial forms (see Ref. 18 and Table 1). Hence, the conformational preference for the *eee* and *eea* forms *in vacuo* appears to be due to their enhanced intramolecular hydrogen bond energy. On the other hand, in the diaxial conformations of both diastereoisomers the hydrogen atoms of the 1-OH and 2-OH groups are available for intermolecular hydrogen bonds. Therefore, their stability should be significantly increased in a molecular environment where all possibilities for hydrogen bonding can be utilized. An additional methyl group or benzene ring in the vicinity of the 1-OH group leads to an additional enhancement of the diaxial conformers (21).

Thus, high-level *ab initio* calculations indicate that the conformers with quasi-diaxial orientation of the 1-OH and 2-OH groups are at least energetically acceptable at room temperature. This provides a quantum theoretical rationalization for the results of the AMBER molecular mechanics calculations presented below.

Fig. 2 represents the AMBER minimum-energy structure of the intercalated complex of the triol carbocation formed from one of the most potent carcinogens, namely (+)-*anti*-3,4-diol-1,2-epoxy-7,12-dimethylbenz[*a*]anthracene. The structural features of the complex highlight the geometric compatibility of the components. (i) The ultimate carcinogen adopts the *aae* conformation. (ii) Both quasi-axial hydroxyl groups form hydrogen bonds with the N3 atoms of the adjacent guanine residues. (iii) The C4 reactive center of the triol carbocation is located very close to the target N2-amino group of guanine; hence the complex is "preorganized" for the following covalent bonding. A change in the absolute configuration of the 1-OH or 2-OH groups destroys the hydrogen bonds and the geometric compatibility. This explains the observation that both carcinogenic stereoisomers of diol epoxides, namely, (+)-*anti* and (-)-*syn*, have the same absolute configuration of these particular hydroxyl groups (6–8).

Fig. 3 presents projections of the equilibrium structures of complexes of triol carbocations formed from carcinogenic bay-region (+)-*anti*-diol epoxides. Fig. 4 presents the structures of complexes with metabolites of inactive PAHs. It is seen in Fig. 3 that the C4 reactive center of potent molecules is located in the most favorable position for covalent bonding with the target N2-amino group of the lower guanine residue. On the other hand, the reactive centers in the complexes with inactive molecules (Fig. 4) are considerably shifted from the ideal position.

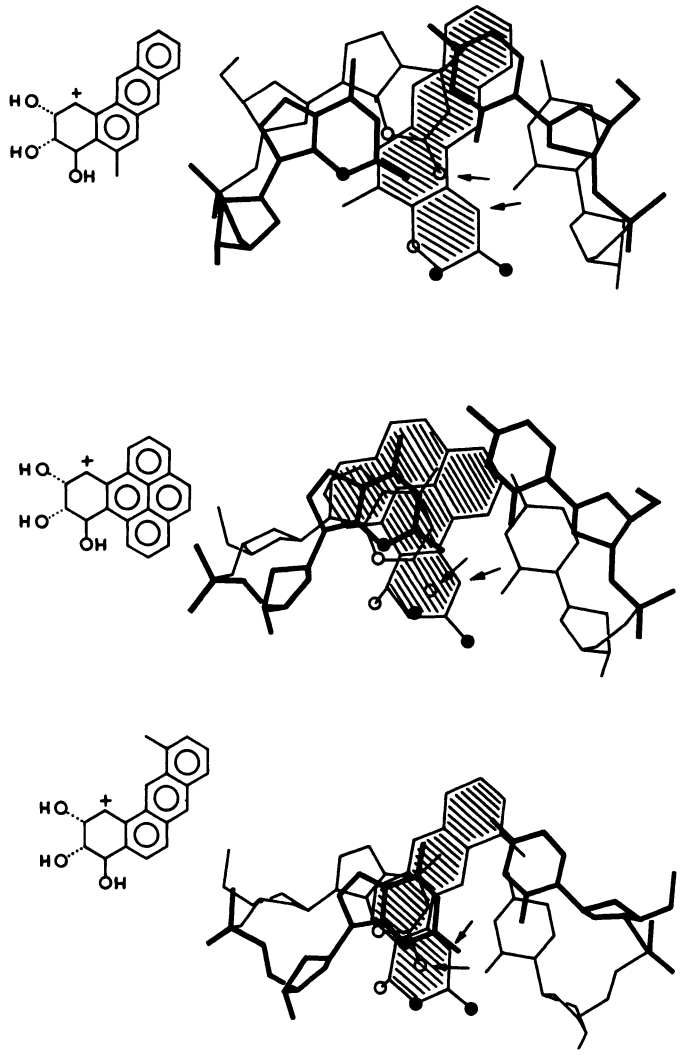

Fig. 4. Equilibrium structures of the intercalated complexes of inactive PAH triol carbocations with the $dG_2 \cdot dC_2$ fragment of DNA. *Arrows*, potential reactive centers.

Fig. 5 and Table 2 present the absolute configurations of bay-region triol carbocations of different PAHs and selected equilibrium structural parameters of their complexes, which may change significantly upon complexation. Table 2 also presents the corresponding observed parameters for intact B-DNA (14). The two-dimensional distance R_{2D} is a projection of the separation of the reactive centers on a plane parallel to the base pairs and is a measure of their readiness for bonding.

These data show that the highly potent structures **1-5** induce only minor changes in B-DNA geometry, encompassing all conformational variables of the DNA fragment even upon complexation. At the same time, these ultimate carcinogens occupy positions of maximum overlap between the *p* orbitals involved in the alkylation. The rest of the molecules produce noticeable conformational changes in DNA and deviate from the ideal position. The structural features of the complexes with inactive structures **14-20** are the least favorable.

Native B-DNA is more rigid than its 2-base pair fragment because of the conformational restrictions imposed by the neighboring bases. As the conformational excitation of the fragment increases, the PAH-DNA incompatibility also increases up to the point of impeding the intercalation of native DNA.

The most interesting examples of PAH metabolite-DNA steric incompatibility are the enantiomers **19** and **20** of the carcinogenic benzo[*a*]pyrene metabolites **8** and **9**, respectively. All four of these structures are electronically highly stabilized (3) and form stable complexes with the DNA fragment, but with **19** and **20** the fragment becomes left-stranded instead of right-stranded. Although such considerable conformational damage is allowed by the flexible DNA fragment, it is impossible in native DNA.

Fig. 6 summarizes equilibrium geometric features of the intercalated complexes. The locations of the most potent structures, **1-5**, differ from those of structures **6-13** in that the former are further shifted toward the target guanine residue to allow the reactive centers to be stacked. In all of the structures **1-5**, area A next to the bay region is occupied by either a methyl group or a benzene ring. This adjunct is pushed from the C2′-methylene group of the deoxyribose residue of the strand of cytosines toward the guanines (Fig. 3).

The strong enhancement of carcinogenicity upon methyl substitution at the *meso*-position next to the bay region is well established (4, 22), but no convincing explanation has been suggested thus far. According to our calculations this "bay-region methyl effect" is a consequence of the improved fit between the triol carbocation and the DNA binding site. The present molecular modeling points to a close parallelism between the effects of a methyl substituent and those of an additional condensed benzene ring in area A (Figs. 3 and 6). The steric requirements dominate over the differences in electronic structure. Two triol carbocation stereoisomers, derived from the (+)-*anti*- and (−)-*syn*-forms of such diol epoxides, fit the spatial requirements with respect to the corresponding guanine residue equally well (Fig. 3; Table 2). This explains the experimental fact that structures **2-5**, are exceptionally potent (10, 11, 23–26).

An increase in the size of the aromatic system promotes the stability of the carbocation and enhances carcinogenicity except in cases where the shape of the PAH precludes its intercalation (3–5). Fig. 6 shows two cases of such PAH-DNA

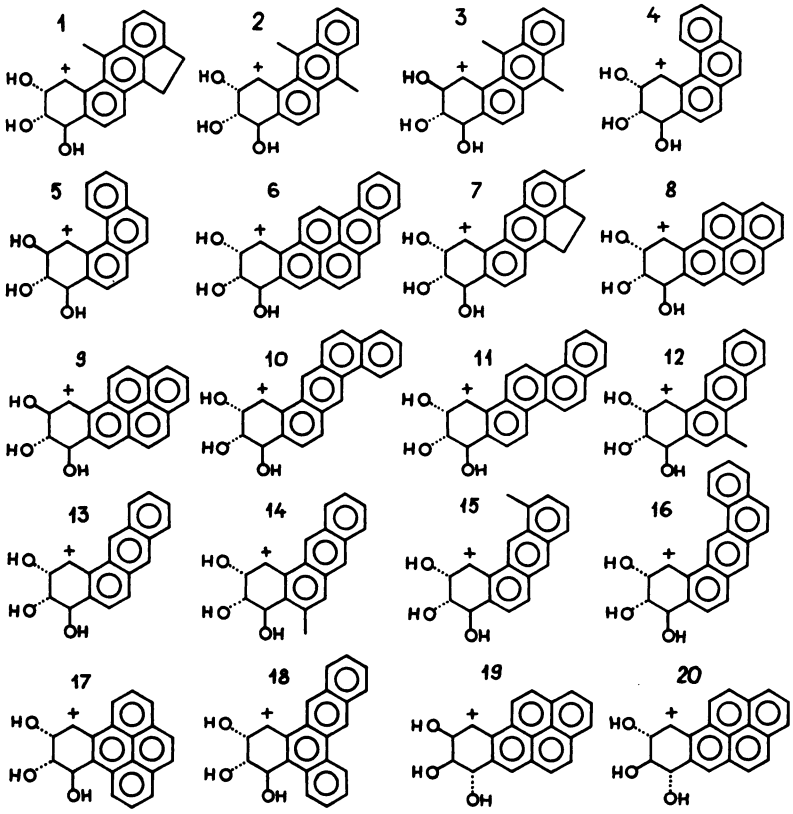

Fig. 5. Structures of triol carbocations of PAHs.

TABLE 2

Selected structural parameters of the physical complexes of PAH triol carbocations with the $dG_2 \cdot dC_2$ fragment of B-DNA

Molecule	R_{2D}[a]	Torsional angles of DNA[b]				Refs.[c]
		Δ_1	χ	ω	Δ_2	
	Å	degrees				
B-DNA		192.1	84.5	159.1	192.1	
Very potent						
1	0.30	133.1	84.3	−163.4	163.1	22
2	0.21	135.1	86.7	−161.7	165.9	10, 11, 23, 24
3	0.14	135.9	87.1	−161.7	168.4	10, 11, 23, 24
4	0.61	142.2	92.2	−161.4	173.5	25, 26
5	0.37	142.8	95.9	−162.2	170.8	25, 26
Potent						
6	0.95	133.3	14.2	−102.2	135.3	3, 5, 26, 31, 32
7	0.88	133.6	7.5	−98.7	142.8	10
8	1.02	135.0	13.8	−101.9	136.9	6–8
9	1.08	134.8	11.8	−97.4	139.7	6–8
10	0.99	137.2	13.1	−101.2	139.8	26, 32, 33
11	0.80	136.3	8.1	−95.6	144.5	3, 5, 33
12	0.84	141.1	8.9	−97.3	142.4	11
13	0.92	136.2	10.0	−99.1	143.2	11, 31, 32
Inactive						
14	1.82	132.9	4.1	−83.4	158.3	11
15	1.69	78.4	49.2	−169.2	150.3	11
16	1.38	75.5	48.0	−168.8	145.2	5, 31, 32
17	0.90	115.0	−3.7	−96.5	150.6	5, 21, 26, 32
18	1.11	106.7	66.5	−169.2	133.4	3, 5, 31
19	1.26	128.0	24.6	−101.7	134.4	6–8
20	0.89	128.8	25.7	−103.7	134.5	6–8

[a] Two-dimensional distance between the reactive centers.

[b] As in Ref. 34, Δ_1 and Δ_2 are the phase angles of pseudorotation of the sugar residues in the strand of guanines at its 5′ and 3′ ends, respectively; χ and ω are angles of rotation around the C1′-N and C3′-O1 bonds of the 5′ sugar, respectively.

[c] References providing information about the potency of the ultimate carcinogens.

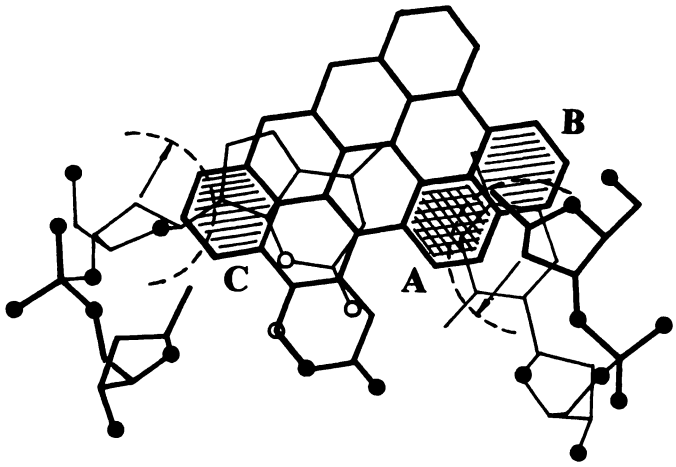

Fig. 6. Orientation of a generalized triol cation formed from the (+)-*anti*-diol epoxide of a PAH in its physical complex with DNA. *Circles*, heteroatoms. Adjuncts in region A (*cross-hatched region*) shift the PAH toward the target guanine N2-amino group, whereas those in regions B and C (*hatched regions*) shift the PAH away from this favorable alignment, due to the repulsions from the C2′-methylene groups of the sugar residues of the DNA backbone. Hydrogen atoms are not shown.

shape incompatibility. The adjuncts in region B are unfavorable because the C2′-methylene group of the deoxyribose residue of the strand of cytosines shifts the PAH metabolite away from the target center. Structures **15** and **16** are examples of such an unfavorable shift. Another case of unfavorable repulsion is found in the structures **14**, **17**, and **18**. Their adjuncts in region C interact with the C2′-methylene group of the deoxyribose residue of the strand of guanines, which pushes the molecules away from the target guanine center toward the strand of cytosines.

The structural features of the physical complexes of PAH triol carbocations with the DNA fragment explain the enantiomeric stereoselectivity and shape dependence of carcinogenicity. We conclude that this particular geometry of the PAH-DNA complex is involved in carcinogenesis. The ability to adopt this particular conformation and orientation in the physical complexation with DNA seems to be a necessary condition for highly potent PAH metabolites. The biologically active conformer of the *anti*-stereoisomer of triol carbocations is predicted to be *aae*, regardless of the conformation of the preceding diol epoxides. Thus, the predominance of the *eea* conformer of diol epoxides cannot be postulated as a necessary condition for high potency, contrary to current opinion (4, 27, 28). In addition, several theoretical models based on PAH diol epoxide intercalation lead to conclusions that are at variance with experiments. Thus, the (+)-*syn*-diol epoxide of benzo[*a*]pyrene should be carcinogenic according to Refs. 29 and 30, in contrast to observations (6–8). The present model avoids such contradictions by relating the tumorigenicity to the diaxial conformers of the triol carbocations, as the true ultimate carcinogens (4). The *biologically active conformation* of triol carbocations formed from (+)-*anti*- or (−)-*syn*-enantiomers of bay-region PAH diol epoxides is energetically acceptable. The potency is thus mainly determined by the ability of the triol carbocations to adopt the *biologically active orientation* near the target center in the physical complex with DNA.

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