Stable ion study of protonated cyclopenta[*a*]phenanthrenes. Structure–reactivity relationships and charge delocalization in the carbocations †

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Protonation studies are reported for a series of cyclopenta[*a*]phenanthrenes C_p[*a*]P in superacid media. Hydrocarbons **1**, **4**, **7**, are ring protonated in FSO_3H–SO_2ClF to form monoarenium ions. The $\Delta^{16,17}$compounds **3**, **6** are protonated at the D-ring double-bond to form stable α-phenanthrene-substituted carbocations. The 17-keto derivatives **2**, **5**, **8**, **9**, **19**, **20** are CO-protonated in FSO_3H–SO_2ClF to form carboxonium ions. Carboxonium ions derived from **8** and **20** undergo ring fluorosulfonation in the biologically important A-ring under thermodynamic control (higher temperatures and prolonged reaction times). Low temperature protonation of **8** and **9** with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF gives their corresponding carboxonium-arenium dications (protonation of **2** with $FSO_3H{\cdot}SbF_5$ (1 : 1)–SO_2ClF gave a mixture of mono- and dications), where ring protonation sites are controlled by the position of the methyl group and occur in the A-ring for the A-ring methylated derivatives (**8**, **9**).

Whereas the 11-methoxy derivative (**16**) forms a carboxonium ion in FSO_3H–SO_2ClF analogous to the 11-Me derivative (**5**), the 11-phenol derivative (**15**), the ethoxy (**17**) and propoxy (**18**) derivatives are more reactive, forming a mixture of mono- and dication (with **15** and **17**) or give mostly a carboxonium-arenium dication (with **18**).

Substituent effects observed under stable ion conditions emphasize relative carbocation stability and relief of *peri*-strain. Under thermodynamic control, carboxonium ions undergo fluorosulfonation in the biologically important A-ring. Charge delocalizations in the resulting mono- and dications (deduced primarily based on magnitude of $\Delta\delta^{13}C$) are discussed and compared. In an effort to further enhance the NMR assignments and for comparison, mono-arenium ions $\mathbf{1H^+}$, $\mathbf{4H^+}$, $\mathbf{6H^+}$, $\mathbf{7H^+}$ and their neutral precursors were calculated at the B3LYP/6-31G(d,p) level of *ab initio* theory; their ^1H and ^{13}C NMR chemical shifts were computed by the GIAO method and their overall charge delocalization paths were deduced *via* differences in the NPA charges (cation minus neutral). The results are compared and discussed.

Stable ion studies of C_p[*a*]P provide useful insights into the contrasting regioselectivities observed in chemical and biological activiation.

Introduction

Structurally, cyclopenta[*a*]phenanthrene C_p[*a*]P bridges polycyclic aromatic hydrocarbons (PAHs) and natural steroids. It has, therefore, been the subject of numerous synthetic, structural and biological studies as they relate to structure–activity relationships and carcinogenesis.[1]

Whereas the parent hydrocarbon **1** (Fig. 1) and the 17-one **2** are not carcinogenic, presence of a D-ring double-bond (15H-C_p[*a*]P) induces activity (as in **3**).[1] Methylation at C-11 (one of the two bay-region carbons) is most effective in increasing biological activity (**4**, **5** and **6**), followed by methylation at C-7 (K-region) (**7**), whereas other methylated derivatives (such as **8** and **9**) remain inactive. Moreover, the combination of methylation at C-11 and 17-CO produces a potent carcinogen (**5**) comparable to benzo[*a*]pyrene; presence of both an 11-methyl and a D-ring double bond also leads to a strong carcinogen (**6**).[1,2]

Metabolic studies have underscored the importance of the diol-epoxide activation path for the C_p[*a*]P derivatives, showing that the more accessible A-ring is metabolized to form 3,4-dihydrodiol **10** and the *anti*- and *syn*-diol-epoxides **11**, **12** as proximate and ultimate carcinogens.[1,3] The distribution of the isolated metabolites varies depending on the species.[3b] Recent synthetic methods for these and their 17-keto derivatives have been developed.[4]

Interestingly, attempts to induce epoxidation in the A-ring were unsuccessful; both peracid oxidation and bio-mimic oxidations occurred at the K-region.[5]

For the alkyl and alkoxy derivatives of **2**, increasing steric crowding at C-11 reduces carcinogenicity, thus 11-ethyl **13** is considerably less active than 11-methyl **5** and 11-*n*-butyl **14** is inactive. The 11-phenol **15** is a carcinogen, 11-methoxy **16** is a strong carcinogen, 11-ethoxy **17** is less active and 11-*n*-propoxy **18** is inactive. The data emphasize the importance of steric hindrance to the approach of target DNA nucleotide.[6]

The 11-trifluoromethyl compound **19** was synthesized and tested to probe the electronic effects. Whereas carcinogenicity was abolished[7] it was still mutagenic, being metabolized at the C-1/C-2 and C-3/C-4 (A-ring) and at C-15 (D-ring) positions.[8]

Combination of a methano-bridge and the 17-CO group (compound **20**) resulted in carcinogenicity despite obstruction of the bay-region. Metabolic studies showed that the A-ring dihydrodiols were still produced as well as products arising from oxidation of the methano-bridge and the D-ring.[1,9]

† Representative ^1H, ^{13}C and C/H HETCOR spectra of mono- and dications and graphs showing the correlation between calculated and experimental chemical shifts are available as supplementary data from BLDSC (SUPPL. NO. 57685, 38 pp.) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

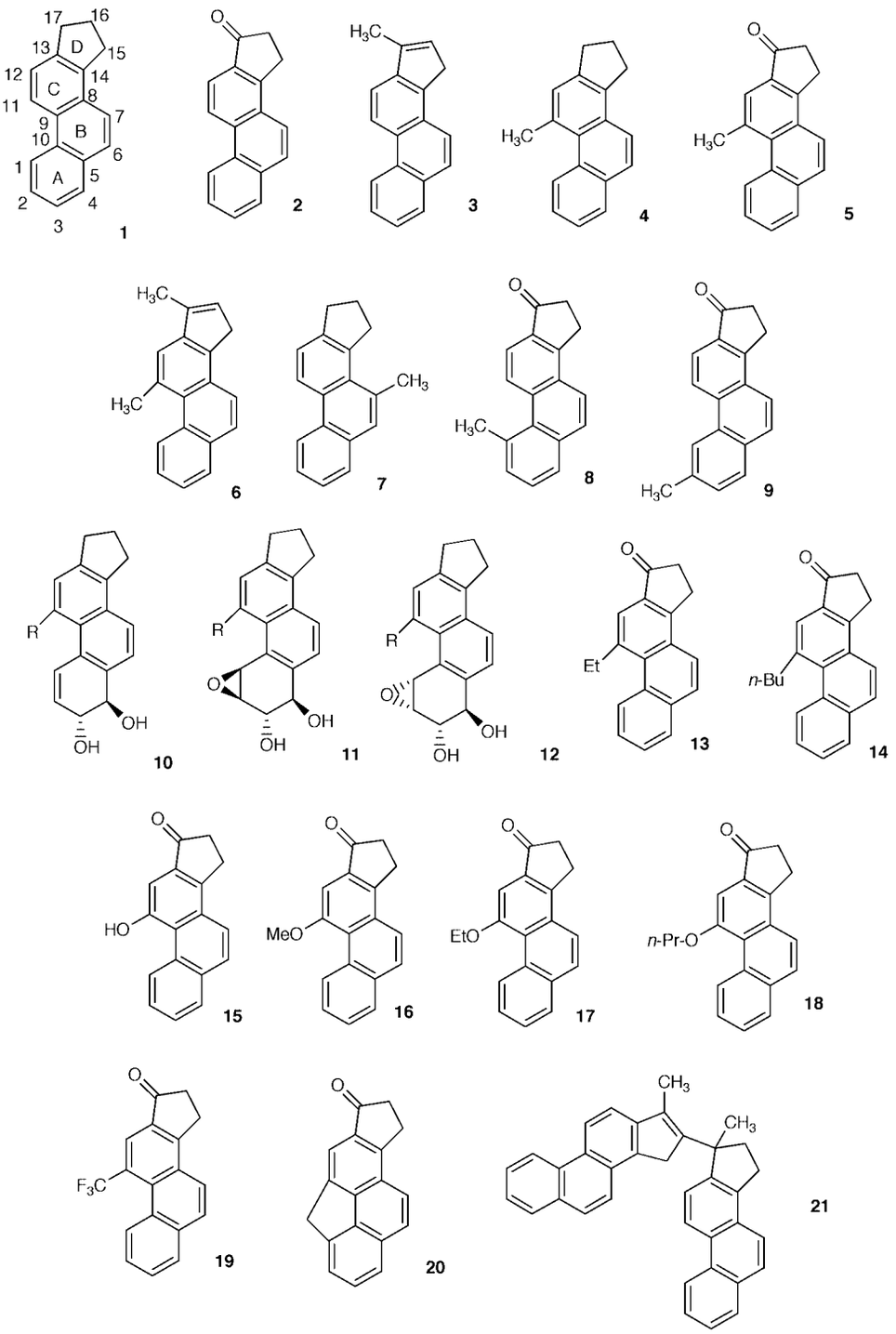

Fig. 1 Cyclopenta[*a*]phenantherene $C_p[a]P$ and its derivatives.

In relation to the available structure–activity data and the importance of the diol-epoxide pathway in the metabolism of $C_p[a]P$ derivatives and in connection to our continuing interest in persistent PAH arenium ions, their charge delocalization and substituent effect, and in continuation of a search for relationships between a carbocation-based structure–activity database and biological data,[10–16] we report here a stable ion study on the $C_p[a]P$ skeleton. It was hoped that the data may provide a mechanistic basis for rationalizing the observed biological structure–activity relationships.

A collection of $C_p[a]P$ substrates (Fig. 1) were provided by the Surrey group for this collaboration. Therefore, except for compounds **10**–**14** all others have been studied. In addition, compound **21** (dimer of the carcinogenic **3**) was also investigated.

Results and discussion

NMR Assignments

Detailed NMR assignments for the precursors, monoarenium ions, carboxonium ions, carboxonium-arenium dications and the fluorosulfonated carboxonium ions (summarized in Figs. 3, 5, 7, 9) were based on ^1H, ^{13}C, (and ^{19}F as applicable), H/H COSY and C/H HETCOR spectra. The low field proton resonances of the bay region (H-1 and H-11) were usually the starting point for the assignments, which together with H/H COSY analysis allowed the A and C ring protons to be assigned. The H-6 and H-7 (B-ring) of the precursors were usually observed as pseudo-singlets. In some cases, the aromatic resonances occurred over a very narrow range, making specific assignments impractical. The ^{13}C resonances of the proton-bearing carbons

were assigned with the help of C/H HETCOR correlations. Since the ^{1}H-resonances of H-6 and H-7 (*meso* positions) were mostly in overlapping regions or appeared as pseudo-singlets, assignments of the C-6 and C-7 carbons could not be established from HETCOR spectra alone even though the difference between the two ^{13}C resonances was usually about 6 ppm. The ambiguity was resolved *via* the NOED spectrum of **18** as model, where the observed NOE between the H-15 (CH_2) and H-7 and the corresponding C/H HETCOR correlations allowed the more deshielded resonance to be assigned to C-6.

Introduction of methyl at the C-11 in the parent hydrocarbon (compound **4**) caused a significant *peri*-deshielding effect on H-1, whereas methyl substitution at C-7 (compound **7**) resulted in shielding of H-6 (K-region).

For the trifluoromethyl compound **19** and its carboxonium ion **19H$^+$**, long-range C/F couplings to C-1 and C-12 are observed which allowed their specific assignments. For the 17-one derivatives in analogy with the 15H-analogs (**3**, **6**), the most deshielded ring junction carbon was assigned to C-14 (in the range *ca*. 155–152 ppm), except for the phenol **15** and the alkoxy derivatives (**16**–**18**), where the *ipso* carbon (C-11) is more deshielded than C-14. For the hydrocarbons **1**, **4**, **7** the most deshielded ring junction carbons were assigned to C-14/C-13. For compounds **15**–**18**, the H-12 singlet in the ^{1}H NMR and C-12 in ^{13}C NMR are the most upfield aromatic resonances. For **18**, an NOE effect was observed between H-12 and O*C*H_2-CH_2CH_3 and between H-7/H-15 indicative of their close proximity.

For the mono- and dications, the calculated charges (AM1) and in particular changes in carbon charges $\Delta q = q_c$(ion) − q_c(neutral) were used as an additional (qualitative) guideline for fine-tuning certain assignments. The success and limitations of the approach have been previously discussed [12,13,16] (see also further). For the monocarboxonium ions, the most deshielded ring junction carbons are C-14 and C-9 (and C-11 in the case of **15H$^+$**–**17H$^+$**), these were assigned taking into account the calculated charges and considering the overall pattern of quaternary carbons chemical shifts which in some cases enabled the remaining ring junction carbons to be grouped. For the monoarenium ions (**1H$^+$**, **4H$^+$**, **7H$^+$**) and the carboxonium-arenium dications (**8H$_2^{2+}$**, **15H$_2^{2+}$**, **17H$_2^{2+}$**, **18H$_2^{2+}$**) more of the ring junction carbons could be assigned due to ring protonation and charge effect, and by taking into account the overall pattern of AM1 charges. In a subsequent step, four representative monoarenium ions (**1H$^+$**, **4H$^+$**, **6H$^+$**, **7H$^+$**) and their neutral precursors were calculated at the B3LYP/6-31G(d,p) level; computed ^{1}H and ^{13}C GIAO chemical shifts and NPA analysis provided an overall comparison with the experimental data and their interpretations (see separate section).

Stable ion studies

The mono-arenium ions derived from 1, 4, 7 (Figs. 2–3). The parent hydrocarbon **1** and its two isomeric methylated derivatives **4**, **7** are ring protonated with FSO_3H–SO_2ClF to give their mono-arenium ions as dark-red solutions. Parent **1** is protonated at C-12 to give **1H$^+$** for which significant upfield shift of the bay-region protons (H-1/H-11) occurs, indicative of out of plane twisting and anisotropic shielding. Positive charge is primarily localized at C-13/C-11/C-8 (*ortho*/*para*) and C-10 (C/B rings), and to a lesser extent in the A ring. The charge delocalization pattern agrees with the overall pattern predicted by AM1.

When methyl is introduced at C-11 (compound **4**) relief of steric strain at the bay-region provides the driving force for *ipso*-attack to give **4H$^+$** (the $^3J_{Me\text{-}H}$ coupling is 7.6 Hz). The diastereotopic nature of the aliphatic protons leads to a complex ^{1}H NMR pattern. Whereas the positive charge is mostly localized at C-14/C-9/C-12 (*ortho*/*para*), the overall delocalization path is phenanthrenium ion-like. Methyl substitution at C-7 changes the site of protonation to C-6 (**7H$^+$**), this makes C-7/C-9/C-12 as well as C-5/C-14 most positive.

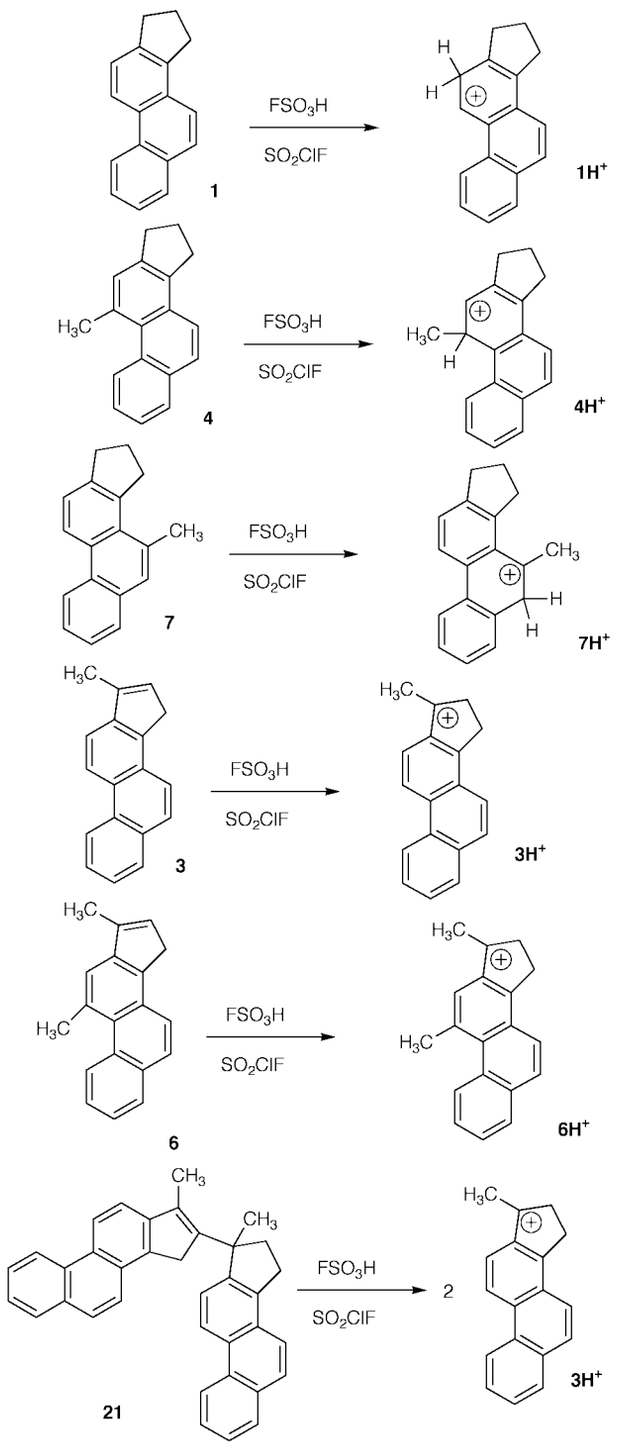

Fig. 2 Generation of monoarenium ions from hydrocarbons (**1**, **4**, **7**), the 15H-derivatives (**3**, **6**) and the dimer (**21**).

There is good overall agreement between the AM1-predicted charge alternation path and the NMR-derived pattern for these carbocations based on magnitude of $\Delta\delta$'s although the latter are usually larger than predicted based on the magnitude of Δq.

Protonation of 3, 6 and the dimer 21 (Figs. 2–3). Compound **3** is protonated at the D-ring double bond to form an α-phenanthrene-substituted carbocation **3H$^+$**. Increased steric crowding at the bay-region *via* the 11-methyl group (compound **6**) does not bring about *ipso* attack; protonation once again occurs at the D-ring double bond. The carbocation centers are at δ 239.6 and 238.1 and the C-14 carbon at δ 185.0 and 180.2 respectively.

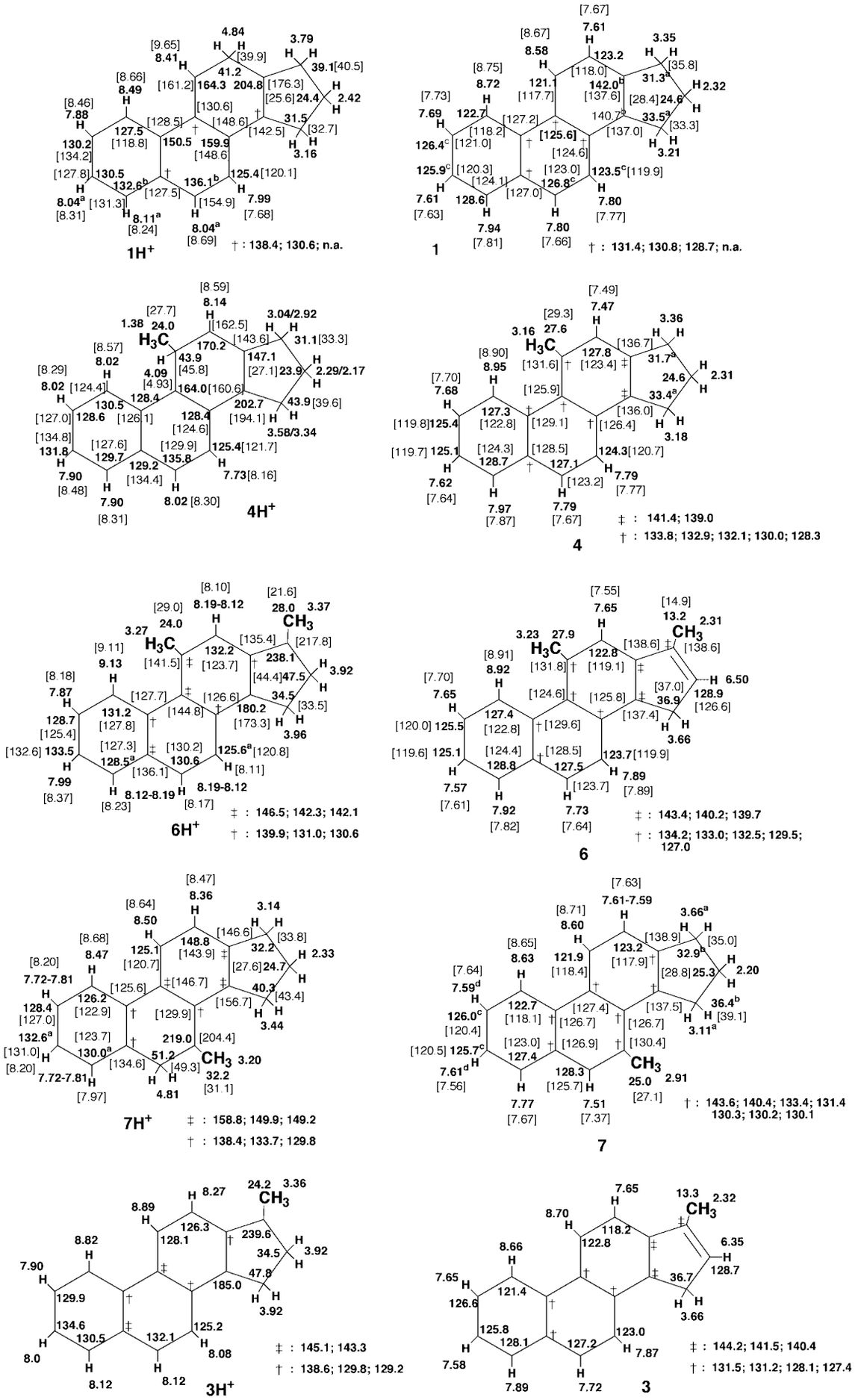

Fig. 3 Summary of ^{13}C and ^{1}H NMR data for cations and precursors in Fig. 2. Computed ^{1}H and ^{13}C chemical shifts are given in [ ] for comparison. a, b, c, d denote interchangeable assignments for a pair or group of proton or carbon resonances. n.a. not assigned. ? Not observed.

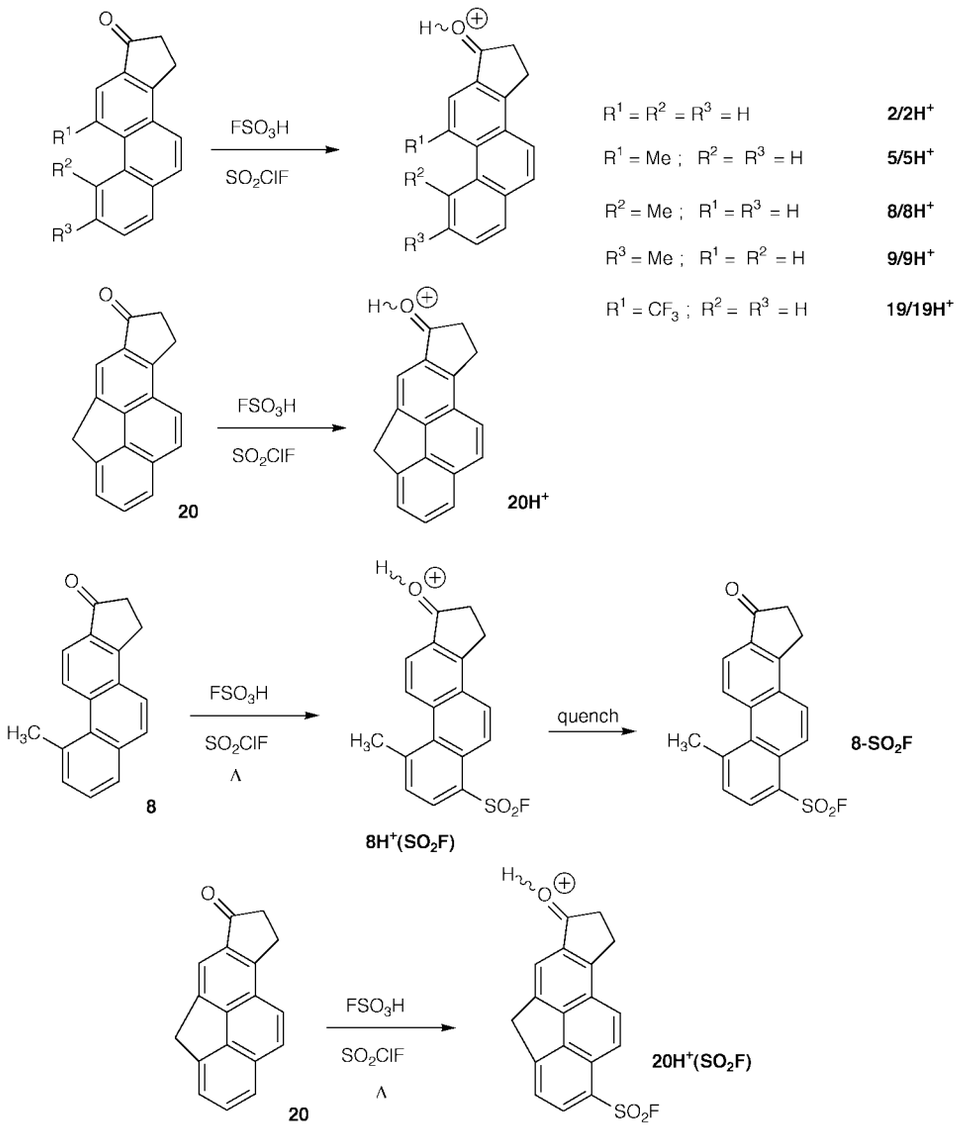

Fig. 4 Generation of carboxonium ions from the 17-one derivatives (**2**, **5**, **8**, **9**, **19**, **20**) and ring fluorosulfonation with **8** and **20**.

In the crowded bay-region of $\mathbf{6H^+}$, H-1 appears at δ 9.13. Although positive charge resides mainly at C-14/C-9 it is spread into the phenanthrene moiety especially the C/B rings, with the A ring showing positive charge development on adjacent carbons! The same overall pattern is revealed taking into account the Δq values from AM1. This effect is apparently unrelated to steric crowding and twisting out of planarity since both carbocations exhibit this feature.

Dimer **21** is formed as a by-product during the synthesis of **3**,[1,17a] attempted purification of **3** on silica gel produced more dimer.[17b] These observations suggest that carbocation $\mathbf{3H^+}$ can be formed even on silica! A dimer analogous to **21** lacking the methyl groups was obtained during the synthesis of the metabolites of the 11-methoxy derivative **16**, upon removing the 17-oxygen from its 17-ol derivative *via* hydrogenolysis in strong acid.[17c] When **21** is allowed to react with FSO_3H–SO_2ClF at dry-ice–acetone temperature the reverse reaction leads to clean formation of $\mathbf{3H^+}$ (identical ^1H and ^{13}C NMR spectra) without direct observation of a protonated dimer ($\mathbf{21H^+}$). Superacid solutions of carbocation $\mathbf{3H^+}$ and $\mathbf{6H^+}$ are dark-red.

Complementary computational studies. The GIAO ^1H and ^{13}C NMR chemical shifts for four representative monoarenium ions $\mathbf{1H^+}$, $\mathbf{4H^+}$, $\mathbf{6H^+}$ and $\mathbf{7H^+}$ and their corresponding neutral precursors calculated at the B3LYP/6-31G(d,p) level are incorporated into Fig. 3 for direct comparison. Overall, the correspondence for the neutral precursors are closer than for the arenium ions. Generally, for the arenium ions, the ^1H chemical shifts are overestimated whereas the ^{13}C shifts are in many cases underestimated. These variations could stem from specific solvation and counter ion effects which are ignored in calculations. In the case of $\mathbf{1H^+}$ rather substantial deviations are observed for the protons and for three carbon resonances. In Fig. 3a and 3b (Supplementary material) the computed GIAO ^{13}C and ^1H chemical shifts for the aromatic carbons and protons of the neutral PAHs and their monoarenium ions are plotted against the assigned values based on the NMR spectra. As for computed changes in NPA charges, for $\mathbf{1H^+}$ it can be deduced that whereas B/C rings exhibit regular charge alternation (like a naphthalenium ion), adjacent positive charges are created in the biologically important A ring (all except C-5 become relatively positive). The situation for $\mathbf{4H^+}$ is very similar; the A ring positions are all relatively positive except for C-10. In $\mathbf{6H^+}$ a severe breakdown of charge alternation is noted, whereby except for three quaternary carbons all others are positive. This effect could be related to *peri*-strain and deviation from planarity. In $\mathbf{7H^+}$, on the other hand, regular charge alternation within a phenanthrenium moiety is observed with C-2 in the A ring being the only exception; in other words not only C-1/C-3/C-5 but also C-2 become positive.

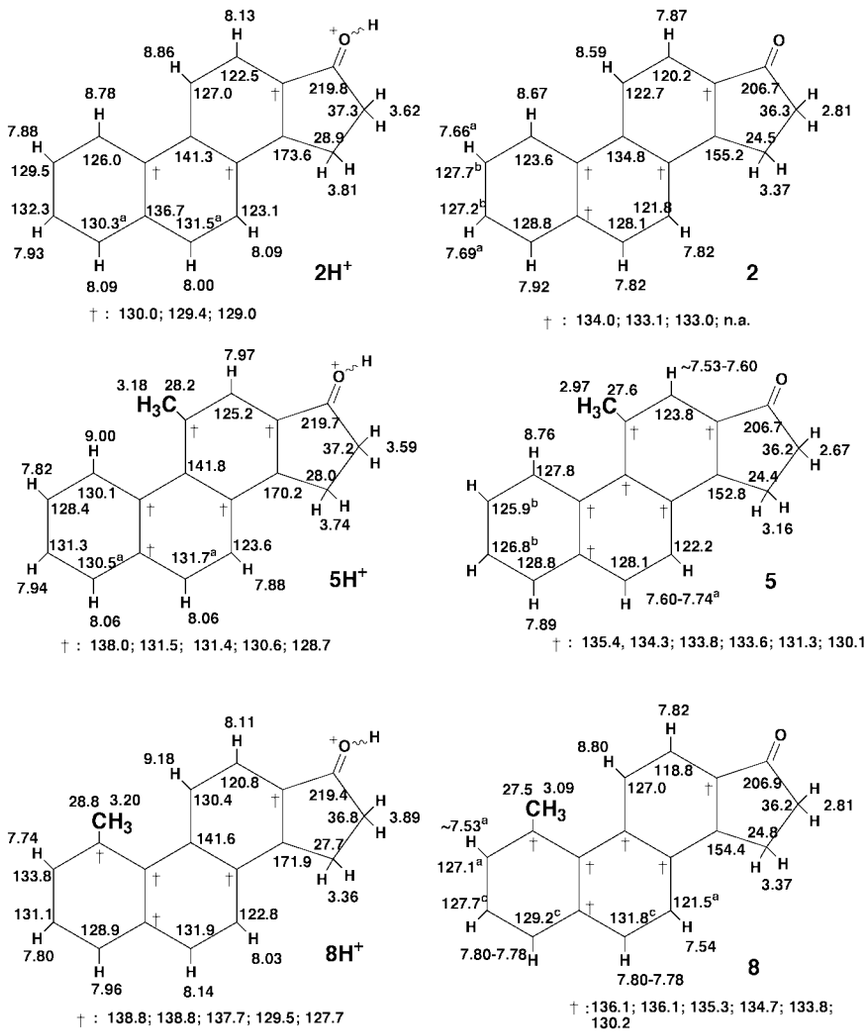

Fig. 5 Summary of ^{13}C and ^{1}H NMR data for cations and precursors in Fig. 4. a, b, c, d denote interchangeable assignments for a pair or group of proton or carbon resonances. n.a. not assigned. ? Not observed.

It can be concluded that whereas the GIAO chemical shifts for these large, highly delocalized arenium ions provide a reasonable overall comparison with experiment, due to variations that exist they cannot be used specifically to reduce the number of interchangeable assignments or to assign quaternary carbons beyond the level already achieved.

Monoprotonation of the 17-one derivatives; carboxonium ions $2H^+$, $5H^+$, $8H^+$, $9H^+$, $19H^+$, $20H^+$ (Figs. 4–5). Smooth low temperature protonation of the 17-ketones **2**, **5**, **8**, **9**, **19** and **20** with FSO_3H–SO_2ClF resulted in generation of their corresponding carboxonium ions as clear homogenous orange-red solutions except for the CF_3-derivative (**19**) which gave a green-brown solution. Although the magnitude of COH^+ deshielding indicates significant oxonium ion character, deshielding at C-14 and shielding at C-13 as compared to the starting substrates suggest that the mesomeric enol form contributes. Positive charge resides mainly at C-14 and C-9 with limited delocalization into other conjugated carbons in the A/B rings. The COH^+ signal was not observed as a separate signal in FSO_3H. Although formation of two geometrical isomers are in principle possible, the NMR spectra are consistent with just one carboxonium ion. AM1 predicts that the energy difference between the *syn* and *anti* isomers for $5H^+$ and $8H^+$ is small (between 1.1–1.3 kcal in favor of the *syn* form), implying that the NMR spectra of the superacid solutions represent average structures. For $19H^+$ long range C/F couplings are clearly observed at C-12 ($^5J_{CF} = 8.4$ Hz) and at C-1 ($^3J_{CF} = 7.3$ Hz) which are slightly reduced as compared to the precursor. In $19H^+$, the CF_3 is deshielded by 3.6 ppm and the $\delta^{19}F$ remains relatively unchanged.

Ring fluorosulfonation of $8H^+$ and $20H^+$ (Figs. 4–5). These carboxonium ions substituted by a carbon atom at C-1, smoothly undergo ring fluorosulfonation in the activated A ring. With $8H^+$, storing the sample at −20 °C for *ca.* 2 h resulted in >95% conversion to $8H^+(SO_2F)$ which exhibits six distinct aromatic doublets in the ^1H NMR, the COH^+ at δ 222.0 and the SO_2F as a singlet at δ 63.1 in the ^{19}F NMR. In a variable temperature ^1H NMR monitoring study, the onset of fluorosulfonation was observed at −30 °C where the new doublets appeared and increased slowly as a function of temperature and finally by allowing the sample to remain at −20 °C. The NMR data are compatible with fluorosulfonation either at C-4 or at C-2, but based on previous studies of fluorosulfonation of arenes in superacids, the *para*-isomer seems more logical[18] (PM3 calculations predict very similar energies for the two regioisomers in the gas phase!). Attempted purification of the ring fluorosulfonated derivative after quenching and isolation of the organic material was unsuccessful. Similar ring fluorosulfonation was observed for $20H^+$ to produce $20H^+(SO_2F)$, which was already detectable in the NMR around −30 °C, eventually leading to a mixture which could not be purified on quenching. In this case, PM3 predicted that ring flurosulfonation at C-2 is lower in energy by 1.2 kcal mol^{-1} as compared to C-4. In control experiments it was established that under the conditions where fluorosulfonation occurred for **8** and **20** a similar reaction did not occur with **2** and **9**.

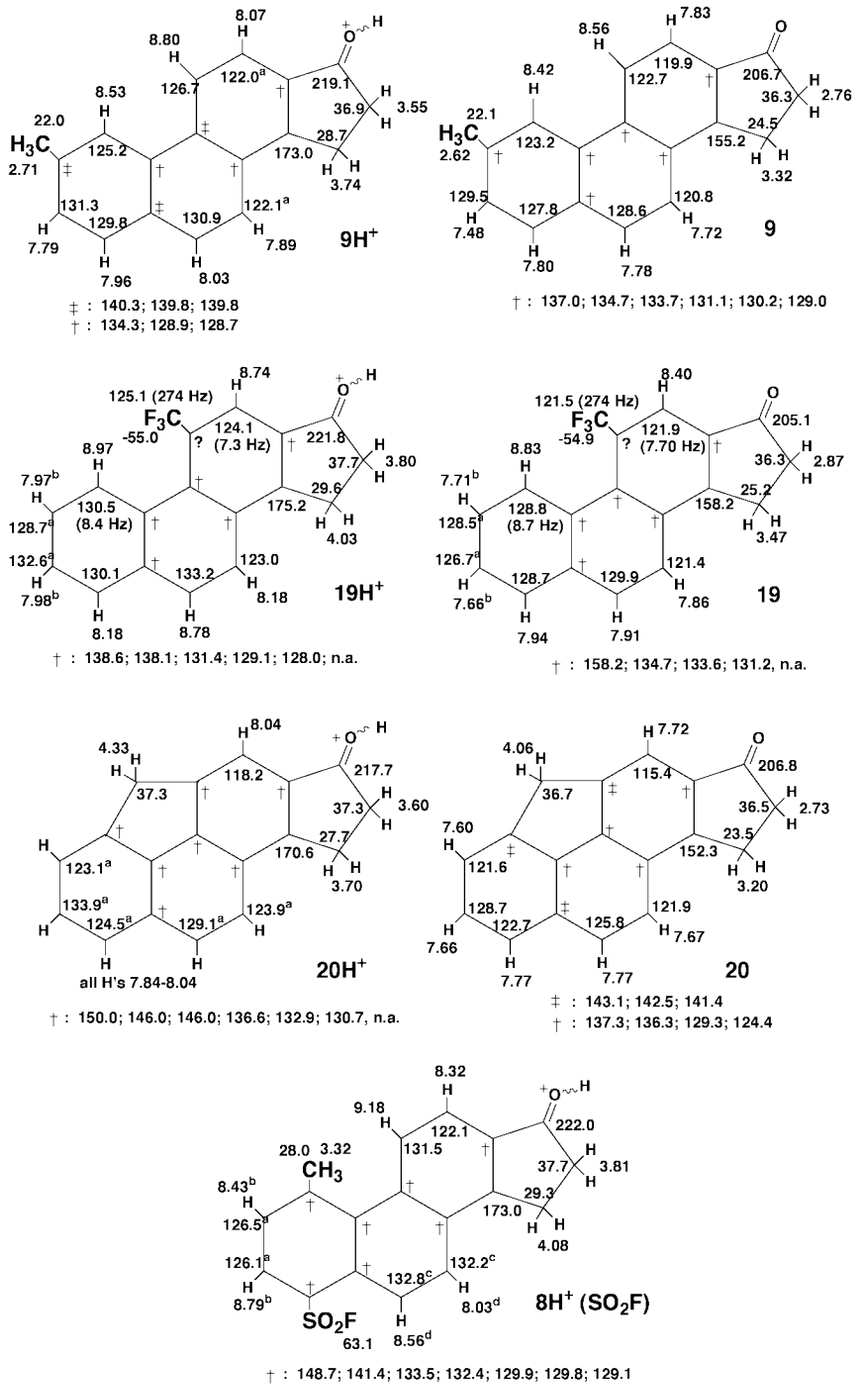

Fig. 5 (Continued.)

Generation of carboxonium-arenium dications from 8, 9 (19 and 2) in $FSO_3H{\cdot}SbF_5$ (4:1)–SO_2ClF or $FSO_3H{\cdot}SbF_5$ (1:1)–SO_2ClF (Figs. 6–7). Compound **8** is cleanly diprotonated in $FSO_3H{\cdot}SbF_5$ (4:1)–SO_2ClF to give $\mathbf{8H_2}^{2+}$ with ring protonation occurring at C-2. The COH^+ is at δ 225.9 and $CO\mathit{H}^+$ is seen as a separate signal at δ 13.46. The most deshielded aromatic carbons are those of C-1, C-3 and C-5 (*ortho*/*para*) together with C-14/C-7. Presence of methyl at C-2 (compound **9**) leads to ring protonation at C-1 to give $\mathbf{9H_2}^{2+}$; with COH^+ at δ 225.5, $CO\mathit{H}^+$ at δ 13.35 and the most deshielded ring carbons at δ 219.2, 178.1 and 175.3. For both dications, magnitude of the positive charge at C-14 decreases as compared to the carboxonium cations. With **19**, in $FSO_3H{\cdot}SbF_5$ (4:1)–SO_2ClF a mixture of mono- and dication was formed which on increasing acidity (addition of $FSO_3H{\cdot}SbF_5$ (1:1)–SO_2ClF) gave only the dication having a $C\mathit{H}_2$ at 5.6 and $CO\mathit{H}^+$ at 13.4 ppm. The observed pattern of 2 singlets and 4 doublets is compatible with protonation at C-2 or at C-4; decomposition set in during ^{13}C data collection. For comparison, the relative AM1 energies were calculated for all possible ring protonated cations derived from $\mathbf{19H}^+$. In concert with experiment, protonation at C-4 and at C-2 (1.8 kcal mol^{-1} higher) are predicted to be the most favored. Finally with **2** a mixture of mono- and dications were formed in $FSO_3H{\cdot}SbF_5$ (1:1)–SO_2ClF.

Protonation studies of the phenol 15 and the alkoxy derivatives 16–18 (Figs. 8–9). Whereas the reactivity of 11-methoxy **16** is comparable to 11-methyl **5**, the C-11 phenol **15** and its alkoxy derivatives **17**–**18** are considerably more reactive. Protonation of the methoxy derivative **16** with FSO_3H–SO_2ClF gave a carboxonium ion $\mathbf{16H}^+$ for which the COH^+ is at δ 218.4 and the most deshielded ring carbons are C-11/C-14. Under similar conditions, protonation of the 11-phenol **15** gave a 1:2 mixture of mono- $\mathbf{15H}^+$ and dication $\mathbf{15H_2}^{2+}$ with protonation taking

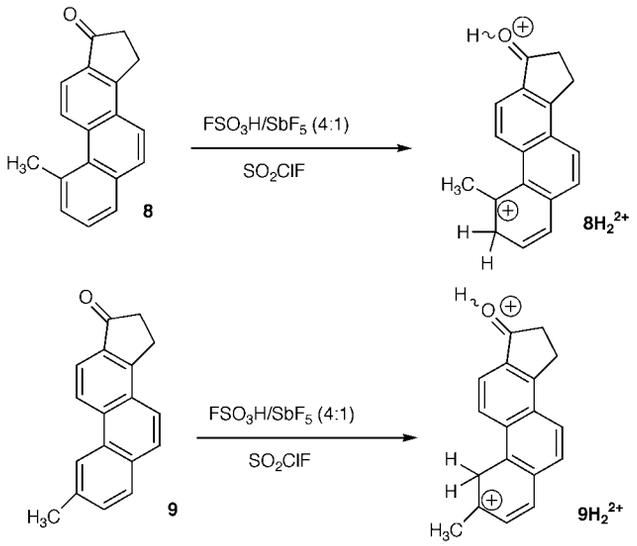

Fig. 6 Generation of carboxonium–arenium dications from **8**, **9**.

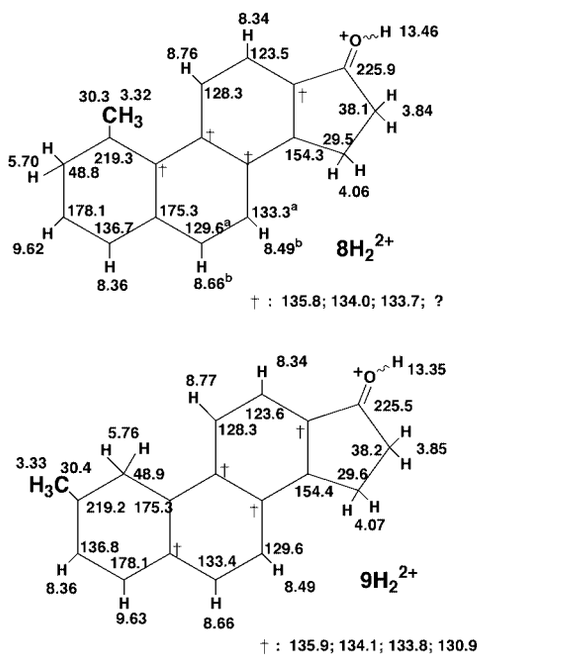

Fig. 7 Summary of ^{13}C and ^{1}H NMR data for the cations in Fig. 6. a, b, c denote interchangeable assignments for a pair or group of proton or carbon resonances. ? Not observed.

place at C-12 (C ring). Addition of 3 drops of $FSO_3H{\cdot}\ SbF_5$ (4:1) to the NMR sample converted the remaining **15H**$^+$ to **15H**$_2^{2+}$ for which *C*OH$^+$ is observed at 221.0 and C-11 at 206.7 ppm. Charge localization at the remaining *ortho* (C-13) and the *para* (C-8) positions has diminished in order to reduce charge–charge repulsion with C-14 which is now more deshielded than in earlier dications. There is a large bay-region (*peri*) shielding effect on H-1. Despite the fact that the B/C ring carbons become most deshielded, the overall delocalization path has phenanthrenium ion character which is in agreement with the pattern deduced based on AM1 charges.

As with **15**, C-12 (the C-ring) is the site of electrophilic attack in **17**–**18**. Protonation of **17** with FSO_3H–SO_2ClF gave a *ca.* 60:40 mixture of **17H**$_2^{2+}$ and **17H**$^+$ which could be fully converted to the dication by addition of 3 drops of $FSO_3H{\cdot}\ SbF_5$(4:1). The *C*OH$^+$ in the carboxonium ion **17H**$^+$ is observed at δ 218.0 whereas in the dication **17H**$_2^{2+}$ it is at δ 221.0. Analogous to **15H**$_2^{2+}$, the most deshielded ring carbons are C-1, C-14 and C-6 and a similar *peri*-shielding effect at H-1 is observed upon C-12 protonation. Increased electrophilic reactivity in **18** leads to *ca.* 90% diprotonation in FSO_3H–SO_2ClF to give **18H**$_2^{2+}$ which shows similar charge delocalization pattern to those of **17H**$_2^{2+}$ and **15H**$_2^{2+}$.

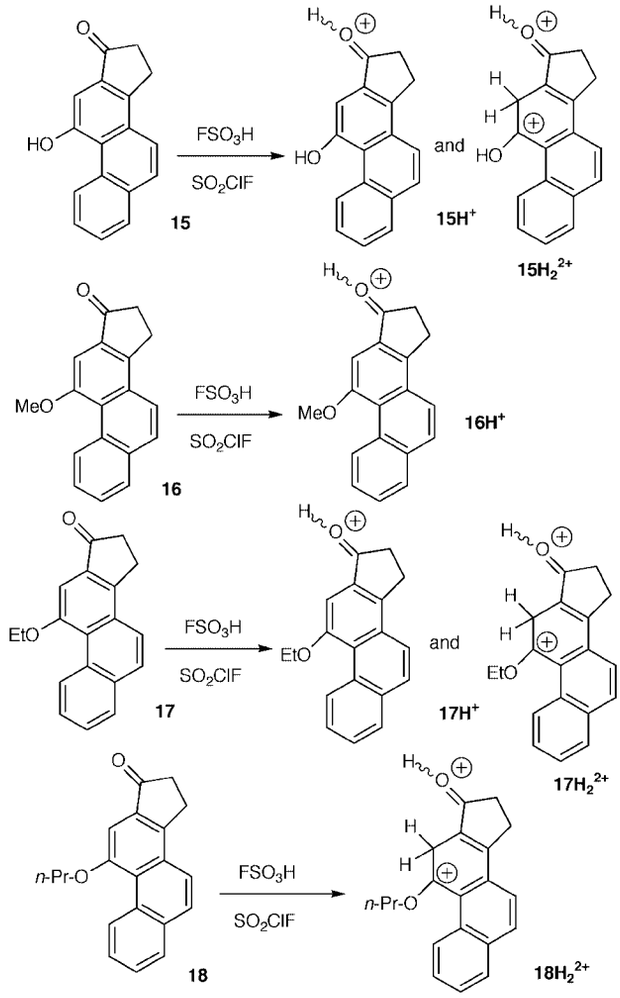

Fig. 8 Mono- and diprotonation of the 11-phenol and the 11-alkoxy derivatives (**15**–**18**).

Comparative discussion of the protonation results and relationship to biological activity

The relationship between "correct substitution" and carcinogenicity in C_p[*a*]P skeleton is well documented.[1] The observed substituent dependency of the site of protonation (FSO_3H–SO_2ClF) in hydrocarbon carbocations **1H**$^+$, **4H**$^+$ and **7H**$^+$ points to relative carbocation stability and relief of steric crowding at the bay-region as important factors in directing electrophilic attack under kinetic control. Despite predominant charge localization in the ring undergoing attack (*ortho*/*para*) the overall delocalization pattern in the monoarenium ions signifies an extended charge alternation path within the phenanthrene moiety, hence phenanthrenium ion character. Whereas ease of formation and stability of both the 16(17)-ene carbocations **3H**$^+$ and **6H**$^+$ implicate their potency, **6** is a stronger tumorigen than **3** which led to the suggestion of an additive effect.[1] Formation of the dimer **21** from **3** on silica and facile generation of **3H**$^+$ from **21** are noteworthy.

Protonation of the keto-analogs (including the CF_3-derivative **19**) with FSO_3H–SO_2ClF occurs at the carbonyl group to form stable carboxonium ions. Charge delocalization mapping in the resulting COH$^+$ ions establishes limited phenanthrenium ion character with C-14 and C-9 becoming most positive. In higher acidity superacids [$FSO_3H{\cdot}SbF_5$ (4:1)–SO_2ClF or $FSO_3H{\cdot}SbF_5$ (1:1)–SO_2ClF] carboxonium–arenium dications were generated from **8** and **9** and mixtures of mono- and dications were formed with **19** and **2**. In the case of A-ring

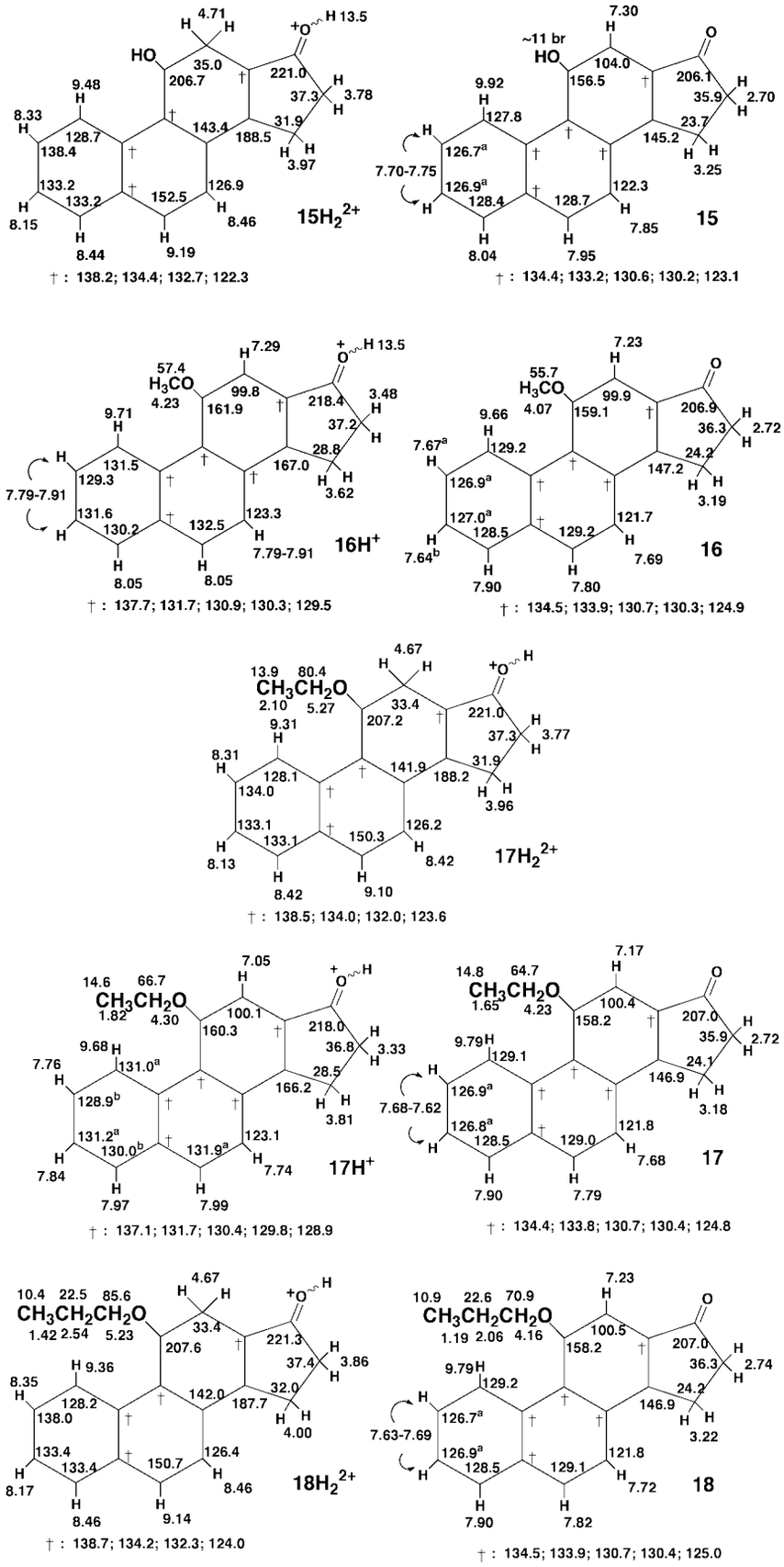

Fig. 9 Summary of ^{13}C and ^{1}H NMR data for cations and precursors in Fig. 8. a, b, c denote interchangeable assignments for a pair or group of proton or carbon resonances. n.a. not assigned. ? Not observed.

methylated analogs **8** and **9**, ring protonation occurs at the A-ring. Previous biological tests showed, however, that A-ring methylation does not increase carcinogencity,[1] probably because it hinders biological oxidation. It is pertinent to point out that based on a molecular model study,[3b] increased activity in **5** is suggested to stem from hydrogen bonding which aligns the A-ring with the catalytic iron center in cyctochrome P450 for epoxidation.

An important observation is that the A-ring activated carboxonium ions **8H**$^+$ and **14H**$^+$ undergo ring fluorosulfonation in

the biologically important A-ring under thermodynamic control. This poses the question whether the biomimic oxidation[5] could have been directed to the A ring if CO was complexed!

Opposite reactivity patterns are revealed for the phenol **15** and its alkoxy **16**–**18** derivatives in comparing stable ion and biological data. Thus the reactivity sequence (ease of ring protonation) propoxy > ethyoxy ≈ phenol > methoxy is observed for their carboxonium ions with protonation occurring at C-11 in the C ring. For **18** and **17** relief of steric strain is an important driving force under kinetic control (it is unclear why **15** is more reactive than **16** in FSO_3H). In contrast, under biological conditions steric factors must prevent metabolic activation of **18** and **17** (only **16** and **15** are active) either because epoxidation is hindered or because subsequent attack by DNA is prevented.

In the carboxonium-arenium dications $\mathbf{8H_2}^{2+}$ and $\mathbf{9H_2}^{2+}$ whereas positive charge is largely localized in the A-ring (*ortho*/*para*) several other conjugated carbons within the phenanthrene moiety are also deshielded. Interestingly, magnitude of positive charge retention diminishes at C-14 upon ring protonation in the A-ring presumably as a means to reduce charge–charge repulsion. An opposite pattern is seemingly in effect in the carboxonium-arenium dications which are protonated in the C-ring ($\mathbf{15H_2}^{2+}$, $\mathbf{17H_2}^{2+}$, $\mathbf{18H_2}^{2+}$), where charge retention has augmented at C-14 and reduced at C-8.

Experimental

The cyclopenta[*a*]phenantherene derivatives are all known compounds whose syntheses had already been reported in the literature.[1–9] They were synthesized and purified at the Imperial Cancer Research Fund Labs in London and at Surrey. Although NMR data on some of these had been reported along with their synthesis, specific assignments had not been made.

NMR spectra of the substrates were recorded in $CDCl_3$ except for **15** which was only soluble in DMSO and for which spectra were recorded in DMSO containing a few drops of $CDCl_3$. Stable ions were generated using a HV-line according to our recently published procedures.[12,14,16] Typically, 20–30 mg of the substrate, 0.5 mL of SO_2ClF, *ca*. 0.05 mL CD_2Cl_2 and 5–10 drops of the superacid were used for each preparation.

NMR spectra were recorded on a GE-GN300 MHz instrument using a 5 mm C/H switchable probe and a 5 mm ^{19}F probe. The procedures for low temperature 1D and 2D-NMR studies of the superacid solutions were similar to our previously published methods.[12,14,16]

NMR data for the carbocations were collected at −70 °C and for carboxonium ions and dications at −20 °C, except for compounds **8** and **20** which were initially studied at −60 °C (to avoid ring fluorosulfonation).

FSO_3H (Allied or Aldrich) was distilled in an all-glass distillation unit under argon and stored in Nalgene bottles with teflon seals under argon. SbF_5 (Aldrich or Fluorochem) was similarly distilled and stored. Preparation of $FSO_3H{\cdot}SbF_5$ mixtures were as previously described.[19]

SO_2ClF was synthesized from SO_2Cl_2, ammonium fluoride and TFAH, according to a modified procedure of Prakash *et al*.[20] Several distillations provided pure SO_2ClF.

Computational methods/procedures

AM1 and PM3 calculations were carried out using standard methods as implemented in the Hyperchem package (Hypercube Inc.). Gaussian 98 software[21] was utilized for *ab initio* calculations. Geometries were optimized and vibrational frequencies were calculated using the HF/6-31G(d,p) method.[22] All species were minima on the potential energy surfaces. The geometries were re-optimized with B3LYP/6-31G(d,p).[23,22] Charges were calculated using Natural Population Analysis (NPA)[24] using NBO 3.1 software.[25] Chemical shifts were calculated with the GIAO method.[26]

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