Persistent oxidation dications of carcinogenic PAHs: charge delocalization mapping in 7,12-dimethylbenzo[*a*]anthracenium, 3-methylcholanthrenium, 1-methylbenzo[*a*]anthracenium and in parent benzo[*a*]anthracenium dications †

Kenneth K. Laali * and Mutsuo Tanaka

Department of Chemistry, Kent State University, Kent, OH 44242, USA

Received (in Cambridge) 21st May 1998, Accepted 16th September 1998

Persistent oxidation dications of 7,12-dimethylbenzo[*a*]anthracene 7,12-DMA ($\mathbf{1}^{2+}$), 3-methylcholanthrene 3-MC ($\mathbf{2}^{2+}$), 1-methylbenzo[*a*]anthracene 1-MBA ($\mathbf{3}^{2+}$) and parent benzo[*a*]anthracene BA ($\mathbf{4}^{2+}$) were generated by low temperature reaction with SbF_5–SO_2ClF and studied directly by NMR. Whereas the positive charge is highly delocalized throughout their periphery, the *meso*-positions of the anthracene moiety (the "L-region") experience the largest $\Delta\delta_{^{13}C}$ values with C-7 being the most positive. Methyl introduction at C-7 results in a dramatic increase in the $\Delta\delta_{^{13}C}$ value at this position (80 ppm in $\mathbf{1}^{2+}$ as compared to 56 ppm in the case of $\mathbf{4}^{2+}$), whereas a methyl group at C-12 is less effective in enhancing carbon deshielding. In 3-methylcholanthrenium dication $\mathbf{2}^{2+}$, the ring carbons attached to the ethano-bridged C-12b/C-2a sustain the largest positive charge, followed by C-6. The $\Sigma\Delta\delta_{^{13}C}$ values for the dications are between 412.6–432.7 ppm and their AM1 calculated $\Delta\Delta_fH°$ values are between 431.2–443.7 kcal mol^{-1}. The resulting 16π-dications exhibit strong proton shielding and are paratropic. Dications $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ derived from potent carcinogens have lower $\Delta\Delta_fH°$ values and are less paratropic as compared to $\mathbf{3}^{2+}$ and $\mathbf{4}^{2+}$. Charge delocalization mapping allows the most likely site(s) for nucleophilic attack to be identified for comparison with the available data on chemical generation and nucleophile trapping of PAH radical cations. Quenching of $\mathbf{1}^{2+}$ with hexane and adamantane to selectively produce the arenium ion of C-7 by hydride abstraction gave inconclusive results.

Introduction

Metabolic activation of PAHs generates electrophiles which can react with nucleophilic sites on DNA bases to form adducts. The diol epoxides, benzylic esters and the radical cations constitute the entire spectrum of electrophiles that can be formed.[1–4] In some systems, diol epoxide ring opening may possess significant carbocationic character.[5–11] Involvement of carbocations can also be important in binding the benzylic esters which are formed from methylated PAHs, whose major metabolites are $PAHCH_2OH$.[1,12] Alternatively, or in competition, PAHs with IP's <7.35 eV could undergo direct oxidation to produce radical cations which can react with cellular nucleophiles.[4] It has been suggested that the relative importance of epoxidation *versus* one-electron oxidation pathways depends on the enzymes present in the target organ.[3]

Benzo[*a*]anthracene together with its regioisomeric di- and monoalkyl derivatives and their ethano-bridged analogs (cholanthrenes), and their corresponding bay- and K-region epoxides have been the subject of numerous solvolytic, structural, theoretical, metabolic and DNA-binding studies in an effort to understand the intriguing structure–activity patterns that they exhibit and in order to shed light on the mechanism of their *in vivo* activation.[1]

7,12-DMBA (**1**) is one of the most potent PAH carcinogens known; its bay-region diol epoxides have been identified as the ultimate carcinogens. Although the 7-CH_2OH and 7,12-$(CH_2OH)_2$ derivatives of **1** are major metabolic products, and this clearly points to the importance of the benzylic side-chain in activation, the corresponding DNA–CH_2–PAH adducts have not been isolated.[1,13*a*] 3-MC (**2**) is also a potent carcinogen which produces the 1-hydroxy derivative (hydroxylation at the ethano-bridge) as the major metabolic product, whose further metabolism produces the 9,10-dihydrodiol.[1,13*b*]

Involvement of a radical cation (RC) pathway has been proposed for both **1** and **2**, and the chemistry of their radical cations (generated chemically or electrochemically) with model bases has been studied in some detail.[3,14,15]

Our work in mechanistic carcinogenesis is concerned with direct studies of PAH arenium ions as models of positive oxygen activation, and with the regioisomeric α-PAH substituted carbocations as diol epoxide ring opening models, with the aim of gauging their charge delocalization mode and substituent modulation of charge alternation.[16–21] We are searching for relationships between the magnitude of carcinogenic activity and the mode of charge alternation.

In relation to the importance of the oxidative pathways for the BA skeleton,[3] we report on the generation and NMR study of the oxidation dications derived from 7,12-DMBA ($\mathbf{1}^{2+}$) and 3-MC ($\mathbf{2}^{2+}$) (both PAHs are potent carcinogens), 1-MBA ($\mathbf{3}^{2+}$) (not a carcinogen) as well as parent BA ($\mathbf{4}^{2+}$) (a marginal carcinogen[5]). The charge delocalization pathways in the dications, substituent effects and tropicity are addressed based on the magnitude of $\Delta\delta_{^{13}C}$ and $\Delta\delta_{^{1}H}$ values. AM1 was used to obtain $\Delta\Delta_fH°$ values, HOMO-coefficients and the HOMO–LUMO gap for the dications, and for a qualitative comparison of the overall charge delocalization pattern. It was hoped that direct studies of the dications would help with a better understanding of the reactivity in the radical cations and provide a more comprehensive picture.

† ^1H, ^{13}C and C/H HETCOR spectra of the dications are available as supplementary material (SUPPL. NO. 57438, 9 pp.). For details of the Supplementary Publications Scheme see '*Instructions for Authors*', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors).

Table 1 $\Sigma\Delta\delta_{^{13}C}$, AM1 $\Delta\Delta_f H°$, ^{1}H center of gravity and the HOMO–LUMO gaps

Dication	$\Sigma\Delta\delta_{^{13}C}$	AM1 $\Delta\Delta_f H°$/ kcal mol^{-1}	^{1}H NMR center of gravity (ppm) [neutral]	HOMO–LUMO gap (ΔE/eV) [neutral]
$\mathbf{1}^{2+}$	432.7	431.2	7.85 [7.85]	6.12 [6.99]
$\mathbf{2}^{2+}$	412.6	431.5	7.70 [7.84]	6.20 [7.06]
$\mathbf{3}^{2+}$	428.0	440.8	7.56 [7.89]	6.26 [7.21]
$\mathbf{4}^{2+}$	424.6	443.7[a]	7.33 [7.96]	6.27 [7.22]

[a] Lit. value 409.2 kcal mol^{-1} (ref. 28).

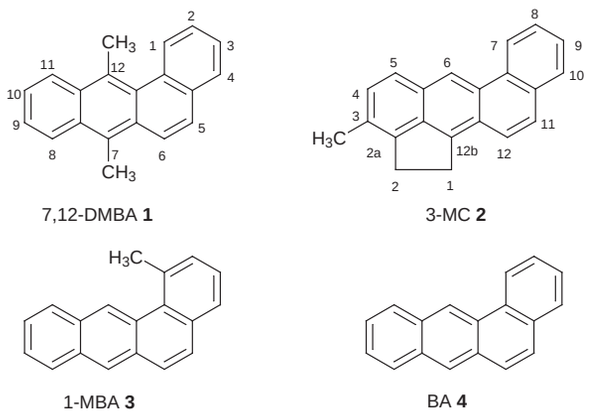


Fig. 1 The substrates.

Results and discussion

Background to the work

Formation of the oxidation dication from parent BA $\mathbf{4}^{2+}$ was first inferred by a Dutch group in 1968 based on its UV spectrum, when SbF_5 was added to a FSO_3H solution of BA.[22,23] The UV spectrum following addition of an alkane was assigned to the C-7 protonated benzo[*a*]anthracenium ion, indicative of selective hydride abstraction at C-7. The ^{13}C NMR spectrum of $\mathbf{4}^{2+}$ was first reported by Forsyth and Olah,[24] as part of an extensive survey of PAH dications. The present study included a detailed ^{1}H and ^{13}C NMR analysis of $\mathbf{4}^{2+}$ for comparison with $\mathbf{1}^{2+}$–$\mathbf{3}^{2+}$ dications.

The substrates (Fig. 1) reacted smoothly with cold SbF_5–SO_2ClF to give their dications as dark-green solutions typically after 12 h at −30 °C. Subsequent storage of the samples for 2 weeks at dry ice–acetone temperature usually improved the quality of the NMR spectra, presumably because of more complete oxidations (converting any remaining radical cations to dications). The resulting spectra exhibited all of the expected ^{13}C resonances as sharp peaks and did not indicate averaging due to a dication–radical cation equilibrium. The proton resonances were also nicely resolved and were devoid of any unusual broadening/averaging (representative spectra are available as Supplementary Material).

Detailed NMR assignments of the dications and their precursors were based on ^{1}H, ^{13}C, H–H COSY, C–H HETCOR (and NOED) spectral data (the results are gathered in Figs. 2 and 3). The quaternary carbons, especially those within a narrow chemical shift range, could not be specifically assigned and are listed separately in Fig. 3.

Comparative discussion of the ^{1}H NMR features and tropicity in the dications

The significant feature in the proton spectra of the dications is the presence of a strong paramagnetic ring current in the resulting 16π-dications which leads to pronounced overall proton shielding as compared to the neutral PAHs (Table 1). The ^{1}H centers of gravity in the dications and the neutrals are shown in Table 1. The largest shielding effects (Fig. 2) are observed for the bay-region protons (H-1/H-12); H-6 shielding diminishes in

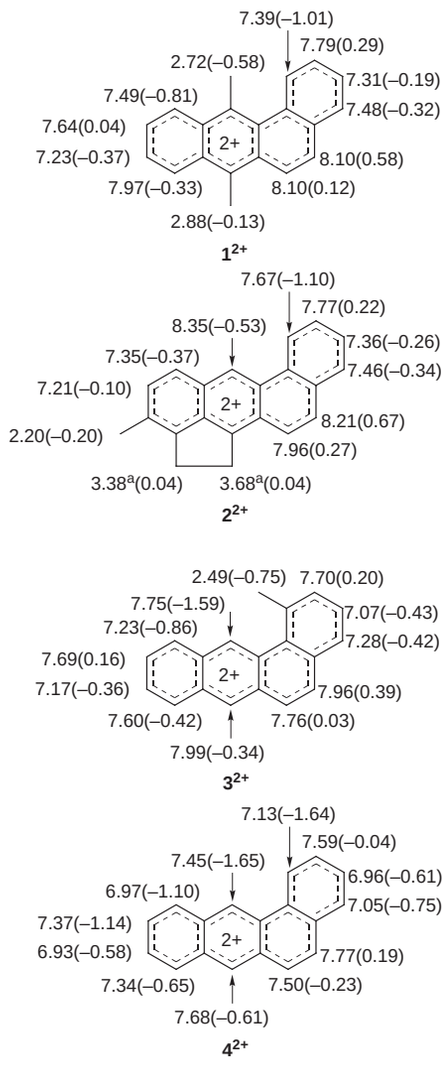
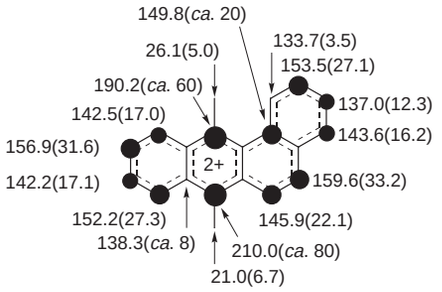


Fig. 2 The ^{1}H NMR assignments for the dications.

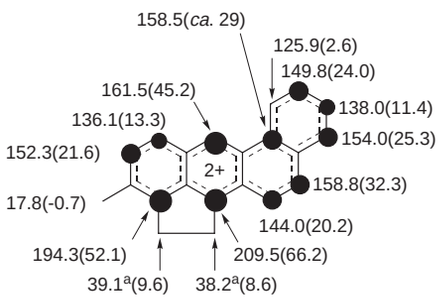
$\mathbf{2}^{2+}$ which has an annelated 5-membered ring. Most K-region protons and the H-2 protons are deshielded.

The bay-region methyl group in $\mathbf{3}^{2+}$ and in $\mathbf{1}^{2+}$ experience strong anisotropic shielding; the *peri*-methyl in $\mathbf{2}^{2+}$ is also shielded. Observation of methyl shielding is indicative of conformational change in the dications for methyl groups in crowded positions. Shielding for a methyl at C-7 is far less ($\mathbf{1}^{2+}$), and for the ethano group ($\mathbf{2}^{2+}$) no such shielding is seen. Methyl shielding in the dications is most pronounced for the dications derived from the non-planar PAHs (**1** and **3**). For **1**, the X-ray structure showed a 20° twist out of the general plane.[1] For $\mathbf{1}^{2+}$, NOE effects were detected between the *meso*-methyl (Me-12) and H-1/H-11, as well as between 7-Me and its *peri*-protons (H-6/H-8). For $\mathbf{2}^{2+}$, NOE enhancement was seen between the methyl (3-Me) and its *ortho*-hydrogen (H-4). A similar NOE effect was observed in $\mathbf{3}^{2+}$ between the bay-region methyl and H-12/H-2.



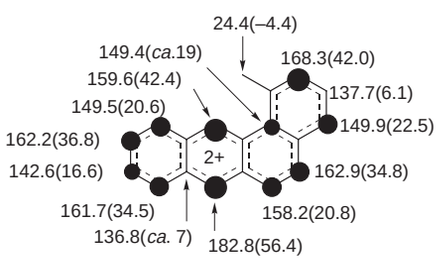
quaternary carbons; 145.7, 145.4, 145.2, 143.2

1^{2+}



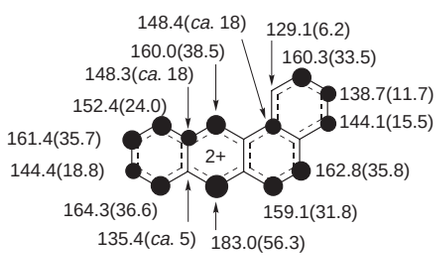
quaternary carbons; 145.6, 144.5, 144.2, 137.4
136.1, 134.9

2^{2+}



quaternary carbons; 148.3, 146.4, 144.5, 144.5
139.8

3^{2+}



quaternary carbons; 143.7, 142.5, 140.9

4^{2+}

a; interchangeable pair

Fig. 3 The ^{13}C NMR assignments for the dications.

In analogy with the conclusions made concerning tropicity in polycyclic dianions,[25–27] it can be seen that the dications derived from non-planar analogs are overall less paratropic. This phenomenon was attributed to poor π-orbital overlap. Since it was shown that the HOMO–LUMO gap (ΔE) and paratropicity correlate,[25–27] the AM1-calculated ΔE values (in eV) are also included in Table 1. In dianions, smaller paratropic shifts are associated with larger HOMO–LUMO gaps, such a relationship apparently breaks down here because of variations in the degree of twisting of the perimeter.

The AM1-predicted $\Delta\Delta_f H°$ values for the dications are between *ca*. 431–444 kcal mol^{-1} with $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ being most favored. These values are well below the 463 ± 3 kcal mol^{-1} maximum for dication formation.[28] As mentioned earlier, no unusual line-broadening was observed in the ^{1}H NMR spectra of the dications (the resonances were sharp and well resolved), consistent with previous arguments on polycyclic dianions that for doubly-charged systems, larger HOMO–LUMO gaps are indicative of little or no contribution from the triplet state which normally results in paramagnetic dilution and concomitant NMR line-broadening.

A comparative discussion of the ^{13}C NMR features

Whereas the positive charge is extensively delocalized throughout the periphery of the benzo[*a*]anthracenium dications there is strong charge localization at the *meso*-positions of the anthracene moiety (Fig. 3). For the unperturbed system $\mathbf{4}^{2+}$, the $\Delta\delta_{^{13}C}$ values at C-7 and C-12 are 56 and 38.5 ppm respectively. Apart from these positions, there is significant charge localization at several other carbons, notably at C-2, C-6, C-8 and C-10. Moreover, charge alternation "breaks down" in some locations where two adjacent carbons both experience fairly large $\Delta\delta_{^{13}C}$ values, especially at the K-region, for example at C-5/C-6. Introduction of a methyl at C-1 ($\mathbf{2}^{2+}$) increases the degree of positive charge retention at both C-12 and C-2. Methyl introduction at C-7 has a pronounced effect in increasing the positive charge at this carbon (from 56 ppm in $\mathbf{4}^{2+}$ to 80 ppm in $\mathbf{1}^{2+}$), whereas a methyl at C-12 is far less effective in increasing $\Delta\delta_{^{13}C}$. Since some quaternary carbons could not be specifically assigned, a complete charge delocalization map cannot be drawn. Nevertheless, it can be clearly seen that a much greater degree of charge localization at C-7 constitutes a major difference between $\mathbf{1}^{2+}$ and $\mathbf{4}^{2+}$ whose PAHs have vastly different carcinogenic potentials. In the absence of steric bias, C-7 must be the most logical site for nucleophilic attack on the dication (see further quenching experiments). Previous studies of quenching of the radical cation of **4** gave products of attack at C-7, C-12 and at C-5.[14]

The total deshieldings ($\Sigma\Delta\delta_{^{13}C}$) in the dications (Table 1) are between *ca*. 413–433 ppm, with $\mathbf{1}^{2+}$ showing the largest total deshielding. For comparison, the AM1-derived HOMO coefficients for $\mathbf{1}^{2+}$–$\mathbf{4}^{2+}$ are illustrated in Fig. 4.

Despite the limitations of semiempirical methods in predicting charge densities, good agreement was previously found between the overall pattern of $\Delta\delta_C$ and AM1 charges in a number of PAH carbocations.[17,20,22] Reasonable qualitative correlations between the NMR shifts and calculated (semiempirical) charge densities have also been observed in delocalized polycyclic dianions.[27,29,30] Despite inherent differences, the correspondence between the overall charge pattern derived from *ab initio* and AM1 methods in modelling PAH ring opening to carbocations has been shown.[31] In the present study, good overall agreement is seen between the charge delocalization paths derived based on the magnitude of $\Delta\delta_{^{13}C}$ values and the AM1-calculated changes in Mulliken carbon charges. The overall pattern remains unchanged if group (CH) charges are considered. These trends are sketched in Fig. 5 for comparison with Fig. 3. Two noteworthy features are a) positive charge retention at the quaternary carbons of the anthracene moiety (C-6a/C-7a/C-11a/C-12a) is at best minimal as these become mostly overall negative; b) in some cases adjacent net positive charges are created.

Quenching experiments

The early work of the Dutch group (see before) suggested that $\mathbf{4}^{2+}$ could selectively hydride abstract from an alkane to give the arenium ion of C-7.[23] Detailed charge delocalization mapping in the present study has identified C-7 as the most likely candidate for nucleophilic attack. It was, therefore, pertinent to examine quenching of the dications with typical hydride donors. Low temperature reaction of $\mathbf{4}^{2+}$ with hexane, and $\mathbf{1}^{2+}$

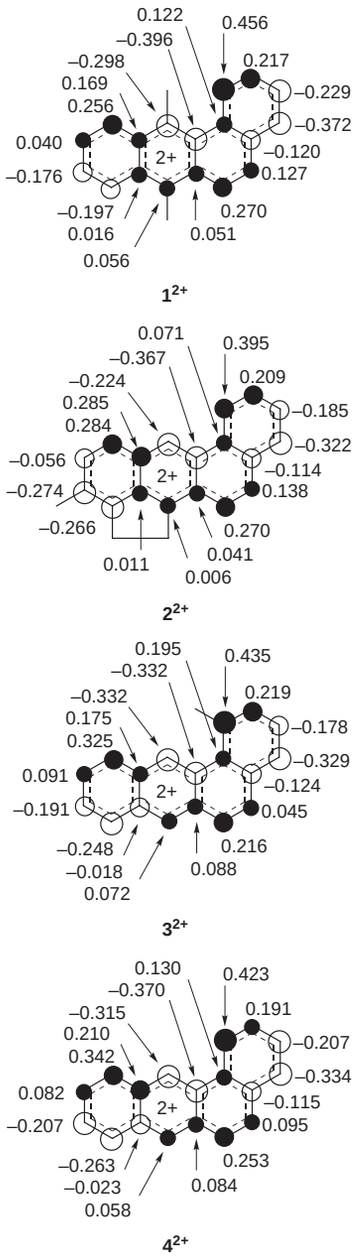


Fig. 4 HOMO coefficients for $\mathbf{1}^{2+}$–$\mathbf{4}^{2+}$.

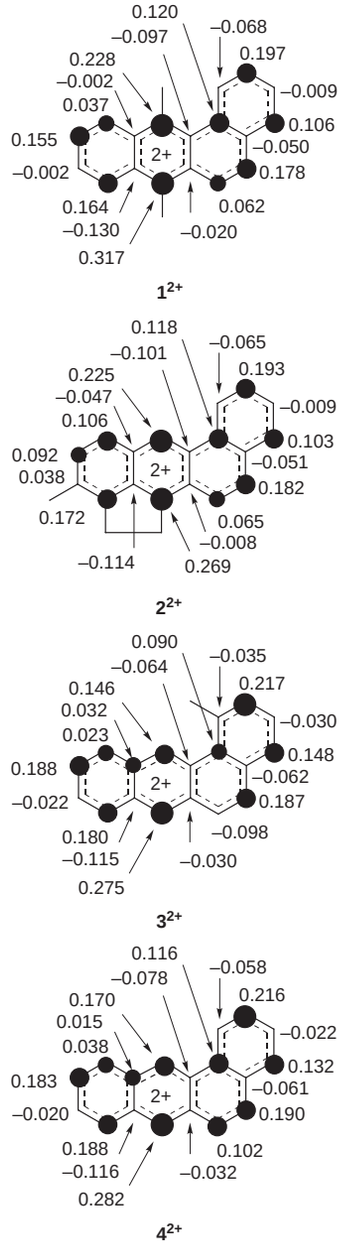


Fig. 5 AM1 changes in carbon charges $\delta q = q_c$ (dication) − q_c (neutral).

with hexane and with adamantane were studied. Upon addition of cold hexane to the dark-green solution of $\mathbf{4}^{2+}$ at dry ice–acetone temperature the color turned dark-red and then black. Low temperature ^{1}H NMR monitoring showed a complex mixture of arenium ions. Lack of selectivity was also encountered with $\mathbf{1}^{2+}$ which gave mixtures of arenium ions upon reaction with hexane or adamantane indicative of hydride abstraction at several sites. The previously reported selective hydride abstraction at C-7 could not therefore be confirmed in our experiments.

Summary

We have generated the persistent dications of potent carcinogens 7,12-DMA and 3-MC, as well as those of 1-MBA and the parent BA. The charge delocalization modes in the resulting 16π-paratropic dications have been examined by NMR. The most important difference between $\mathbf{1}^{2+}$ and $\mathbf{4}^{2+}$ is the presence of a significantly larger localized positive charge at C-7 in the former. For $\mathbf{3}^{2+}$ the ring carbons attached to the ethano bridge exhibit a large charge localization. In all cases, there is extensive charge delocalization and several sites have been identified as possible candidates for nucleophilic attack. Substituent effect on charge distribution, tropicity and conformation have been addressed; AM1 energies, changes in carbon charges, HOMO–LUMO gaps and the HOMO coefficients were also determined for comparison with NMR data. Studies of the arenium ions derived from the BA skeleton and α-BA-substituted-carbocations as models of epoxide ring opening are the subject of a separate investigation which is being reported elsewhere.[32]

Experimental

The PAHs

7,12-DMBA, 3-MC and BA were purchased from Aldrich and used without further purification after determining (by NMR) that their purities were no less than 98%. 1-MBA [1,33] was available in our laboratory from a related study.

SbF_5 (Aldrich or Fluorochem) was doubly distilled in an all-glass distillation unit under argon and stored in Nalgene bottles with Teflon cap seals under argon.

SO_2ClF was prepared from SO_2Cl_2 by reaction with NH_4F and TFAH using a modified procedure of Prakash *et al.*[34]

The Hyperchem package (hypercube 1994) was utilized for energy minimizations and AM1 calculations. The semi-

empirical package built into GAMESS (version 1995) was used for determining the AM1 HOMO-coefficients.

NMR spectra were recorded on a wide-bore GE-GN300 instrument utilizing a 5 mm C/H switchable probe and using very short (*ca*. 3 mm) external sealed capillary tubes (made from melting point tubes) containing acetone-d_6–TMS which were added to the 5 mm NMR tubes containing the dication solutions. The reported ^1H NMR shifts are corrected for the use of capillary ($\delta\ ^1H_{int} = \delta\ ^1H_{ext} + 0.82$ ppm).

Preparation of the dications

SbF_5 (1 mL) was charged into a 10 mm NMR tube under an argon atmosphere. SO_2ClF (2 mL) was condensed into a 5 mm NMR tube using a vacuum line and was subsequently poured directly into SbF_5 in the 10 mm tube at dry ice–acetone temperature. By vigorous mixing (vortex) and slight periodic warming a clear homogeneous solution was obtained. In a similar fashion, SO_2ClF (0.3 mL) was condensed *via* a vacuum line into a 5 mm NMR tube charged with the PAH substrate (30 mg) to form a slurry. The SbF_5–SO_2ClF solution in the 10 mm NMR tube was then added to the resulting slurry under argon with vigorous mixing (vortex) to produce the dications as dark-green homogeneous solutions. The samples were kept at −30 °C for 12 hours and then stored at dry ice–acetone temperature for 2 weeks.

Quenching experiments

These were performed by the addition of dry hexane (5 drops) or a few crystals of adamantane (10 mg) to the dication solutions in the 5 mm NMR sample tubes at dry ice–acetone temperature with vigorous (vortex) mixing whereupon the green colour turned dark-red and then black over time. The samples were kept at dry ice–acetone temperature for 3 days and then analyzed by NMR. In all cases mixtures of arenium ions were formed which could not be specifically assigned.

Acknowledgements

Support of our work in the area of reactive intermediates of carcinogenesis of PAH by the NCI of NIH (R15 CA 63595) is gratefully acknowledged. We thank Dr Todd Reaker for computational assistance.

References

1 R. G. Harvey, *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*, Cambridge University Press, Cambridge, UK, 1991.
2 *Polycyclic Aromatic Hydrocarbons and Carcinogenesis*, ACS Symposium Series 283, ed. R. G. Harvey, ACS, Washington DC, 1985.
3 E. L. Cavalieri and E. G. Rogan, in *Free Radical in Biology*, ed. W. A. Pyror, 1984, vol. 5, ch. 10, pp. 323–369.
4 K. H. Stansbury, J. W. Flesher and R. L. Cupta, *Chem. Res. Toxicol.*, 1994, **7**, 254.
5 N. T. Nashed, A. Bax, R. J. Loncharich, J. M. Sayer and D. M. Jerina, *J. Am. Chem. Soc.*, 1993, **115**, 1711.
6 N. T. Nashed, S. K. Balani, R. J. Loncharich, J. M. Sayer, D. Y. Shipley, R. S. Mohn, D. L. Whalen and D. M. Jerina, *J. Am. Chem. Soc.*, 1991, **113**, 3910.
7 N. T. Nashed, T. V. S. Rao and D. M. Jerina, *J. Org. Chem.*, 1993, **58**, 6344.
8 N. T. Nashed, J. M. Sayer and D. M. Jerina, *J. Am. Chem. Soc.*, 1993, **115**, 1723.
9 H. Yagi, J. M. Sayer, D. R. Thakker, W. Levin and D. M. Jerina, *J. Am. Chem. Soc.*, 1987, **109**, 838.
10 J. W. Keller, N. G. Kundu and C. Heidelberger, *J. Org. Chem.*, 1976, **41**, 3487.
11 J. W. Keller and C. Heidelberg, *J. Am. Chem. Soc.*, 1976, **98**, 2328.
12 R. E. Royer, T. A. Lyle, G. G. Moy, G. H. Daub and D. L. Vander Jagt, *J. Org. Chem.*, 1979, **44**, 3202.
13 (*a*) M. Koreeda and R. Gopalaswamy, *J. Am. Chem. Soc.*, 1995, **117**, 10 595; (*b*) S. A. Jacobs and R. G. Harvey, *Tetrahedron Lett.*, 1981, **22**, 1093.
14 E. Cavalieri and R. Roth, *J. Org. Chem.*, 1976, **41**, 2679.
15 W. V. J. RamaKrishna, E. L. Cavalieri, E. G. Rogan, G. Dolnikowski, R. L. Cerny, M. L. Gross, H. Jeong, R. Jankowiak and G. L. Small, *J. Am. Chem. Soc.*, 1992, **114**, 1863.
16 K. K. Laali, S. Hollenstein, R. G. Harvey and P. E. Hanson, *J. Org. Chem.*, 1997, **62**, 4023.
17 K. K. Laali, M. Tanaka, S. Hollenstein and M. Cheng, *J. Org. Chem.*, 1997, **62**, 7752.
18 K. K. Laali and P. E. Hansen, *J. Org. Chem.*, 1997, **62**, 5304.
19 K. K. Laali, S. Hollenstein and P. E. Hansen, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 2207.
20 K. K. Laali and S. Hollenstein, *J. Chem. Soc.*, *Perkin. Trans. 2*, 1998, 897.
21 K. K. Laali, P. E. Hansen, J. J. Houser and M. Zander, *J. Chem. Soc.*, *Perkin Trans. 2*, 1995, 1781.
22 K. K. Laali, *Chem. Rev.*, 1996, **96**, 1873.
23 W. Th. A. M. Van der Lugt, H. M. Buck and J. Oosterhoff, *Tetrahedron*, 1968, **24**, 4941.
24 D. A. Forsyth and G. A. Olah, *J. Am. Chem. Soc.*, 1976, **98**, 4086.
25 M. Rabinovitz and Y. Cohen, *Tetrahedron*, 1988, **44**, 6957.
26 M. Rabinovitz, *Top. Curr. Chem.*, 1988, **146**, 99.
27 M. Rabinovitz and A. Ayalon, *Pure Appl. Chem.*, 1993, **65**, 111.
28 N. J. Mills, *J. Org. Chem.*, 1992, **57**, 1899.
29 Y. Cohen, J. Klein and M. Rabinovitz, *J. Am. Chem. Soc.*, 1988, **110**, 4634.
30 L. Zelikovich, R. E. Hoffman, A. Ayalon and M. Rabinovitz, *J. Chem. Soc.*, *Perkin Trans. 2*, 1992, 1785.
31 (*a*) J. R. Rabinovitz and S. B. Little, *Int. J. Quantum Chem.*, 1994, **52**, 681; (*b*) J. R. Rabinovitz and S. B. Little, *Chem. Res. Toxicol.*, 1992, **5**, 285.
32 K. K. Laali and M. Tanaka, *J. Org. Chem.* 1998, in the press.
33 W. F. Dunning and M. R. Curtis, *J. Natl. Cancer Inst.*, 1960, **25**, 385.
34 V. P. Reddy, D. R. Bellow and G. K. S. Prakash, *J. Fluorine Chem.*, 1992, **56**, 195.

Paper 8/03856B