Calculations Related to the Reactivity of Polycyclic Aromatic Hydrocarbon Episulfides

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The opening reaction of *S*-protonated polycyclic aromatic hydrocarbon episulfides has been evaluated by means of *ab initio*, density-functional, and semiempirical calculations. Episulfides are predicted to open more easily than the corresponding *O*-protonated derivatives, epoxides, and diol epoxides. On the other hand, diol episulfides would present the slowest rate for opening, the *syn* isomers being expected to be more reactive than the *anti* isomers. Bay-region and methyl-substituted bay-region compounds were found to open more readily among the sulfur derivatives, following the same reactivity pattern as the oxygen analogs. The exothermicity of the opening process correlated with the charge delocalization in the resulting carbocation. This reaction step is very important in the carcinogenic pathway of the epoxide analogs. Thus, according to the present calculations, episulfides could possibly exert carcinogenic activity.

Introduction. – Polycyclic aromatic hydrocarbons (PAHs) are an important group of chemical carcinogens, as much because of their relatively high tumorigenic potency [1] as for their widespread environmental prevalence [2]. Several studies support the hypothesis that the ultimate metabolically active form of these compounds that give rise to the alkylation of DNA are diol epoxides [1e][3]. The *anti* isomers (those that present the benzylic OH group and the epoxide O-atom on opposite faces of the molecule) of the *trans*-diols exhibit a higher activity in relation to the *syn* isomers (benzylic OH and the epoxide O-atom on the same face) [4]. The critical step for the mechanism involved in this carcinogenic process is considered to be the epoxide ring opening to yield a carbocation at the benzylic position of the epoxide function [5]. It is likely that electrophilic attack on DNA by hydrocarbon epoxides is S_N1-like and proceeds through proton-stabilized transition states in which the hydrocarbon exhibits significant carbonium-ion character [6].

Polycyclic aromatic episulfides, the sulfur analogs of PAH epoxides, maintain the basic requirements of PAH carcinogenicity [1b]. However, the thermodynamic [7] and kinetic [8] instability of the aromatic episulfides has complicated the synthesis of such compounds [9], and only a few have been isolated [10]. An attempted experimental work together with theoretical calculations oriented to direct the efforts for synthesizing polycyclic arene episulfides to make them available for cancer-related research has been reported lately [11a]. More recently, the synthesis as well as studies of the cytotoxicity and mutagenicity of some aromatic diol episulfides have been carried out [11b].

Recent quantum-chemical calculations concerning the carcinogenic pathway of PAH epoxides and diol epoxides have shown very good agreement with the experi-

mental reactivity of this type of compound [12]. In this work, calculations related to the reactivity of the target episulfides and diol episulfides of PAHs are reported in order to infer their possible carcinogenic potency by comparison with the results obtained for the epoxide derivatives.

Computational Methods. – *Ab initio* calculations at the *Hartree-Fock* (HF) and DFT/B3LYP [13] levels with the 6-31G* split-valence-shell basis set [14] were performed with the Gaussian 98 package of programs [15]. Calculations with the 6-31G(3df) basis on sulfur were also carried out. Geometries were fully optimized and stationary points were characterized as minima (no imaginary frequencies) or transition states (one imaginary frequency) by calculation of the harmonic vibrational frequencies. The geometries optimized at the HF level were used for single-point calculations at the third-order *Møller-Plesset* perturbation correction (MP3) [16] for treatment of electron correlation effects. Optimizations at the MP2 [17] level were also performed. The semiempirical methods AM1 [18] and PM3 [19] were used as implemented in the AMPAC 5.0 package of programs [20]. The solvent effect was estimated by computations at the RHF/6-31G* level by means of the isodensity surface polarized continuum model (IPCM) [21] without geometry optimizations.

Results and Discussion. – The episulfide ring-opening reactions for *S*-protonated 1β,2β-dihydrobenzene episulfide (benzene episulfide; **1**) and 1α,2β-dihydroxy-3β,4β-tetrahydrobenzene episulfide (benzene diol episulfide, **3a**) were taken as model systems for the sake of analyzing the behavior of episulfides and diol episulfides derived from PAH2 (the *Scheme*). Total energies are shown in *Table 1*, while activation energies and energies of reaction are displayed in *Table 2*, along with a comparison of the epoxide derivatives. Calculations with the 6-31G(3df) basis on sulfur, to account for the greater polarizability of this atom, showed no significant differences, which confirms the reliability of the 6-31G* basis for the whole study. Structures are shown in *Figs. 1* and *2*, and information related to them is presented in *Tables 3* and *4*.

The *S*-protonated benzene episulfide presented C_S symmetry and a planar six-membered ring, the S–H bond pointing toward the ring in an *endo* disposition. The corresponding species for benzene diol episulfide exhibited a H-bond interaction

Scheme. *Calculated Opening Reactions for Protonated Benzene Episulfide and Benzenediol Episulfide*

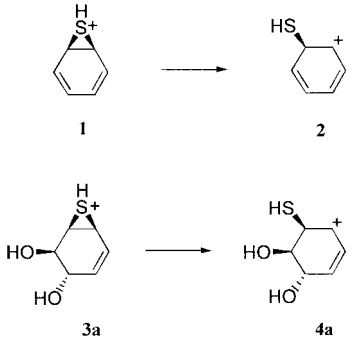

Table 1. *Ab Initio and DFT Total Energies* (Hartree), *Zero-Point Energies* (ZPE, kcal/mol), *and Semiempirical Heats of Formation* (kcal/mol) *for the Protonated Species*

Method	Benzene episulfide (**1**)			Benzene diol episulfide (**3a**)		
	Closed minimum	Transition state	Open carbocation	Closed minimum	Transition state	Open carbocation
RHF/6-31G*	– 628.49886	– 628.49856	– 628.51221	– 779.37565	– 779.37176	– 779.37674
MP2/6-31G*//6-31G*	– 629.37286	– 629.37047	– 629.36868	– 780.61534	– 780.60154	– 780.59239
MP3/6-31G*//6-31G*	– 629.41625	– 629.41388	– 629.41478	– 780.66387	– 780.65089	– 780.64486
ZPE (RHF/6-31G*)	75.45	75.09	74.72	97.73	96.66	96.27
RHF/6-31G*[a])	– 628.51126	– 628.51071	– 628.52376			
MP2/6-31G*//6-31G*[a])	– 629.42654	– 629.42410	– 629.42193			
MP3/6-31G*//6-31G*[a])	– 629.47223	– 629.46999	– 629.47141			
ZPE (RHF/6-31G*)[a])	75.28	74.94	74.65			
MP2/6-31G*	– 629.37649	– 629.36921	– 629.37135	– 780.62098		[b])
B3LYP/6-31G*	– 630.72836	– 630.72801	– 630.73236	– 782.36060		[b])
ZPE (B3LYP/6-31G*)	70.11	69.92	69.74	90.05		[b])
RHF/6-31G*/IPCM	– 628.58465	– 628.58426	– 628.60035	– 779.46997	– 779.45992	– 779.47418
AM1	223.36	223.42	220.23	115.73		[b])
PM3	227.34	231.74	229.14	128.44	142.11	141.30

[a]) 6-31G(3df) basis on S-atom. This basis was not employed for (3a), as no significant differences were observed comparing with the 6-31G(d) basis results. [b]) The open geometry collapses into the closed structure.

Table 2. *Calculations for the Opening Reactions of the Protonated Benzene Episulfide and Benzene Epoxide Derivatives* (kcal/mol)

Method	Benzene episulfide		Benzene diol episulfide		Benzene epoxide[a])		Benzene diol epoxide[b])	
	$\Delta E^{\ddagger}$	ΔE_r	$\Delta E^{\ddagger}$	ΔE_r	$\Delta E^{\ddagger}$	ΔE_r	$\Delta E^{\ddagger}$	ΔE_r
RHF/6-31G*	0.19	– 8.38	2.44	– 0.69	1.06	– 19.57	0.41	– 11.36
MP2/6-31G*//6-31G*	1.50	2.62	8.66	14.40	1.84	– 10.29	1.64	2.34
MP3/6-31G*//6-31G*	1.49	0.92	8.14	11.92	2.29	– 11.79	2.05	– 0.38
RHF/6-31G*[c])	< 0.01	– 9.11	1.37	– 2.15	0.40	– 21.15	< 0.01	– 12.47
RHF/6-31G*[d])	0.35	– 7.85						
MP2/6-31G*//6-31G*[d])	1.53	2.90						
MP3/6-31G*//6-31G*[d])	1.40	0.51						
RHF/6-31G*[c])[d])	0.01	– 8.19						
MP2/6-31G*	4.57	3.23	[e])	[e])	3.88	– 9.61	5.89	3.86
B3LYP/6-31G*	0.22	– 2.51	[e])	[e])	0.30	– 14.84	[f])	[f])
B3LYP/6-31G*[c])	0.03	– 2.88			0.02	– 15.83		
RHF/6-31G*/IPCM	0.24	– 9.85	6.31	– 2.64	0.92[g])	– 30.59[g])	0.63[g])	– 22.10[g])
AM1	0.06	– 3.13	[e])	[e])	0.11	– 31.38	< 0.01	– 23.28
PM3	4.40	1.80	13.67	12.86	< 0.001	– 30.71	[f])	[f])

[a]) From [12]. [b]) This work. [c]) Including zero-point vibrational contribution. [d]) 6-31G(3df) basis on sulfur atom. This basis was not employed for (**3a**), as no significant differences were observed compared with the 6-31G(d) basis results. [e]) The open structure collapses into the closed one. [f]) The closed geometry opens spontaneously upon protonation. [g]) AM1-SM2.1 [29] results.

between the H-atom attached to the sulfur and the oxygen of the closest OH group; this feature increases the asymmetry of the protonated episulfide ring, whose C–S bond distances differed from each other. Due to this interaction, in the most stable isomer, the involved hydroxy group was axial, as in the diol epoxide case. However, with both

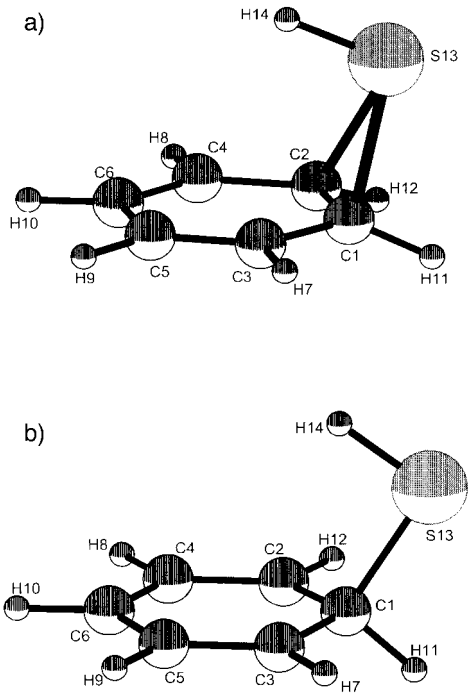

Fig. 1. *Calculated structures for* S-*protonated benzene episulfide* (**1**). a) *Closed minimum.* b) *Open carbocation.*

semiempirical methods, the species with that OH group in the equatorial position was slightly more stable for the diol episulfide, in spite of weaker H-bonding.

The activation energy for the opening of the episulfide ring of *S*-protonated benzene episulfide was very small at all levels of calculations, even lower than the values that had been observed for *O*-protonated benzene epoxide and diol epoxide [12]. Exothermicity was notably less than for the epoxide, even slightly endothermic, depending on the method. The acid-catalyzed solvolysis in aqueous solutions of benzylic episulfides to yield benzylic hydroxy thiols occurred at much lower rates than the solvolysis of the corresponding epoxides [11b]. This could be ascribed to sulfur being less basic than oxygen. Protonation affinities calculated at the RHF/6-31G* level showed that protonation is more favorable for benzene epoxide over benzene episulfide by *ca.* 3 kcal/mol. Hence, the protonation step would seem to be rate determining for the opening of the sulfur derivatives. Episulfides are *ca.* 10 kcal/mol less strained than epoxides [22]. Nevertheless, C–S bonds are *ca.* 20 kcal/mol weaker than C–O bonds [23], and this difference has been established to be more important in determining the lower thermodynamic and kinetic stability of the episulfide ring [11a].

Surprising behavior was observed with *S*-protonated benzene diol episulfide. This compound, which would presumably be the most reactive considering the greater reactivity of the diol epoxide over the epoxide, showed the highest activation energy for the opening. This reaction was also the most endothermic of the series according to the *Hartree-Fock* and PM3 results. Furthermore, the open carbocation collapsed into the

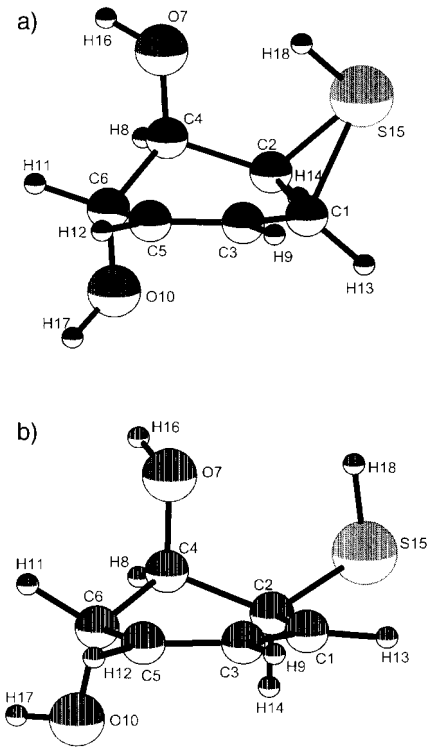

Fig. 2. *Calculated structures for* S-*protonated* anti-*benzenediol episulfide* (**3a**). a) *Closed minimum.* b) *Open carbocation.*

closed structure according to the MP2 and B3LYP calculations, reinforcing the evidence that the closed intermediate is much more stable than the open species. This spontaneous closure was also observed with AM1.

An explanation for this unexpected relative stability of the closed and open diol episulfide protonated structures could be found by taking into account the H-bond interaction that was observed between the H-atom attached to the S-atom and the O-atom of the closest OH group. For the epoxide derivatives, the enhanced reactivity of the diol epoxide had been ascribed to H-bonding between the H-atom of the epoxide and its closest OH group [12]. This interaction induces the asymmetry of the epoxide ring, with the breaking C–O bond becoming longer, which diminishes the barrier for opening. However, for the episulfide derivative, the H-bond-stabilizing interaction is considerably stronger in the closed intermediate because of the greater size of the S-atom. In this way, the O···H distance is 2.1765 Å in the closed species, while in the open one this H-bond lengthens to 2.5988 Å (RHF/6-31G* level). On the other hand, in the closed protonated diol epoxide, the H-bond distance is 1.9214 Å, while, in the open form, this length is 2.2633 Å, which still represents a strong interaction. In this way, the asymmetry of the episulfide ring seems not to compensate for the loss in stability of the open structure, which gives rise to a higher barrier for the opening process.

Table 3. *Selected Calculated Geometrical Parameters for the Structures Corresponding to* S-*Protonated Benzene Episulfide* (**1**)[a])

Structure	Parameter	AM1	PM3	RHF/6-31G*	MP2/6-31G*	B2LYP/6-31G*
Closed minimum:	C(1)–C(2)	1.4893	1.4945	1.4475	1.4738	1.4727
Bond length	C(1)–C(3), C(2)–C(4)	1.4485	1.4542	1.4624	1.4511	1.4520
	C(3)–C(5), C(4)–C(6)	1.3568	1.3529	1.3358	1.3645	1.3605
	C(5)–C(6)	1.4440	1.4458	1.4598	1.4433	1.4477
	C(1)–S(13)[b])	1.9157	1.9155	1.9726	1.9478	2.0111
	C(1)–H(11)	1.1140	1.1108	1.0750	1.0890	1.0874
	S(13)–H(14)	1.3266	1.3060	1.3246	1.3458	1.3516
Bond angle	C(1)–C(2)–S(13)	67.2	67.0	68.5	67.8	68.5
	C(3)–C(1)–S(13)	119.6	121.0	116.8	117.9	117.6
Episulfide-opening	C(1)–C(2)	1.4862	1.4719	1.4466	1.4585	1.4697
transition state:	C(1)–S(13)	1.8829	1.8630	1.9270	1.9099	1.9472
Bond length	C(2)–S(13)	2.0050	2.3379	2.1266	2.4133	2.1953
Open carbocation:	C(1)–C(2)	1.4687	1.4703	1.4799	1.4647	1.4731
Bond length	C(3)–C(5)	1.3730	1.3706	1.3531	1.3769	1.3726
	C(5)–C(6)	1.4093	1.4065	1.4099	1.4093	1.4130
	C(1)–S(13)	1.7827	1.8425	1.8523	1.8824	1.9005
	S(13)–H(14)	1.3233	1.3074	1.3271	1.3447	1.3522

[a]) Bond lengths in angstroms, bond angles in degrees. [b]) Equivalent to C(2)–S(13). [c]) Equivalent to C(2)–C(1)–S(13). [d]) Equivalent to C(4)–C(2)–S(13).

Table 4. *Selected Calculated Geometrical Parameters for Structures Corresponding to* S-*Protonated* anti-*Benzenediol Episulfide* (**3a**)[a])

Structure	Parameter	AM1	PM3	RHF/6-31G*	MP2/6-31G*	B3LYP/6-31G*
Closed minimum:	C(1)–C(2)	1.4861	1.4945	1.4530	1.4679	1.4671
Bond length	C(1)–S(15)	1.9025	1.9027	1.9311	1.9045	2.0119
	C(2)–S(15)	1.8355	1.8706	1.8583	1.8522	1.8734
	S(15)–H(18)	1.3261	1.3062	1.3243	1.3514	1.3641
	O(7)–H(18)	2.9662	3.2428	2.1765	1.9663	1.9657
Bond angle	C(1)–C(2)–S(15)	69.0	67.8	70.1	68.9	72.9
	C(3)–C(1)–S(15)	121.9	122.3	118.4	119.7	120.8
Episulfide-opening	C(1)–C(2)		1.4666	1.4589		
transition state:	C(1)–S(15)		2.5477	2.3156		
Bond length	C(2)–S(15)		1.8441	1.8456		
	S(15)–H(18)		1.3118	1.3231		
	O(7)–H(18)		2.4920	2.2265		
Open carbocation:	C(1)–C(2)		1.4672	1.4895		
Bond length	C(2)–S(15)		1.8306	1.8233		
	S(15)–H(18)		1.3103	1.3256		
	O(7)–H(18)		2.7240	2.5988		

[a]) Bond lengths in angstroms, bond angles in degrees.

In view of the foregoing observations, the *syn* isomer of the *S*-protonated benzene *trans*-diol episulfide (**3b**) was calculated to observe the behavior of the species in the absence of the intramolecular H-bond. The activation energy for this opening was lower and the energy of reaction more exothermic than for the *anti* isomer, confirming,

thus, the influence of the H-bond interaction hindering the opening of the last one (*Table 5*). According to this, the *syn* isomers of *trans*-diol episulfides would exhibit a higher reactivity than the *anti* compounds, in contrast with the reactivity pattern known for diol epoxides. These results agree with the lower mutagenic activity shown by the *anti* isomer of benzo[*a*]pyrene-7,8-diol-9,10-episulfide in relation with the *syn* isomer [11b]. Furthermore, both isomers presented a much lower activity than the corresponding *anti* diol epoxide [11b], which reinforces the conclusions drawn on the basis of the present calculations.

Table 5. *Calculations for the Opening Reaction of the* anti- *and* syn- *Isomers of* S-*Protonated* trans-*Benzene diol Episulfide*

Method	*anti*-isomer (**3a**)			*syn*-isomer (**3b**)		
	ΔH_f[a]) [kcal/mol]	$\Delta E^{\neq}$ [kcal/mol]	ΔE_r [kcal/mol]	ΔH_f[a]) [kcal/mol]	$\Delta E^{\neq}$ [kcal/mol]	ΔE_r [kcal/mol]
RHF/6-31G*	– 779.37565	2.44	– 0.69	– 779.36740	1.78	– 6.62
MP2/6-31G*//6-31G*	– 780.61534	8.66	14.40	– 780.60409	7.35	7.03
MP3/6-31G*//6-31G*	– 780.66387	8.14	11.92	– 780.65372	6.82	5.03
AM1	115.73	[b])	[b])	117.37	6.08	0.40
PM3	128.44	13.67	12.86	129.58	12.66	9.80

[a]) Total energy (hartree) for the *ab initio* calculations. [b]) The open structure collapses into the closed one.

Calculations in aqueous solution afforded a slight increase in the activation energy for **1**, although the barrier remained very low. The increase in the activation barrier was more noticeable for the diol episulfide (**3a**). Nevertheless, as the solvent effect did not appear to be important, the reactivity in biological systems would be expected to present the same trend as that predicted for the gas-phase results.

It should be noted that both *ab initio* and semiempirical methods afforded the same trend in the comparison of the reactivity of both systems. This can be considered as evidence of the reliability of these semiempirical methods for the study of the behavior of this type of compounds, as it had also been proved for the oxygen derivatives [12].

The so-called 'bay-region theory' [24] provides rationalization that PAHs, which contain a bay-region angular benzo ring dihydrodiol epoxide with one C-atom of the epoxide ring in the bay region, exhibit increased mutagenic activity [25], establishing a relationship between the ease of formation of a carbonium ion at the benzylic position of a bay region and the carcinogenicity of the hydrocarbon. Taking this into account, the enthalpy change involved in the ring-opening process for several protonated episulfides and diol episulfides was computed. Moreover, as Me substitution in the nonbenzo ring of a bay region tends to markedly increase the reactivity [1e], compounds of this type were also considered. According to the sizes of the structures, semiempirical methods were employed. The AM1 method has proved to afford

molecular geometries that are in good agreement with experimentally measured values for PAHs [26a][27], and has been found to be well-suited to study specific effects of the methyl-group substitution on them [26b]. Structures are shown in *Fig. 3* and calculation results are summarized in *Table 6*.

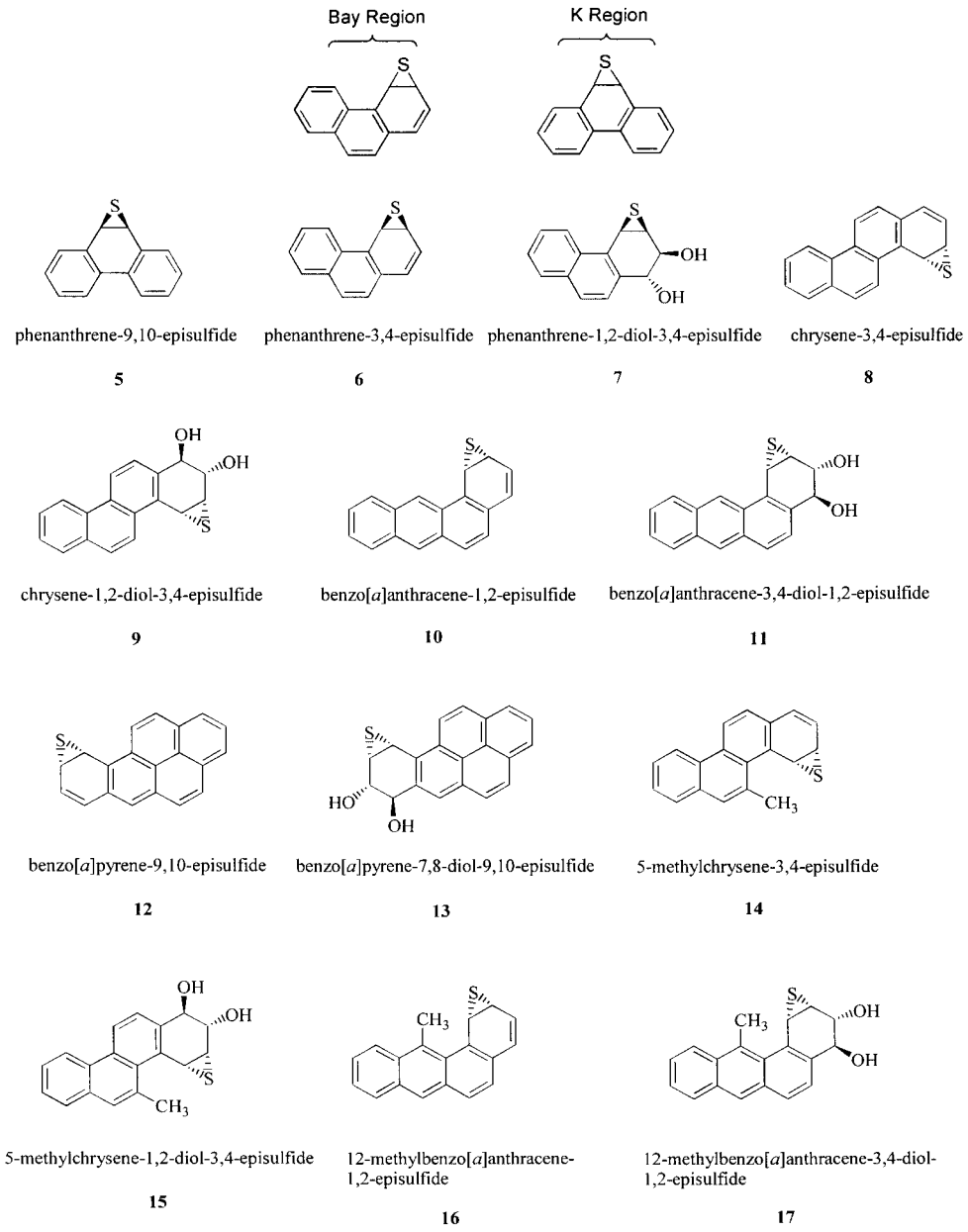

Fig. 3. *Episulfides and diol episulfides considered in* Table 6

Table 6. *Calculations for the Episulfide Ring Opening Reaction of the* S*-Protonated Compounds*

Compound	ΔH_r [kcal/mol] AM1	PM3	AM1 Charge at the carbocationic center
1	– 3.13	1.80	0.049
5	– 1.27	4.88	0.130
6	– 6.12[a])	– 2.23	0.060
8	– 5.37[a])	– 1.62	0.077
10	– 9.33[a])	– 5.46	0.018
12	– 8.43[a])	– 5.19	0.056
14	– 6.64[a])	– 2.25	0.068
16	– 10.80[a])	– 6.84[a])	0.008
4	[b])	12.86	
7	– 4.23[a])	[b])	0.114
9	– 5.16[a])	– 0.24	0.114
11	– 7.72[a])	– 1.29	0.072
13	– 13.59[a])	– 9.14[a])	0.046
15	– 6.00[a])	– 0.22	0.101
17	– 14.42[a])	– 9.71[a])	0.018

[a]) Value estimated by keeping fixed the S–C–C angle of the spisulfide ring, as the fully-optimized protonated species collapsed into the open carbocation. [b]) The open structure collapses into the closed one.

The opening reaction became more exothermic on going from a K-region to a bay-region episulfide, as can be seen by comparing the values for phenanthrene-9,10-episulfide (**5**) and phenanthrene-3,4-episulfide (**6**); this observation being in accordance with the trend previously found for the corresponding epoxides [12]. Previous calculations had indicated that bay-region episulfides are thermodynamically less stable than their K-region isomers [11a]. No protonated bay-region episulfide was characterized as a minimum on the respective potential-energy surfaces but opened spontaneously upon protonation, affording the open carbocations, by the AM1 results. The same observation had been made for bay-region epoxides [12]. The corresponding ΔH values for opening were estimated by fixing the S–C–C angle of the episulfide ring in the protonated forms. Conversely, the bay-region protonated minima were isolated by PM3, as this method yielded less-exothermic values for the reaction, with the exception of 12-methylbenzo[*a*]anthracene-1,2-episulfide (**16**), which opened.

Bay-region diol episulfides opened upon protonation according to AM1, as it had been observed with the corresponding diol epoxides [12]. For the diol epoxide analog of benzo[*a*]pyrene-7,8-diol-9,10-episulfide (**13**) there is considerable experimental evidence that protonation and ring opening to the carbocation probably occur in a concerted fashion (general acid catalysis) [28]. The PM3 calculations rendered the same spontaneous opening for **13** and 12-methylbenzo[*a*]anthracene-3,4-diol-1,2-episulfide (**17**), which afforded the most exothermic ΔH values of the series, while the other closed protonated structures were found to be stable minima; surprisingly, the open phenanthrene-1,2-diol-3,4-episulfide (**7**) could not be isolated as it collapsed to the closed species. Although both semiempirical methods produced roughly the same general reactivity trend, AM1 seemed to perform more properly for this reaction with this class of compounds.

Considering the bay-region Me compounds, they showed a larger tendency to open than the corresponding unsubstituted molecules. Thus, the same conclusions related to the greater reactivity of the Me-substituted epoxide derivatives applied to the episulfides. This observation had been ascribed to distortion by nonplanarity of the aromatic system and consequent instability of the closed protonated structures, and not to stabilization by hyperconjugative effects on the open carbocations [12].

The exothermicity of the opening reaction, which accounts for the ease of carbonium ion formation, correlated with a decrease in the net positive charge at the benzylic C-atom of the open structure. This stabilization of the resulting carbocation by delocalization of the charge applied for both the episulfide and diol episulfide series. The same observation had been made for the epoxide derivatives, for which the charge at the carbocationic center was less positive, in correspondence with the more exothermic reaction of those compounds [12]. In this way, stabilization by delocalization of the positive charge into the π system as the molecule becomes more conjugated by the presence of fused aromatic rings explains the reactivity pattern.

Conclusions. – According to the theoretical results in this study, protonated PAH episulfides are predicted to open at a higher rate than that corresponding to both the epoxides and diol epoxide analogs. On the other hand, diol episulfides would be the least reactive derivatives of the series, and their *anti* isomers would be less reactive than the *syn* compounds. The H-bond interaction between the H-atom of the protonated episulfide and the O-atom of the closest OH group in the *anti* structure is very much stabilized in the closed species and, hence, hinders the opening of the episulfide ring. This would be in contrast to the reactivity pattern of the diol epoxide derivatives. It should be noted, however, that the slower protonation of the S-atom could influence the overall activity of the episulfides, considering their slower acid-catalyzed solvolysis [11b].

For the larger molecules, the increase in the exothermicity of the opening reaction correlated with the decrease of the net positive charge at the benzylic position by a greater delocalization in the carbocation formed as the structure becomes more conjugated. Bay-region structures opened more readily, and Me substitution at the bay region also favored the opening of the episulfide ring. These obervations are in accordance with the known reactivity of the oxygen analogs, and would allow us to infer the potential activity of the episulfides by taking into account the relative reactivity of the corresponding epoxides. According to the present computations, benzo[*a*]anthracene-1,2-episulfides (compounds **10**, **16**, and **17**), as well as benzo[*a*]pyrene-7,8-diol-9,10-episulfide (**13**) are expected to be the most reactive.

It should be remarked that reactivity cannot be related directly to carcinogenicity, as excessive reactivity can result in destruction by reactions with other cellular nucleophiles. The active bay-region diol epoxide metabolites are characterized by their resistance to detoxification by epoxide hydrase and other enzymes, which permits them to survive sufficiently long to reach and react with DNA [1e]. Nevertheless, from the results reported in this study, it is suggested that the sulfur derivatives of PAHs could be of interest in cancer research. Therefore, these calculations encourage further experimental efforts for the synthesis of this type of compound.

The same trend observed between the semiempirical methods and the more rigorous *ab initio* and density-functional results supports the validity of the perform-

ance of the former for this type of molecule, and proposes that they are reliable enough to be applied to the study of larger systems. According to this, the reactivity of different episulfide derivatives of PAHs could be theoretically predicted by the methods employed in this work. As aqueous-phase calculations did not reveal an important solvent effect, the present gas-phase results appear as a good approximation to the potential activity in biological systems.

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