Persistent Carbocations from Bay Region Methoxy-Substituted Cyclopenta[*a*]phenanthrene and Its Derivatives. A Structure/Reactivity Study

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Received April 10, 2000

Using 500 MHz NMR, we have carried out a stable ion protonation and model nitration study of the methoxy-substituted hydrocarbon **6**, its 15-ol **7**, and the dimer **10**, in order to evaluate OMe substituent effects on directing electrophilic attack and on charge delocalization mode/conformational aspects in the resulting carbocations. It is found that the C-11 methoxy group directs the electrophilic attack to C-12 and C-14. Thus protonation of **6** with FSO_3H/SO_2ClF gives a 4:1 mixture of monoarenium ions $\mathbf{6H^+}/\mathbf{6aH^+}$. Prolonged reaction times and increased temperature induced fluorosulfonylation at C-14 ($\mathbf{6^+}$-$\mathbf{SO_2F}$), whereas ambient nitration with $NO_2^+BF_4^-$ occurred at C-12. The 15-ol derivative **7** is cleanly ionized to $\mathbf{11^+}$, providing the first example of an α-phenanthrene-substituted carbocation from phenanthrene C-1 position. Contrasting behavior of the D-ring methyl-substituted **9** and the C-11 methoxy-substituted **10** dimers is remarkable in that unlike **9** which is readily cleaved to produce the monomeric arenium ion $\mathbf{3H^+}$, **10** is diprotonated at the two C-12 sites and at C-12/C-14 in each unit. The latter dication−dimer exists as a mixture of diastereomers. Reactivity of **7** underscores the importance of $\mathbf{11^+}$. Attack at the C-14 ring junction is in concert with the proposal that electrophilic oxygen would attack at C-14/C-15 (epoxidation) followed by ring opening to give the biologically active 15-ol as a major metabolite.

Introduction

Because of its structural relationship to both PAHs and steroids, the cyclopent[*a*]phenanthrene skeleton **1** (Scheme 1) has received considerable attention.[1] Metabolic studies have indicated that the diol-epoxide activation path is important and that two ends of the molecule (A-ring and five-membered D-ring) are metabolized.[2−7] Synthetic routes to the A-ring dihydrodiols and diol-epoxide metabolites have also been developed.[8,9] Whereas parent **1** is inactive, biological activity is exhibited when a small alkyl group is substituted at the bay region (C-11) (as in **2**) or a double-bond is placed at C-16/C-17 (as in **3**). Carcinogenicity is greatly enhanced by combining methyl at C-11 with a CO group at C-17 (**3**a) or a double bond at C-16/C-17 (**4** and **4a**). Compound **5** with an 11-methoxy substituent and the 17-keto group is also potent. Surprisingly though, the 11-methoxy hydrocarbon **6** is equally potent (but **2** is only weakly active!).[10,11] Compound **7** is a major metabolite of **6** and is a strong direct-acting bacterial mutagen.[11]

In continuation of our studies on PAH arenium ions and α-PAH carbocations[12,13] and in search of correlations among site(s) of attack, carbocation stability/charge delocalization mode, and biological activity, in a previous stable ion study,[14] we examined the carbocations and carboxonium ions derived from various derivatives of **1**. The observed increased potency of the methoxy derivative **6** as compared to **2** and the importance of **7** in the metabolism of **6** were the impetus for the present investigation which focuses on **6**, **7**, and the dimer **10**. The latter is formed as a major product when the 17-ol **8** was exposed to weak acid.[10] In our previous work[14] it was found that dimer **9** gave $\mathbf{3H^+}$, i.e., the same carbocation derived from **3** by protonation at the double bond (see Scheme 2). Dimer **10** lacks the methyl groups at the five-membered rings and instead contains methoxy substituents at C-11.

Our goal was to explore if the unusual potency of **6** compared to **2** is manifested in their differing behavior under stable ion conditions where protonation is used to

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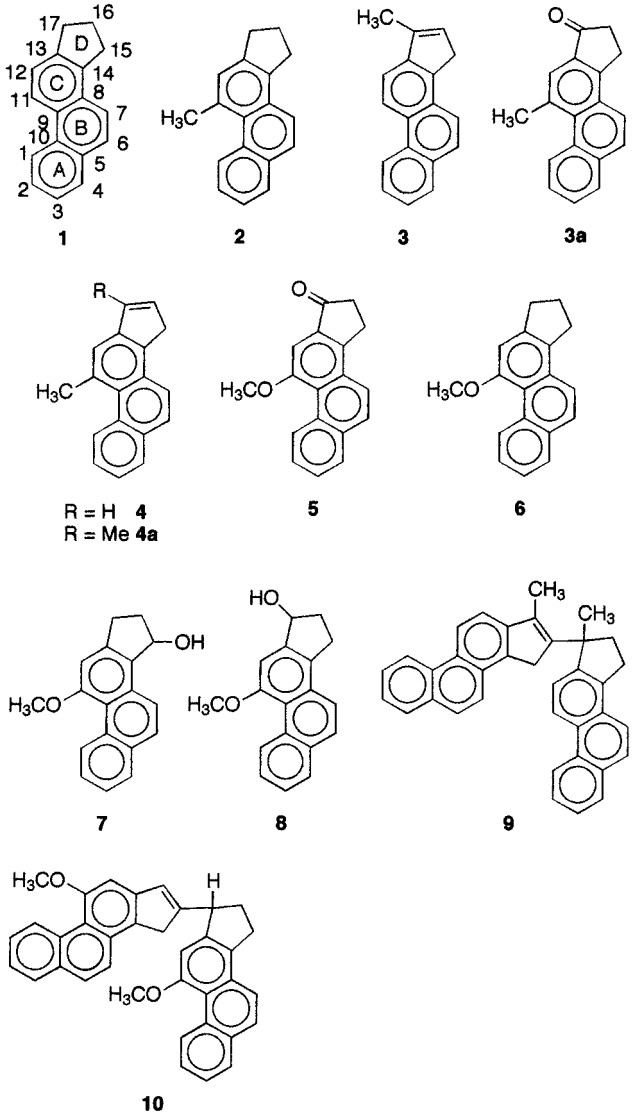
10.1021/jo000534i CCC: $19.00
Published on Web 10/05/2000

Scheme 1



mimic attack by electrophilic oxygen. Nitration of **6** and ionization of **7** resulting in the 15-carbocation $\mathbf{11}^+$ are also reported.

Results and Discussion

NMR Assignments. Detailed NMR assignments for the neutral precursors, their resulting mono- and dications and the nitro derivative were based on ^{1}H, ^{13}C, H/H COSY, C/H HETCOR, and NOED spectra. For the neutral compounds and major mono- and dications COLOC spectra assisted the specific assignment of the ring junction carbons (via ^3J C/H correlations). The data are summarized in Figure 1.

A significant feature in the ^{1}H NMR spectra of the 11-methoxy derivatives **6**, the 15-ol **7**, and the dimer **10** is the extreme low-field shift of the bay region proton H-1, whereas H-12 is the most shielded. Presence of a strong NOE effect between O*Me* and H-12 and weak NOE between O*Me* and H-1 establishes a conformation in which the methyl group moves away from the bay region toward H-12. This conformation does not change in the resulting carbocations (see below).

Stable Ion Studies (Scheme 2). We showed previously that compound **5** (a carcinogen) reacts with FSO_3H/SO_2ClF to give a carboxonium ion ($\mathbf{5H}^+$) (Scheme 2). The weakly carcinogenic 11-methyl hydrocarbon **2** is protonated at the ipso position to give the monoarenium ion $\mathbf{2H}^+$. In contrast, low-temperature protonation of **6** with FSO_3H/SO_2ClF under the same set of conditions produced a 4:1 mixture of monoarenium ions $\mathbf{6H}^+$ and $\mathbf{6aH}^+$, respectively (ortho/para to methoxy), as a clear orange solution.

AM1 predicts that protonation at C-14 and C-12 are most favored but it computes $\mathbf{6aH}^+$ ~1 kcal/mol lower than $\mathbf{6H}^+$. Protonation at C-1 is predicted to be the next best possibility (1.5 kcal/mol higher than $\mathbf{6H}^+$).[15] Other arenium ions including that of ipso attack had significantly higher energies.

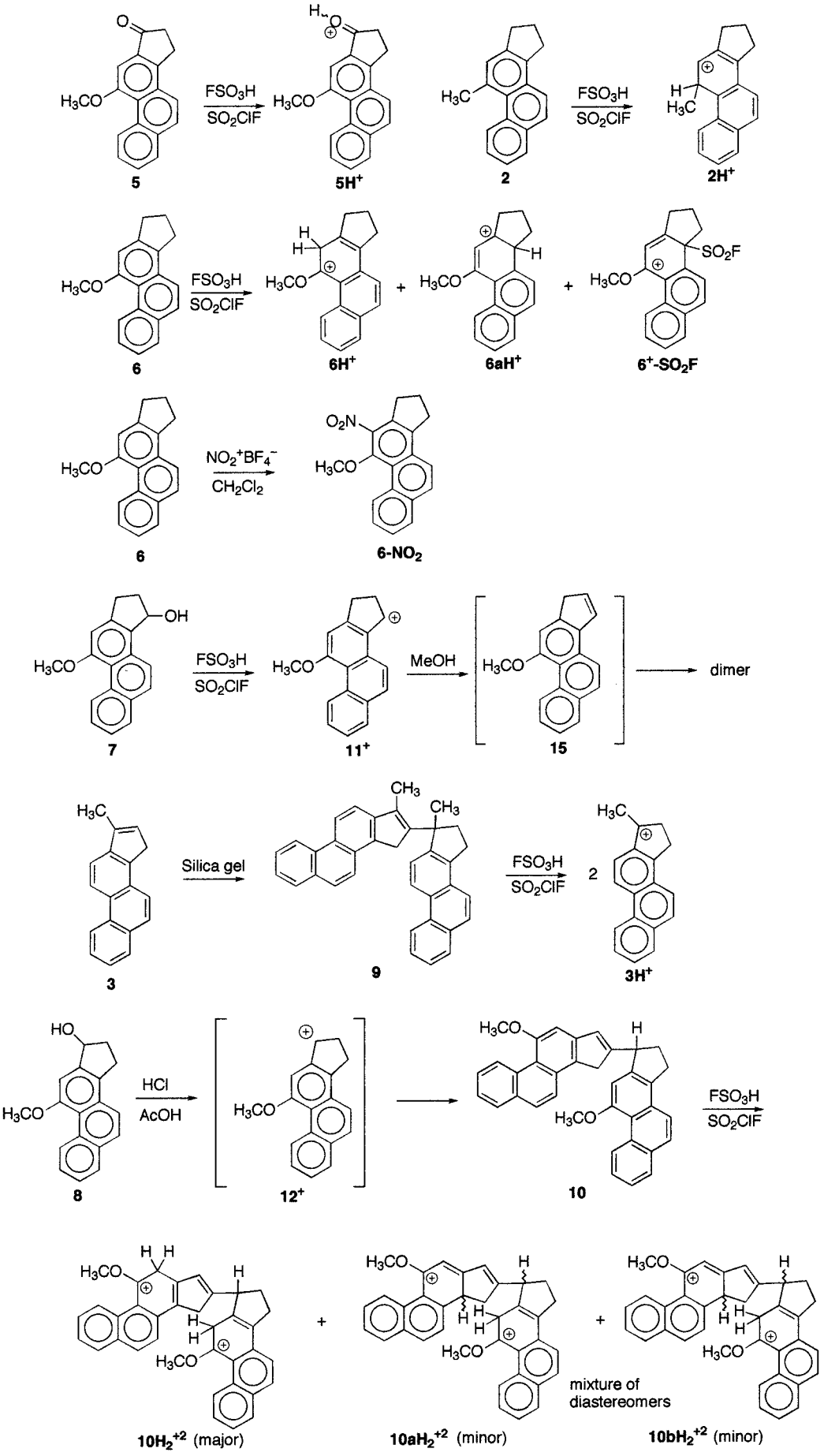
A noteworthy feature in the proton spectrum is the upfield shift of the H-1 ring proton in the arenium ions while other protons are all deshielded. Whereas it is tempting to attribute this to a geometrical change, there is no noticeable change in H-1/H-2 vicinal couplings which changed from 8.8 Hz in **6** to 8.9 Hz in $\mathbf{6H}^+$ and $\mathbf{6aH}^+$. In $\mathbf{6H}^+$ there is a strong NOE effect for O*Me*/CH_2 whereas NOE between O*Me*/H-1 is small. The same situation is observed for the minor cation. Therefore, methoxy orientation is not altered upon cation formation. In $\mathbf{6aH}^+$, the H-14 (at C/D ring junction) appears as a doublet of doublet at 4.20 ppm. Since C-14 is a stereocenter, the five-membered ring CH_2 protons are diasterotopic. One of the CH_2's at C-15 is unusually shielded. The AM1-minimized structure of $\mathbf{6H}^+$ shows it to be nearly planar with slight twisting at the bay region, whereas $\mathbf{6aH}^+$ is bent at the C-ring. The methoxy groups in both cases are pointing toward C-12 (this agrees with the NOED spectra). For $\mathbf{6aH}^+$, one of the CH_2 protons at C-15 is predicted to be located above the A/B ring plane (the space-filling model for $\mathbf{6aH}^+$ is shown in Figure 2). This corroborates the notion that it is anisotropically shielded. The most deshielded ^{13}C resonance in $\mathbf{6H}^+$ is the methoxy-bearing C-11 at δ 204.6 followed by C-8, C-13, and C-6. In $\mathbf{6aH}^+$, the most deshielded ^{13}C resonance is that of C-13 at δ 202.1. Quenching of the ion solution returned the intact hydrocarbon **6**.

When, in a separate experiment, the superacid solution containing $\mathbf{6H}^+/\mathbf{6aH}^+$ was allowed to warm-upto −20 °C, slow formation of the arenium ion of fluorosulfonation $\mathbf{6}^+\mathbf{\text{-}SO_2F}$ was observed by attack at C-14 which after 2 weeks accounted for 29% of the mixture. Prolonged storage of the superacid solution (0 °C for 15 h) increased its yield to 50%. Observation of slow fluorosulfonylation at C-14 under thermodynamic control provides a novel example pointing to C-14 as an active site. Cation $\mathbf{6}^+\mathbf{\text{-}SO_2F}$ exhibits an ^{19}F resonance at δ 67.8 which is in the expected range.[14] The D-ring CH_2's appear as multiplets, and the *C*-SO_2F is at δ 80.5. The PM3-minimized structure of $\mathbf{6}^+\mathbf{\text{-}SO_2F}$ is included in Figure 2.

In an attempt to isolate a neutral fluorosulfonation addition product at the C/D ring junction, the superacid solution was allowed to react with methylcyclohexane (a hydride donor) followed by H_2O/bicarbonate. However, only the hydrocarbon **6** was isolated. To explore the possibility that $\mathbf{6H}^+$ and $\mathbf{6aH}^+$ could be further protonated at the higher acidities to produce dications, pro-

(15) While protonation at C-1 gives a slightly less-stable cation, analysis of the AM1 MO's of **6** shows its pz to make no contribution to the HOMO so protonation at C-1 would be kinetically noncompetitive (we thank one of the reviewers for providing this information).

Scheme 2


FSO3H
SO2ClF
NO2+BF4−
CH2Cl2
MeOH
dimer
Silica gel
HCl
AcOH
2
mixture of
diastereomers

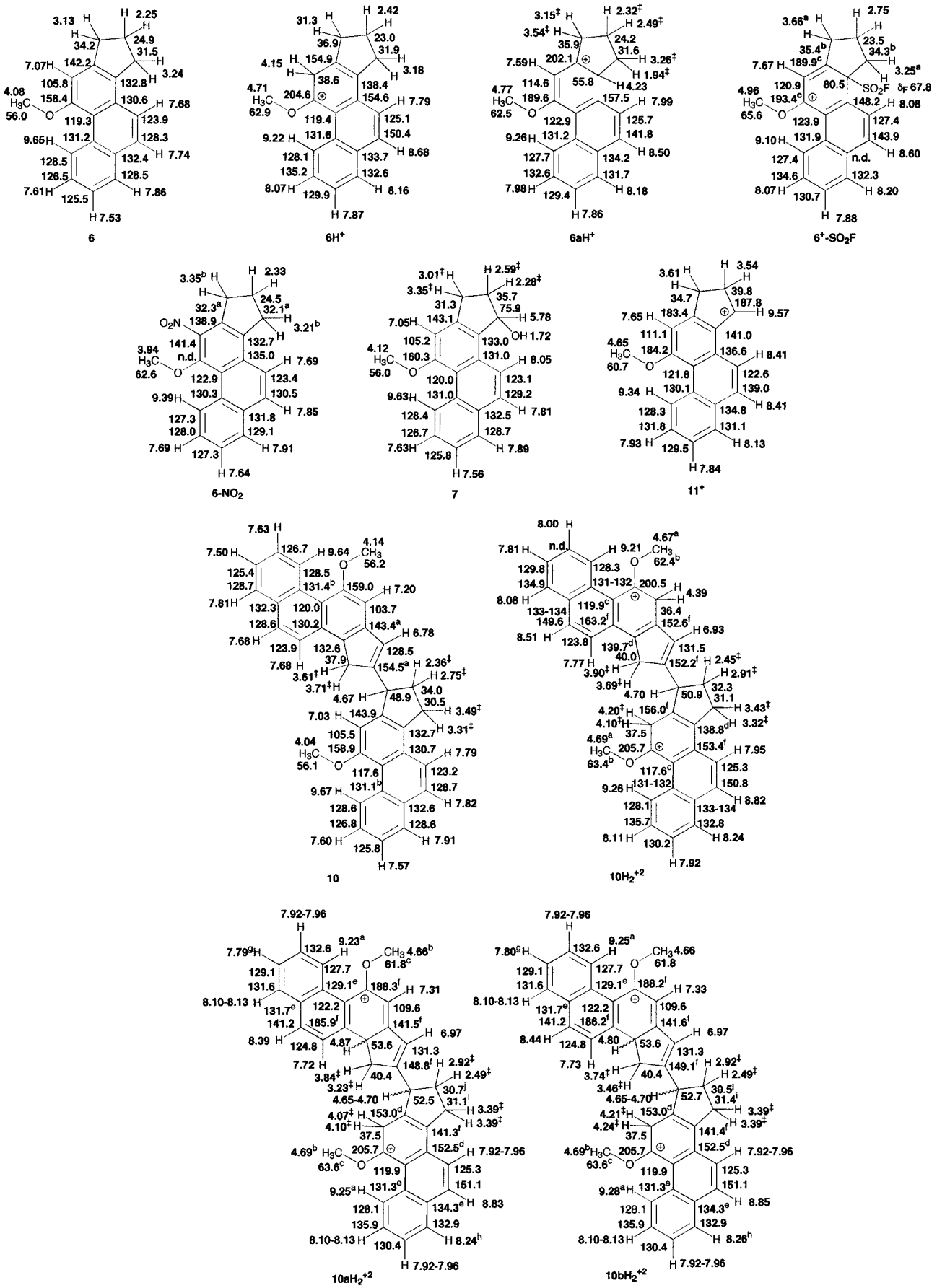


Figure 1. Summary of ^{13}C and ^{1}H NMR data for cations, precursors, and **6·NO₂**. [a, b, c, d, e, and f denote interchangeable assignment for a pair or group of proton or carbon resonances within a compound; g, h, i, and j denote interchangeable assignments within **7aH₂**$^{+2}$ and **7bH₂**$^{+2}$, ++ denotes that specific assignments of the diastereotropic protons in the five-membered rings are unknown.]

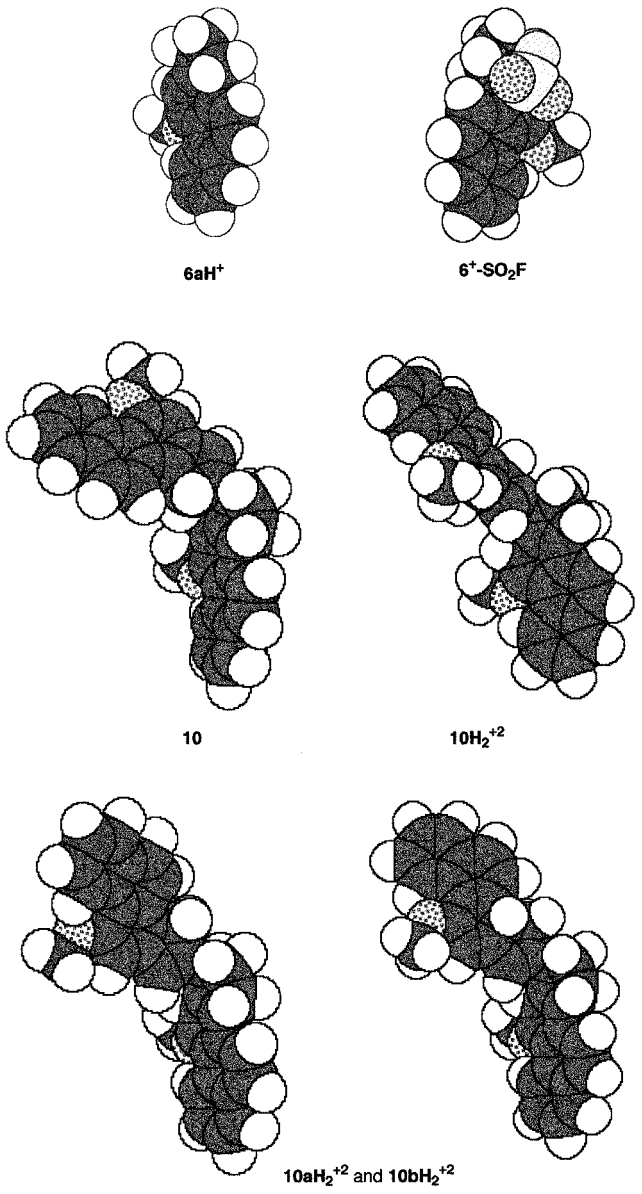


Figure 2. AM1-minimized structures of **6aH**$^+$, **10**, **10H**$_2^{+2}$, **10aH**$_2^{+2}$, and **10bH**$_2^{+2}$ and PM3-minimized structure for **6**$^+$-**SO$_2$F**.

tonation of **6** with FSO_3H-SbF_5 (4:1) and FSO_3H-SbF_5 (1:1) was also examined. This led to the formation of the same two carbocations (but yellow precipitates were also formed indicative of side reactions). The NMR spectra exhibited line-broadening suggesting competing oxidation and radical cation formation; polymerization set in shortly thereafter.

Aprotic Nitration of 6. For comparison, the room-temperature nitration of **6** was studied with NO_2BF_4 in CH_2Cl_2 solvent and reaction mixture was examined directly by NMR which showed that **6-NO$_2$** was formed in high selectivity by attack at C-12. Absence of an aromatic singlet (H-12) ruled out attack at C-14; no unreacted **6** remained.

Protonation of the 15-ol Derivative 7. The metabolitically significant alcohol **7** reacted with FSO_3H/SO_2ClF to produce **11**$^+$ exclusively (a clear red solution). This is the first example of a persistent α-phenanthrene-substituted carbocation from the phenanthrene C-1 position.[12b] In the ^{1}H NMR spectrum the C$^+$-*H* is the most deshielded resonance (at δ 9.57) and exhibits NOE with H-7 (at δ 8.41). The most deshielded carbon resonances are those of C-15/C-13/C-11.

Quenching in MeOH and H$_2$O. A 15-OMe derivative was not isolated upon quenching of **11**$^+$ with MeOH, instead a mixture of products was formed. Quenching with H_2O/bicarbonate also produced a mixture (**15** was not present in the mixture). The major component of the mixture was the same in both cases. Presence of diagnostic deshielded doublets at δ 9.69 and 9.64 (1H each) suggested that it is a dimer formed via **15** (analogous to **9** which is formed from **3**).

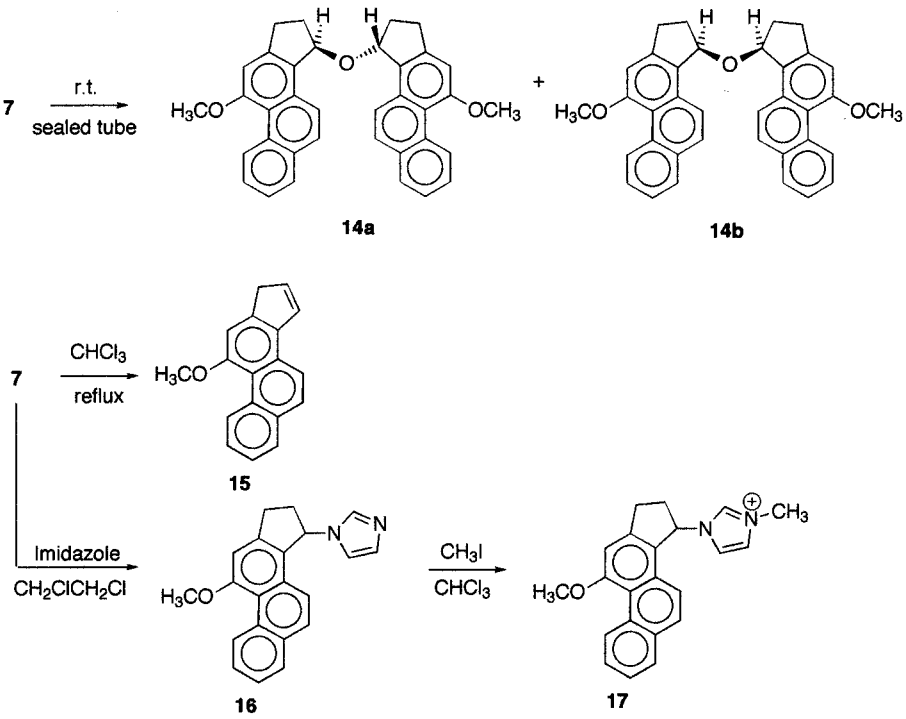
Reactivity Studies on the 15-ol 7. Compound **7** forms a white crystalline solid and has been previously characterized.[10,11]

Samples of **7** stored in sealed glass tubes turned brown. After 18 months, TLC analysis indicated that only a trace of **7** remained and revealed two major nonpolar products. These were separated and identified on the basis of UV and mass spectra (see Experimental Section) to be diastereomeric ethers **14a**/**14b** (Scheme 3). In the mass spectrum *m*/*z* 264 is the base peak which corresponds to the radical cation of **15**. Surprisingly, attempts to bring about ether formation by heating **7** in an inert solvent was not successful. Mild reflux in $CHCl_3$ led to quantitative conversion to **15** with its characteristic olefinic C*H* at δ 7.47 and 6.66. In an attempt to trap **11**$^+$ in competition, **7** was carefully heated in CH_2ClCH_2Cl or cyclohexane in the presence of imidazole (a biologically relevant nucleophile). This led to the formation of a new product, whose NMR spectral characteristics agree with that of imidazole adduct **16**. Since **16** is somewhat unstable, removal of excess imidazole was not attempted. In an attempt to provide corroborative information, the mixture was reacted with MeI and the reaction mixture was examined directly by electrospray mass spectrometry. This showed the *N*-methylated imidazolium adduct **17** (*m*/*z* 329) and a fragment ion at *m*/*z* 247 corresponding to **11**$^+$. MS/MS experiment on the isolated *m*/*z* 329 gave *m*/*z* 247 as the principle daughter ion.

Contrasting Behavior of the Dimers 9 and 10. Dimer **9** is readily formed from **3** during purification on silica gel and protonation of **9** under stable ion conditions cleanly produces **3H**$^+$.[14] These findings point to the high stability of **3H**$^+$ which is derived from a carcinogen. Dimer **10** is produced in good yield on exposure of the 17-ol **8** to acid.[10] Dimerization presumably occurs in the expected way via an elimination−addition process involving **12**$^+$. The NMR characteristics of the dimer **10** are analogous to those of **6**, for example, extreme low-field-shifted bay region H-1 protons in each unit and methoxy orientation which is pointing toward H-12 in each unit (determined from NOED spectra) occur in both. The olefinic proton H-17 (δ 6.78) exhibits NOE with both H-12 (δ 7.20; same unit) and the H-17 (δ 4.67; the other unit).

Protonation of **10** with FSO_3H/SO_2ClF (a dark-red solution) yielded three dimeric dications, **10H**$_2^{+2}$ (protonation occurring at two C-12 sites) and **10aH**$_2^{+2}$/**10bH**$_2^{+2}$ (protonation at C-12 and C-14 sites) in 2:1:1 ratio respectively as persistent carbocations *without* C/C cleavage to give **12**$^+$. Dications **10aH**$_2^{+2}$/**10bH**$_2^{+2}$ are diastereomers with two chiral centers, but their specific configurations could not be determined. The reactive sites are the same as those of **6**. When the temperature was increased to −20 °C, the dication ratios changed to 1:1:

Scheme 3



1. The chemical shift patterns for each of the arenium units were similar to those of **6H**$^+$ and **6aH**$^+$, indicating that there is little interaction between them. Anisotropic shielding of the H-1 protons in each unit is noteworthy. NOE enhancement was observed between O*Me* and H-12. The most deshielded aromatic carbons are C-11, C-8, C-13, and C-16. Quenching of superacid solution cleanly returned the intact **10**.

The AM1-minimized structures of **10**, **10H$_2$**$^{+2}$, **10aH$_2$**$^{+2}$, and **10bH$_2$**$^{+2}$ are included in Figure 2. The methoxy groups are directed toward C-12. The cyclopenta[*a*]-phenanthrene units are only slightly twisted out of plane except for the D-rings in **10aH$_2$**$^{+2}$/**10bH$_2$**$^{+2}$, where protonation occurs at the ring junction, which are bent.

Protonation of **10** with FSO_3H-SbF_5 (1:1)/SO_2ClF showed line broadening in the ^{1}H NMR spectra and led to side reactions and polymerization. Thus attempts to increase the charging in the dimers were unsuccessful.

Steric crowding caused by methyl groups at C-17 must be an important driving force for the formation of **3H**$^+$ from **9**.[16]

Comparative Discussion and Summary. A common feature of the arenium ions studied is their limited charge delocalization domain. For both carbocation **6H**$^+$ and **6aH**$^+$ the charge is localized in the C-ring ortho/para to the site of attack together with one other conjugated carbon (C-6), whereas the A-ring is least positive. Charge delocalization in the **6**$^+$**-SO$_2$F** carbocation is also limited to the C-ring. Dimer dications behave analogously whereby for each unit, positive charge resides in the C-ring plus C-6 and there is little interaction between the units.

Bay region H-1 is strongly deshielded in the neutrals and moves upfield in the carbocations indicative of conformation change and anisotropic shielding.

The methoxy conformation remains unchanged in the hydrocarbons and in the arenium ions with methyl pointing away from the bay region toward H-12. Protonation at the biologically important C-14 causes the D-ring to move out of aromatic plane.

On the basis of magnitude of $\Delta\delta$ ^{13}C values, charge delocalization in **11**$^+$ is limited to the cation center (δ 187.8), C-13 (δ 183.4), the methoxy-bearing C-11 (δ 184.2) and to a lesser extent to C-6. On the basis of our previous work,[12b] carbocation **12**$^+$ is also expected to have limited phenanthrenium ion character. AM1 calculations predict that **11**$^+$ is 10.2 kcal/mol more stable than **12**$^+$ whereas the difference in the relative stabilities for the regioisomeric carbocations in the absence of methoxy substituents decreases to 2.1 kcal/mol in favor of the C-15 carbocation. Therefore the OMe group has a substantial stabilization effect on **11**$^+$; this underscores its significance in biological activation.

Differing behavior of the dimers **9** and **10** allowed the generation of novel dimeric dications from the latter where each units maintains its charge delocalization mode.

The electrophilic reactivity of **6** is unique in that it is directed to both C-12 and C-14. Direct observation of model carbocations **6aH**$^+$ and **6**$^+$**-SO$_2$F** lends support to the notion that increased activity of **6** stems from attack by electrophilic oxygen at C-14/C-15 producing **7** as a major metabolite. Ambient reactivity of **7** is signified by facile dehydration to produce **15**, and trapping of the carbocation becomes feasible when **7** is heated in the presence of imidazole to form the adduct **16**.

Experimental Section

NMR spectra were recorded on a 500 MHz spectrometer. Ambient temperature spectra were recorded in $CDCl_3$. Low-temperature stable ion spectra (^{1}H, ^{13}C, H/H COSY, C/H HETCOR, COLOC, and NOED experiments) were recorded between −70 and −20 °C.

(16) As for difference in relative stabilities between **3H**$^+$ and **12**$^+$, taking hydride transfer reaction as an indicator, AM1 predicts the $\Delta\Delta H_f^o$ for **3H**$^+$ and **12**$^+$ to be 182.8 and 190.9 kcal/mol, respectively.

AM1 and PM3 calculations were performed using standard methods implemented in the Hyperchem package version 5.11 (Hypercube Inc, 1999) or Insight II Release 97.0 (MSI, 1999).

FSO_3H and SbF_5 were freshly distilled in an all-glass distillation unit under dry nitrogen at atmospheric pressure. FSO_3H-SbF_5 (4:1) and (1:1) were prepared by transfer of freshly distilled SbF_5 into a Nalgene bottle and by direct addition of the required amount of FSO_3H which was weighed inside a second Nalgene bottle. Dry CH_2Cl_2 was prepared by distillation over P_2O_5. Other commercially available reagents were used as received.

SO_2ClF was synthesized from SO_2Cl_2, ammonium fluoride, and trifluoroacetic acid, according to a modified procedure of Prakash et al.[17] Several distillation provided pure SO_2ClF.

Procedures for the synthesis of compounds **6** (15,16-dihydro-11-methoxy- 17H-cyclopenta[*a*]phenanthrene), **7** (15, 16-dihydro-11-methoxy-17H-cyclopenta[a]phenanthren-15-ol), and the dimers **9** and **10** have already been reported.[10,11]

General Procedure for Stable Ion Generation. SO_2ClF (ca 0.4 mL) was distilled into a 5-mm NMR tube containing the substrate (10−20 mg) cooled to dry ice−acetone temperature. Either FSO_3H or FSO_3H-SbF_5 (2 drops) was carefully added under dry N_2 to the resulting suspension, and the mixture was mixed (vortex) until homogeneous. Two drops of cold CD_2Cl_2 then were added on the top of the solution followed by efficient vortex mixing. The FSO_3H solutions of **6**, **7** and **9** were clear-orange, clear-red, and dark-red, respectively.

Quenching Experiment in Protonation of 6 and 10. The NMR tube containing the superacid was carefully poured into ice−$NaHCO_3$ with vigorous mixing, and the organic layer was extracted with ether. The extract was washed (10% NaCl) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was analyzed by NMR, which indicated that starting material, **6** or **10**, was recovered. In the case of **6^+-SO_2F**, to the superacid solution was added cold methylcyclohexane, and the solution was mixed (vortex). It was then poured into ice−$NaHCO_3$ and extracted (CH_2Cl_2). The combined organic extract was dried ($MgSO_4$), and the solvent was removed to give a purple oil, which was assayed by ^1H NMR showing intact **6**.

Nitration of 6 with NO_2BF_4. NO_2BF_4 (3 mg, 0.02 mmol) was added at room temperature to a solution of **6** (5 mg, 0.02 mmol) in dry CH_2Cl_2 (0.5 mL). and the solution was mixed. After 5 min the mixture was poured into water. The resulting solution was extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$). Removal of the solvents gave a pale yellow oil, which was passed through a short column (SiO_2, CH_2Cl_2). NMR analysis was consistent with the formation of **6-NO_2** (see Scheme 2). IR ($CHCl_3$): 1533, 1363 cm^{-1}. ES-MS [CH_3CN−water (1:1), 0.1% NH_4NO_3] *m*/*z*: 294 $(M + H)^+$. MS/MS experiment on *m*/*z* 294 cation produced daughter ions at *m*/*z* 248 (loss of nitro) and *m*/*z* 277.

Quenching of 11^+ with Methanol or H_2O. The superacid solution was carefully poured into methanol or ice−$NaHCO_3$ at dry ice-acetone temperature, and the organic layer was extracted with CH_2Cl_2. The extract was washed (10% NaCl) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. ^1H NMR analysis showed that in both cases mixtures were formed and that the major component of the mixtures was the same in both cases. This was identified as a dimer. Partial ^1H NMR data: δ 9.69 (d, $J = 9.0$ Hz, 1 H), 9.64 (d, $J = 9.0$ Hz, 1 H), 7.18 (s, 1 H), 6.90 (s, 1 H), 4.94 (m, 1 H), 4.19 (s, 3 H), 7.08 (s, 3 H).

Analysis of 14a/14b. A sample of **7** (white crystalline) was kept at room temperature in a sealed tube for 18 months whereby it turned to brown. TLC analysis showed the presence of two "less-polar" new compounds and only a trace of **7**. Compounds **14a**/**14b** could be separated by column-chromatography (silica gel/hexane). They had identical UV spectra (λ_{max} 216, 254, 273.5, 306.5, 341, 358 nm) almost the same as that of **7** itself. Their EI mass spectra were virtually identical giving rise to a weak M^+ at *m*/*z* 510 ($C_{36}H_{30}O_3$) with a base peak at *m*/*z* 246 ($C_{18}H_{14}O$, radical cation of **15**) and intense cations at *m*/*z* 231 and *m*/*z* 202. The molecular formula is supported by the isotope ions at *m*/*z* 511 (∼40% abundance of M^+) and a small peak at 512, and from the UV evidence these nonpolar compounds must therefore be the isomeric dimers (diastereomers).

Ambient Reactivity of 7. A drop of 2 M HCl was added to a solution of **7** in $CHCl_3$, and the resulting suspension was mixed. NMR analysis indicated that the 15,16-ene **15** was formed; gentle heating of **7** in $CHCl_3$ also converted it to **15**. ^1H NMR: δ 9.70 (d, $J = 9.0$ Hz, 1 H), 8.06 (d, $J = 9.0$ Hz, 1 H), 7.90 (d, $J = 8.0$ Hz, 1 H), 7.79 (d, $J = 9.0$ Hz, 1 H), 7.64 (dd, $J = 9.0$, 7.5 Hz, 1 H), 7.57 (dd, $J = 8.0$, 7.5 Hz, 1 H), 7.47 (m, 1 H), 7.42 (s, 1 H), 6.66 (m, 1 H), 4.16 (s, 3 H), 3.61 (s, 2 H). ^{13}C NMR: δ 157.4 (C), 142.7 (C), 135.3 (C), 132.6 (C), 132.1 (CH), 131.1 (C), 130.0 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.7 (C), 126.6 (CH), 125.7 (CH), 123.3 (CH), 119.3 (C), 106.2 (CH), 56.3 (CH_3), 40.4 (CH_2).

Heating **7** in CH_2ClCH_2Cl (∼2 h) or cyclohexane (5 h) in the presence of imidazole gave an adduct, **16**. ^1H NMR: δ 9.65 (d, $J = 9.0$ Hz, 1 H), 7.84 (d, $J = 8.0$ Hz, 1 H), 7.69 (d, $J = 9.0$ Hz, 1 H), 7.64 (dd, $J = 9.0$, 8.0 Hz, 1 H), 7.57 (dd, $J = 8.0$, 8.0 Hz, 1 H), 7.42 (s, 1 H), 7.39 (d, $J = 9.0$ Hz, 1 H), 7.15 (s, 1 H), 7.00 (s, 1 H), 6.71 (s, 1 H), 6.18 (d, $J = 6.5$ Hz, 1 H), 3.38 (m,1 H), 3.18 (m, 1 H), 2.82 (m, 1 H), 2.48 (m, 1 H).

Acknowledgment. Support of our work in the area of reactive intermediates of carcinogenesis of PAHs by the NCI of NIH (R15 CA 78235-01A1) is gratefully acknowledged. We thank Dr. Gary Boyd (Imperial Cancer Fund) for the EI-MS of **14a**/**14b**.

Supporting Information Available: Selected NMR spectra for the protonation of **6**, **7**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000534I

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