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Polycyclic Arene Episulfides. Attempted Synthesis, Molecular Orbital Calculations and Comparison with Arene Oxides

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Abstract. In pursuit of the elusive polycyclic arene episulfides, the synthesis of phenanthrene-9,10-episulfide (**5b**) was attempted. However, the reactions of phenanthrene-9,10-oxide and of phenanthrene with sulfur transfer agents and of 5,7-dihydrodibenzo[c,e]thiepine (**9**) with butyllithium did not afford **5b**, although its intermediacy could be detected by NMR and inferred from the products isolated. Quantum-mechanical *ab initio* and density functional methods were used to calculate the thermodynamic stability of representative arene episulfides and arene oxides. The arene episulfides were found to be thermodynamically significantly less stable than the corresponding oxides, towards elimination of sulfur and oxygen respectively. K-region arene episulfides are found to be thermodynamically more stable towards sulfur extrusion than their bay-region isomers. The thermodynamic stabilities of analogous arene oxides and arene episulfides parallel each other, and the relative thermodynamic stabilities of arene oxides and episulfides can be deduced from the degree of the aromatic character of the rings which do not carry the heteroatom.

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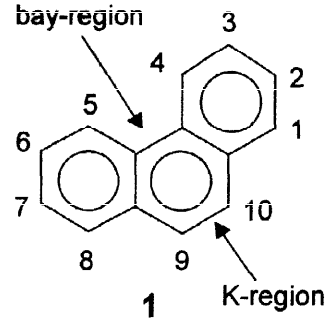
Introduction

Polycyclic aromatic hydrocarbons (PAHs) are products of incomplete combustion of organic matter and are widely distributed in the environment.[1,2] Several of these ubiquitous environmental contaminants are highly carcinogenic[3,4] and play an important role in human cancer.[5,6] It is believed that the first step in the tumorigenic and mutagenic process initiated by PAHs is the covalent modification of DNA by polycyclic aromatic diol epoxides (DEs) which are formed metabolically[7] from the parent PAHs (e. g. **1-3**) via enzymatic activation.[1,2]



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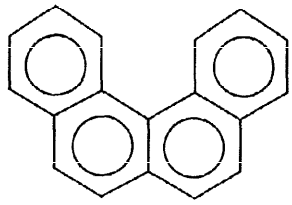

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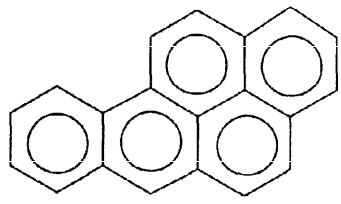

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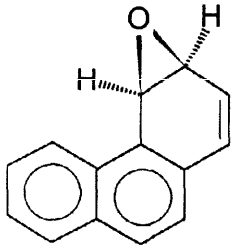
Consequently, structure-activity relationships for PAHs have been extensively investigated[6,8-11] and indeed, several studies support the hypothesis that DE metabolites are the principal active carcinogenic forms of these PAHs.[1,8,11,12] As a result, the synthesis of such metabolites has played an important role in cancer-related chemical research[1,6,9] and a great number of polycyclic arene epoxides [e.g. **4**[13] (bay-region); **5a**[14] (K-region, see **1**)] and diol epoxides [e.g. **6a** (bay-region)][15] have been synthesized and extensively studied.[1,2]

The development of the "bay-region theory" of carcinogenesis by aromatic hydrocarbons was one of the first successful applications of quantum chemistry to biological problems.[16] To date, more than a dozen hydrocarbons have been studied in sufficient detail either to prove or implicate bay-region diol epoxides as their metabolically formed ultimate carcinogens.[17]



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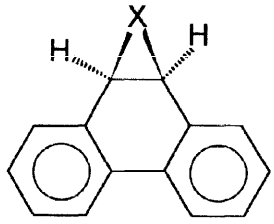
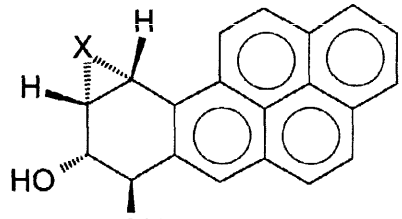


5a (X=O)
5b (X=S)



6a (X=O)
6b (X=S)

Numerous studies have investigated covalent adduct formation from the reactions of DEs and DNA.[18] This adduct formation was found to occur mainly, though not exclusively, via addition of the exocyclic amino groups of deoxyadenosine and deoxyguanosine residues of DNA to the benzylic carbon atoms of the epoxide functions.[18] This reaction occurs mainly, but not exclusively, via trans opening of the epoxide by the exocyclic amino group.[19] Although, the findings of these studies provide a useful tool to probe the mechanism of cancer induction, the details of the process involved remain obscure[20] and many questions concerning the structure-

activity relationships as well as the molecular mechanism of PAH carcinogenesis remain to be elucidated.[18]

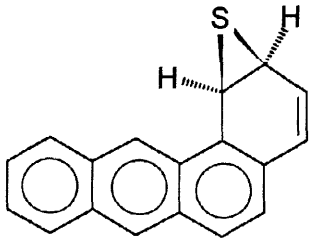
In view of the above, it is rather surprising that only a few, just recently synthesized polycyclic aromatic episulfides - the sulfur analogs of the PAH epoxides, (e.g., **25**) - are known thus far. Arene episulfides should be highly interesting in this context because: (a) the episulfides maintain the basic requirement of PAH carcinogenicity;[8] and (b) the well-established important role of organo-sulfur compounds in biological systems. Moreover, the particular steric, electronic and electrophilic requirements in the formation of the DNA adducts[20] may be even "in favour" of the arene episulfides compared with that of the corresponding arene oxides.

The lack of information concerning the PAH-episulfides (PeSs) is due to the instability of the aromatic episulfides (thiiranes) both thermodynamically[21] and kinetically[22] and consequently, to their synthetic nonavailability until very recently, particularly of the arene episulfides. Previously they have been reported only as intermediates.[23] Twelve years ago a reaction product was assigned the structure of phenanthrene 9,10-episulfide,[24] but this assignment has been shown by us to be in error.[25] Numerous attempts by others[26] and us (see later) to prepare PeSs by applying the commonly used methods for the synthesis of thiiranes[22,27] were unsuccessful. In view of the expectedly easy (nucleophilic) catalytic and/or thermal desulfurization of thiiranes, and the driving force towards aromatization in arene episulfides, these failures are not unexpected. Thus, although PeSs might be formed during the metabolism of carcinogenic PAHs from the interaction of PAH-epoxides (PEs) or DEs with sulfur nucleophiles available in the cells/tissues, the extent of their biological significance is questionable due to their instability.

We hoped that a theoretical quantum mechanical study of the chemical consequences of the replacement of the oxygen atom in arene oxides by the larger, more polarizable and more nucleophilic sulfur atom would provide an in-depth understanding of the nature of bonding, thermal stability and stereospecific structure-reactivity relationships in these systems, and would help direct the experimental efforts to the most relevant systems.

Objectives

The main objectives of our study at this initial stage were: (1) to synthesize the thus far elusive polycyclic arene episulfides (e.g. **5b**, **7** and **8**), in order to make them available for cancer-related bioorganic studies; (2) To gain fundamental information about polycyclic arene episulfides by reliable molecular orbital quantum mechanical calculations. Extensive research in the last 15 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.[28] Thus, the delineation of agreements and discrepancies between theoretical predictions and experimental results concerning the polycyclic arene episulfides will be made possible. We hoped that such a theoretical study would be helpful in directing future experimental efforts to the most relevant systems.



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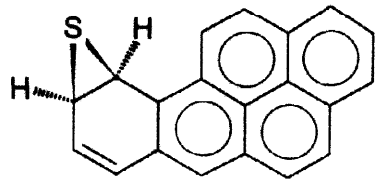

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The results of our experimental and theoretical studies are reported below.

Methodology

1. Synthesis methodology

The K-region and bay-region arene oxides (e.g., **5a**[14] and the O-analog of **8**,[13] respectively) or the parent hydrocarbons (e.g., phenanthrene in the case of **5b**) were used as precursors for the synthesis of the targeted arene episulfides. The arene oxides and the "olefinic"-PAH were treated with various sulfur transfer agents.[21,27,29] Following the erroneous report (see below) on the isolation of **5b** from the lithiation products of 5,7-dihydrodibenzo[c,e]thiepine **9**,[24] the latter was also used as a key starting material in the attempted synthesis of **5b**.

2. Computational methods

Standard *ab initio* molecular orbital[28] and Density Functional Theory (DFT) calculations (using the B3LYP[30] functional) were performed using the Gaussian 94 series of programs.[31] The polarized 6-31G* basis set was used in all the calculations.[31] With both theoretical methods the geometries were fully optimized (at the Hartree-Fock level for the *ab initio* calculations) and characterized as minima by calculating the harmonic vibrational frequencies and characterizing the corresponding Hessian matrix.[31] The HF/6-31G* optimized geometries were used for single point calculations at the third-order Möller-Plesset perturbation correction (MP3(full)),[32] for treatment of electron correlation effects. The DFT/B3LYP[30] method enables calculations on relatively large systems with inclusion of electron correlation.

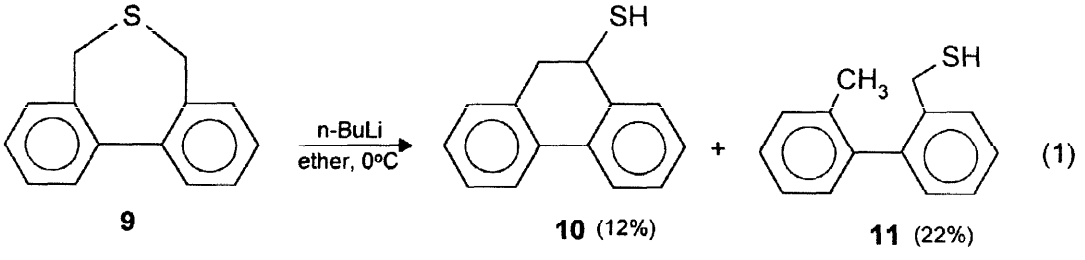
The following thermodynamic quantities were determined using the Gaussian statistical-mechanics routines (which use the standard expressions for an ideal gas in the canonical ensemble):[31] zero-point energies (ZPE), entropies at 298 K ($S°_{298}$) and Gibbs free energies at 298 K ($G°_{298}$). At the MP3 level of theory the $G°_{298}$ values were calculated as the sum of the MP3/6-31G* electronic energy and the thermal Gibbs energy calculated at B3LYP. The calculated absolute energies and zero-point energies (ZPE) of all the species calculated in this study are given in the Supplementary Material (available from the corresponding author).

Results and discussion

1. Experimental Studies

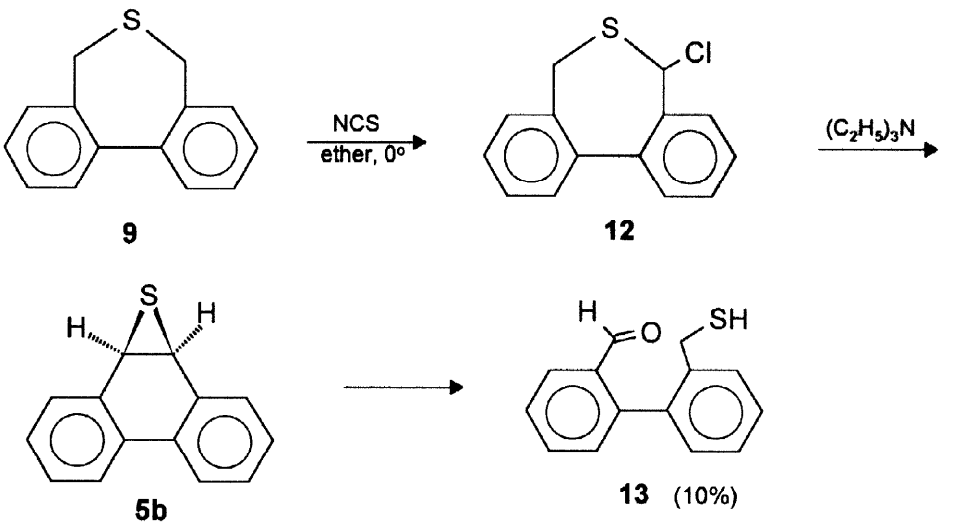
Our preliminary attempts to obtain the target model compound, phenanthrene-9,10-episulfide **5b,** involving the reactions of the corresponding epoxide precursor **5a** with: potassium thiocyanate, hydrogen sulfide, or with 2-methylbenzothiazole-2-thione, under a variety of conditions, failed. NMR monitoring of these reactions suggested that only in the reaction of **5a** with 3-methylbenzothiazole-2-thione under acidic conditions[33] **5b** might be an intermediate. Thus, the NMR 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, CH_3), ppm of which the singlet at 3.93 ppm might be assigned to **5b**. However, all attempts to actually isolate **5b** were unsuccessful.

Following the report[24] on the isolation of **5b**, via the reaction of 5,7-dihydrobenzo[c,e]-thiepine **9** with butyllithium at low temperatures, we have attempted in vain to prepare the latter via this procedure. Disappointingly, the only isolated products, except recovered starting material and phenanthrene, were the thiols **10** and **11**, as shown in equation 1. The formation of both **10** and **11** can be accounted for as resulting from **5b**, e.g., by invoking a 2H-reductive cleavage of **5b** leading to **10** and a consecutive 2H-reductive cleavage leading to **11**, or alternatively, based on the marked tendency of arene oxides to rearrange to phenols,[13] the thiol **10** may result from the ring opening of the intially formed **5b**. However, at this point, there is no support for any of these mechanisms.



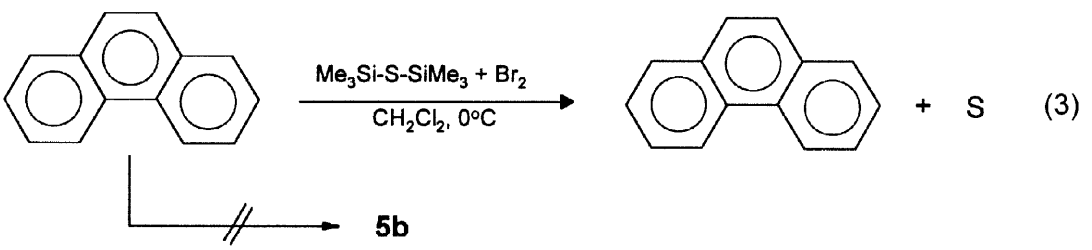
9 **10** (12%) **11** (22%)

The α-chlorination of the thiepine **9** in dry ether with N-chlorosuccinimide (NCS) followed by treatment of the reaction mixture with triethylamine yielded after work-up, the thiolaldehyde **13** in a very low yield (~ 10 %) and recovered **9**. It is possible that **5b** is formed as an intermediate via the dehydrohalogenation of the α-chlorosulfide **12**, and is responsible for the formation of **13** (equation 2). Compound **13** could also arise from the direct hydrolysis of **12**. Thus, also in this reaction the presence of the targeted **5b** could be only circumstantially inferred, but it was not directly detected in the reaction mixture.



(2)

Following the procedure of Capozzi et al.,[34] which is applicable to cis-olefins only, we reacted phenanthrene (**1**) with the effective sulfur transfer agent: bis-trimethylsilyl sulfide in the presence of bromine (equation 3).[29] Only the precursor phenanthrene and elemental sulfur were quantitatively recovered from the reaction mixture. Since the reaction of bis-trimethylsilylsulfide with bromine afforded quantitatively elemental sulfur, either in the presence or in the absence of phenanthrene, we conclude that the target phenanthrene episulfide (**5b**) is not involved in this process.



(3)

2. *Theoretical Studies*

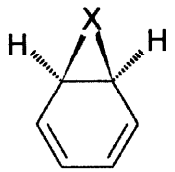
At this point we turned to theoretical calculations in order to gain reliable information on the thermodynamic stability of arene episulfides, especially in comparison with that of known analogous arene oxides.[2,13]

(a) The parent benzene epoxide and benzene episulfide

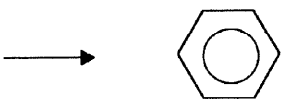
What are the relative thermodynamic stabilities of analogous arene expoxides and episulfides? Let us examine first the parent benzene epoxide (**14a**) and benzene episulfide (**14b**). Benzene epoxide was synthesized and isolated (although its isolation from its mixture with the isomeric oxepines is difficult),[35] while benzene episulfide has not been isolated as yet.[36]

One way to estimate the thermodynamic stability of **14** is by equation 4, which describes its dissociation to give benzene and atom X, which is either oxygen or sulfur in its triplet ground electronic state.[37] $\Delta G°$ for this reaction reflects the thermodynamic stabilities of **14a** and **14b**

towards this simple dissociation process. The calculated energies of equation 4 are summarized in Table 1.



14a (X=O)
14b (X=S)



+ X: (X=O, S) (4)

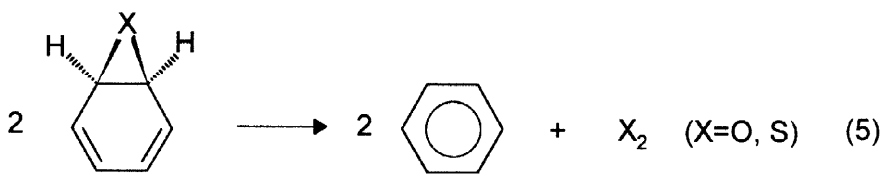
Table 1. Calculated ΔH° [a] for reactions 4-16.

eq.	X	ΔH°		eq.	X	ΔH°	
		MP3 [b]	B3LYP [c]			MP3 [b]	B3LYP [c]
4	O	41.54 [d]	51.83 [f]	11	O		-16.35[h,i]
	S	18.70 [e]	21.47 [g]		S		-15.37[h,i]
5	O	-10.73	-18.72	12	O		-14.36 [i]
	S	-40.08	-52.00		S		-14.50 [i]
6		-47.99	-58.75	13	O		-5.78 [i]
7	O	-29.23	-30.85		S		-6.69 [i]
	S	-30.42	-33.04	14	O		-10.07 [i]
8	O	-25.93	-29.09		S		-10.81 [i]
	S	-23.06	-27.05	15	H	-26.36	-22.60
9	O	49.48	34.53		CH_3	-25.49	-22.42
	S	38.61	27.58	16	H		-21.83
10	O	52.64	52.12		CH_3		-21.65
	S	47.35	46.24				

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

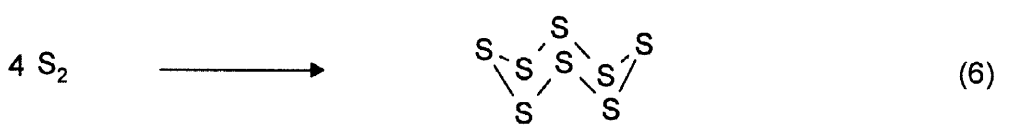
Equation 4 is calculated to be endothermic for both X=O and X=S. However, the calculations reveal a marked difference between the arene oxide and the arene episulfide, the latter being much less thermodynamically stable towards this dissociation reaction. Thus, while ΔG° of equation 4 for **14a** is endothermic by 34.4 kcal/mol at MP3/6-31G*//6-31G* (44.6 kcal/mol at B3LYP/6-31G*), for benzene episulfide (**14b**) ΔG° is endothermic by only 11.6 (14.3) kcal/mol at MP3/6-31G*//6-31G* and B3LYP/6-31G*, respectively. The low ΔG° of equation 4 for the episulfide **14b**, indicates a very low thermodynamic stability towards dissociation, implying that **14b** should be difficult to isolate even at low temperatures, where the contribution of entropy is small.

We are, of course, aware of the fact that the extrusion of sulfur from **14b** is probably significantly more complicated than the single-step mechanism shown in equation 4. The extrusion reaction may involve, for example, two molecules of **14b** and extrusion of molecular S_2 (equation 5) or of extended clusters of sulfur atoms which are thermodynamically more stable than S_2 (see for example the paper by Miller et al.[38]). However, the qualitative conclusions about the relative thermodynamic stabilities of **14a** and **14b** towards the extrusion of oxygen and sulfur respectively, are very similar whether their thermodynamic stabilities are calculated via equation 4 or via equation 5 (which compares the stabilities of **14a** and **14b** relative to that of benzene and triplet O_2 or S_2, respectively). Equation 5 is exothermic for both X=O and X=S, but it is much more exothermic for the episulfide **14b** (-40.1 and -52.0 kcal/mol at MP3/6-316*//6-31G and B3LYP/6-31G*, respectively) than for the epoxide **14a** (-10.7 and -18.7 kcal/mol at MP3/6-31G*//6-31G* and B3LYP/6-31G*, respectively, see Table 1).

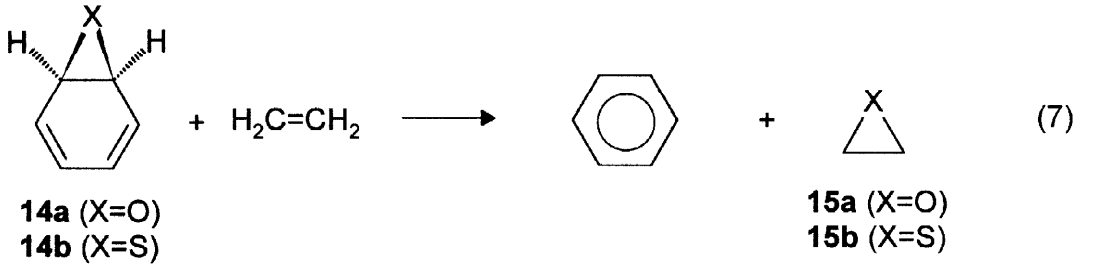


14a (X=O)
14b (X=S)

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). This reaction is very exothermic, by -48.0 (-58.8) kcal/mol at MP3/6-31G*//6-31G* (B3LYP/6-31G*), and thus it is expected to further decrease the thermodynamic stability of **14b** with respect to sulfur extrusion, as it will make equation 5 (leading to S_8 instead of S_2) exothermic by ca. 52-67 kcal/mol. These considerations do not affect the thermodynamic stability of **14a**, because O_2 is a thermodynamically stable entity. According to model MINDO/3 calculations on related systems, the activation energies for sulfur extrusion leading to S_8 are lower than 5 kcal/mol.[38] If this conclusion applies to **14b** then one can conclude that the kinetic stability of **14b** towards the extrusion of sulfur is very low. This may explain why all attempts made so far to isolate **14b** have failed.



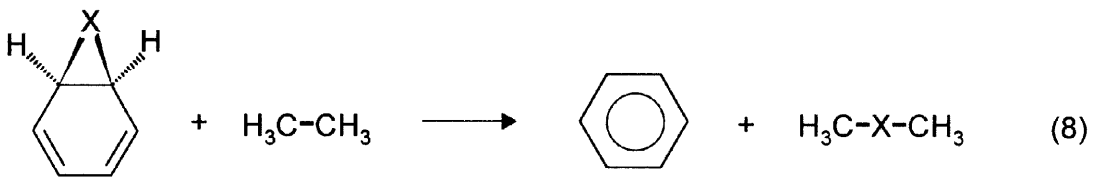
Two other comparisons between the thermodynamic stability of benzene oxide and benzene episulfide are given by the isodesmic equations 7 and 8 (Table 1).



(7)

14a (X=O)
14b (X=S)

15a (X=O)
15b (X=S)



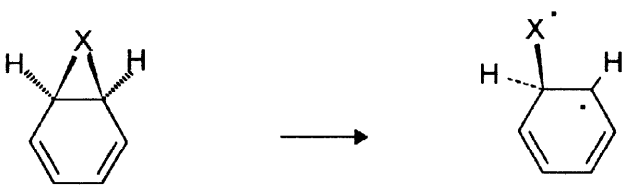
(8)

14a (X=O)
14b (X=S)

16a (X=O)
16b (X=S)

Equations 7 and 8 are exothermic for both X=O and X=S (Table 1), revealing again the thermodynamic instability of **14a** and **14b** towards the transfer of X. The exothermicity of equations 7 and 8 results mainly from the aromatic stabilization of the benzene ring formed in these processes. Equations 7 and 8 do not reveal any significant differences between the oxygen and the sulfur compounds, leading to the conclusion that the strain of the bicyclic skeleton in **14b** and **14a** is similar. Furthermore, this suggests that the lower thermodynamic stability of the episulfide **14b** compared to that of the oxide **14a** towards extrusion of X or X_2 (i.e., equations 4 and 5, respectively), does not result from an inherent instability of the polycyclic episulfide but, to a large extent is due to fact that C-S bonds are generally weaker than C-O bonds by ca. 20 kcal/mol[39a] (see also equation 9), and to the higher stability of the triplet state of atomic sulfur compared with that of triplet oxygen.[37] In equations 7 and 8 the different strengths of the C-S and C-O bonds play a minor role as they appear on both sides of these equations. Using the calculated energies of equation 8 for X=O and X=S and the experimentally known[39b] gas-phase heats of formations at 298 °K (i.e., ΔH_f° (298)) of the other molecules in these equations (i.e.,: benzene (19.82 kcal/mol), ethane (- 20.24 kcal/mol), CH_3OCH_3 (- 43.99 kcal/mol) and CH_3SCH_3 (- 8.97 kcal/mol)), the heat of formation of benzene episulfide (**14b**) is predicted to be 54.1 – 58.1 kcal/mol (at MP3/6-31G* or B3LYP/6-31G* respectively) and that of benzene oxide (**14a**) is 22.0 – 25.2 kcal/mol at (MP3/6-31G* or B3LYP/6-31G* respectively).

We have also probed the kinetic stability of benzene oxide **14a** and of benzene episulfide **14b**, by calculating the energy required to cleave one of their strained C-X bonds to produce the corresponding triplet biradicals **17a** and **17b**, respectively (see equation 9).



(9)

14a (X=O)
14b (X=S)

17a (X=O)
17b (X=S)

The results of the calculations at the MP3/6-31G*//6-31G* and the B3LYP/6-31G* levels differ by some 10-15 kcal/mol (Table 1), but both methods predict that the cleavage of a C-S bond in **14b** is significantly more facile (i.e., by 7-11 kcal/mol) than the cleavage of a C-O bond in **14a**. These results, in agreement with the thermodynamic data of equations 4 and 5, suggest that also kinetically **14b** should be much more reactive and thus more difficult to isolate than **14a**. Cleavage of the C-X bond in either **14a** or **14b** is significantly more facile (less endothermic) than the analogous C-X bond cleavage in oxirane (**15a**) and thiirane (**15b**), respectively (equation 10). This is expected, since in **17a** and **17b** the odd-electron centred on carbon is stabilized by conjugation with the adjacent diene unit, while in **18a** and **18b** such delocalization is not possible.

(10)

15a (X=O)
15b (X=S)

18a (X=O)
18b (X=S)

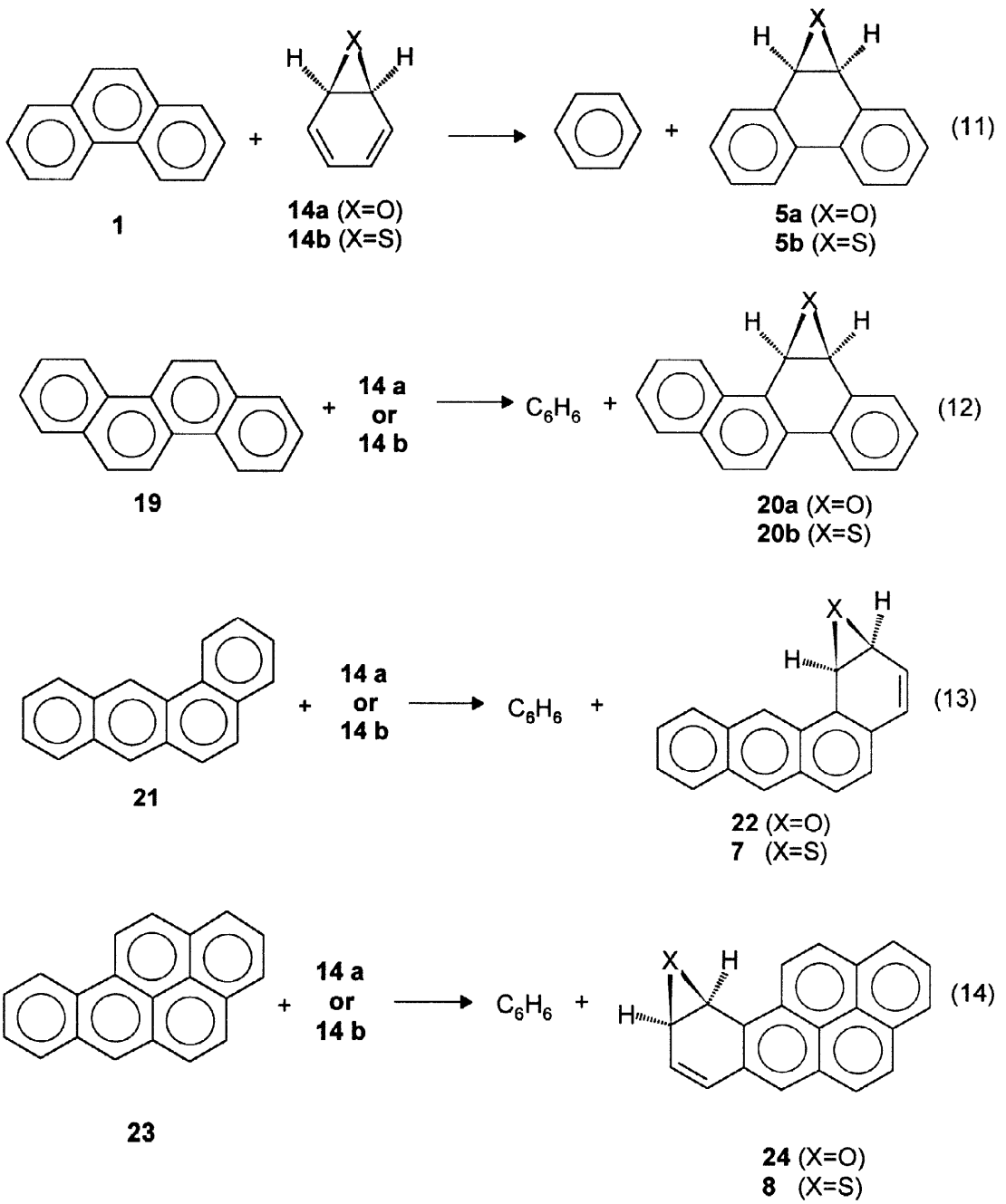
In conclusion, all the calculations point clearly to a very low thermodynamic and kinetic stability of **14b**, a conclusion consistent with the failures to isolate it.[36]

(b) Larger arene epoxides and episulfides

We have extended the calculations to oxides and episulfides of several larger K- and bay-region polycyclic arene episulfides, particularly to those, for which the corresponding oxides have been successfully synthesized. These calculations may allow us to predict which arene episulfides are more likely to be synthetically accessible. As the size of the polycyclic aromatic moiety increases, the number of possible expoxides and episulfides increases dramatically. In this study we examine only a few representative regioisomers and do not intend to cover all the possible regioisomers.

Equations 11-14 compare the thermodynamic stability of several larger arene oxides and episulfides with those of the parent benzene oxide (**14a**) and benzene episulfide (**14b**), respectively. Note that equations 11-14 are obtained by the subtraction of two oxygen (or sulfur) extrusion equations, i.e., equation 11 is obtained by substracting from equation 4 an analogous equation for the larger polycyclic compounds **5a** and **5b**. A more negative (exothermic) value of $\Delta H°$ indicates a higher thermodynamic stability of the larger polycyclic compound (e.g., **20a** or **20b**) relative to **14a** or **14b**. Furthermore, as equations 11-14 are isodesmic (unlike equations 4 or 5), it is expected that computational errors to a large extent

cancel out, leading to more reliable results.[28] The calculated energies of equations 11-14 are reported in Table 1.

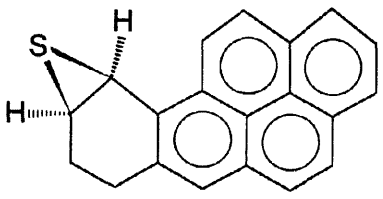


The most important conclusion from the results of the calculations for reactions 11-14 is that the thermodynamic stabilities of analogous arene oxides and arene episulfides (relative to the parent **14a** and **14b,** respectively) are very similar (Table 1). *This suggests that the relative thermodynamic stabilities of the already known arene oxides (**5a**, **20a**, 22 and 24)*[14] *are a good guide for indicating which arene episulfides have a better chance to be isolated.* Thus, the higher the thermodynamic stability of the arene oxide the higher is the thermodynamic stability of the corresponding arene episulfide. Our calculations also predict that the K-region

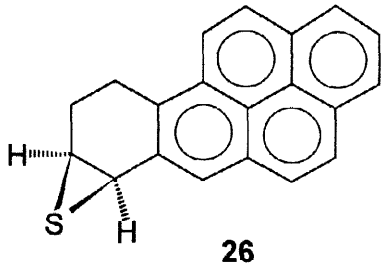
polycyclic arene episulfides are more stable thermodynamically, and thus have a better chance to survive isolation, than their bay-region isomers. For example, compare the calculated $\Delta H°$ values for equations 11 and 12 with those of equations 13 and 14, the former two equations being significantly more exothermic.

Of the representative episulfides considered in equations 11-14 the most stable thermodynamically is the phenanthrene episulfide **5b**, which is calculated to be by ca. 15.4 kcal/mol more stable with respect to S-transfer than the parent benzene episulfide (**14b**). We therefore believe that **5b**, may be sufficiently stable to survive isolation. However, we note that even in this favourable case $\Delta G°$ for the dissociation of **5b** to phenanthrene and atomic S is endothermic by only ca. 28 kcal/mol and its dissociation to produce phenanthrene and S_2 or S_8 is highly exothermic, so that the isolation of **5b** should be attempted only at very low temperatures and undoubtedly it presents a major synthetic challenge. Note that the calculated energies of equations 11-14, can be used to predict the heats of formation of the larger arene epoxides and episulfides which appear in these equations, using the $\Delta H_f°$ values of **14a** and **14b** evaluated above and the experimentally known $\Delta H_f°$ values of the corresponding hydrocarbons (e.g., of **1** for calculating $\Delta H_f°$ of **5a** and **5b** via equation 11).

Our theory-based conclusion that K-region epoxides and episulfides are thermodynamically more stable than their bay-region isomers is in agreement with the limited available experimental knowledge. Thus, for example, the bay-region arene oxide **4** was found to be significantly less stable than its 1,2-oxide isomer.[13] Similarly, the recently synthesized bay-region 9,10-episulfide of tetrahydro-benzo[a]pyrene (**25**), slowly loses elemental sulfur when left to stand for several days, whereas its 7,8- isomer **26** is stable at room temperature.[40]



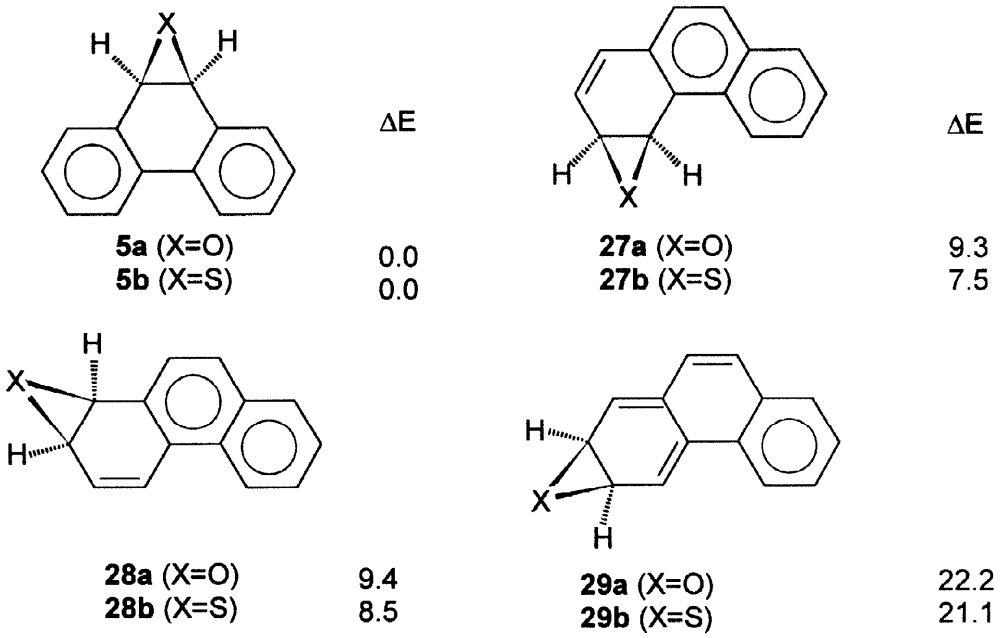
25



26

Our calculations for reactions 13 and 14 (Table 1) also suggest that within the bay-region arene episulfide series, the thermodynamic stability and thus the chances of a compound to survive isolation, increase the higher is the aromatic character[41] of its ring system. To test this hypothesis we have calculated several isomeric oxides and episulfides.

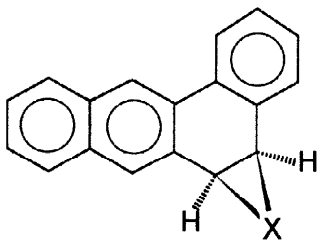
For the phenanthrene system we have calculated all the 4 possible epoxide and episulfide isomers: i.e., **5**, **27**, **28**, **29**. Their calculated relative stabilities ΔE (in kcal/mol) at the B3LYP/6-31G* level of theory are summarized in Scheme 1.



Scheme 1. Relative energies (kcal/mol) of phenanthrene oxides and episulfides.

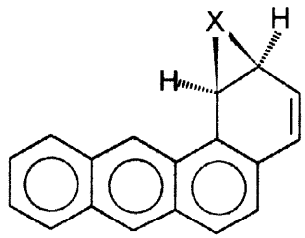
The calculated stability order of the isomers follows the order expected on the basis of simple aromatic resonance arguments.[41] The most stable isomer for both X=O and X=S is the K-region isomer **5** in which two benzene rings retain their aromaticity. The second most stable isomers are **27** and **28** in which the aromaticity of a naphthalene ring is preserved. The aromatic stabilization of a naphthalene ring is intermediate between that of a single benzene ring and of two benzene rings.[41] The least stable isomer, lying ca. 21-22 kcal/mol higher in energy than **5**, is **29,** in which only the aromaticity of one benzene ring is preserved.

This qualitative criterion is applicable also to larger systems. Thus, for example, we have compared the relative energies of the bay-region arene oxide **22** and episulfide **7** with the corresponding K-region isomers **30** and **31**, and also the relative energies of the bay-region arene oxide **24** and episulfide **8** with the corresponding K-region isomers **32** and **33**, respectively. The results, which are shown in Schemes 2 and 3 respectively, follow the above-mentioned simple aromatic resonance arguments. Thus, in Scheme 2 the most stable isomers for both X=O and X=S are the K-region **30a** and **30b,** which retain the aromaticity of a benzene and of a naphthalene ring. The isomers **22** and **7** are less stable, because they possess an anthracene ring which has a lower aromatic character. **31a** and **31b** are the least stable isomers as they possess the most disturbed aromatic system, allowing aromaticity only in a single benzene ring.



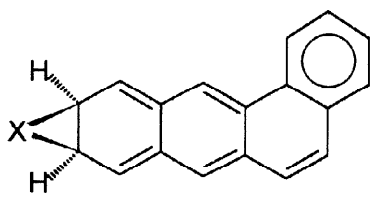
ΔE

30a (X=O) 0.0
30b (X=S) 0.0



ΔE

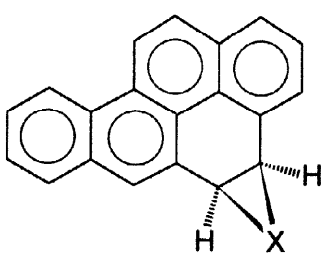
22 (X=O) 12.8
7 (X=S) 10.8



31a (X=O) 30.4
31b (X=S) 29.5

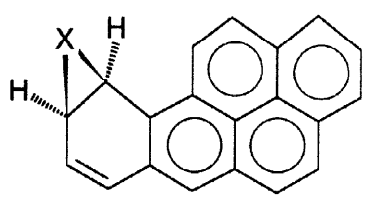
Scheme 2. Relative energies (kcal/mol) of benz[a]anthracene oxides and episulfides.

Another example which follows the "aromaticity-order" is shown in Scheme 3. The most stable isomers are **32a** and **32b**, in which the aromaticity of a chrysene system is preserved. **24** and **8** which possess the aromaticity of a pyrene, are less stable. The least stable isomers are **33a** and **33b** in which the aromatic conjugation is strongly disturbed, with only one of the benzene rings remaining intact.



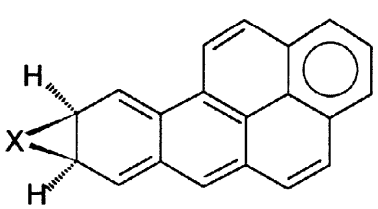
ΔE

32a (X=O) 0.0
32b (X=S) 0.0



ΔE

24 (X=O) 8.8
8 (X=S) 6.9

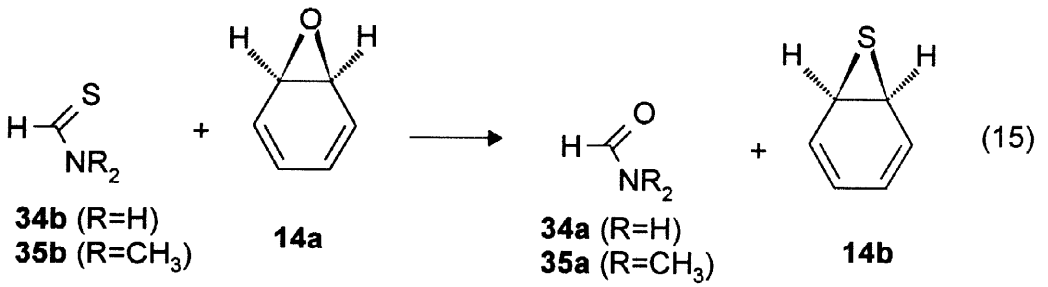


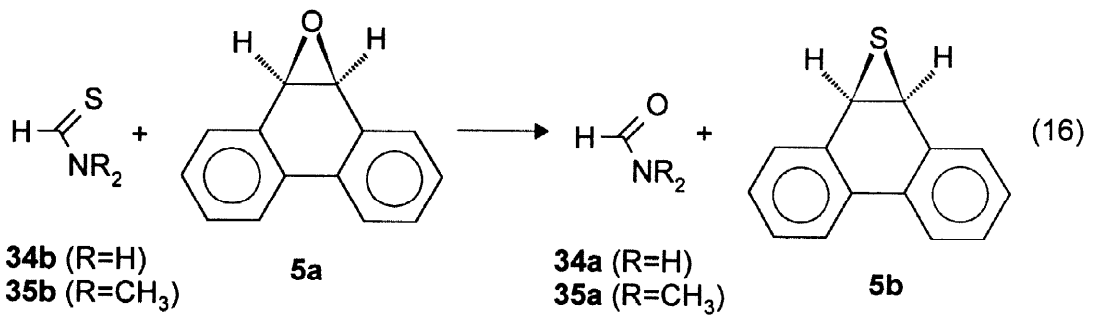
33a (X=O) 27.7
33b (X=S) 26.7

Scheme 3. Relative energies (kcal/mol) of benz[a]pyrene oxides and episulfides.

(c) Sulfur-transfer reagents

We have also probed the ability of the nucleophilic reagents $HC(=S)NH_2$ (**34b**) and $HC(=S)N(CH_3)_2$ (**35b**) to serve as efficient sulfur-transfer agents to arene epoxides, to produce the corresponding arene episulfides (see equations 15 and 16).





The sulfur transfer reactions for both R=H and $R=CH_3$ are calculated to be quite exothermic; i.e., by 22-26 kcal/mol (depending on the theoretical level), suggesting that at least thermodynamically **35b** (and also **34b**), which was recently used successfully by us for this transformation, in the benzo[a]pyrene series,[42] can serve in these reactions as an efficient sulfur transfer reagent.

Conclusions

The results of our experimental work suggest that the reaction of sulfur transfer agents with arene oxide or the parent PAH precursors may lead to the synthesis and isolation of the target polycyclic arene episulfides. However, as the thermodynamic and kinetic stability of arene episulfides towards the loss of sulfur is significantly lower than that of arene oxides, as clearly shown by the calculations, their synthesis and isolation must be attempted at substantially lower temperatures.

Our calculations have also shown that the thermodynamic stabilities of different arene oxides parallel the relative stabilities of the corresponding arene episulfides. This finding could be very useful as it can indicate which arene episulfides are more likely be isolated. The calculations predict that: (a) arene episulfides of the K-region type are more stable towards sulfur extrusion than their bay-region isomers; (b) within the bay-region episulfide series the larger the number of the intact aromatic rings in the molecule, the more thermodynamically stable it is; (c) the order of thermodynamic stability of various arene oxides and episulfides can

be deduced by examining the degree of the "aromatic character" of the rings which do not carry the heteroatom.

In view of the above and the recent successful synthesis[40a] of the tetrahydrobenzo[a]pyrene episulfides **25** and **26** (via modification of the procedure of Takido et al.[43]), and of **6b**,[43] we expect that the treatment of the arene oxide **24** with N-dimethylthioformamide will yield the arene episulfide **8**, one of our target compounds. This work is currently in progress.

Experimental section

Reagents and solvents used were either commercially available or prepared, purified, or dried, as appropriate according to well-established lab procedures. Proton NMR spectra were recorded at 250 or 300 MHz in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to internal TMS. Mass spectra were run on a Varian 711 double-focusing mass spectrometer with an electron energy of 70 eV.

Selected important data of NMR-tube reaction mixtures (a & b) are provided below:

(a) NMR spectra of the reaction of **5a** with 3-methylbenzothiazole-2-thione (**36**):

5a + **36**: 7.15-8.12(m), 4.55(s), 3.83(**36**:s, 3H, CH_3).

5a + **36** $\xrightarrow{H^+/CF_3CO_2H}$: 7.21-8.73(m), 6.37(d), 5.50(d), 3.93(s), 3.83(**36**:s, 3H, CH_3).

(b) NMR spectra of the reaction of **5a** with H_2S:

5a + H_2S: 7.25- 8.13(m), 4.55(s), 0.81(H_2S: s, 2H):

5a + H_2S ⟶ :7.49-7.70(m), 7.00(s), 0.80 (H_2S: s, 2H):

5a $\xrightarrow{H^+}$:7.54-8.55(m), 6.39(s), 6.32(s), 5.88(d), 5.01(d).

Preparation of thiols 10 and 11 (reaction 1): Reactions were carried out under N_2 atmosphere, in anhydrous ether (7.5 -15 ml), on a 0.5-4 mmol scale mostly at 0°C → 25°C (some reactions at -78°C → 25°C.), using an equimolar ratio between **9** and BuLi (except for a few runs with excess of BuLi) and time duration of 4-6 hrs. After the reaction was completed (determined by TLC monitoring), the reaction mixture was washed with water, the organic phase was separated and dried (Na_2SO_4) and the crude product was separated by column chromatography (silica-gel; eluant: PE:CH_2Cl_2=70-95: 30-5 v/v) to obtain recovered **9**, phenanthrene (35-40%), **10**, (12%) and **11** (22%).

10: ^{1}H NMR, 7.23-7.44 (m, 8H; arom), 3.24-3.56 (m, 3H; CH_2, CH), 1.56 (s, 1H, SH); MS, 212.0663 (M^+, 90.4%), 211.0592 (M^+-H, 23%), 180.0900 (M^+-S, 19.1%) 179.0862 (M^+ -SH, 100%).

11: ^{1}H NMR, 7.03-7.46 (m, 8H; arom.), 3.33-3.61 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.64 (t, 1H; SH); MS, 214.0808 (M^+, 73%), 181.1001 (M^+ -SH, 96.1%), 180.0933 (M^+-SH_2, 80%), 179.0871 (M^+-H_2O-H, 50.5%), 178.0785 (M^+-H_2S-2H, 27%). 165.0711 (M^+ -H_2S-CH_3, 100%).

Preparation of 13 (reaction 2): Thiepine **9** was treated with N-chlorosuccinimide (1:1.1 mole ratio; 0.5-4 mmole scale) in dry ether under nitrogen, at 0°C. The reaction mixture was treated with Et_3N, the Et_3NHCl precipitate was filtered and the filtrate was dried (Na_2SO_4). Column chromatography (silica gel) afforded (in addition to recovered **9**) **13** (~10% yield).

13: IR ($CHCl_3$), 3075, 2400, 1685, 1590, 1210 cm^{-1}. ^{1}H NMR, 9.6 (1H; CHO), 7-8 (m, arom.), 3.3 (s, 2H, CH_2).

Acknowledgements

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37. We are aware of the fact that the extrusion reaction in equation 4 is spin-forbidden and that a spin-allowed process would lead to the higher energy singlet X. Thus, for S and O the singlet state is by 45.4 and 26.4 kcal/mol higher in energy than the triplet state, see Li, Y.; Wang, X.; Jensen, F.; Houk, K.N.; Olah, G.A. *J. Am. Chem. Soc.*, **1990**, *112*, 3922. However, we ignore here this point, as well as the possibility of intersystem crossing, because the energies of equation 4 serve only to gain qualitative information on the thermodynamic stabilities of **14a** and **14b** towards the elimination of X.
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