Stereoelectronic Effects in the Deprotonation of Arylalkyl Radical Cations: *meso*-Ethylanthracenes[1]

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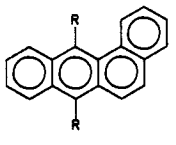
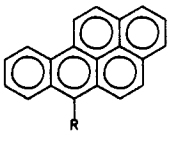
Abstract: In contrast to *meso*-methylanthracenes, which are oxidized by one-electron oxidants to hydroxymethyl derivatives, *meso*-ethylanthracenes such as 9,10-diethylanthracene (DEA) undergo a facile chemical or biochemical oxidative elimination of ethylene to yield an anthrone. No trace of ethyl side chain oxidation to a 1-hydroxyethyl derivative is observed. The rationale for this dramatic selection between methyl and ethyl reactivity is a stereoelectronic effect on radical cation deprotonation. 9-Ethyl-10-methylanthracene (EMA) undergoes both oxidative pathways, but the competition between the two pathways is mediated by water. This effect is attributed to the intervention of a water cluster in the deprotonation reaction.

Stereoelectronic control in proton-transfer reactions is accepted as a primary constraint in rates of such reactions. The particular case of arylalkyl radical cations would be expected to provide no exception to this postulate. However, the recent observation that such radical cations have enormous acidities (pK_as <-12)[2] while exhibiting relatively sluggish proton transfer rates[2a] suggested that stereoelectronic control in such thermodynamically driven systems might test the limits of conventional mechanistic dogma. Indeed, recent mechanistic investigations have revealed ambiguities in the evidence for stereoelectronic control in radical cation deprotonation and have paved the way for this investigation into *meso*-ethylanthracenes, for which the stereochemistry of precursor radical cations is less ambiguous.

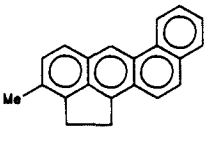
Our investigation of the problem of stereoelectronic control in the deprotonation of arylalkyl radical cations was prompted by several observations in the biochemical literature on the "ethyl" effect, that is, the abolition of carcinogenic activity when certain otherwise carcinogenic polynuclear aromatic hydrocarbons are substituted at the meso position by an ethyl group. For instance, 7,12-dimethylbenz[*a*]anthracene (DMBA) and 6-methylbenz-[*a*]pyrene (6-MBP), both potent carcinogens, become relatively innocuous when substituted instead by ethyl (DEBA and 6-EBP).[3,4] Conversely, when the meso substituent is an *ethano* bridge to another ring carbon, e.g., 3-methylcholanthrene (3-MC),[5] carcinogenicity is as great as that for DMBA. Thus the orientation of the ethyl group appears to play a role in metabolism and, ultimately, promotion or abolition of carcinogenicity.



DMBA, R = Me
DEBA, R = Et



6-MBP, R = Me
6-EBP, R = Et



3-MC

The accepted metabolic pathway for activation of polynuclear aromatic hydrocarbons is enzymatic oxidation to a dihydrodiol epoxide through the intervention of cytochrome P450,[6] although an alternative pathway involving side-chain oxidation to a hydroxymethyl derivative has not been completely excluded.[7] Moreover, P450 oxidations of low potential substrates are thought to involve radical cations[8] which "should" undergo facile deprotonation–side-chain oxidation.[2] The presence of this subtle ethyl effect could thus be viewed as evidence for stereoelectronic control in a radical cation pathway. Specifically, the ethyl group in a *meso*-ethylanthracene derivative is maintained perpendicular to the anthracene plane by strong flagpole interactions with the peri hydrogen atoms, thus preventing facile overlap of in incipient benzylic radical center with the aromatic π-system. When the ethyl group is "tied back" to yield a cholanthrene, no such constraint exists. To the extent that radical cation deprotonation is involved in metabolic activation, prevention of such deprotonation would abolish the carcinogenicity. While our results in this regard remain permissive, even supportive, of the dihydrodiol activation pathway, we have now firmly established the existence of stereoelectronic control in radical cation deprotonations. We have discovered a novel chemical and enzymatic elimination of ethylene in an unprecedented seven-centered transition state, and we have developed new insight into the oxidation pathways of microsomal systems.

Background. The most convincing and most widely quoted evidence in favor of stereoelectronic control in radical cation deprotonations devolves from the 1972 work of Onopchenko and Schulz.[9] These workers report that *p*-cymene undergoes oxidation almost exclusively at the methyl group under conditions plausibly involving the *p*-cymene radical cation, i.e., cobalt(III) in acetic acid. They attribute this regiochemistry to a conformation in which the isopropyl group bisects the plane of the *p*-cymene, thus preventing facile deprotonation from the tertiary center. Although this work has been widely quoted, other results present troubling inconsistencies. Thus Walling and co-workers[10] observe products during peroxydisulfate oxidation of *p*-cymene which involve breaking the tertiary carbon–hydrogen bond, although primary oxidation of the isopropyl group also suggests that radical intermediates may be involved. Most suggestive are the ESR studies

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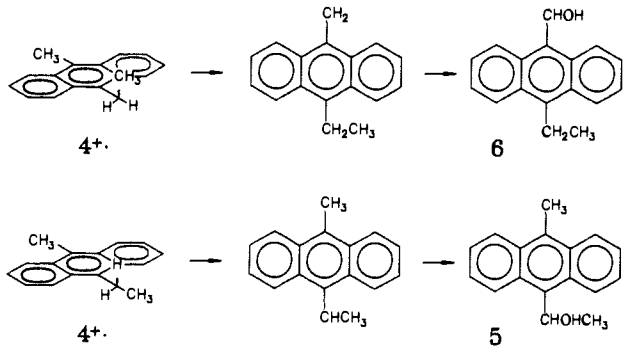

Figure 1. Stereoelectronic effect in deprotonation of EMA.

of Symons,[11] for which the hyperfine coupling constants in the *p*-cymene radical cation indicate the presence of two conformations in which one clearly exhibits perpendicular geometry of the C–H group with respect to the aromatic plane. Moreover, the magnitude of the hyperfine coupling constant indicates considerable stabilization of hyperconjugation by the nearly in-plane methyl groups. Indeed, Bacciochi observes that, in the gas phase, the isopropyl group was more reactive than the methyl group toward deprotonation and that the source of the apparent stereoelectronic effect is, rather, a solvent effect.[12] We only wish to reemphasize the increasingly recognized fact that radical cation conformations may differ considerably from those of the corresponding neutrals.[13]

This conformational ambiguity is apparently avoided by *meso*-ethylanthracene radical cations. In such cases, the ethyl group is maintained in a conformation perpendicular to the anthracene plane by the peri hydrogens, which prevent planarization of the molecule through significant flagpole interactions. Indeed, the ESR spectra of *meso*-ethylanthracene radical cations exhibit a hyperfine coupling constant for the methylene protons clearly in accord with a perpendicular disposition of the ethyl group.[14] Conversely, 9-methylanthracene radical cation has a large methyl proton hyperfine coupling constant indicating significant hyperconjugation,[15] which is congruent with the notion that this radical cation is a strong thermodynamic acid.

Previously we have shown that 9,10-dimethylanthracene (DMA, **1**) undergoes facile oxidation by iron(III) salts to 9-(hydroxymethyl)-10-methylanthracene (**2**).[1,16] Given the additional biochemical imperative for understanding the origin of the ethyl effect in *meso*-ethylanthracene derivatives, addition of 9,10-diethylanthracene (DEA, **3**) and 9-ethyl-10-methylanthracene (EMA, **4**) to our studies of DMA was a useful starting point for our investigation of stereoelectronic effects in deprotonation of arylalkyl radical cations. We reasoned that oxidation of EMA to 9-(1-hydroxyethyl)-10-methylanthracene (**5**) in competition with 9-ethyl-10-(hydroxymethyl)anthracene (**6**) would provide a direct measure of the significance of the stereoelectronic effect insofar as the major contributor to the regiochemistry consisted of the nearly planar orientation of the acidic CH moiety (see Figure 1). In addition, we might provide some insight into the origin of the biochemical "ethyl" effect.

Results. Conformational and Steric Effects in Neutral Anthracenes. In order to define the limits of the stereochemical constraints on the neutral molecules, we elected to perform single-crystal X-ray diffractometry and nuclear magnetic resonance investigations on the conformation of DEA itself. Our X-ray results are reported elsewhere,[17] but indicate the presence of an anti conformation, with the ethyl groups oriented at 87° with respect to the anthracene plane to form a centrosymmetric conformation. Since the ethyl groups can either be anti or syn to each other, the existence of the alternate syn conformation in equilibrium with the anti conformation could be probed by low-temperature proton NMR spectroscopy at 400 MHz. Indeed, the methyl group, which appears as a triplet centered at δ 1.54 at ambient temperature, at −110 °C broadened into an unresolved multiplet. Decoupling of the methylene resonances allowed dissection of the methyl resonances into two broadened singlets (see Figure 2). No further sharpening of signals occurred at lower temperatures, which we attributed to the insolubility of the anthracene at the low temperature limits of the solvent. Making reasonable assumptions as to the actual chemical shifts, we were able to reproduce the observed signals using the temperature-dependent exchange rates shown in Figure 2 (see Experimental Section). Application of the Eyring equations allowed us to calculate the exchange free energy according to the following equation:[18]

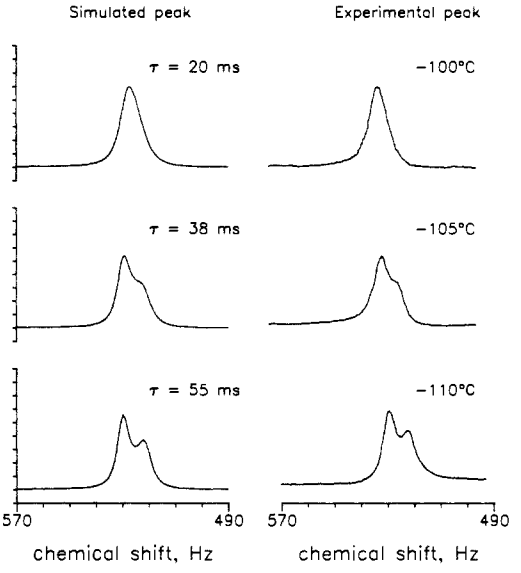

Figure 2. Temperature dependent NMR of DEA.

$$\Delta G^{\ddagger} = 2.303RT(10.319 + \log T - \log k)$$

We associate the resulting free energy of 8.7 kcal/mol with the barrier to rotation about the ethyl–anthracene bond.

Results. Chemical Oxidations. The most generally useful oxidation medium for our studies was tris(phenanthroline)iron(III) tris(hexafluorophosphate) in aqueous acetonitrile.[1,19] The oxidant undergoes slow decomposition in aqueous solvent, although reaction with the substrate is faster than decomposition. With less easily oxidizable substrates, decomposition of oxidant predominates, echoing Kochi's caution against the use of wet solvent.[19] In a typical oxidation, 0.06 mmol of the anthracene was dissolved in 18 mL of 5–20% aqueous acetonitrile. Freshly prepared Fe(III)(phen)$_3$ complex (0.09 mmol) was added in 2 mL of dry acetonitrile; the reaction mixture was stirred for 30 min, and the reaction mixture was quenched by addition of diethyl ether to precipitate iron salts. Under our conditions, oxidation of anthracenes to products occurred in high yield with uniformly excellent mass balance. Oxidation of DMA to 9-(hydroxymethyl)-10-methylanthracene (**3**) occurred cleanly, and thus

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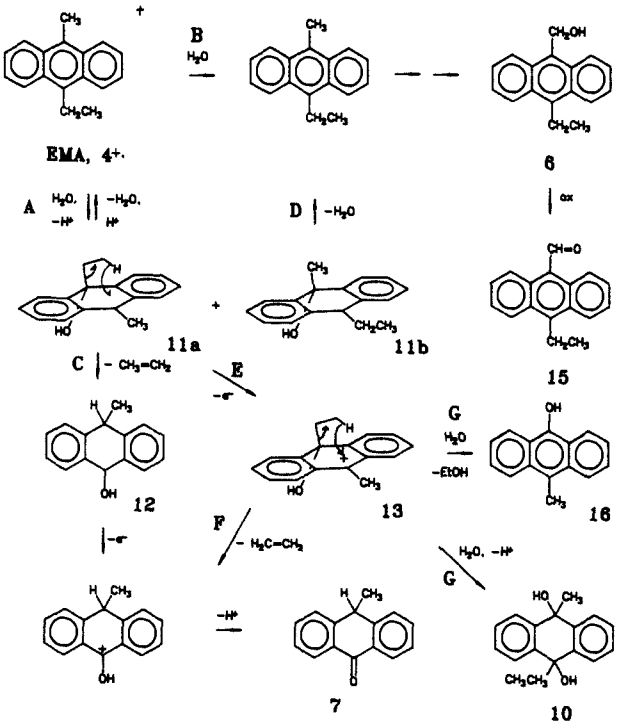

Figure 3. EMA$^{\bullet+}$ reaction scheme.

allowed us to use oxidation of the methyl group in EMA (**4**) as a convenient molecular "clock" to compare the rates of competing reactions.

Inasmuch as we expected partial but not absolute stereocontrol in our ethylanthracenes, we anticipated formation of 9-(1-hydroxyethyl)-10-methylanthracene (**5**) in the oxidation of EMA along with 9-ethyl-10-(hydroxymethyl)anthracene (**6**). Indeed, (hydroxymethyl)anthracene **6** was produced in 20–40% yield, presumably through a sequential oxidation, deprotonation, oxidation, and hydrolysis mechanism (path B of Figure 3). However, no trace of the independently prepared hydroxyethyl product **5** was observed by capillary gas chromatography. Rather, the mechanistically unprecedented oxidation product, 10-methylanthrone (**7**), was produced (see Figure 3). With 9,10-diethylanthracene (DEA), only the cleavage product, 10-ethylanthrone (**9**), was produced. No trace of independently prepared 9-ethyl-10-(1-hydroxyethyl)anthracene (**5**) or 9,10-dihydro-9,10-dihydroxy-9,10-diethylanthracene (**10**) was detected.

The product mix between (hydroxymethyl)anthracene **6** and 10-methylanthrone (**7**) was dependent upon water concentration. At moderate (>10%) water concentrations, the hydroxymethyl derivative was the major product. At lower water concentrations, the anthrone prevailed (see Table I).

Results. Microsomal Oxidation. Inasmuch as oxidation by cytochrome P450 is presumed to be the major metabolic pathway by which polynuclear aromatic hydrocarbons are activated or converted into excretable byproducts, we elected to investigate oxidation in a microsomal system, for which P450 is the de facto oxidant.[20] Treatment of 2 mM solutions of either EMA or DEA with rat-liver microsomes resulted in efficient oxidation to 10-methyl- or 10-ethylanthrone (see Table I). In the former case, a trace of 9-ethyl-10-(hydroxymethyl)anthracene (**6**) was produced as well. When an identical solution of EMA was treated with the cytosolic (aqueous supernatant) fraction of the microsomal preparation medium, the (hydroxymethyl)anthracene became the major product.

Discussion. Mechanism of Anthrone Formation. Of possible mechanisms for the formation of 10-methylanthrone, three seemed most plausible, each involving preliminary attack by water or other nucleophile to yield a 9-ethyl-9-hydroxy-10-methylanthracenyl radical (**11**) (see Figure 3). This intermediate could undergo elimination of ethylene through a cyclic seven-centered transition state to yield a 9-methyl-9-hydro-10-hydroxyanthracenyl radical (**12**). Oxidation–deprotonation of this intermediate would yield the anthrone **7**. Alternatively, oxidation of radical **11** to the cation **13**, followed by hydride transfer and elimination of ethylene through a similar seven-centered transition state would yield 10-methylanthrone directly. Finally, water-assisted cleavage of cation **13** could yield ethanol and 9-hydroxy-10-methylanthracene that, under the conditions of the reaction, could tautomerize to 10-methylanthrone. In order to sort through these mechanistic possibilities, isolation of ethylene and determination of intramolecularity through the use of deuterated materials was in order.

Results. Isolation of Ethylene and Deuterium Labeling Studies. Since two of the postulated mechanisms involved ethylene as a byproduct, determination of its presence was essential. This was accomplished by two analytical and chemical techniques. The first involved a straightforward analysis of the effluent gases produced in the oxidation. Indeed, ethylene was detected in significant amounts by mass spectroscopy despite the small scale of the reaction. No attempt was made to quantify the ethylene yield. The second technique involved the trapping of the effluent gases in a solution of bromine in carbon tetrachloride. In this case, the product 1,2-dibromoethane was detected by capillary gas chromatography calibrated with independently obtained material.

For isotope studies, 9-(perdeuteroethyl)-10-methylanthracene was prepared from (10-methylanthracenyl)lithium and ethyl-d_5 iodide. The 10-methylanthrone recovered after oxidation was 99.8% d_1 by mass spectroscopy, while NMR spectroscopy indicated the absence of the C-10 proton from anthrone **7**. Thus 100% transfer of deuterium occurs from the ethyl group to C-10 of the hydroanthracenyl radical **12**. Making the reasonable assumption that formation of 9-(perdeuteroethyl)-10-(hydroxymethyl)-anthracene occurs without a deuterium isotope effect, we could use this product as an internal clock for the relative rate of anthrone formation and thus determine the deuterium isotope effect

Table I. Oxidation of 9-Ethyl-10-methylanthracene and 9,10-Diethylanthracene[a]

substrate	$[H_2O]$, M	$[Fe^{3+}]$, mM	% yield[b] 6	15	7
EMA	2.78	4.5	11.1	4.0	76.5
EMA	5.56	4.5	24.9	5.7	62.9
EMA-d_5	5.56	4.5	58.4[c]	9.9	24.9
DEA	5.56	3.0	–	–	87.5[d]
DEA	5.56	4.5	–	–	87.2[d]
EMA	8.33	4.5	37.1	7.0	50.2
EMA	11.12	4.5	46.2	8.4	40.6
EMA	rat liver microsomes[e,f] (1 h)		3.2		83.4
EMA	rat liver microsomes[e,f] (20 h)		4.1		77.3
DEA	rat liver microsomes[e,f] (1 h)				89.7
EMA	rat liver cytosol[e] (20 h)		85.7		8.9

[a] Reaction in 20 mL of H_2O–MeCN with 3.00 mM substrate and tris(phenanthroline)iron tris(hexafluorophosphate) at 25 °C for 30 min was followed by ether precipitation. [b] Yields based upon recovered starting material. [c] 99.8% deuterium incorporation. [d] 10-Ethylanthrone (**8**); anthraquinone was also formed in 2–4% yields. [e] Solutions of dialkylanthracene in MeCN (50 mL) to give a final concentration of 2 mM were incubated at room temperature. [f] Anthraquinone was also formed in yields of 6.5% (1 h) and 10.7% (20 h) with DMA and 7.8% with DEA.

Table II. Rate Constants for Anthracene Radical Cation Disappearance[a]

compound	k (M^{-1} s^{-1})[a]
DMA (**1**)	0.296 ± 0.018
DMA-d_6 (**1**-d_6)	0.257 ± 0.024
DEA (**3**)	0.318 ± 0.023
EMA (**4**)	0.275 ± 0.010

[a] Error limits represent 95% confidence levels for 48-point linear regression analyses of radical cation disappearance rates with respect to water concentration.

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for ethylene elimination from the ratio of product yields. Our experimentally determined number was 5.7.

Results. Electrochemical Studies. Our previous study using 9,10-dimethylanthracene-d_0 and -d_6 allowed us to determine the absence of a primary deuterium kinetic isotope effect and the presence of a secondary deuterium isotope effect near unity (1.05 ± 0.06 per deuterium; see Table II) for the rate of disappearance of the radical cation as a function of water concentration.[16] In the case of the ethylated anthracenes in which divergent products are produced, more significant effects on radical cation disappearance might be anticipated. Indeed, just as in the dimethyl case, cyclic voltammetric analysis of EMA and DEA radical cation disappearance gave clean pseudo-first-order kinetics, with a rate constant linearly dependent upon water concentration. Thus we were able to determine the second-order rate constant for reaction of the radical cation with water (see Table II). In each case, the rate constant was within experimental error of that determined for DMA itself.

Discussion. Kinetics of Anthrone Formation and Radical Cation Deprotonation. The lack of dependence of radical cation disappearance rates upon structure requires that attack by solvent (water) be the primary event affecting radical cation lifetime. Attack at the meso (9 or 10) anthracenic position is consistent with these structural features, with the small secondary deuterium kinetic isotope effect for DMA-d_6, with theoretical and experimental data indicating high cationic character at this position,[21] and with recent experimental data indicating sluggish rates of deprotonation of radical cations despite favorable thermodynamics.[19,22] In order to account for the effect of water on the product distribution for EMA, however, such addition must be reversible. In the absence of reversibility, addition of nucleophile would be product determining, and given the apparent negligible steric effect of ethyl substitution, the ratio of hydroxymethyl to anthrone product would be 1/1.

Oxidation of the hydroxyanthryl intermediate **11** to cation **13**, followed by hydride transfer through path F does not to explain either our electrochemical or chemical results. First, no change in mechanism from EC to ECE is observed as water is increased. That is, the coulometry remains constant, indicating that intermediate **11** does not undergo rapid secondary oxidation on the electrochemical time scale and that, therefore, step E does not compete with other, presumably faster, processes. Second, no trace of bisdiol **14**, a plausible product from formation of cation **13**, is observed. Similarly, no analogous diol is formed during oxidation of DMA (**1**), for which elimination of ethylene is not available as a rapid competing pathway.

The change in product distribution for EMA as the water concentration increases provides the most intriguing and useful mechanistic information, given that both hydroxymethyl and anthrone products depend upon water in a formally unimolecular sense, with one dependent upon water acting as a base and the other as a nucleophile. Thus the formation of hydroxymethyl-derived products, i.e., alcohol **6** plus aldehyde **15** as well as anthrone **7** should be first order with respect to water, and their ratio ([**6** + **15**]/**7**) should be independent of water concentration in the absence of strong medium effects. Our electrochemical observation is that the overall rate of disappearance of radical cation is indeed linear with water concentration. However, the ratio of products yields a plot that is *not* constant but roughly linear, with a significant second-order component (see Figure 4). We must conclude that the rate of hydroxymethyl product formation is (at least) second order in water.

Two explanations seem plausible. The first of these assumes that formation of the anthracenylmethyl radical leading to hydroxymethyl product arises from an E_2-like elimination of water (path D) from the initial meso adduct **11b**. Since water is both base and nucleophile, it appears as second order in the rate expression. If this mechanism is operative, however, one might expect a similar elimination of water from intermediate **11a** to yield an ethyl-abstracted radical. The second explanation takes advantage of the apparent reversibility of radical cation solvolysis and incorporates growing evidence that proton transfer reactions in aqueous solvents involves a cluster of water molecules.[23] It is well known that the proton hydration energy increases nearly linearly with each subsequent molecule of water after the first.[24] Thus a model in which at least a water dimer is required for proton transfer would accommodate our results. Moreover, the third-order effect can be neatly accommodated by more efficient transfer to a water trimer. Finally, we note that, at even larger water concentrations, rates of proton transfer for an organic photoacid (2-naphthol) are rationalized by intervention of a water tetramer.[23] Thus the most appealing explanation of our anomalous solvent effect is that water when a nucleophile acts kinetically as a discrete molecule, but when a base, as a cluster of order at least two. This cluster effect is simply a kinetic consequence of the thermodynamics of proton solvation![25]

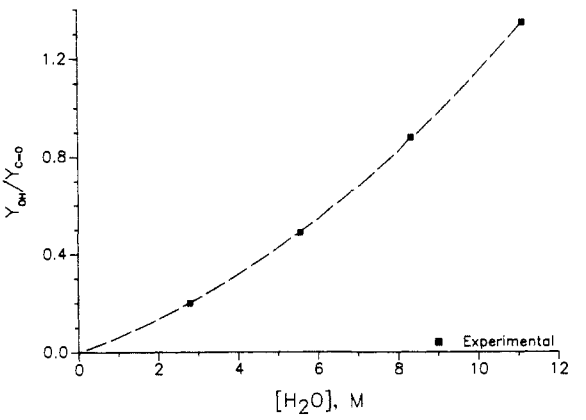

Figure 4. Ratio of deprotonation to elimination.

Given these chemical and electrochemical effects of water on radical cation decomposition pathways, we are now in a position to account for the origin of the ethyl effect. Formation of radical cations from low potential hydrocarbons is now an accepted pathway in the biochemistry of cytochrome P450,[26] as well as a number of other oxygenases. In the hydrophobic environment of microsomes in general and cytochrome P450 in particular, radical cations do not undergo facile proton loss. Rather, nucleophilic pathways involving oxygen nucleophiles intervene. In the particular case of EMA, such nucleophilic attack introduces a new pathway for ethylene elimination, which produces excretable anthrone metabolites. We believe this pathway accounts for the lack of carcinogenicity of 7,12-diethylbenz[*a*]anthracene and 6-ethylbenz[*a*]pyrene.

Conclusion. Radical cations are viewed as key intermediates in a number of chemical, electrochemical, and biochemical oxidation pathways. This intermediacy has produced a conundrum, since production of arene and olefin oxides in biooxidations would appear to be unrelated to radical cation formation. As Bruice has recently shown, such products can indeed be formed if the nucleophile is an oxoiron porphyrin.[27] We now see that an important additional component in mediating this chemistry is the nature of the macromolecular water structure. Efficient proton abstraction by water from biologically generated acids, e.g., radical cations, would play havoc with enzymatic specificity. The fact that such proton transfer requires more ordered (at least dimeric) water environments allows the efficient mediation of proton transfer by other biological bases.

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Experimental Section

Instrumentation. Cyclic voltammograms were obtained by using the experimental apparatus previously described.[28] During all electrochemical experiments, the solutions were blanketed with solvent-saturated, water-free argon. All experiments were carried out in acetonitrile containing 0.10 M lithium perchlorate at 25 ± 1 °C. Water was introduced into the electrochemical cell via syringe. The concentration of the electroactive solute was maintained at a constant level throughout the titration with H_2O. Although voltammograms were recorded versus the saturated calomel electrode, ferrocene was used as an internal standard according to the method of Gagne et al.[29]

NMR spectra were recorded on a Varian Gemini 300 (300 MHz) instrument and low temperature NMR experiments were performed on a Varian XL-400 (400 MHz) spectrometer. GC analysis was performed on a HP 5890A gas chromatograph using a 25-m 5% methylphenyl silicone gum capillary column (0.32-mm diameter). Mass spectra were recorded on a VG-7070SE mass spectrometer equipped with a VG-11-250J data system.

Simulations. NMR line shape simulations were performed by use of the NMREXCHH program kindly provided by Prof. Herbert O. House. This program, written in BASIC for the IBM-PC, is based upon the Gutowsky and Holm derivation.[30] For further discussion, see ref 18. The "best fit" parameters used to generate Figure 2 employed chemical shifts of 521.0 (44%) and 530.5 Hz (56%).

Materials. Acetonitrile (Fisher reagent grade) was dried over CaH_2 and distilled. 9-Methylanthracene-10-carboxaldehyde and C_2D_5I were purchased from Aldrich and used without further purification. 9-Methyl-10-bromoanthracene,[31] 9-ethyl-10-bromoanthracene,[31] and 9,10-dihydro-9,10-dihydroxy-9,10-diethylanthracene were prepared by literature procedures.

Procedure for Tris(phenanthroline)iron(III) Oxidations. In a typical procedure, 0.06 mmol of dialkylanthracene in 18 mL of acetonitrile–water was purged for 45 min with deoxygenated argon (*Caution!* Purging for less time results in complex oxidation mixtures from molecular oxygen) and 0.06–0.09 mmol of the blue tris(phenanthroline)iron tris(hexafluorophosphate) complex in 2 mL of MeCN was added with stirring. The solution was stirred for 30 min under argon and 0.06 mmol of biphenyl was added as an internal standard. The reaction was quenched by pouring into 500 mL of diethyl ether. The resulting red iron(II) precipitate was removed by filtration, and the filtrate was dried over Na_2SO_4. The residue was redissolved in 2 mL of tetrahydrofuran, and the products were identified by gas chromatography–mass spectroscopy and quantified by capillary gas chromatography. In all cases, the retention times and mass spectra of the products were identical with those of authentic samples. In the oxidation of 9-ethyl-10-methylanthracene, 9-ethyl-10-(hydroxymethyl)anthracene and 10-methylanthrone were produced, in addition to a small amount of 9-ethyl-10-anthracenecarboxaldehyde (see Table I). 9,10-Diethylanthracene yielded only 9-ethylanthrone and small amounts of anthraquinone (Table I). Neither 9-(1-hydroxyethyl)-10-methylanthracene, which was otherwise stable to the reaction conditions, nor 9,10-dihydro-9,10-dihydroxy-9,10-diethylanthracene was detected within the detection limits of capillary gas chromatography (<0.1%).

Oxidation of 9-(Perdeuteroethyl)-10-methylanthracene. The deuterated hydrocarbon (0.0600 mmol) was dissolved in 16 mL of acetonitrile and 2 mL of water and was oxidized with 0.0900 mmol of tris(phenanthroline)iron tris(hexafluorophosphate) by the above procedure. The yields of the products (Table I) were calculated by capillary chromatography with the use of response factors obtained from undeuterated samples, assuming a negligible deuterium isotope effect for the response factors of the various products. Mass spectral analysis indicated that the 10-methylanthrone recovered after oxidation was 99.8% d_1, after correcting for the deuterium content of the starting material. The yields of the products obtained in a separate run with the nondeuterated hydrocarbon were compared with those obtained from the deuterated hydrocarbon (see Table I), and $(k_H/k_D)_{app}$ for the formation of the anthrone was determined by assuming that the rate of formatin of 9-(hydroxymethyl)-10-ethylanthracene was independent of deuteration at ethyl, i.e., $(k_H/k_D) = [62.9/(24.9 + 5.7)]/[24.9/(58.4 + 9.9)] = 5.67$.

Isolation of Ethylene. 9-Ethyl-10-methylanthracene (1.20 mmol) was dissolved in 80 mL of deoxygenated MeCN·H_2O (76:4 v/v), and 1.8 mmol of tris(phenanthroline)iron tris(hexafluorophosphate) in 20 mL of MeCN was added. The solution was purged continuously with argon during the 30-min reaction period. The effluent gases were passed through two serial traps maintained at −10 °C with an ice–salt bath to condense MeCN vapors and two traps maintained at ethanol–dry ice temperatures to condense volatile gases. The latter traps were disconnected from the reaction vessel, sealed with a pinch clamp at one end, and connected at the other end to an evacuated cooled gas sampling bulb with a two-way Teflon seal. The traps were allowed to warm to room temperature and the gases collected in the sampling bulb. The collected gases were analyzed by mass spectroscopy, which confirmed the presence of ethylene in the mixture; MS *m/e* (relative intensity): 29 (2.27), 28 (100), 27 (73.7), 26 (57.4), 25 (8.84).

In another experiment the effluent gases were passed through a solution of Br_2 in ether, upon which the solution decolorized. The ether solution was washed with water and concentrated. 1,2-Dibromoethane was identified as the product by comparison of its retention time with that of an authentic sample by capillary gas chromatography.

Isolation of Microsomes.[32] Untreated, fed male SHR rats aged 15 weeks (average weight 295 g) obtained from Charles River Breeding Laboratories (SHR/NCrlBR) were used in all experiments. Test animals were anesthetized with 35 mg/kg sodium phenobarbital by ip injection prior to sacrifice. Microsomes were prepared by removing the livers and homogenizing them at 0–3 °C in 3 volumes of 50 mM potassium phosphate buffer containing 200 mM NaCl (pH 6.5). The homogenate was centrifuged in a Beckman J2-21 centrifuge with a JA-17 rotor at 3600*g* for 5 min. The supernatant S_1 was centrifuged at 29000*g* with a JA-17 rotor for 20 min, and the pellet was washed and discarded. The supernatant S_2 was spun in a Beckman L8-M ultracentrifuge with a Ti-75 rotor at 104000*g* for 50 min. The pellet was resuspended in phosphate buffer (10 mL/g of microsomes) and used immediately for incubations. The 104000*g* supernatant was used as the cytosol.

In another experiment the supernatant S_2 was centrifuged with a Ti-75 rotor at 5000*g* for 30 min. The band of microsomes at the top of the tube was removed carefully from the cytosol by pipet and was used as such for incubations. Microsomes obtained by both the methods exhibited similar activity.

Enzymatic Oxidations. Incubations were conducted in 16 × 150 mm culture tubes equipped with rubber stoppers. Each microsomal incubation contained 4.0 mL of microsomal suspension and sufficient substrate dissolved in 50 mL of MeCN to give a final concentration of 2 mM. The cytosolic incubations contained 5 mL of the cytosol and the substrate in 50 mL of MeCN to give a final concentration of 2 mM.

For extraction each incubation was saturated with Na_2SO_4, extracted with 6 mL of diethyl ether, and centrifuged as needed to break emulsions. This procedure was repeated with 5, 4, and 4 mL of solvent, and the combined ethereal extract dried over Na_2SO_4 and concentrated. The residue was redissolved in tetrahydrofuran and analyzed by capillary gas chromatography and gas chromatography–mass spectrometry.

9,10-Diethylanthracene. 9-Ethyl-10-bromoanthracene (2.86 g, 10.0 mmol) in 30 mL of diethyl ether was treated with 6.5 mL (13.0 mmol, 1.3 equiv) of 2.0 M PhLi in cyclohexane–ether for 2.5 h at room temperature. The reaction mixture was treated with 6.24 g (3.20 mL, 40.0 mmol) of ethyl iodide and heated under reflux for 3 h. The cooled ether solution was washed with water and dried. Evaporation of the ether solution and recrystallization of the residue from ethanol yielded 1.34 g (5.73 mmol, 57%) of 9,10-diethylanthracene as light yellow prisms: mp 145–145.5 °C [lit.[33] mp 146–147 °C]; H^1 NMR (Me_2CO-d_6) δ 1.43 (t, 6 H, J = 7.6 Hz), 3.67 (q, 4 H, J = 7.6 Hz), 7.4–7.67 (m, 4 H), 8.2–8.55 (m, 4 H).

9-Ethyl-10-methylanthracene. Treatment of 2.72 g (10.0 mmol) of 9-methyl-10-bromoanthracene in 30 mL of diethyl ether with 6.5 mL (13.0 mmol, 1.3 equiv) of PhLi in cyclohexane–diethyl ether at room temperature was followed by addition of 6.24 g (3.20 mL, 40.0 mmol) of iodoethane. Quenching with water and extraction with ether yielded, after drying and concentrating, 1.43 g (6.11 mmol, 65%) of solid 9-ethyl-10-methylanthracene. Recrystallization from ethanol yielded yellowish prisms: mp 141–143 °C [lit.[33] mp 142–144 °C]; H^1 NMR ($CDCl_3$) δ 1.42 (t, 3 H), 3.10 (s, 3 H), 3.65 (q, 2 H), 7.3–8.5 (m, 8 H); MS (relative intensity) *m/e* 221 (8.5), 220 (49.0), 206 (15.9), 205 (100), 203 (21.3), 189 (10.7), 101 (18.9), 96 (10.2).

9-Methyl-10-ethylanthracene-d_5. The procedure for 9-methyl-10-ethylanthracene was followed. Reaction of (9-methyl-10-anthracenyl)-lithium, prepared from 1.36 g (5.00 mmol) of 9-methyl-10-bromoanthracene, with 3.22 g (1.60 mL, 20.0 mmol) of iodoethane-d_5 yielded 0.680 g (3.02 mmol, 60% yield) of 9-methyl-10-(1,1,2,2,2-pentadeuterioethyl) as yellowish prims, mp 141–143 °C. The spectral data

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were as follows: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3 H), 7.24-7.53 (m, 4 H), 8.28-8.36 (m, 4 H); MS analysis 98.9 mol % d_5.

9-Ethyl-10-anthracenecarboxaldehyde. (9-Ethylanthracenyl)lithium, prepared from 2.86 g (10.0 mmol) of 10-ethyl-9-bromoanthracene and 6.5 mL (13.0 mmol, 1.3 equiv) of 2.0 M phenyllithium in 30 mL cyclohexane-ether, was allowed to react with 10.0 mL (0.13 mol) of dimethylformamide at room temperature for 30 min. Water (30 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with two 25-mL portions of ether, and the combined organic extracts were dried over Na_2SO_4. The concentrate was recrystallized from petroleum ether to yield 1.27 g (54%) of yellow needles: mp 96-97 °C [lit.[34] mp 96-96.5 °C]; ^{1}H NMR ($CDCl_3$) δ 1.49 (t, 3 H), 3.70 (q, 2 H), 7.4-8.65 (m, 8 H), 11.47 (s, 1 H).

9-(Hydroxymethyl)-10-ethylanthracene.[33] 10-Ethyl-9-anthracenecarboxaldehyde (0.590 g, 2.50 mmol) in 25 mL of diethyl ether was treated with 0.12 g (3.1 mmol) $LiAlH_4$ and the mixture refluxed for 1 h. After treatment with 5 mL of ethyl acetate and 20 mL of H_2O the organic fraction was separated, chlorobenzene (25 mL) was added and ether was removed at reduced pressure. The product (0.33 g; 56% yield) crystallized from the hot chlorobenzene solution as pale yellow needles, mp 182-183 °C [lit.[35] mp 180-183 °C].

9-Methylanthrone.[36] 2-(1-Phenylethyl)benzoic acid, prepared by the reaction of 4.51 g (20.0 mmol) of *o*-benzoylbenzoic acid with 17 mL (51.0 mmol) of 3.0 M MeMgl in ethyl ether followed by reduction of the product with Zn and alcoholic NH_3 (yield 4.20 g; 93%), was stirred in 50 mL of concentrated H_2SO_4 for 30 min at room temperature. The mixture was poured on ice, and the solid was recrystallized from MeOH-H_2O to give 1.40 g (6.73 mmol) of 9-methylanthrone (38% yield) as light yellow needles: mp 63-64 °C [lit.[37] mp 65 °C]; ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3 H), 4.33 (q, 1 H), 7.45-8.43 (m, 8 H); MS *m/e* (relative intensity) 208 (100), 207 (9.6), 192 (11.3), 180 (63.3), 152 (53.5), 151 (30.0), 150 (11.7), 76 (19.3), 75 (11.1), 42 (10.4).

9-Ethylanthrone.[35] The procedure of Heymann et al. was used. Recrystallization from MeOH-H_2O gave the pure anthrone in 31% yield: mp 50-52 °C (lit.[38] mp 50-52 °C); H^1 NMR ($CDCl_3$) δ 0.34 (t, 3 H), 1.96 (m, 2 H), 4.25 (t, 1 H), 7.2-8.5 (m, 8 H).

9-(1-Hydroxyethyl)-10-methylanthracene. 10-Methylanthracene-9-carboxaldehyde (2.20 g, 9.32 mmol) was allowed to react with 7.0 mL (0.02 mol) of 3.0 M MeMgl in ethyl ether. The product isolated by ether extraction was recrystallized from petroleum ether-methylene chloride: yield 1.7 g (73%); mp 107-109 °C [lit.[39] mp 108-110 °C]; ^{1}H NMR (CCl_4) δ 1.92 (d, 3 H), 2.38 (s, 1 H), 3.13 (s, 3 H), 6.55 (q, 1 H), 7.34-7.67 (m, 4 H), 8.30-8.61 (m, 4 H).

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High-Pressure ^{19}F NMR Study of the Degenerate Isomerization of Hexafluoroacetone Anils. Evidence for the Existence of Two Different Inversion Transition States

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Abstract: Solvent, temperature, and pressure effects on the rate of the degenerate isomerization of hexafluoroacetone anils were studied by ^{19}F NMR. The results unequivocally demonstrated that the mechanism is not rotation about the carbon-nitrogen bond even in the presence of a strongly electron-donating substitutent in the para position of the phenyl group because the polarity of the reactant did not increase in the activation step. Combined with the substituent effects, the present results can be explained most reasonably by assuming two different conformations for the phenyl group in the inversion transition state, i.e., perpendicular and planar conformations for the electron-attracting and -donating substituents, respectively.

The mechanism of geometrical isomerization about the nitrogen-nitrogen,[3] carbon-nitrogen,[4] and carbon-carbon[5,6] double bond has been actively investigated in recent years in many laboratories. The argument was focused on whether the reaction proceeds by inversion at the nitrogen atom or by rotation about the nitrogen-nitrogen or the carbon-nitrogen bond. For example, Perrin and Thoburn[7] studied the substituent effects on the *E-Z* and *Z-E* isomerization rates of *N*-arylformamidates (eq 1) and

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concluded that the reaction proceeds by nitrogen inversion. As can be seen in this recent example, it has been agreed that the inversion mechanism is more common than the rotation mechanism. A number of arguments have been adduced in support of

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