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REVIEW

Three-membered benzylic thia-rings of polycyclic aromatic hydrocarbons: synthesis, molecular calculations and properties

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In cancer research/organic synthesis related studies, several hitherto unknown three-membered benzylic thia-ring-containing polycyclic aromatic hydrocarbons, PAH-episulfides (PeSs) and PAH diol episulfides (DeSs), have been synthesized and their relevant chemistry explored. These compounds represent the sulfur analogs of the corresponding diol epoxide carcinogens. A highly efficient general synthetic methodology has been developed for the conversion of epoxides and, stereoselectively, diol epoxides into their corresponding episulfides using the nucleophilic sulfur transfer agent DMTF. The newly-synthesized DeSs show remarkable stability towards aqueous acid whereas both PeSs and DeSs are thermodynamically unstable (loss of sulfur) – consistent with the predictions of previously performed molecular orbital calculations. This review constitutes an account of what has been achieved in this area, focusing on aspects related to cancer research and the implications for further research.

Keywords: Polycyclic aromatic hydrocarbons (PAHs); Episulfides; Arene episulfides; Diol episulfides; Episulfoxides: synthesis, molecular calculations and chemistry

1. Introduction

1.1 *Cancer research-related connection*

Polycyclic aromatic hydrocarbons (PAHs) such as **1–3** are products of incomplete combustion of organic matter and are widely distributed in the environment [1–3]. Several of these ubiquitous environmental contaminants are highly carcinogenic [4, 5] and, therefore, play an important role in human cancer [5, 6]. The metabolically formed bay- and fjord-region diastereomeric diol epoxides (DEs) *e.g.*, **4** and **5**, are known ultimate carcinogens of the

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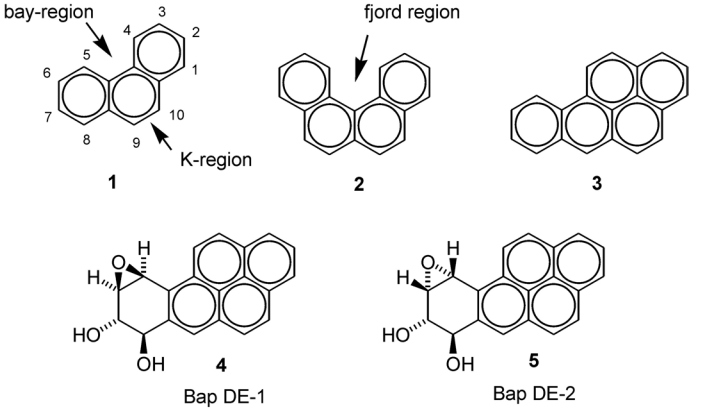
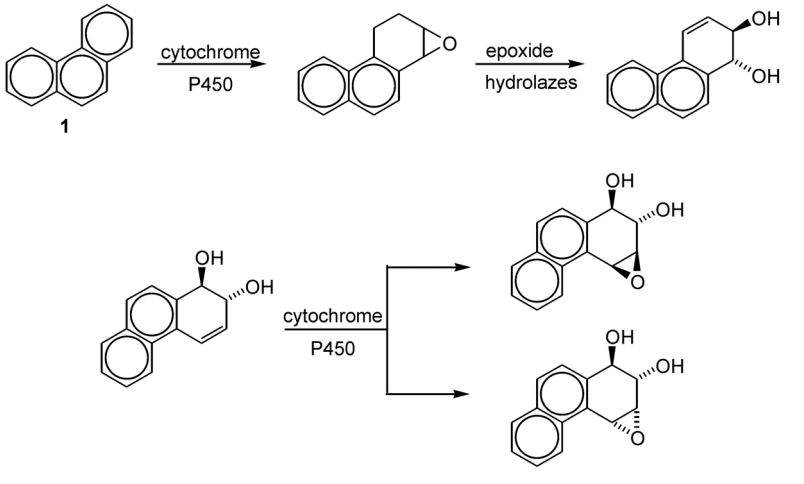
environmentally prevalent PAHs [2]. These diol epoxides are formed from *trans*-dihydrodiols, so that the epoxide oxygen is either *cis* (DE-l) or *trans* (DE-2) to the benzylic hydroxyl group [7]. Interestingly, the highly hindered fjord-region DEs are much more tumorigenic than their bay-region counterparts [2, 8].



It is believed that the first step in the tumorigenic and/or mutagenic process initiated by PAHs is the covalent modification of DNA by these polycyclic aromatic DEs, which, in turn, are formed metabolically [7–10] from the parent PAHs (*e.g.* **3**) *via* enzymatic activation [2, 3]. Consequently, structure-activity relationships for PAHs and their diols have been extensively investigated [6, 9–12] and, indeed, several studies support the hypothesis that DE metabolites are the principal active carcinogenic forms of these PAHs [2, 9–12]. This is illustrated for **1** in scheme 1.

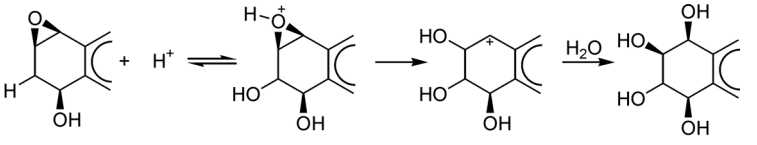


SCHEME 1 Enzymatic transformation of PAHs into diol epoxides (DEs).

There are marked stereochemical preferences associated with the metabolism of bay-region PAH-diols. Thus, as typified by the metabolism of benzo[*a*]pyrene (BaP, **3**) by cytochrome P450c and epoxide hydrolase, the (*R, S, S, R*)-diol epoxide-2 from BaP and several other PAHs predominate, although four optically active bay-region diol epoxides are metabolically possible [2]. With only one known exception, high tumorigenicity, when observed, has been limited to diol epoxide-2 diastereomers, whereas the diol epoxide-l diastereomers are weak or inactive [2]. In the absence of specific steric or electronic factors, DEs-2 prefer equatorial OHs and DEs-1 prefer axial OHs, whereas benzo-ring dihydrodiols have a marked preference for the conformation in which their hydroxyl groups are pseudo-equatorial [13]. Thus, both

absolute configuration and *conformation* play a crucial role in the mutagenic/carcinogenic mechanisms initiated by the PAH-DEs.

Solvolytic reactivity of the electrophilic DEs in aqueous media has been subjected to considerable experimental scrutiny, since it provides the simplest chemical model for the reaction in which the DEs alkylate specific nucleophilic sites in the cell, initiating the mutagenic or tumorigenic process [2, 9, 14]. Both DEs-1 and DEs-2 undergo acid-catalyzed hydrolysis in water at low pH and 'spontaneous' reaction with solvent at higher pH, according to the rate law $k_{obsd} = k_H[H^+] + k_0$, where k_H is the second-order rate constant for the spontaneous reaction [2, 15]. Furthermore, the solvolytic reactivity is well correlated over a 10^3-fold range of activity with $-E_{deloc/b}$ (a measure of the ease of formation of the resonance stabilized benzylic carbocation) for DEs having similar conformational preferences. These results accord with the mechanism shown in scheme 2 [15].



SCHEME 2 Mechanism of acid-catalyzed solvolysis of diol epoxides.

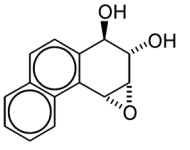
The rate of hydrolysis of BaP DE-2 in aqueous solution, in the presence of DNA, is enhanced markedly, whereas only a small amount of covalent binding of the DE (<15%) to the DNA occurs. For other diol epoxides, such as those derived from the nonplanar benzo[*c*]phenanthrene (BcP, **2**), covalent adduct formation is much more competitive with DNA-catalyzed hydrolysis [16].

Numerous studies have investigated covalent adduct formation between DEs and DNA with particular emphasis on adducts derived from BaP and BcP (**3** and **2**, respectively). Thus, the chemical structures have been elucidated of 16 principal adducts formed from the deoxyadenosine (dA) and deoxyguanosine (dG) residues of DNA upon reaction *in vitro* with the four configurationally isomeric 3,4-diol 1,2-epoxides derived from benzo[*c*]phananthrene-*trans*-3,4-dihydrodiol. These adducts, one *cis*- and one *trans*-addition product, are formed from each of the four configurationally isomeric diol epoxides with either deoxyguanosine or deoxyadenosine. In these major adducts the site of covalent attachment of the diol epoxide moiety to the nucleoside residue is at the exocyclic amino group. Recently, in capitalizing on the above, a novel and efficient synthesis has been reported of the eight possible, diastereomerically pure, *cis* and *trans R* and *S* O^6-allyl protected N^2-dGuo phosphoramidite building blocks, through the *cis* and *trans* opening of BcP DE-1 and -2 [17].

In conclusion, DNA adduct formation from DEs occurs mainly, though not exclusively, *via* addition of the exocyclic amino groups of dG and dA to the benzylic carbon atoms of the epoxide functions [18] and mainly, but not exclusively, *via trans* opening of the epoxide by the exocyclic amino group [19]. The *planar* DEs, like those of BaP, covalently bind predominantly to dG sites of nucleic acids, whereas the DEs derived from nonplanar PAHs, such as that of BcP, bind equally or to a greater extent to the dA residues. The findings of all these extensive, detailed studies provide a useful tool for probing the mechanism of cancer induction, although the details of the process at the molecular level remain obscure [6]. Thus, many questions concerning the molecular basis of these structure–activity relationships, as well as the molecular mechanism of PAH carcinogenesis at the molecular-genetic level, remain to be elucidated [18].

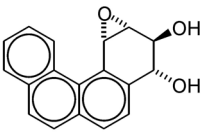
Both the bay- and fjord-region DEs are well-established metabolites of PAHs responsible for their mutagenicity [20] and carcinogenicity. Stereospecific synthesis of such metabolites, *e.g.*, **5–7**, has played a key role in cancer-related chemical research [2, 3, 6, 10, 21]. Indeed, numerous polycyclic arene oxides [22–25] and DEs [10–25] have been synthesized and extensively

studied. However, only relatively recently have a few studies of their episulfide counterparts been reported [6, 26].



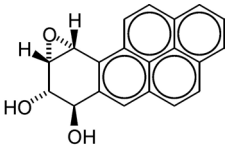
diol epoxide-2

6



(-)-(4*R*,3*S*)-diol-(2*R*,1*S*)-epoxide-1

(-)-7



(+)-diol epoxide 2

(+)-5

1.2 *From numerous attempts to the first successful synthesis*

Notably, polycyclic aromatic hydrocarbon episulfides, the sulfur analogs of the PAH epoxides, were unknown and, therefore, not tested for carcinogenicity until very recently, in spite of the well-established important role of organosulfur compounds in biological systems. This lack of information concerning the PAH episulfides (PeSs) is, undoubtedly, due to the instability of the benzylic episulfides (thiiranes) both thermodynamically [27] and kinetically [28] and, consequently, to their difficult accessibility synthetically [29]. Thus, although PeSs might be formed during the metabolism of the carcinogenic PAHs from the interaction of PAH-epoxides (PEs) or DEs with sulfur nucleophiles available in the cells/tissues, they appear to have no biological significance, due to either their thermodynamic instability or problematic solvolytic reactivity.

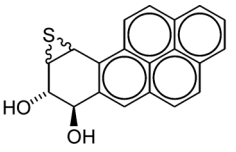
After numerous failures [27, 29], the first successful synthesis and characterization of PeSs was reported by Blum *et al*. [29]. In addition, theoretical molecular orbital calculations suggest that the dihydro, bay-region arene episulfides containing three or more rings should be thermodynamically stable enough to be isolated [30]. Therefore, tetrahydro bay- and fjord-region PeSs, such as **9–11** and their corresponding diol episulfides (DeSs), should be synthetically attainable.

1.3 *Relevant guiding considerations*

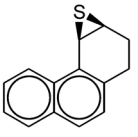
The above considerations and the following points provided a considerable impetus for further studies in this area: (a) the first successful synthesis of BaPeS (**12**) [29], *via* a modification of the procedure of Takido *et al*. [31]; (b) our successful totally stereoselective synthesis of diol episulfides (DeSs) **8a**, **b** [32]; (c) that both bay- and fjord-region DEs are well-established metabolites of PAHs, responsible for their mutagenicity [20] and carcinogenicity, the latter highly hindered being much more tumorigenic than their bay-region counterparts [2, 8]; and (d) DNA adduct formation occurs, mainly, *via trans*-opening of the epoxide function of the DEs by the exocyclic amino group of the former [3, 6, 10, 17–19, 33–38]. Facilitating the whole study was the development of an effective synthetic methodology for the stereochemically controlled preparation (under mild conditions!) of PeSs such as **9–11** and even more so, in relation to cancer research, their corresponding DeSs, *e.g.*, **8b**, the sulfur analogs of the ultimate DE-2 carcinogens.

The basic structural requirements for PAHs carcinogenicity [9] are fully maintained in the PeSs and their corresponding DeSs, giving rise to the intriguing possibility of replacing the epoxide oxygen of PAH-epoxides and, even more so, of their corresponding DEs with sulfur, in order to evaluate the chemical and biological properties of the resulting corresponding PeSs and, particularly, DeSs. The preparation of these DeS–oligonucleotide adducts, the sulfur analogs of the corresponding DEs-adducts, is also of significant interest.

Although the particular steric, electronic and electrophilic requirements for carcinogenicity of the PEs and DEs are expected to be maintained in the corresponding PeSs and DeSs,



8a,**b** (DeS-1 & 2)



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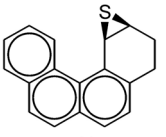

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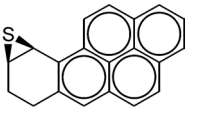

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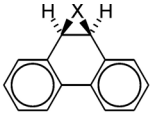
substantial differences in chemical and biological properties of the latter relative to the former are anticipated. This is due to the lower electronegativity and much higher nucleophilicity (and polarizability) of sulfur compared with oxygen. Thus, protonation at sulfur is expected to be much less favorable than at oxygen. Also, the C−S bond in episulfides is ∼20 kcal mol^{-1} weaker than the C−O bond [39], and the episulfides are ∼10 kcal mol^{-1} less strained than epoxides [40]. Furthermore, sulfur possesses vacant d-orbitals that can accommodate up to ten electrons, with all the implications involved [28]. The cancer research-related interest in the synthesis and chemistry of PeSs and DeSs is thus apparent. However, both the PeSs and the DeSs were until very recently unknown and, therefore, not tested for carcinogenicity/mutagenicity until very recently.

The conversion of epoxides with inorganic sulfur transfer agents to yield the corresponding episulfides appears to be the method of choice for the synthesis of the latter, *via* a five-membered 1,3-oxathiolane intermediate [28]. Indeed, this methodology has been applied to prepare PAH-episulfides.

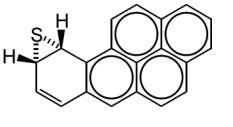
2. Polycyclic arene episulfides

Arene episulfides should be highly interesting in cancer research since (a) they maintain the basic requirement of PAH carcinogenicity [9] and (b) organosulfur compounds have an important role in biological systems. Therefore, the synthesis of the thus-far elusive polycyclic arene episulfides, *e.g.*, **12b** and **13b**, would make them available for cancer-related bioorganic research and reinforce theoretical studies for the acquisition of fundamental information about them by way of reliable molecular orbital quantum mechanical calculations.

Extensive research in the last 20 years has established that theory is an extremely useful and reliable source of fundamental chemical information, such as molecular structure, thermodynamic data and electronic structure [41]. Thus, the delineation of agreements and discrepancies between theoretical predictions and experimental results concerning the synthesis, thermodynamic stability and chemistry of polycyclic arene episulfides will be made possible. Further, molecular calculations may help direct future experimental efforts to the most relevant, as well as synthetically accessible, systems. The essence of both our experimental and theoretical studies in this respect is given below.



12 a: X = O
b: X = S



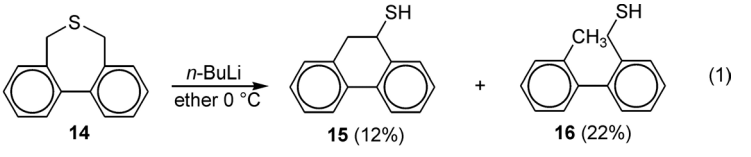
13b

2.1 *Attempted synthesis*

The K- and bay-regions arene oxides (*e.g.*, **12a** [22]) or the parent hydrocarbons (*e.g.*, phenanthrene in the case of **12b**), have been used as precursors for the synthesis of the targeted arene episulfides. Initial attempts involved treating **12a** and phenanthrene (**1**) with sulfur transfer agents [30, 3l, 42]. Following the erroneous report on the presumed isolation of **12b** from the lithiation products of 2,7-dihydrodibenzo[*c*, *e*]thiepine **14** [43], the latter was also used as a key starting material in the attempted synthesis of **12b**.

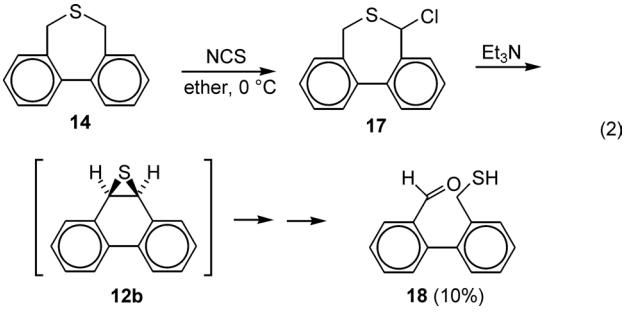
All our attempts failed to obtain the arene episulfide **12b** upon reacting the corresponding epoxide precursor **12a** with either the nucleophilic inorganic potassium thiocyanate and hydrogen sulfide or with the organic sulfur transfer agent 2-methylbenzothiazole-2-thione under various conditions. However, NMR monitoring suggested that **12b** might be an intermediate in the reaction of **12a** with 3-methylbenzothiazole-2-thione under acidic conditions [44]. The NMR spectra of the products showed peaks at δ 8.73–7.21 (m, arom.), 6.37 (d), 5.50 (d), 3.93 (s), 3.83 (s, 3H, CR_3), ppm [30]. Accordingly, the singlet at 3.93 ppm may suggest the formation of **12b** as a thermodynamically unstable intermediate along the reaction coordinate. This is further corroborated by our later ^{1}H NMR spectroscopic study in which the epoxide **12a**, in $CDCl_3$, was treated with *N*, *N*-dimethylthioformamide (DMTF). The new peaks, which appeared at 3.51 and 3.67 ppm, were assigned to the oxathiolane intermediate **32** (scheme 3 below), the precursor of **12b** [45].

We have attempted in vain to prepare **12b** *via* the treatment of **14** with butyllithium at low temperatures [43]. The result was unsuccessful as only isolable thiols **15** and **16** accompanied recovered starting material and phenanthrene in the reaction mixture (equation 1) [27, 30].

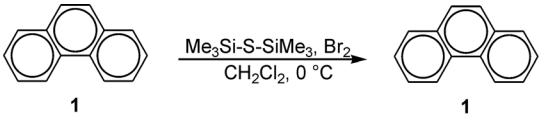


Thiirane **12b** is a possible intermediate on the pathway leading to thiols **15** and **16**. Intermediate **12b** would have to succumb to two 2H reductive cleavages to give **15** and **16**, respectively. As an alternative mechanism one is reminded of the tendency of arene oxides to rearrange to phenols [46]; thiol **15** may result from a similar fate of **12b**.

Attempts were made to mimic this chemistry through synthetic manipulation. Thus thiepine **14** was chlorinated in the α position with *N*-chlorosuccinimide (NCS) in dry ether. Subsequent treatment of **17** with triethylamine yielded thioaldehyde **18**, but in low yield (∼10%), and an amount of starting material [27, 30]. It is possible that **18** results from hydrolysis of **12b** which may be formed by an initial dehydrohalogenation step (equation 2). However, since direct hydrolysis of **17** can also give **18**, we were unable to garner direct evidence for **12b** and its intermediacy in equation 1 can only be inferred.



Treatment of phenanthrene (**1**) with the sulfur transfer agent bis-trimethylsilyl sulfide in the presence of bromine [47, 48] afforded only the precursor phenanthrene and elemental sulfur, both quantitatively recovered from the reaction mixture (equation 3). However, in the presence *or* the absence of phenanthrene, the reaction of bis(trimethylsilyl) sulfide with bromine afforded elemental sulfur quantitatively, meaning that episulfide **12b** is not formed in this reaction [30].

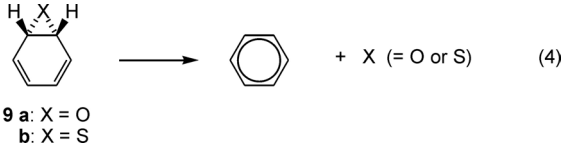


2.2 *Molecular orbital calculations*

Previous high level *ab initio* calculations of the structure, vibrational energies and thermodynamic properties of all carbon- and sulfur-atom-containing three-membered ring systems [49] have resulted in excellent agreement between theoretically predicted and experimental data. This lent confidence to our *ab initio* calculation-based predictions for the characteristics of polycyclic arene episulfides. Thus, standard *ab initio* molecular orbital [41] and density functional theory (DFT) calculations (using the B3LYP [50] functional) were performed using the Gaussian 94 series of programs and the polarized 6-3lG* basic set in all the calculations, with geometries fully optimized and characterized as minima, by calculating the harmonic vibrational frequencies and characterizing the corresponding Hessian matrix [30, 51]. The HF/6-31G* optimized geometries were used for single point calculations at the MP3(full) level [52], for treatment of electron correlation effects. Further details of the calculations are provided elsewhere [30].

The first question we addressed, in applying theoretical calculations, concerned the relative thermodynamic stabilities of arene epoxides and their analogous episulfides. The reactions studied at the outset addressed the fragmentation of the parent, the already known benzene epoxide (**19a**) [53] and the thus-far illusive benzene episulfide (**19b**) [54]. The reaction outcome would provide benzene and either oxygen or sulfur in their triplet ground electronic state (equation 4). The calculated ΔG° for this reaction reflects the thermodynamic stabilities of **19a** and **19b** towards this process. The calculated enthalpies of equation 4, endothermic for both X = O and X = S, are summarized in table 1 [30].

The data indicate that benzene episulfide is much more prone to loss of the lone atom than benzene oxide. Specifically the loss of O from **19a** as in equation 4 is endergonic by 34.4 kcal mol^{-1} while loss of S from **19b** is endergonic by only 11.6 kcal mol^{-1} at the same MP3/6-31G*//6-31G* level. The low ΔG° for the episulfide **19b** is indicative of a strong thermodynamic propensity toward dissociation. Hence **19b** is predicted to be difficult to isolate even at low temperatures where entropy factors are minimal.



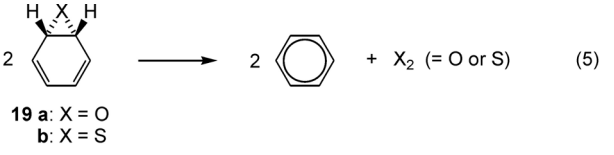
Should the chemistry of equation 4 be viewed as an unsuitable model for the extrusion of sulfur or oxygen from **19**, calculations were also performed using double the stoichiometry (equation 5). Equation 5 may reflect better the chemistry at hand since molecular S_2 or extended clusters of sulfur atoms, known to be more thermodynamically stable than S_2 [55], are expected to offer a more accurate view of the nature of the sulfur being extruded. However, regardless of whether the data pertaining to equations 4 or 5 is employed, the same qualitative conclusions can be made about the relative stabilities of benzene episulfide and benzene oxide. The loss

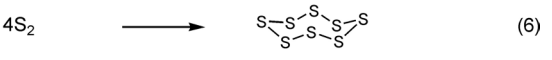
Table 1. Calculated energies; ΔH° and selected related ΔG° and ΔS° (in footnotes) for reactions 4–11 (at MP3 and B3LYP levels) [30].

Equation	X	ΔH° (kcal mol^{-1}) MP3[a]	B3LYP[b]	Equation	X	ΔH° (kcal mol^{-1}) MP3[a]	B3LYP[b]
4	O	41.54[c]	51.83[d]	8	O	– 25.93	−29.09
	S	18.70[e]	21.47[f]		S	– −23.06	−27.05
5	O	−10.73	−18.72	9	O		– −16.35[g,h]
	S	−40.08	−52.00		S		– −15.37[g,h]
6		−47.99	−58.75	10	O		−10.07[h]
7	O	−29.23	−30.85		S		−10.81[h]
	S	−30.42	−33.04	11[i]			−21.83

[a]MP3(full)/6-31G*//HF/6-31G* + ZPE (HF/6-31G*); [b]B3LYP/6-31G* + ZPE (B3LYP/6-31G*); [c]$\Delta S^\circ_{298} = 27.70$ cal mol^{-1} K^{-1} at HF/6-31G* and $\Delta G^\circ_{298} = 34.35$ kcal mol^{-1} at MP3/6-31G*//HF/6-31G* (thermal Gibbs energy at B3LYP/6-31G*); [d]$\Delta S^\circ_{298} = 27.41$ cal mol^{-1} K^{-1} and $\Delta G^\circ_{298} = 44.64$ kcal mol^{-1} at B3LYP/6-31G*; [e]$\Delta S^\circ_{298} = 26.74$ cal mol^{-1} K^{-1} at HF/6-31G* and $\Delta G^\circ_{298} = 11.55$ kcal mol^{-1} at MP3/6-31G*//HF/76-31G* (thermal Gibbs energy at B3LYP/6-31G*); [f]$\Delta S^\circ_{298} = 26.27$ cal mol^{-1} K^{-1} and $\Delta G^\circ_{298} = 14.32$ kcal mol^{-1} at B3LYP/6-31G*; [g]ΔH° at B3LYP/6-31G* + ZPE (B3LYP/6-31G*) is: $= -15.80$ and -15.03 kcal mol^{-1} for X = O and X = S, respectively; [h]ΔE (*i.e.*, without ZPE). [i]R = H.

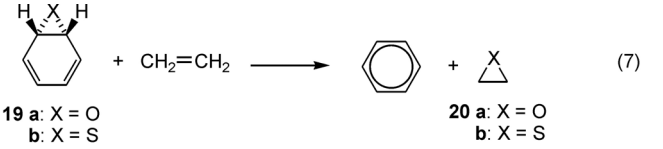
of X_2, while exothermic for X = O and X = S, is much more so for episulfide **19b** (table 1). Notably, S_2 (in contrast to O_2) is not a thermodynamically stable form of sulfur and it reacts further to give S_8 (equation 6).

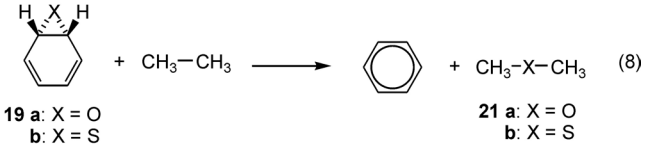




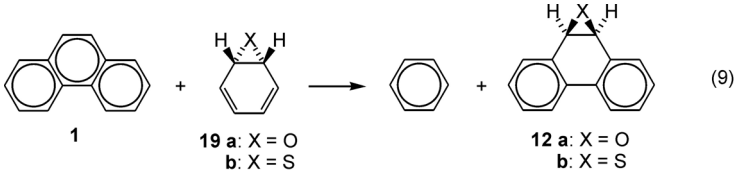
Since the chemistry of equation 6 is very exothermic (see table 1) it is expected to further decrease the thermodynamic stability of **19b** with respect to sulfur extrusion. Hence an adaptation of equation 5, one that yields S_8 instead of S_2, is in fact more exothermic. The *kinetic* stability of **19b** towards the extrusion of sulfur was calculated to be very low [55], which may explain why all the attempts so far to isolate **19b** have failed. Also, it may similarly explain our [27, 30] and others [29] unsuccessful attempts to prepare the arene episulfide **13b** (see equations 9 and 10 and table 1). A different way to compare the relative thermodynamic stability of benzene oxide and benzene episulfide is *via* their isodesmic equations 7 and 8. The chemistry of these equations is exergonic for both X = O and X = S (table 1), the evidence in favor of the thermodynamic instability of both **19a** and **19b** towards the transfer of X. The driving force in this chemistry is clearly the aromatic stabilization of the benzene ring formed and there is little noteworthy difference between the oxygen and the sulfur compounds. Moreover, it can be suggested that the lower thermodynamic stability of the episulfide **19b** towards extrusion of X or X_2, compared with that of the oxide **19a**, (*i.e.* equations 4 and 5, respectively), is not

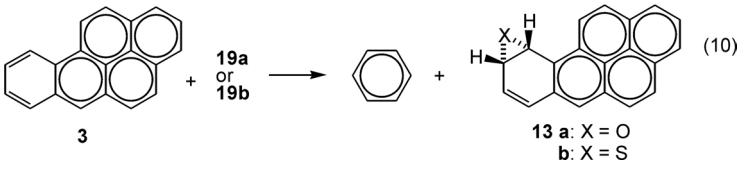
due to an intrinsic instability of **19b** but, for the most part, is based on two factors. One is that C−S bonds tend to be weaker than C−O bonds by *ca.* 20 kcal mol^{-1} [39, 56] and the other reason pertains to the triplet state of atomic sulfur and its the high stability compared with that of triplet oxygen [57].





Several related calculations were also performed on the other larger K- and bay-region polycyclic arene epoxides and episulfides, with a focus on those systems where the arene oxide has been previously synthesized. Equations 9 and 10 compare the thermodynamic stability of **19a/b** with that of some larger arene oxides and episulfides. These equations are obtained by amalgamating two extrusion reaction equations and arranging the result of their combination so that the X element is eliminated. For instance, equation 9 arises from setting up a reaction analogous to equation 4 for phenanthrene-derived compounds **12a** and **12b** and then subtracting that new equation from the actual equation 4. Equation 10 uses a similar manipulation for compounds **3/13**. The outcome is that a more exothermic ΔH° indicates a higher thermodynamic stability of the larger polycyclic compound, *e.g.*, **13a** or **13b**, relative to **12a** or **12b**, respectively (table 1). ΔG°s for equation 10 at the MP3 level have been calculated as −8.26 and −6.39 kcal mol^{-1} for the arene oxides and arene episulfides, respectively [30].



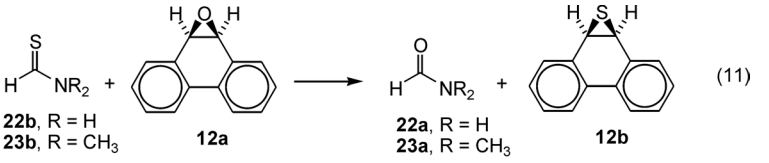


The key conclusion to draw from the calculations pertaining to equations 9 and 10 is that the trends of thermodynamic stabilities of analogous arene oxides and arene episulfides are comparable to that for **19a** and **19b**. Hence, one can use the relative thermodynamic stabilities of known arene oxides (*e.g.*, **12a** *and* **13a**) as a guide to predict which episulfides are most likely to be isolable. The data suggest that a high thermodynamic stability for an arene oxide is a reliable indicator of a high thermodynamic stability of the corresponding arene episulfide [30]. Moreover, the calculations (ignoring the kinetic stability) allow a comparison between K-region polycyclic arene episulfides and their bay-region isomers. In general, the K-region congeners are more stable thermodynamically (*e.g.*, **12b** $\Delta H^\circ = ca.$ −15 kcal mol^{-1}) and have a better chance of being isolated (*e.g.*, **13b** $\Delta H^\circ = ca.$ − 10.8 kcal mol^{-1}). Similarly, the synthesized

bay-region 9,10-episulfide **11** slowly loses elemental sulfur when left to stand for several days, whereas its 7,8-isomer is stable at room temperature [29]. Yet caution is required since ΔH° for the dissociation of **12b** to phenanthrene and atomic sulfur is endothermic by only *ca.* 28 kcal mol^{-1} whereas its breakdown to phenanthrene and S_2 or S_8 is highly exothermic [30]. Therefore, its isolation should be attempted only at a very low temperature.

With respect to thermodynamic stability our calculations also suggest that, in the bay-region arene episulfide series, as the thermodynamic stability (and thus the chance of an episulfide to survive isolation) increases, the higher is the aromatic character [58] of its ring system.

Finally, the potential of the nucleophilic reagents HC(=S)NH_2 (**22b**) and HC(=S)$N(CH_3)_2$ (**23b**) to transfer sulfur to arene epoxides, and produce the corresponding arene episulfides, has been probed (equation 11). Depending on the theoretical level, the reactions depicted in equation 11 were calculated to be noticeably exothermic by 22–26 kcal mol^{-1}. Should the thermodynamic data serve practice well, **22b** and **23b** should act as very efficient sulfur transfer agents in the DEs-to-DeSs and PEs-to-PeS transformations [32].



(11)

A recent study based on molecular calculations points to the importance of DeSs in cancer/carcinogenesis research and provides predictions concerning the relative reactivities of Des-1 and -2 [59]. These calculation-based predictions are in accord with ours as summarized above.

In conclusion, our calculations have proved quite useful in this analysis. First, the data suggests that the thermodynamic stabilities of the arene oxides are a good gauge for the relative stabilities of the corresponding arene episulfides, a finding that should serve as a guide by indicating which arene episulfides are likely to survive isolation. We have also learned that bay-region arene episulfides are more prone to loss of sulfur by way of extrusion than are K-region isomers. For the bay-region episulfide series, more fused intact aromatic rings impart greater thermodynamic stability to the system. Finally, one can establish the order of thermodynamic stability of various arene oxides and episulfides by examining the degree of 'aromatic character' of the rings that *do not* carry the sulfur atom [30].

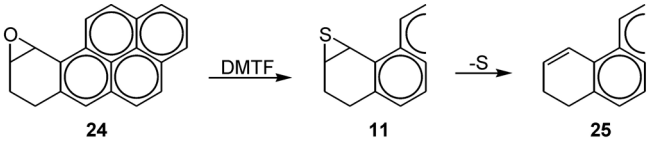
3. Polycyclic aromatic hydrocarbon episulfides and diol-episulfides

3.1 *Synthetic methodology and effective synthesis*

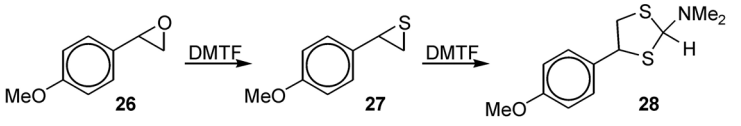
A general method for the conversion of epoxides into the corresponding episulfides using *N*,*N*-dimethylthioformamide (DMTF) in CH_2Cl_2 as a nucleophilic sulfur transfer agent in the presence of a catalytic amount of trifluoroacetic acid has been developed by Takido *et al.* [31]. Subsequently, the synthesis of 7,8,9,10-tetrahydro-BaP 9,10-episulfide (**11**) in 37% yield as well as of its isomers, all from the corresponding epoxides, was achieved using this protocol [29]. When we applied this method to DE-2 (**5**) in THF as a solvent we could not detect any formation of the desired DeS, neither by NMR spectroscopy nor by HPLC analysis of the reaction mixture [32].

However, we have developed a simple and efficient general method for the conversion of epoxides into the corresponding episulfides using DMTF as both solvent and sulfur-transfer agent in the presence of trace amounts of $BF_3{\cdot}Et_2O$ as a catalyst. The use of $BF_3{\cdot}Et_2O$ (0.01 equiv.) with a 40-fold excess of DTMF (−20 °C for 15 min) dramatically increased the conversion of the precursor epoxide into its corresponding episulfide **11** from the previously reported

37 to >90% [32]. The product (**11**) was easily separated from excess DMTF and generated DMF, by silica-gel column chromatography, using 15% EtOAc in *n*-hexane. In the absence of $BF_3{\cdot}Et_2O$, the reaction of epoxide **24** is complete in 3 days at room temperature, but the desired PeS **11** is accompanied by a substantial amount (>50%) of 7,8-dihydro-BaP (**25**) which arises by thermal desulfurization [28] of **11** (equation 12).



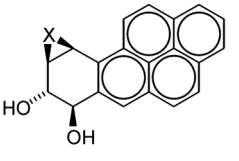
(12)



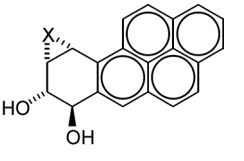
(13)

4-Methoxystyrene oxide (**26**) [60] when treated with DMTF (1 equiv.) and $BF_3{\cdot}Et_2O$ (0.01 equiv.) at −20 °C for 2 h afforded the corresponding episulfide (**27**) [60] in 90% yield [32]. However, in this case, use of excess DMTF and prolonged reaction time afforded a diastereomeric mixture (1:1) of the 1,3-dithiolanes (**28**), which were formed by further addition of DMTF to the initially formed episulfide (**27**).

The newly developed method worked very well for both DE-l (**4**) and DE-2 (**5**), which were stereoselectively converted into DeS-2 (**8b**) and DeS-1 (**8a**), respectively [30]. Solvent-dependent changes of preferred conformation observed in the NMR spectra of **4** and **8a**, but not of **5** and **8b**, were used to assign the relative stereochemistry to these diastereomeric DeSs [30, 62].

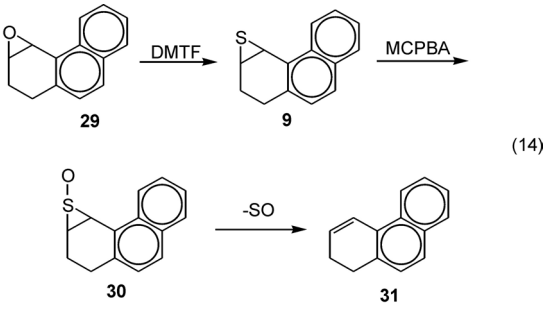


X = O: DE-1, **4**
X = S: DeS-1, **8a**



X = O: DE-2, **5**
X = S: DeS-2, **8b**

In applying a modified version of our synthetic methodology, we have synthesized PeS **9** by treating its precursor epoxide **29** with DMTF, in dichloromethane (DCM) at −65 °C in the presence of $BF_3{\cdot}Et_2O$ for 4 h. Compound **9** was isolated in 80% yield after silica-gel column chromatography [45]. The same yield of **9** was obtained by the treatment of the epoxide with DMTF at −75 °C (equation 14).



(14)

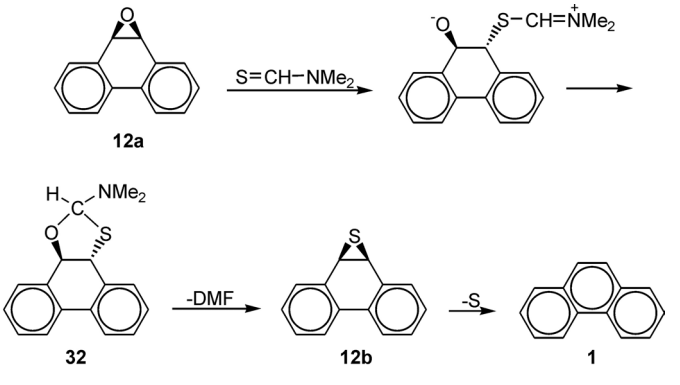
In a similar vein, we have attempted the synthesis, or at least the detection *via* NMR, of the so-far elusive **12b** [27, 29, 30]. However, it proved to be too unstable to be isolated. Instead, the decomposition products obtained, elemental sulfur (72%) and phenanthrene (**1**) (74%) in about a 1:1 molar ratio, are in accord with the intermediacy of **12b** [45].

Oxidation of episulfide **9** with *m*-CPBA afforded the corresponding episulfoxide **30**, but isolation was not possible since **30** succumbed to SO loss rapidly at room temperature to give **31**. However, the IR spectrum of the reaction mixture showed a strong absorption at 1065 cm^{-1}, a band characteristic of the sulfur-oxygen (S=O) stretching frequency in thiirane oxides [45]. EI-MS of the compound presumed to be **30** showed a base peak of m/z 180 [$M^+ - SO$]. Regardless of whether the sulfoxide group was eliminated following an initial ionization by the electron impact on **30**, or that thermal decomposition is responsible for this elimination [63], the base peak of m/z 180 and the expected absence of peak at m/z 212 strongly suggests that the expected episulfoxide **30** has been formed. Formation of the latter has been further corroborated *via* the low-temperature NMR studies of **30** in which H_4 and C_3 were detected at 6.07 and 53.3 ppm, respectively. To the best of our knowledge, **30** is the first detected PAH benzylic episulfoxide.

We are currently further exploring the possibilities of preparing both benzylic polycyclic aromatic hydrocarbon-episulfides and -episulfoxides that are more thermodynamically stable than **12b** and **30** in order to facilitate our study of their chemistry and biological activity.

3.2 *Mechanism of PAH-epoxides to -episulfides transformations*

Given all of the above experimental results, particularly (a) the stereospecific conversion of the DE-l and -2 (**4** and **5**) into the DeS-1 and -2 (**8a** and **8b**), respectively, and (b) the isolation of the five-membered 1,3-dithiolanes in these and analogous transformations [32]; *e.g.*, **26** → **27** (equation 13), a mechanism can be proposed [45]. Using the episulfidation of epoxide **12a** as an example, scheme 3 outlines the epoxides-to-episulfides transformation [45]. This mechanism is in accord with the accepted mechanism for conversions of epoxides into their corresponding episulfides by sulfur-transfer agents [28].



SCHEME 3 Proposed mechanism for the transformation of PAH epoxides to episulfides.

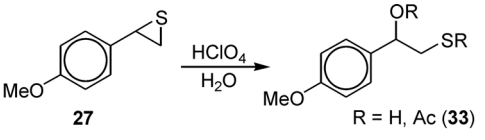
3.3 *Properties*

Inconsistent with molecular calculations-based theoretical predictions [30], both newly synthesized PeSs and DeSs, were found experimentally to be thermodynamically unstable, losing their sulfur fast and readily at room temperature to provide the corresponding fully aromatic or conjugated, unsaturated systems (*e.g.*, equation 12 and scheme 3) [29, 30, 32, 45].

They do, however, maintain their integrity while being kept in the refrigerator, particularly under (deep) freezing conditions.

In view of the use of the PEs and DEs as model compounds in cancer research-related biochemical studies, mainly associated with their solvolytic reactivity, the respective solvolytic behavior of the analogous PeSs and DeSs is of particular interest. In aqueous solutions, benzylic epoxides undergo acid-catalyzed solvolysis to the corresponding dihydroxy compounds *via* benzylic carbocations, with an observed rate constant given by the equation $k_{obsd} = k_H[a_{H+}]$ [2, 15]. We anticipated that the episulfides would undergo an analogous reaction to yield benzylic hydroxy thiols.

Although solvolysis of these episulfides does occur, its rate is extraordinarily slow [32, 62] compared with that of the corresponding epoxides. Solvolysis of the reactive 4-methoxystyrene oxide **26** is too fast to measure by conventional spectrophotometry below pH $\sim$ 5($t_{1/2} < 7$s), whereas k_H for its thia-analog **27** required a pH of 1–2 for reasonable rates ($t_{1/2}$4–40 min) to be observed. Similarly, epoxide **24** has a half-life of $\sim$6 s at pH 5, whereas $t_{1/2}$ for solvolysis of episulfide **11** is $\sim$10 min in 1 M acid. Thus, k_H (table 2) for 4-methoxystyrene episulfide (**27**) in water is more than 3×10^5-fold slower than k_H for the corresponding epoxide (**26**) under the same conditions [60a] (table 2). The sole product of the acid-catalyzed hydrolysis of **27** was 2-(4-methoxyphenyl)-2-hydroxyethanethiol, which was characterized as its diacetate (**33**).



27 R = H, Ac (**33**) (15)

A similar large difference (>10^7) in k_H was observed between the episulfide (**11**) and the epoxide (**24**). These rate differences correspond to a difference of 7–8 kcal mol^{-1} in activation energy. Preliminary results indicate that the DeSs are also very unreactive towards acid-catalyzed hydrolysis compared with the DEs [32].

Studies in Chinese hamster V-79 cells indicated the DeSs have very low toxicity and mutagenicity compared with DE-2 (**5**). This low biological activity may be related to their markedly reduced solvolytic reactivity relative to epoxides [32]. When the relative cytotoxicity was compared in terms of LD_{50}(μM), DeS-1 (**8a**) and DeS-2 (**8b**) were 68- and 160-fold less cytotoxic, respectively, than DE-2 (**5**). When relative mutagenicity was compared in terms of 8-azaguanine resistant colonies per 10^5 surviving cells per μM, **8a** and **8b** were 2,300- and 4,600-fold less mutagenic, respectively, than **5** [32].

Table 2. Rate constants for the hydrolysis of epoxides and episulfides [32].

Compound	K_H($M^{-1}s^{-1}$)	Solvent
Epoxides (**24**) [60[b]]	1.2×10^1	25% dioxane-water
Episulfide (**11**)[a]	1.7×10^{-2}	20% acetonitrile-water[b]
Epoxide (**26**) [61[a]]	1.1×10^4	water
Episulfide (**27**)[c]	2.8×10^{-2}	water

[a]Rate constant for the spectral change at 354 nm measured at 25 °C in 1M $HClO_4$/20% acetonitrile–water. Products were not characterized. [b]We believe the comparison of **27** and **12** in different solvent systems to be acceptable since solvent (25% dioxane–water *vs*. water alone) had only a small effect (<2-fold) on the rate of acid-catalyzed hydrolysis for the analogous diol epoxides [50b]. [c]Rate constants measured at 25 °C in water (ionic strength 0.1 M, sodium perchlorate) at pH 1.0–2.3. Reactions monitored at 237 nm [62].

4. Summary – future perspectives

Bay- and fjord-region diol epoxides (DEs) are the ultimate carcinogenic metabolites of the environmentally widespread PAHs. Their tumorigenic activity is believed to result from the alkylation of the cyclic amino groups of deoxyadenosine (dA) and deoxyguanosine (dG) sites in the DNA. Therefore, DEs and their precursor PAHs and PEs have been, and are being, used in numerous cancer/carcinogenesis studies, worldwide. Analogous PeSs and DeSs were unknown until very recently and, therefore, were not used or even probed in cancer-related research. Our work, reported herein, has aimed to fill this gap; *i.e.*, to synthesize the thus-far elusive PeSs and DeSs as well as selected arene episulfides *via* newly-developed effective methodology. Following this we sought to thoroughly study the chemical and biological properties *per se*, but particularly in relation to the relevant cancer research, *i.e.*, region- and stereospecific-modes and kinetics of chemical reactivity. Moreover, we aimed to predict their thermodynamic and kinetic stability *via* appropriate *ab initio* molecular calculations. Finally, we still plan to synthesize model DeS–oligomeric DNA adducts. This report updates our efforts thus far on the PeS–DeS trail.

In summary, (a) a highly efficient general synthetic methodology has been developed and successfully applied for the preparation of PeSs and, totally stereoselectively, of DeSs from their corresponding epoxides using the nucleophilic sulfur-transfer agent DMTF; (b) quantum-mechanical *ab initio* calculations have been used successfully to predict thermodynamic and kinetic stabilities of PeSs, DeSs and their corresponding arene episulfides that are consistent with experimental results and, therefore, facilitate more judicious choices for future research; and (c) the newly synthesized BaP-DeS-1 and -2 show remarkable stability towards aqueous acid and very low toxicity and mutagenicity compared with their corresponding DEs.

Replacement of the oxygen atom in the DEs by the "bulkier", more polarizable and more nucleophilic sulfur atom provides a unique opportunity to evaluate the nature of bonding, thermodynamic stability and stereospecific structure–chemical/biochemical reactivity relationships in these systems and their related DNA adducts. PeSs, DeSs and their study are expected to contribute to our understanding of the mechanisms of carcinogenesis. They not only open a new area of PAH cancer-related research but may also lead to novel, electrophilic anti-tumor drugs. Also, their synthesis and study is expected to contribute to the understanding of the chemistry of three-membered ring heterocycles, particularly that of the benzylic PAHs.

We intend to continue our explorative research work in this area accordingly, particularly in the synthesis and study of as-yet unknown PeSs, DeSs and their oligomeric DNA adducts.

Acknowledgment

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