ization of the acids in the gas phase.[14] Entropies of solution come from vapor pressure vs composition data for aqueous solutions.[22] The last appear to be the limiting factor at present; values were found in the literature only for R = H, Me, Et, and *n*-Pr. An entropy of solvation for the proton of 30.9 eu is used.[16] These data are summarized in Table V.

For the entropies, increasing alkyl chain length results in more ordered solvation for both the acid and the conjugate base, but now the increment for each homologation is larger for the anion than the neutral. This disfavors the bulkier anions, resulting in the larger acid being less acidic for entropic reasons. If the analogous separation, based on eq 3, of the anions' solvation entropies into electrostatic and neutral terms is done, the electrostatic entropies of solvation shown in Table V are obtained. We estimate the relative uncertainty in $\Delta S_s^{g\to aq}(A^-)^{el}$ as at least 4 eu, so nothing definite can be said about the apparent trend observed.

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Conclusions

It has been found that the enthalpy of acidity of aliphatic carboxylic acids becomes stronger with an increase in substituent bulk in RCO_2H, in both gas-phase and aqueous solution. The reasons for this are completely different in the two phases, however. As noted,[2] polarizability is the controlling force in the gas phase, while relative solvation energies appear to be the major factor in solution. Larger alkyl groups result in increased solvation enthalpies both for the acid and for the anion. The relatively greater solvation enthalpy of most of the neutral aliphatic carboxylic acids with increasing steric bulk, compared to the effect in the corresponding anions, when added to the gas-phase acidity favoring the larger acid, results in a close balance for the enthalpy of acidity in solution. It is the entropic effect of the anion resulting in a more ordered solution with increasing substituent bulk, relative to the neutral acid, that actually makes the larger carboxylic acids weaker in aqueous solution. Chemical intuition, in the form of the concept of steric hindrance to solvation,[3,17] reflects not an enthalpic process but an ergonic one.

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One-Electron Oxidation of 9-Methylanthracene and 9-[(Trimethylsilyl)methyl]anthracene: Reversal of Radical-Cation Selectivity by the Trimethylsilyl Group

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Abstract: Oxidation of 9-methylanthracene by pyridine/iodine proceeds mainly through nucleophilic attack on the intermediate anthracene radical cation rather than deprotonation. Replacement of a methyl proton by trimethylsilyl completely reverses the regiochemistry.

One-electron oxidation of hydrocarbons produces startling effects on reactivity that have only recently been recognized. Among these are activation toward electrocyclic[1] reactions, enhanced electrophilicity, and increased acidity.[2] Pharmacologically, such behavior is dramatically illustrated by the metabolic activation of certain methylated polycyclic aromatic hydrocarbons (PAH's) to form potent carcinogens[3] in which radical cations are mechanistically implicated.[4] However, it is not yet clear whether carcinogenicity of PAH's is coherent with the properties of their radical cations. Nevertheless, their metabolic activation follows reactivity patterns, i.e., deprotonation leading ultimately to formation of benzylic nucleic acid residues[5] and epoxidation leading to similar adducts, which are consistent with the duality of alkylaromatic radical cations as both strong acids and strong electrophiles. Activation and covalent binding of chemical carcinogens either via their radical cations or, more probably, through oxidation to strong electrophiles capable of alkylating macromolecular cellular nucleophiles is one of the triggering processes in carcinogenesis. Therefore, it is clear that a thorough understanding of the variables associated with deprotonation of alkylated PAH radical cations is necessary for the elucidation of the oxidative mechanisms in general and PAH carcinogenesis in particular.

We have been interested in elucidating oxidative mechanisms operating in PAH metabolism. Our investigations have been focused on studies on the role of solvent, stereoelectronics, and other effects that mimic changes in metabolic pathways using noncarcinogenic anthracene derivatives. For example, we reported

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dramatic solvent and stereoelectronic effects in biomimetic oxidation of 9,10-dialkylanthracenes.[6] Deprotonation as a significant mechanistic pathway in radical-cation reactions has been demonstrated both kinetically[7] and pharmacologically through deuterium isotope effects on the potentially acidic site.[8] However, our studies have demonstrated, at least in the case of *m*-alkylanthracene radical cations,[7b] that proton transfer leading to methyl oxidation is sluggish relative to nucleophilic attack by solvent leading to ring oxidation. In part, this reflects the considerable stereoelectronic constraints required for cleavage of the C–H σ-bond perpendicular to the aromatic ring. Our aim is to develop a highly acidic radical cation to explore changes in the oxidative metabolism. Eventually, this will enable us to examine whether acidity of PAH radical cations and carcinogenicity are convergent.

As our model compound, we chose 9-methylanthracene (9-MA), which, by virtue of an open meso position, should allow both nucleophilic attack and deprotonation, although nucleophilic attack would be expected to dominate. In electrochemical studies, Parker has shown that 9-phenylanthracene radical cation undergoes nucleophilic attack by pyridine at nearly diffusion-controlled rates.[9] Formation of pyridine adducts has also been demonstrated by Cavalieri and Roth, who used iodine as the one-electron oxidant and pyridine alkylation as a model for metabolic activation and binding of carcinogenic aromatic hydrocarbons[10] such as 7,12-DMBA and 3-MC. Both benzylic and meso pyridinium adducts were formed, presumably through nucleophilic trapping of the corresponding radical cations.

Mariano and co-workers have shown that the electrophilicity of a silicon atom is greatly enhanced when a radical cation is generated β to the silicon atom.[11] This property of the trialkylsilyl group has been exploited in developing suicide inhibitors for oxidases such as cytochrome P-450[12] and monoamineoxidase.[13] In this context, a trimethylsilyl group can be thought of as a "latent proton",[14] and replacement of a methyl proton in a radical-cation-mediated oxidation should alter the reaction pathways in favor of side-chain oxidation. Would a trimethylsilyl group (i.e., 9-[(trimethylsilyl)methyl]anthracene, 9-(TMS)MA) exhibit this effect? A comparative study of nucleophilic trapping of 9-MA and 9-(TMS)MA radical cations by pyridine, with use of the model reaction developed by Cavalieri and Roth, should provide the answer.

Results

Trapping of Radical Cations Generated by Iodine and Ceric Ammonium Nitrate (CAN). Cavalieri's conditions for iodine-mediated oxidation were employed with minor modifications. A cosolvent was incorporated into the mixture in order to minimize the amount of pyridine used. 9-MA and 9-(TMS)MA underwent clean oxidation by iodine in dry chloroform containing pyridine. NMR analysis indicated that the product was a mixture of two compounds. The major product (85–90% of mixture) from 9-MA oxidation was isolated by repeated recrystallization from chloroform/ether. Characterization by NMR and single-crystal X-ray diffraction of the perchlorate derivative confirmed that the major product (9-MAP) had arisen from nucleophilic attack on the 10 position of the 9-MA radical cation. The computer-generated ORTEP drawing of the 9-MAP molecule is shown in Figure 1. The minor product was identified as *N*-(9-anthracenylmethyl)-pyridinium iodide (9-AMP) by spectroscopic comparison with an authentic sample independently synthesized from 9-(chloromethyl)anthracene and pyridine. Since both oxidation products exhibited nonoverlapping NMR peaks, NMR analysis of the gross mixture of oxidation mixture allowed evaluation of the ratio of two isomers. As evinced from the NMR spectral analysis of the gross mixture, 9-MA yielded 9-AMP and 9-MAP in a ratio of 10:90. 9-(TMS)MA gave a mixture of the same compounds, but with a completely reversed regioselectivity, i.e., a ratio of 85:15. Oxidation of 9-MA and 9-(TMS)MA with the one-electron oxidant ceric ammonium nitrate (CAN) was also performed to examine any variation of selectivity with the oxidant. Oxidation of 9-MA with CAN in acetonitrile resulted in a mixture of the same compounds in the ratio of 15:85. However, oxidation of 9-(TMS)MA with CAN apparently yielded only 9-AMP. That this is a solvent effect was indicated by an oxidation of 9-(TMS)MA with I_2/pyridine in acetonitrile, which again yielded only 9-AMP.

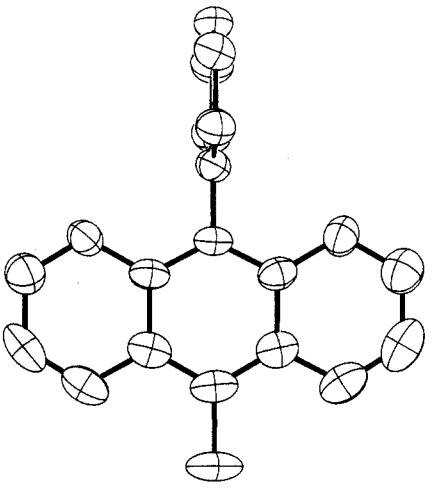

Figure 1. ORTEP drawing of the crystal structure of 9-MAP.

Discussion

Origin of Products. Involvement of radical cations in frozen solutions of iodine and several polycyclic aromatic hydrocarbons has been observed directly by ESR spectroscopy,[15] and the formation of these pyridinium adducts can be readily interpreted in terms of the involvement of radical cations. Radical cations of 9-phenylanthracene generated electrochemically have been trapped with pyridines to give pyridinium salts.[11,16] Upon the initial electron transfer, 9-MA radical cation undergoes predominantly nucleophilic attack by pyridine and, less efficiently, deprotonation. In either case, a second one-electron oxidation and deprotonation or pyridination of the resultant carbocation yields the observed products (see Scheme I) in a mechanism analogous to that proposed by Cavalieri and Roth.[11] In the case of 9-(TMS)MA, desilylation is much more rapid than deprotonation of the 9-MA radical cation, and side-chain oxidation predominates. This conclusion is supported by initial stopped-flow experiments that indicate that the decay of radical cation of 9-(TMS)MA formed with CAN is a very rapid process as compared to that of 9-MA.[17]

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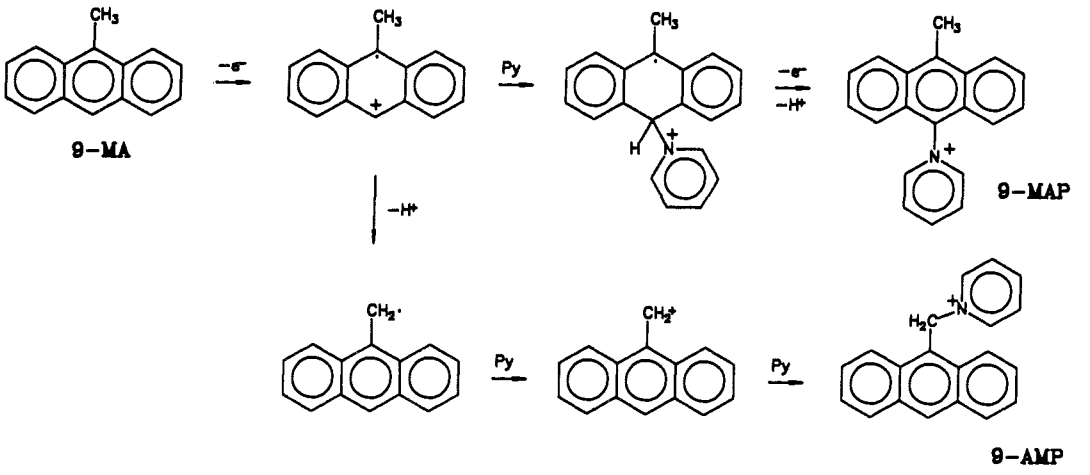
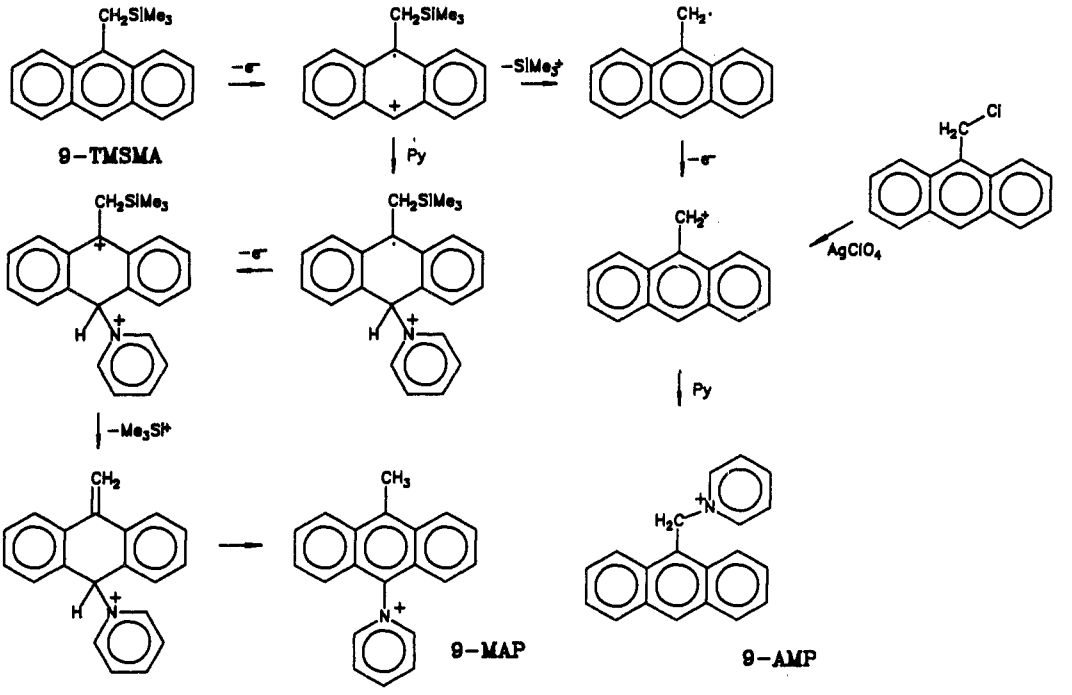
Scheme I



Scheme II



Studies with benzyltrialkylsilanes have also indicated that photosensitized oxidation leads to extremely rapid fragmentation of the corresponding radical cations as a result of nucleophile assistance,[18] which may also be a factor in 9-(TMS)MA. In the particular case of 9-(TMS)MA, peri interactions force the TMS group perpendicular to the aromatic plane, thus allowing maximum orbital overlap of aromatic p-orbitals and the σ-orbitals of the breaking C–Si bond. Maximum positive charge on meso positions should also make desilylation facile by making the silicon atom more electrophilic.[19] Upon one-electron oxidation, 9-(TMS)MA presumably undergoes extremely facile desilylation to form 9-methylanthryl radical followed by a second one-electron oxidation and pyridination (Scheme II).

The formation of 9-MAP as a minor product presents an interesting mechanistic issue. That is, does desilylation arise before or after nucleophilic attack by pyridine? In the former case, subsequent oxidation to the anthrylmethyl cation followed by ring pyridination of the ambient cation would explain this product. However, reaction of 9-(chloromethyl)anthracene with pyridine in the presence of $AgClO_4$, conditions for which the anthrylmethyl cation is the presumed intermediated, yielded 9-AMP as the exclusive product. Thus, we conclude that pyridine attack precedes desilylation for this minor product. The absence of this product in oxidation in acetonitrile solvent coincides with recent evidence that desilylation occurs with solvent assistance.[18] In the more nucleophilic solvent acetonitrile, which is present at much higher concentrations than pyridine, attack by solvent at silicon is much faster than attack at carbon by pyridine.[20]

Our results with 9-(TMS)MA demonstrate that it is possible to overcome a sluggish radical-cation deprotonation by replacement of proton with trimethylsilyl, redirecting the partition from ring oxidation to side-chain oxidation. Use of a trimethylsilyl group in this fashion has obvious implications for radical-cation-mediated biooxidations, both for design of suicide enzyme inactivators and in alteration of oxidative pathways. Given that the competition between side-chain oxidation and ring oxygenation of polynuclear aromatic hydrocarbons is still an unresolved component of their carcinogenicity, the ability to control the oxidative pathway by use of (trimethylsilyl)methyl rather than methyl substituents on

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(19) 2-(TMS)MA, which lacks both these features, undergoes oxidation with iodine/pyridine to result in mainly nucleophilic attack on meso positions (Sirimanne, S.; Tolbert, L. M. Unpublished results).

(20) We thank a reviewer for pointing out this possibility.

Table I. X-ray Crystallographic Data

formula	$C_{20}H_{16}NCl_4$
fw	369.68
cryst syst	triclinic
space gp	$P\bar{1}$
a, Å	7.6160 (20)
b, Å	10.2380 (20)
c, Å	12.110
V, Å^3	878.45
Z	2
cryst size, mm	0.68 × 0.24 × 0.14
λ(Mo Kα), cm^{-1}	0.24
d_{calcd}, g/cm^3	1.398
temp, °C	24 °C
radiation (graphite monochromator)	0.71073 Å (Mo Kα)
2θ range, deg	11.47–20.94
scan mode	ω
no. of refl collected	3086
no. of refl used	1608
R_F	0.78
R_W	0.065

such substrates may provide insight. Studies in this regard are in progress.

Experimental Section

Materials. 9-Methylanthracene, 9-(bromomethyl)anthracene, [(trimethylsilyl)methyl]magnesium chloride, 9-(chloromethyl)anthracene, and silver perchlorate were purchased from Aldrich. 9-[(Trimethylsilyl)methyl]anthracene was synthesized according to Tamao et al.[21]

Oxidation with Iodine in the Presence of Pyridine. In a typical experiment, pyridine (6 mL) in 10 mL of dry chloroform was added to 9-MA or 9-(TMS)MA (1.00 mmol) and iodine (10 mmol) in 5 mL of dry chloroform. The mixture was stirred in the dark for 24 h at 25 °C. The products were diluted with methylene chloride, washed with 2 × 50 mL of 1 M sodium thiosulfate solution, and isolated in 40–75% yield by precipitation with ether. NMR analysis of the reaction mixture prior to precipitation revealed the formation of products in near-quantitative yield and ratio identical with that after precipitation. The brownish yellow product was dried in a vacuum desiccator. Thus, 200 mg (1.04 mmol) of 9-MA produced 297 mg (0.748 mmol, 72%) of pyridinium adducts in an 90:10 ratio by NMR analysis. Redissolution in chloroform and reprecipitation with ether produced 169 mg (0.411 mmol, 41%) of pyridinium adducts in the same ratio. Conversion of the iodide salt to the perchlorate allowed isolation of the major product in analytically pure form through repeated crystallization of the mixture. NMR and X-ray analysis allowed assignment of the major product as *N*-(10-methyl-9-anthracenyl)pyridinium perchlorate (9-MAP): mp 249.5–250 °C; ^{1}H NMR (Me_2DO-d_6) δ 9.45 (d, 2 H), 9.28 (t, 1 H), 8.63 (d, 2 H), 8.56 (t, 2 H), 7.78–7.66 (m, 4 H), 7.22 (d, 2 H), 3.26 (s, 3 H); IR ($CHCl_3$) 3103, 3051, 3027, 2936, 1619, 1463, 1369, 1335, 1266, 1237 cm^{-1}; UV (EtOH) λ_{max} (nm) (log ε) 357.5 (3.93), 376 (4.04), 395 (3.95). Anal. Calcd for $C_{20}H_{16}NI$: C, 60.47; H, 4.06; N, 3.52; I, 31.94. Found: C, 59.82; H, 4.11; N, 3.45; I, 31.51.

Oxidation with CAN in the Presence of Pyridine. In a typical experiment, 9-MA or 9-(TMS)MA (0.40 mmol), CAN (0.80 mmol), and pyridine (4.0 mmol) in 7.5 mL of dry acetonitrile were stirred 24 h at 25 °C in a screw-capped vial. The products were extracted with methylene chloride and washed with water, the methylene chloride solution was then poured into ether, and the product was separated by filtration, washed well with more ether, and dried under vacuum. In the case of 9-MA, 77.0 mg (0.403 mmol) produced 93.0 mg (0.233 mmol, 59%) of 9-AMP and 9-MAP in a 1:6 ratio by NMR analysis. In the case of 9-(TMS)MA, 75.0 mg (0.284 mmol) produced 26.5 mg (0.0665 mmol) of 9-AMP as a poorly crystalline solid. A similar reaction with 132 mg (0.500 mmol) of 9-(TMS)MA in acetonitrile yielded 9-MAP as the single isolable product (68 mg, 0.17 mmol) in 34.5% yield.

***N*-(9-Anthracenylmethyl)pyridinium Chloride (9-AMP). A. Without $AgClO_4$.** 9-(Chloromethyl)anthracene (100 mg, 0.441 mmol) was stirred with pyridine (0.4 mL. 0.49 mmol) overnight, and the pyridinium salt was precipitated by adding dry ether (50 mL). The yellow solid was filtered and washed well with ether (3 × 50 mL) to remove unreacted pyridine and 9-(chloromethyl)anthracene. The product was recrystallized from $CHCl_3$/ether to yield 121 mg (0.396 mmol, 90%) of light yellow prisms: mp 184.5–185 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.94 (s, 1 H), 8.87 (d, 2 H), 8.57 (t, 1 H), 8.42 (d, 2 H), 8.28 (d, 2 H), 8.07 (t, 2 H), 7.71–7.61 (m, 4 H), 6.97 (s, 2 H); IR ($CHCl_3$) cm^{-1} 3100, 3055, 3013, 2943, 1632, 1527, 1485, 1449, 1252, 1146; UV (CH_3OH) λ_{max} (nm) 353.0 (3.7), 369.5 (3.82), 390.5 (3.73). Anal. Calcd for $C_{20}H_{16}NCl$: C, 78.55; H, 5.27; N, 4.58, Cl, 11.59. Found: C, 78.19; H, 5.65; N, 4.27; Cl, 11.00.

B. With $AgClO_4$. Silver perchlorate (0.100 g, 0.482 mmol) was added to 9-(chloromethyl)anthracene (75.0 mg, 0.331 mmol) in chloroform (5 mL). Pyridine was added after stirring for 10 min, and stirring was continued for 2 h. The insoluble matter was removed by filtration, and the pyridinium salt was separated by precipitation with dry ether. The product was washed with ether and dried under vacuum to yield 98.0 mg (0.26 mmol, 79%) of *N*-(9-anthracenylmethyl)pyridinium chloride (9-AMP), 100% pure by NMR analysis.

X-ray Crystal Structure Analysis of MAP. Crystals of 9-MAP perchlorate suitable for X-ray diffraction studies were obtained by slow crystallization from chloroform. The intensity data were collected on a Syntex $P2_1$ diffractometer. The structure was solved with use of the SOLV direct methods program of the SHELXTL system on a Data General Eclipse computer. Crystallographic parameters are listed in Table I. Figure 1 shows a computer-generated drawing of 9-MAP.

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Registry No. 9-MA, 779-02-2; 9-TMSMA, 88920-42-7; 9-MAP·ClO_4^-, 131618-27-4; 9-AMP·Cl^-, 54375-34-7; CAN, 10139-51-2; I_2, 7553-56-2.

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