One-Electron Oxidation of Dibenzo[a]pyrenes by Manganic Acetate

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The dibenzo[a]pyrenes (DB[a]Ps) are carcinogenic polycyclic aromatic hydrocarbons (PAH) found as environmental pollutants. DB[a,l]P is the most potent carcinogenic PAH ever tested. To investigate the bioactivation of DB[a]Ps by one-electron oxidation, oxidation of DB[a,e]P, DB[a,h]P, DB[a,i]P, DB[a,l]P, and anthanthrene with $Mn(OAc)_3$ was conducted and compared to that of benzo[a]pyrene (B[a]P). All five DB[a]Ps produced monoacetoxy derivatives, and all of them except DB[a,l]P also produced diacetoxy derivatives. Kinetic studies of the formation of monoacetoxy and diacetoxy derivatives of DB[a]Ps were carried out, and the results were compared to those of the parent compound B[a]P. DB[a,l]P was similar to B[a]P. DB[a,e]P reacted inefficiently to form monoacetoxy and diacetoxy products. The other three DB[a]Ps resembled one another. These results provide preliminary essential information for studies of the bioactivation of the very potent carcinogen DB[a,l]P to form DNA adducts.

Introduction

Dibenzo[a]pyrenes (DB[a]Ps), formed by condensation of a benzo ring on benzo[a]pyrene (B[a]P), are environmental pollutants generally considered carcinogenic.[1-3] These compounds include anthanthrene, dibenzo[a,e]pyrene (DB[a,e]P), dibenzo[a,h]pyrene (DB[a,h]P), dibenzo[a,i]pyrene (DB[a,i]P), and dibenzo[a,l]pyrene (DB[a,l]P)[4] (Figure 1). In tumorigenicity experiments, anthanthrene is inactive; DB[a,e]P is very weak at best, whereas DB[a,i]P and DB[a,h]P are relatively potent, although less than B[a]P.[5,6] DB[a,l]P is the strongest carcinogenic aromatic hydrocarbon (PAH) ever tested.[7]

One-electron oxidation is a major mechanism of PAH activation, producing radical cations that can bind covalently to DNA.[8-10] Oxidation of PAH by $Mn(OAc)_3$ represents a very useful model for producing radical cations and their subsequent trapping by acetate ions.[9] An extensive study of one-electron oxidation of B[a]P and 6-substituted B[a]P derivatives by $Mn(OAc)_3$ was conducted with the purpose of studying some of the chemical properties of their radical cations.[11] B[a]P reacts specifically and efficiently at C-6 with formation of 6-OAcB[a]P.

In the present study, DB[a]Ps were oxidized by $Mn(OAc)_3$ with the initial purpose of identifying the major products of this reaction. In addition, the relative reactivity in acetoxylation of the radical cations of DB[a]Ps and B[a]P, obtained by manganic oxidation, is reported.

Experimental Procedures

^1H NMR spectra were recorded in $CDCl_3$ with $(CH_3)_4Si$ as the internal standard as previously described.[11] Mass spectra (MS) were recorded as previously described.[11] Anodic peak potentials were measured by cyclic voltammetry, as reported elsewhere.[12] HPLC analyses were performed with a photodiode array detector (PDA) as previously described.[13] A library of spectra was constructed on the PDA (wavelength range, 210–600 nm; resolution, 2 nm). Reverse-phase analyses were conducted on a YMC AQ-313 ODS 5-μm column, 6.0 × 250 mm (YMC, Morristown, NJ), eluted with a 60-min linear gradient of 60% CH_3OH in H_2O to 100% CH_3OH at a flow rate of 1 mL/min. Medium-pressure liquid chromatography (MPLC) was performed on a Büchi preparative liquid chromatograph composed of a pump Model B681, 6-way changeover valve, and columns Model B685 (Brinkmann Instruments, Westbury, NY), and absorbance–fluorescence monitor, Model UA-5 (ISCO, Lincoln, NE). Detection was at 254 nm. Columns were packed with silica gel LPS-1, 13–24 μm (Whatman, Inc., Clifton, NJ), and eluted with *n*-hexane at appropriate flow rates to maintain the pressure within the 30–35 bar range.

$Mn(OAc)_3 \cdot 2H_2O$ was prepared as previously described.[11,14] AcOH was dried and distilled over P_2O_5, and benzene over Na. B[a]P was available in our laboratory and purified as previously described.[11] DB[a]Ps were available in our laboratory and were purified by column chromatography on silica gel eluted with hexane/benzene (8:2). All were recrystallized from xylenes, except for DB[a,l]P, which was recrystallized from benzene.

DB[*a*,*e*]P: mp 236–238 °C (lit.[15] mp 233–234 °C); ^1H NMR δ 7.72–7.76 (m, 2 H, 11-H, 12-H), 7.77–7.85 (m, 2 H, 2-H, 3-H), 8.01 (t, 1 H, 8-H), 8.23 (bd, 1 H, 7-H), 8.29 (d, 1 H, 6-H), 8.32 (bd, 1 H, 1-H), 8.74–8.78 (m, 1 H, 10-H), 8.83 (d, 1 H, 9-H), 8.90–8.93 (m, 1 H, 13-H), 8.99 (bd, 1 H, 4-H), 9.02 (d, 1 H, 5-H), 9.21 (s, 1 H, 14-H).

DB[*a*,*h*]P: mp 306–308 °C (lit.[15] mp 308 °C); ^1H NMR δ 7.75–7.86 (m, 4 H, 2-H, 3-H, 9-H, 10-H), 8.33 (bd, 2 H, 1-H, 8-H), 8.36 (d, 2 H, 6-H, 13-H), 8.70 (s, 2 H, 7-H, 14-H), 8.99 (d, 2 H, 5-H, 12-H), 9.05 (bd, 2 H, 4-H, 11-H).

DB[*a*,*l*]P: mp 280–281 °C (lit.[15] mp 280 °C); ^1H NMR δ 7.74–7.86 (m, 4 H, 2-H, 3-H, 10-H, 11-H), 7.80 (s, 2 H, 6-H, 7-H), 8.22 (bd, 2 H, 4-H, 9-H), 8.32 (s, 2 H, 5-H, 8-H), 9.04 (bd, 2 H, 1-H, 12-H), 9.21 (s, 2 H, 13-H, 14-H).

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(4) We have used the commonly recognized names. The IUPAC systematic names are anthanthrene, dibenzo[*def*,*mno*]chrysene; DB[a,e]P, naphtho[1,2,3,4-*def*]chrysene; DB[a,h]P, dibenzo[*b*,*def*]chrysene; DB[a,i]P, benzo[*rst*]pentaphene; and DB[a,l]P, dibenzo[*def*,*p*]chrysene.

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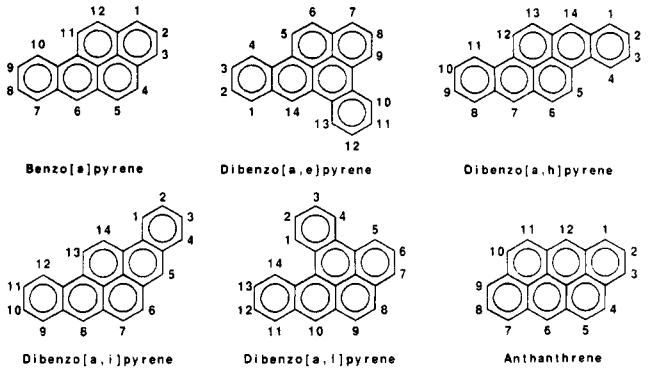


Figure 1. Structures of DB[*a*]Ps.

DB[*a*,*l*]P: mp 224–226 °C (lit.[15] mp 224–226 °C); ^{1}H NMR δ 7.70–7.81 (m, 4 H, 2-H, 3-H, 12-H, 13-H), 7.87 (d, 1 H, 8-H), 7.99 (d, 1 H, 9-H), 8.01 (t, 1 H, 6-H), 8.09 (bd, 1 H, 7-H), 8.28–8.31 (m, 1 H, 11-H), 8.52 (s, 1 H, 10-H), 8.92 (bd, 2 H, 4-H, 5-H), 9.13 (dd, 1 H, 1-H), 9.22–9.25 (m, 1 H, 14-H).

Anthanthrene: mp 261–262 °C (lit.[15] mp 261 °C); ^{1}H NMR δ 8.09 (d, 2 H, 4-H, 10-H), 8.14 (t, 2 H, 2-H, 8-H), 8.17 (d, 2 H, 5-H, 11-H), 8.23 (bd, 2 H, 3-H, 9-H), 8.55 (bd, 2 H, 1-H, 7-H), 8.81 (s, 2 H, 6-H, 12-H).

Standard Procedure for PAH Oxidation by Manganic Acetate. Manganic oxidation of the DB[*a*]Ps was conducted with 50–150 mg of each compound to isolate products in sufficient amount for analyses. The experimental conditions were similar to those previously described,[11] with the exception that AcOH/benzene (1:1) was used in place of AcOH alone, due to the poor solubility of DB[*a*]Ps in AcOH. The concentration of starting material was 25 mM and that of $Mn(OAc)_3 \cdot 2H_2O$ was 50 mM. Reactions were run at 40 °C under argon and were continued until $Mn(OAc)_3$ was depleted. In particular, reaction times were the following: for DB[*a*,*e*]P, 7 h; DB[*a*,*h*]P, 4 h; DB[*a*,*i*]P, 5 h; DB[*a*,*l*]P, 4 h; and anthanthrene, 5 h. Reaction mixtures were purified by silica gel column chromatography, followed by recrystallization. In some instances, impure fractions collected from column chromatography were further purified by MPLC. Purity was >98% as analyzed by HPLC. The structure determination of the products was made by ^{1}H NMR (available as supplementary material) and MS.

DB[*a*,*e*]P. The yields of the two products obtained, 14-OAcDB[*a*,*e*]P and 6,14-$(OAc)_2$DB[*a*,*e*]P, were 27 and 8%, respectively.

14-OAcDB[*a*,*e*]P was recrystallized from benzene/hexane: mp 269–271 °C; MS 360 (4.2, M) in agreement with $C_{26}H_{16}O_2$, 318 (100, M – CH_2CO); 317 (22.5, M – Ac); ^{1}H NMR δ 2.63 (s, 3 H, OAc), 7.63–7.73 (m, 2 H, 11-H, 12-H), 7.78–7.90 (m, 2 H, 2-H, 3-H), 7.98 (t, 1 H, 8-H), 8.21 (bd, 1 H, 7-H), 8.25 (d, 1 H, 6-H), 8.27–8.30 (m, 1 H, 1-H), 8.75 (bd, 1 H, 10-H), 8.77 (bd, 1 H, 9-H), 8.99 (d, 1 H, 5-H), 9.01 (dd, 1 H, 4-H), 9.25 (dd, 1 H, 13-H).

6,14-$(OAc)_2$DB[*a*,*e*]P was obtained from MPLC: MS 418 (M, 10.7) in agreement with $C_{28}H_{18}O_4$, 376 (35.7, M – CH_2CO), 334 (100, M – $2CH_2CO$), 332 (7.3, M – 2Ac); ^{1}H NMR δ 2.62 (s, 3 H, 6-OAc), 2.63 (s, 3 H, 14-OAc), 7.61–7.72 (m, 2 H, 11-H, 12-H), 7.79–7.86 (m, 2 H, 2-H, 3-H), 8.01 (t, 1 H, 8-H), 8.23 (d, 1 H, 7-H), 8.26–8.29 (m, 1 H, 1-H), 8.73 (dd, 1 H, 10-H), 8.76 (s, 1 H, 5-H), 8.81 (d, 1 H, 9-H), 8.85–8.88 (m, 1 H, 4-H), 9.25 (dd, 1 H, 13-H).

DB[*a*,*h*]P. The yields of the three products obtained, 7-OAcDB[*a*,*h*]P, 7,14-$(OAc)_2$DB[*a*,*h*]P, and DB[*a*,*h*]P-7,14-dione were 47, 10, and <1%, respectively.

7-OAcDB[*a*,*h*]P was recrystallized from benzene/hexane: mp 287–289 °C; MS 360 (M, 7.9) in agreement with $C_{26}H_{16}O_2$, 318 (100, M – CH_2CO), 317 (43.2, M – Ac); ^{1}H NMR δ 2.76 (s, 3 H, OAc), 7.69–7.81 (m, 4 H, 2-H, 3-H, 9-H, 10-H), 8.22 (bd, 2 H, 1-H, 8-H), 8.25 (d, 2 H, 6-H, 13-H), 8.62 (s, 1 H, 14-H), 8.87 (d, 2 H, 5-H, 12-H), 8.93–9.01 (m, 2 H, 4-H, 11-H).

7,14-$(OAc)_2$DB[*a*,*h*]P was obtained from MPLC: MS 418 (6.6, M) in agreement with $C_{28}H_{18}O_4$, 376 (11.6, M – CH_2CO), 334 (100, M – $2CH_2CO$), 332 (83.2, M – 2Ac); ^{1}H NMR δ 2.76 (s, 6 H, 7-OAc, 14-OAc), 7.80–7.89 (m, 4 H, 2-H, 3-H, 9-H, 10-H), 8.26–8.31 (m, 4 H, 4-H, 6-H, 8-H, 13-H), 9.02 (d, 2 H, 5-H, 12-H), 9.04–9.08 (m, 2 H, 4-H, 11-H).

DB[*a*,*b*]P-7,14-dione was recrystallized from nitrobenzene: mp 397–398 °C (lit.[15] mp 391–392 °C); MS 332 (100, M) in agreement with $C_{24}H_{12}O_2$, 304 (14.1, M – CO), 276 (17.5, M – 2CO); ^{1}H NMR δ 7.64 (t, 2 H, 3-H, 10-H), 7.78–7.83 (m, 2 H, 2-H, 9-H), 8.40 (d, 2 H, 1-H, 8-H), 8.51 (dd, 2 H, 4-H, 11-H), 8.65 (d, 2 H, 5-H, 12-H), 8.83 (d, 2 H, 6-H, 13-H).

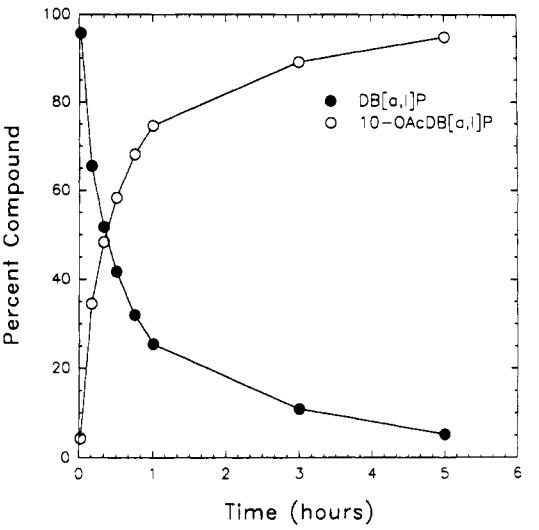


Figure 2. Kinetics of acetoxylation of DB[*a*,*l*]P by $Mn(OAc)_3$.

DB[*a*,*i*]P. The yields of the three products obtained, 5-OAcDB[*a*,*i*]P, 5,8-$(OAc)_2$DB[*a*,*i*]P, and DB[*a*,*i*]P-5,8-dione, were 44, 34, and 14%, respectively.

5-OAcDB[*a*,*i*]P was recrystallized from benzene/hexane: mp 271–273 °C; MS 360 (18.8, M) in agreement with $C_{26}H_{16}O_2$, 318 (100, M – CH_2CO), 317 (11.4, M – Ac); ^{1}H NMR δ 2.70 (s, 3 H, OAc), 7.74–7.87 (m, 6 H, 2-H, 3-H, 6-H, 7-H, 10-H, 11-H), 8.16–8.22 (m, 2 H, 4-H, 9-H), 8.31 (s, 1 H, 8-H), 9.01–9.06 (m, 2 H, 1-H, 12-H), 9.16 (s, 2 H, 13-H, 14-H).

5,8-$(OAc)_2$DB[*a*,*i*]P was recrystallized from benzene/hexane: mp 303–306 °C; MS 418 (4.0, M) in agreement with $C_{28}H_{18}O_4$, 376 (8.6, M – CH_2CO), 334 (77.2, M – $2CH_2CO$), 332 (100, M – 2Ac); ^{1}H NMR δ 2.66 (s, 6 H, 5-OAc, 8-OAc), 7.80–7.89 (m, 4 H, 2-H, 3-H, 10-H, 11-H), 7.83 (s, 2 H, 6-H, 7-H), 8.18 (bd, 2 H, 4-H, 9-H), 9.07 (d, 2 H, 1-H, 12-H), 9.18 (s, 2 H, 13-H, 14-H).

DB[*a*,*i*]P-5,8-dione was recrystallized from nitrobenzene: mp 378–380 °C (lit.[15] mp 365 °C); MS 332 (100, M) in agreement with $C_{24}H_{12}O_2$, 304 (8.8, M – CO), 276 (15.4, M – 2CO); ^{1}H NMR δ 7.57–7.62 (m, 2 H, 3-H, 10-H), 7.76–7.82 (m, 2 H, 2-H, 11-H), 8.35 (bd, 2 H, 4-H, 9-H), 8.49 (bd, 2 H, 1-H, 12-H), 8.54 (s, 2 H, 6-H, 7-H), 8.92 (s, 2 H, 13-H, 14-H).

DB[*a*,*l*]P. The yield of the one product, 10-OAcDB[*a*,*l*]P, was 86%. It was recrystallized from benzene/hexane: mp 124–125 °C; MS 360 (16.1, M) in agreement with $C_{26}H_{16}O_2$, 318 (100, M – CH_2CO), 317 (22.5, M – Ac); ^{1}H NMR δ 2.73 (s, 3 H, OAc), 7.70–7.80 (m, 4 H, 2-H, 3-H, 12-H, 13-H), 7.92 (d, 1 H, 8-H), 7.97 (d, 1 H, 9-H), 8.02 (t, 1 H, 6-H), 8.10 (bd, 1 H, 11-H), 8.89–8.95 (m, 2 H, 4-H, 5-H), 9.04 (dd, 1 H, 1-H), 9.23–9.26 (m, 1 H, 14-H).

Anthanthrene. The yields of the three products obtained, 6-acetoxyanthanthrene, 6,12-diacetoxyanthanthrene, and anthanthrene-6,12-dione, were 47, 19, and <1%, respectively.

6-Acetoxyanthanthrene was recrystallized from benzene/hexane: mp 203–204 °C; MS 334 (14.5, M) in agreement with $C_{24}H_{14}O_2$, 292 (100, M – CH_2CO), 291 (31.5, M – Ac); ^{1}H NMR δ 2.77 (s, 3 H, OAc), 8.05 (d, 1 H, 10-H), 8.10–8.24 (m, 5 H, 2-H, 3-H, 8-H, 9-H, 11-H), 8.11 (s, 2 H, 4-H, 5-H), 8.44 (bd, 1 H, 1-H), 8.53 (bd, 1 H, 7-H), 8.76 (s, 1 H, 12-H).

6,12-Diacetoxyanthanthrene was recrystallized from benzene/hexane: mp 307–309 °C; MS 392 (4.5, M) in agreement with $C_{26}H_{16}O_4$, 350 (8.4, M – CH_2CO), 308 (77.2, M – $2CH_2CO$), 306 (100, M – 2Ac); ^{1}H NMR δ 2.77 (s, 6 H, 6-OAc, 12-OAc), 8.12–8.23 (m, 2 H, 2-H, 8-H), 8.15 (s, 4 H, 4-H, 5-H, 10-H, 11-H), 8.28 (dd, 2 H, 3-H, 9-H), 8.50 (dd, 2 H, 1-H, 7-H).

Anthanthrene-6,12-dione was recrystallized from xylene: mp 400–402 °C; ^{1}H NMR δ 7.88 (t, 2 H, 2-H, 8-H), 8.13 (d, 2 H, 4-H, 10-H), 8.26 (dd, 2 H, 3-H, 9-H), 8.54 (d, 2 H, 5-H, 11-H), 8.77 (dd, 2 H, 1-H, 7-H). Melting point and NMR data were identical to those of the authentic standard.

Table I. Preparative-Scale Manganic Oxidation of Dibenzo[a]pyrenes: Yields of Isolated Reaction Products

PAH	E_{ap}[a]	% reaction products		
		monoacetoxy	diacetoxy	diones
DB[a,e]P	1.239	27 (14)[b]	8 (6, 14)	0
DB[a,h]P	0.967	47 (7)	10 (7, 14)	traces (7, 14)
DB[a,i]P	1.042	44 (5)	34 (5, 8)	14 (5, 8)
DB[a,l]P	1.143	86 (10)	0	0
anthanthrene	0.990	47 (6)	19 (6, 12)	traces (6, 12)

[a] Anodic peak potentials (E_{ap}), expressed in V vs Ag/AgCl, are taken from ref 12. [b] Numbers in parentheses are positions of substitution.

Table II. Rate Constants of Manganic Oxidation of Dibenzo[a]pyrenes[a]

PAH	k, min^{-1}
DB[a,h]P	6.3×10^{-1}
anthanthrene	5.4×10^{-1}
DB[a,i]P	8.4×10^{-2}
DB[a,l]P	3.8×10^{-2}
B[a]P	1.8×10^{-2}
DB[a,e]P	3.9×10^{-3}

[a] PAH (25 mM) were oxidized by $Mn(OAc)_3 \cdot 2H_2O$ (50 mM) in AcOH/benzene (1:1) at 40 °C under argon. First-order rate constants were calculated from the first 10% of reaction.

Determination of Reaction Rates. Kinetic information about the reactivity of the different substrates was obtained. The manganic oxidations were run under the conditions described above on a much smaller scale, namely 5 mg of starting material (25 mM) in AcOH/benzene (1:1) with 50 mM $Mn(OAc)_3 \cdot 2H_2O$ at 40 °C under argon. The reaction mixtures were sampled at 1, 11, 21, 31, and 45 min and 1, 3, 6, 9, and 24 h. After a standard microscale workup, each sample (200 μL) was analyzed by HPLC. The different components were identified by comparison against the library of spectra previously constructed. The best matches of spectra were in the range of 950–995 per 1000. Uncorrected peak areas were used for reaction rate plots. No determination of molar extinction coefficients was done. However, for each DB[a]P the spectra of starting material and reaction products were analyzed for a wavelength corresponding to a common absorbance maximum. In particular, the wavelengths used were 254 nm for B[a]P, 302 nm for DB[a,e]P, 294 nm for DB[a,i]P, 309 nm for DB[a,h]P, 302 nm for DB[a,l]P, 307 nm for anthanthrene. For comparison, the reaction rate of B[a]P under these conditions was also measured.

Results and Discussion

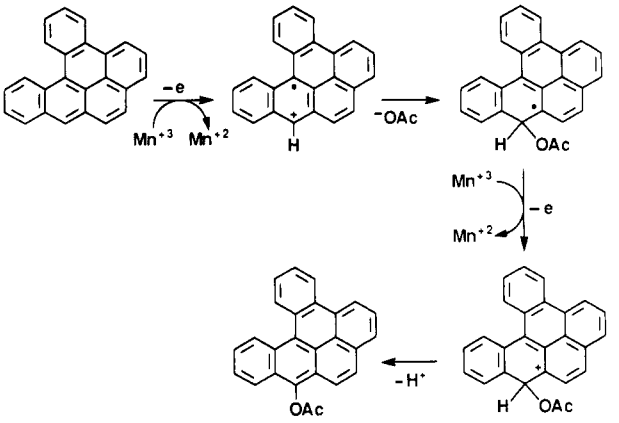
Preparative-Scale Reactions. The selected PAH, DB[a,e]P, DB[a,h]P, DB[a,i]P, DB[a,l]P, and anthanthrene (Figure 1), were first oxidized to isolate and characterize the reaction products (Table I). The PAH radical cations generated by Mn^{3+} undergo nucleophilic attack by acetate ion to yield acetoxylated derivatives. The degree of charge localization in the radical cation intermediate determines the position(s) of substitution.

DB[a,l]P produces only the 10-monoacetoxy derivative, whereas the other four PAH yield diacetoxy derivatives. DB[a,i]P, DB[a,h]P, and anthanthrene yield quinones. These products can arise by decomposition of the diacetoxy derivatives on silica gel chromatography or by further manganic oxidation of the diacetoxy derivatives.[11]

Determination of Reaction Rates. The principal aim of this study was to obtain information about the reaction rates of the DB[a]Ps relative to each other and B[a]P, the parent structure of these DB[a]Ps. Comparison of DB[a,l]P and B[a]P is of particular interest because the former is much more carcinogenic than the parent compound.[7] These kinetic reactions were run on a much smaller scale, and first-order rate constants were calculated from the first 10% of reaction (Table II).

DB[a,l]P. Oxidation/nucleophilic attack occurs rapidly on this PAH, and acetoxylation is regioselective for C-10

Scheme I. Nucleophilic Substitution of DB[a,l]P$^{\cdot+}$ Generated by Manganic Oxidation of DB[a,l]P



(Table I, Figure 2). This PAH resembles B[a]P very closely, and indeed, it reacts even faster (Table II). Initial one-electron oxidation of DB[a,l]P by Mn^{3+} produces a radical cation which undergoes nucleophilic attack by acetate ion. The resulting acetoxy-substituted radical is further oxidized by Mn^{3+} to the corresponding arenium ion, and the latter yields the final acetoxy-substituted derivative by loss of a proton (Scheme I). These results imply that the extent of charge localization at C-10 of DB[a,l]P must be at least as high as that of C-6 in B[a]P,[11] thus accounting for the high regioselectivity of substitution.

DB[a,e]P. This substrate is quite unreactive (Table II). The fact that acetoxylation still occurs at the *meso*-anthracenic C-14 (Table I) indicates that this site has enough charge localized onto it for reaction; however, steric hindrance at C-14 (caused by benzo substitution at the *meso*-phenanthrenic site) and a relatively high anodic peak potential (1.239 V) render this reaction very slow, allowing the diacetoxylation reaction to be competitive. After 7 h the rates of formation and further oxidation of the monoacetoxy derivative are comparable (not shown). Thus, the diacetoxy derivative increases, whereas the amount of monoacetoxy does not.

DB[a,i]P. The relatively low value of its anodic peak potential (Table I) indicates that this PAH is easily oxidized. Indeed, reaction is faster than that of DB[a,l]P (Table II). Unlike B[a]P and DB[a,l]P, diacetoxy derivatives are formed from the start of the reaction. This is logical considering that DB[a,i]P has two *meso*-anthracenic positions with the same extent of charge localization in the radical cation.

Anthanthrene. The behavior of this PAH parallels very closely that of DB[a,i]P, although reaction is even faster (Table II). This is in agreement with the lower value of the anodic peak potential (0.990 vs 1.042 V, Table I). Diacetoxy derivatives are formed, as also seen with DB[a,i]P.

DB[a,h]P. This PAH continues the trend seen with DB[a,i]P and anthanthrene and shows the fastest reaction rate (Table II); over 95% of the starting material is consumed in the first 10 min (not shown).

Conclusions

The results obtained in this study allow us to draw the following conclusions.

First, only DB[a,l]P among the DB[a]Ps resembles very closely the parent B[a]P[11] under one-electron oxidation/nucleophilic substitution conditions. The regioselectivity of substitution indicates a high degree of charge localization at C-10 in the DB[a,l]P radical cation. Furthermore, the single-electron nature of the initial oxidative step was clearly demonstrated by fast cyclic voltammetry.[12]

This information is of great relevancy in preparing DB[a,l]P-nucleoside adducts with the purpose of determining the involvement of one-electron oxidation in the biological formation of adducts. Similar studies have demonstrated that B[a]P adducts are formed predominantly by one-electron oxidation in biological systems.[16]

Second, the DB[a,e]P radical cation is rather inert to nucleophilic substitution. This lack of reactivity presumably derives from a relatively high oxidation potential combined with steric hindrance at the *meso*-anthracenic position, which still possesses a fair degree of charge localization. Thus, formation of DB[a,e]P-DNA adducts is expected to be inefficient.

Third, DB[a,h]P, DB[a,i]P, and anthanthrene basically show similar behavior during oxidation by $Mn(OAc)_3$. Their rates of reaction are extremely fast, and disubstitution products are also present. This reflects the fact that all three PAH possess two identical *meso*-anthracenic positions available for nucleophilic substitution and relatively low anodic peak potentials.

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Supplementary Material Available: ^1H NMR spectra of the products (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Electrophilic Substitution of Methylene-Bridged Polycyclic Aromatic Hydrocarbons

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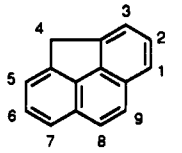
The electrophilic bromination and formylation of the methylene-bridged polycyclic aromatic hydrocarbons 11*H*-benz[*bc*]aceanthrylene (**2**), 4*H*-cyclopenta[*def*]chrysene (**3**), 13*H*-dibenz[*bc,l*]aceanthrylene (**4**), and 4*H*-benzo[*b*]cyclopenta[*mno*]chrysene (**5**) were investigated. All reactions proceeded with high regioselectivity to afford predominantly a single major isomeric product. The sole exception was bromination of **3** which gave a small amount of a second isomeric product. The sites of electrophilic substitution were correlated with theoretical predictions from semiempirical molecular orbital calculations using the MNDO method. The observed sites of electrophilic substitution were in excellent agreement with the theoretical predictions in the cases of **2**-**4**. However, in the case of **5**, substitution took place in the 6-position, whereas the site predicted to be most reactive is the 5-position. In addition, the aryl aldehyde products were converted into the corresponding methyl derivatives for studies of their potential carcinogenicity.

Methylene-bridged polycyclic aromatic hydrocarbons (PAHs) are principal components of coal tar and crude petroleum, and significant levels occur as environmental pollutants.[1] However, few PAHs of this class are known, and their chemical properties are relatively unexplored.[2,3] As part of a program to investigate the chemistry and carcinogenic properties of the methylene-bridged polyarenes, we reported recently the syntheses of several PAHs of this class.[4] Syntheses of additional examples have been described by other investigators.[5] The available evidence suggests that the sites of electrophilic substitution of bridged hydrocarbons may differ significantly from those of the related unbridged polyarenes. Thus, electrophilic bromination,[6] acylation,[7] and nitration[8] of the prototype methylene-bridged hydrocarbon 4*H*-cyclopenta[*def*]-phenanthrene (**1**) take place preferentially in the 1-position. In contrast, analogous reactions of the parent aromatic ring system, phenanthrene, occur predominantly in the 9-position.



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We now report electrophilic bromination and formylation of the methylene-bridged PAHs 11*H*-benz[*bc*]aceanthrylene (**2**), 4*H*-cyclopenta[*def*]chrysene (**3**), 13*H*-dibenz[*bc,l*]aceanthrylene (**4**), and 4*H*-benzo[*b*]cyclopenta[*mno*]chrysene (**5**) (Figure 1). These hydrocarbons were synthesized by methods described previously.[4a-c] The observed sites of electrophilic substitution were correlated with theoretical predictions from semiempirical molecular

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