two quite different activating groups (cyano and 4-nitrophenyl). The significant difference in the reactivities of the *N*-(4-nitrophenethyl)pyridinium and quinuclidinium cations (**3** and **2**, respectively) is unexpected, particularly in terms of the lack of a change in the rate-determining step for the latter at about the same nucleofuge basicity for which such a change is clearly apparent for the former. More comprehensive studies of these two general classes of nucleofuge will be required to elucidate the detailed reasons behind their quite different reactivities, despite their similarities as nitrogen-derived leaving groups of the same electrical charge and similar basicity.

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Registry No. **3a**·Br, 135041-77-9; **3b**·Br, 135041-78-0; **3c**·Br, 135041-79-1; **3d**·Br, 120392-43-0; **3e**·Br, 135041-80-4; **3f**·Br, 135105-70-3; **3g**·Br, 135041-81-5; **3h**·Br, 135041-82-6; **3i**·Br, 135041-83-7; **3j**·Br, 135041-84-8; **3k**·Br, 135041-85-9; **3l**·Br, 135041-86-0; **4**·Br, 135041-87-1; 1-bromo-2-(4-nitrophenyl)ethane, 5339-26-4; 3-chloropyridine, 626-60-8; 3-(cyanomethyl)pyridine, 6443-85-2; 3-phenylpyridine, 1008-88-4; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 2-methylpyridine, 109-06-8; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-amino-3-bromopyridine, 13534-98-0; 4-morpholinopyridine, 2767-91-1; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; 1-methylimidazole, 616-47-7.

Cation Radical–Nucleophile Combination Reactions. Reactions of Nitrogen-Centered Nucleophiles with Cation Radicals Derived from Anthracenes

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Abstract: Cation radicals derived from anthracene and 9-substituted anthracenes react with pyridine and substituted pyridines to form pyridinium salts. 9-Nitro- and 9-cyano-substituted cation radicals were observed to be about 10^2 times as reactive as unsubstituted anthracene (AH) cation radicals while the 9-phenylanthracene (PAH) cation radical was found to be from 2 to 7 times less reactive than $AH^{\bullet+}$. The reactivities of the nitrogen-centered nucleophiles were observed to depend upon both electronic and steric factors. The mechanism of the reactions involves nucleophilic attack by the nitrogen lone pair at the 10-position of the cation radical. The reactions are accompanied by a change in hybridization, sp^2 to sp^3, at the anthracene 10-position, giving rise to inverse deuterium kinetic isotope effects ranging from 0.7 to 0.8 when the 10-position is substituted with deuterium. An electron-transfer mechanism for the substitution reactions was ruled out on the basis of energetic considerations.

Introduction

Although cation radical–nucleophile combination reactions have been studied extensively,[1] the mechanism of the reactions remains an active topic of discussion. A central issue has been concerned with the energetics of the attack of a nucleophile on a cation radical. Work reported from our laboratory[2-4] indicates that the overall reaction (1), where Ar–H is an aromatic compound and compound N is a nucleophile, in the absence of special constraints such as steric factors, can be an essentially barrier-free reaction.

$$Ar\text{–}H^{\bullet+} + N \rightarrow Ar^{\bullet}(H)(N^{+}) \qquad (1)$$

This is in spite of the fact[5,6] that since the product of reaction 1 is a doubly excited configuration with respect to reactants, the reaction is formally "forbidden" and can only have a low barrier under certain conditions. Specifically, when Ar–H is anthracene or 9-phenylanthracene and N is pyridine, reaction 1 is predicted to be slow.[6]

The early studies on cation radical–nucleophile reactivity[7,8] involved cation radicals of low reactivity such as those from 9,10-diphenylanthracene (DPA). This was an intentional feature of these studies made necessary by the fact that it was not possible to study the kinetics of more reactive cation radicals with the available kinetic techniques. The kinetic studies showed that in these systems, complex rate laws are followed that implicate the intermediacy of doubly charged species.[1] The apparent low reactivity[9] of cation radicals toward nucleophiles led Pross to examine the reaction theoretically, by using the configuration-mixing (CM) model.[5]

Cation radicals derived from 9-phenylanthracene (PAH), in contrast to $DPA^{\bullet+}$, are highly reactive toward nucleophiles.[2,10,11]

Table I. Oxidation Peak Potentials of Anthracenes and Nitrogen-Centered Nucleophiles in Acetonitrile–Bu_4NPF_6 (0.1 M)

substance	$E^{p\,a}$
anthracene	0.88
9-phenylanthracene	0.85
9-cyanoanthracene	1.25
9-nitroanthracene	1.26
4-methylpyridine	2.44
pyridine	2.46
2-methylpyridine	2.31
4-cyanopyridine	2.90[b]
2,6-dimethylpyridine	2.13

[a] Peak potentials for the oxidation of the substrate in V vs $Fc/Fc^{\bullet+}$ in CH_3CN–$LiClO_4$ (0.1 M) at 298 K. Fc refers to ferrocene. [b] 4-Cyanopyridine did not show a well-defined oxidation peak. A shoulder was observed at about 2.9 V vs $Fc/Fc^{\bullet+}$.

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Table II. Second-Order Rate Constants for the Reactions of Pyridine Nucleophiles with 9-Phenylanthracene Cation Radical

substrate	nucleophile	log k(AN)/ M^{-1} s^{-1} [a]	log k(DCM)/ M^{-1} s^{-1} [b]
ANO_2	4-methylpyridine	9.56	9.60
	pyridine	9.14	9.34
	2-methylpyridine	8.60	8.62
	4-cyanopyridine	8.34	8.30
	2,6-dimethylpyridine	5.53	5.08
ACN	4-methylpyridine	9.41	9.32
	pyridine	9.08	9.32
	2-methylpyridine	8.88	8.70
	4-cyanopyridine	8.79	8.48
	2,6-dimethylpyridine	5.49	5.36
AH	4-methylpyridine	7.89	9.08
	pyridine	7.36	8.73
	2-methylpyridine	6.68	7.11
	4-cyanopyridine	6.72	6.08
	2,6-dimethylpyridine	[c]	4.38
PAH	4-methylpyridine	7.60	7.51
	pyridine	7.04	6.91
	2-methylpyridine	6.04	5.17
	4-cyanopyridine	5.86	4.57
	2,6-dimethylpyridine	3.04	2.62

[a] Measured in acetonitrile–Bu_4NPF_6 (0.1 M) at 298 K. [b] Measured in dichloromethane–Bu_4NPF_6 (0.2 M) at 298 K. [c] Interference by a background reaction.

Other recent studies have revealed essentially barrier-free cation radical–nucleophile combination reactions.[12,13] The gas-phase reactions of ketene cation radical[13] and aromatic cation radicals with trinitromethyl anion, some of which involve cage combination,[12] are predicted to be facile by the CM model treatment in spite of the doubly excited product configurations involved.[6] This is due to the fact that the energetics of the single electron shift from nucleophile to cation radical are favorable in these cases in contrast to the situation for the $PAH^{\bullet+}$ pyridine reaction.

In this paper we report the results of a detailed investigation of the reactions of anthracene and 9-substituted anthracene cation radicals with pyridine and substituted pyridines. The preliminary results reported earlier[2] did not specifically rule out the possibility of a mechanism involving electron transfer (2) followed by radical combination (3). We address this possibility by examining the

$$Ar\text{–}H^{\bullet+} + N \rightleftarrows Ar\text{–}H + N^{\bullet+} \quad (2)$$

$$Ar\text{–}H^{\bullet+} + N^{\bullet+} \rightarrow Ar^{+}(H)(N^{+}) \quad (3)$$

energetics of reaction 2 and by studying deuterium kinetic isotope effects for reactions of $PAH^{\bullet+}$ and $PAD^{\bullet+}$. We reexamine the CM model analysis of cation radical–nucleophile combination reactions in the light of recent work.

Results and Discussion

Electron Transfer between Cation Radicals and Nucleophiles. The electrode potentials for reduction of the cation radicals (4) along with those for oxidation of the nucleophiles (5) provide data for the calculation of equilibrium constants for the electron-transfer reactions (2). Peak potentials for oxidation of substrates and nucleophiles are listed in Table I, and rate constants for a number of cation radical–nucleophile combinations in acetonitrile and dichloromethane are summarized in Table II.

$$Ar\text{–}H^{\bullet+} + e^{-} \rightleftarrows Ar\text{–}H \quad (4)$$

$$N \rightleftarrows N^{\bullet+} + e^{-} \quad (5)$$

Equilibrium constants for electron-transfer reactions (2) in acetonitrile between 9-substituted anthracene (see below for structures) cation radicals with pyridine, 4-methylpyridine, and 4-cyanopyridine are very small. The equilibrium constants (K_2) were calculated from the potential differences for half-reactions 4 and 5. The maximum possible rate constants for electron-transfer reactions (2) were then calculated from eq 6, which assumes that reverse reactions (2) are diffusion-controlled. The

$$(k_2)_{max} = K_2 k_{diff} \quad (6)$$

latter assumption is justified since the free energy changes for reaction 2 are 10 kcal/mol or more positive. In all cases, the observed rate constant (k_{COMB}) greatly exceeds the $(k_2)_{max}$, providing strong evidence that reaction 2 does not lie on the reaction coordinate for the formation of combination products.

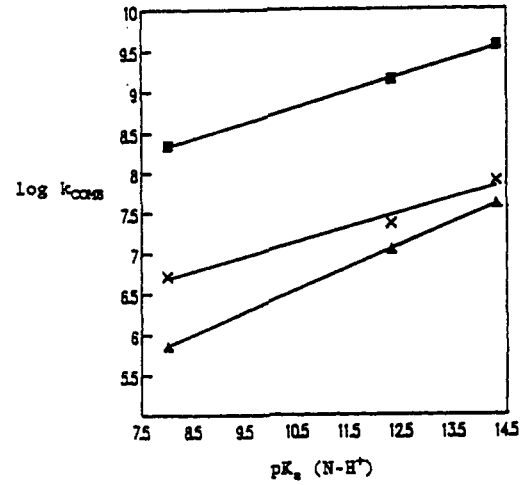
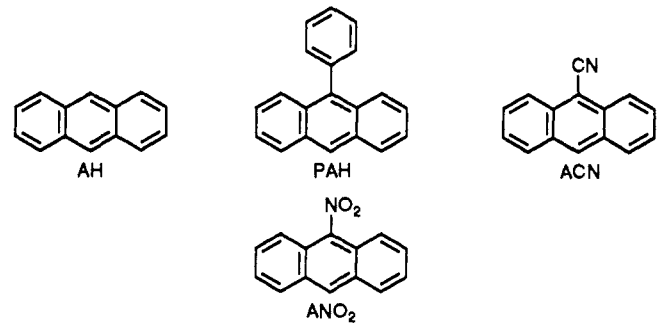


Figure 1. Plot of log k_{COMB} vs pK_a of the conjugate acids of the pyridines for the reactions with $ANO_2^{\bullet+}$, (■), $AH^{\bullet+}$ (×), and $PAH^{\bullet+}$ (▲) in acetonitrile. The data for the reactions of $ACN^{\bullet+}$ were omitted for clarity.



Polar Substituent Effects. Second-order rate constants for the reactions of the cation radicals of 9-phenylanthracene, anthracene, 9-cyanoanthracene, and 9-nitroanthracene with pyridine and a number of substituted pyridines in CH_3CN–Bu_4NBF_4 (0.1 M) and in CH_2Cl_2–Bu_4NPF_6 (0.2 M) at 298.2 K are summarized in Table II. The data show that there is very little difference in rate constants in the two solvents and that the reactions are relatively insensitive to substituent effects. Hammett ρ values ranging from −0.65 (9-cyanoanthracene) to −1.79 (9-phenylanthracene), derived from plots of log k_{COMB} vs σ^+ for the reactions with 4-methylpyridine, pyridine, and 4-cyanopyridine in acetonitrile, were observed. The low value of ρ for the reactions of the 9-cyanoanthracene cation radical could be explained in part by the fact that the reactions with 4-methylpyridine and pyridine are within 1 order of magnitude of the diffusion-controlled limit. On the other hand, the rate constants for the reactions of 9-nitroanthracene cation radical are of similar magnitude while ρ in this case was observed to be equal to −1.26, very near the value (−1.21) observed for the reactions of $AH^{\bullet+}$. The most significant feature of the data is that all of the reactions are very rapid.

Plots of log k_{COMB} vs pK_a of the conjugate acids of the pyridine bases in acetonitrile are illustrated in Figure 1. The slopes of the Brönsted type correlations were 0.192 (ANO_2), 0.0935 (ACN), 0.180 (AH), and 0.276 (PAH). These results are consistent with

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Table III. Arrhenius Activation Energies for the Reactions of Nitrogen-Centered Nucleophiles with Cation Radicals Derived from Anthracenes in Acetonitrile–Bu_4NPF_6 (0.1 M)

	E_a/kcal/mol			
nucleophile	$ANO_2^{\bullet+}$	$ACN^{\bullet+}$	$PAH^{\bullet+}$	$AH^{\bullet+}$
4-methylpyridine			0[a]	
pyridine	1.7	2.7	2.6[a]	−1.8
2-methylpyridine	1.7		1.9	−2.1
4-cyanopyridine	2.9	−0.5	0.1[a]	−4.4
2,6-dimethylpyridine	1.6	−0.3	4.0	

[a] Values from ref 2.

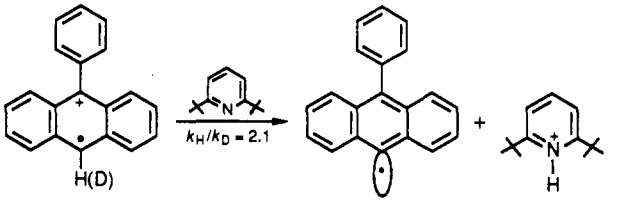
the Hammett correlations discussed in the previous paragraph. The small values of the slopes suggest a weak dependence of the rates of the cation radical–nucleophile combination reactions on the nucleophilicity of the substituted pyridine.

Temperature Effects. The apparent Arrhenius activation energies observed for the reactions of $AH^{\bullet+}$, $PAH^{\bullet+}$, $ACN^{\bullet+}$, and $ANO_2^{\bullet+}$ in acetonitrile are summarized in Table III. The feature of interest here is that the values are very small and sometimes negative. We have previously interpreted this to be indicative of a two-step mechanism involving an initial π-complex formation (7) followed by bond formation (8).[2,4] Whether or not the

$$Ar\text{–}H^{\bullet+} + N \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} Ar\text{–}H^{\bullet+}/N \qquad (7)$$

$$Ar\text{–}H^{\bullet+}/N \xrightarrow{k_8} Ar^{\bullet}(H)(N^{+}) \qquad (8)$$

π-complex is manifested in the observed kinetics depends upon the relative magnitudes of k_8 and k_{-7}. A negative or very low observed enthalpy of activation can arise from the masking of the positive enthalpy of activation for reaction 8 by a negative enthalpy of reaction 7. An extreme case of this phenomenon has recently been observed during the proton transfer reaction between $PAH^{\bullet+}$ and 2,6-di-*tert*-butylpyridine (9).[14] In this case, the Arrhenius activation energy was observed to be −7 kcal/mol. There is ample evidence that the initial step in many cation radical reactions is the formation of a π-complex between the reactants.[1]



(9)

The π-complexes formed in reaction 7 have eluded detection by spectroscopic techniques.[1] We have attempted to detect $PAH^{\bullet+}N$ (where N is pyridine) by linear-sweep voltammetry measurements. At a voltage sweep rate of 1000 V/s we were unable to observe any difference in the peak potential for the oxidation of PAH (1.0 mM) in the presence and the absence of pyridine (2.0 mM). If we assume that our limit of detection of a potential change upon addition of pyridine under these conditions is 1.0 mV, this corresponds to a maximum equilibrium constant for reaction 10 of about 20 M^{-1}. Larger values of K_{10} would be

$$PAH^{\bullet+} + \text{pyridine} \rightleftarrows PAH^{\bullet+}/\text{pyridine} \qquad (10)$$

expected to give rise to a negative shift in the peak potential when pyridine is added. Thus, it is possible that k_8 could be as much as 1 order of magnitude lower than the observed rate constants ($k_{obsd} = k_8K_9$) without equilibrium 7 being detectable by our voltammetric measurements.

Steric Effect of Substituents at the 2-Position of the Pyridine Ring. Alkyl and phenyl substituents in the 2-position exert a substantial steric effect upon the rates of reactions of the nitrogen-centered nucleophiles with cation radicals derived from the anthracenes. Second-order rate constants for the reactions of $PAH^{\bullet+}$ with pyridine and a number of 2-substituted and 2,6-disubstituted pyridines in acetonitrile–Bu_4NPF_6 (0.1 M) at 298 K are summarized in Table IV. The results show that a single substituent on the 2-positions of the pyridines has a moderate effect on the rate constants while a very dramatic decrease in the rate constants is observed when both the 2- and 6-positions are substituted.

Table IV. Second-Order Rate Constants and Deuterium Kinetic Isotope Effects for the Reactions of 9-Phenylanthracene Cation Radical with Alkyl-Substituted Pyridines in Acetonitrile–Bu_4NPF_6 (0.1 M) at 298 K

	nucleophile	log k/ M^{-1} s^{-1}	k_{rel}	k_H/k_D
1	4-methylpyridine	7.60	36300	
2	pyridine	7.08	10900	0.7
3	2,4-dimethylpyridine	6.32	1910	0.8
4	2-methylpyridine	6.04	1000	0.8
5	2-ethylpyridine	5.68	436	0.8
6	2-phenylpyridine	4.49	28.2	0.8
7	2,4,6-trimethylpyridine	3.18	1.36	0.7
8	2,6-dimethylpyridine	3.04	1.00	0.75

It is interesting to compare the polar effect of a 4-methyl group on the nucleophile reactivity of the nitrogen center as the steric environment is changed. 4-Methylpyridine is about 4 times more reactive than pyridine toward $PAH^{\bullet+}$ (Table II), while the polar effect of the 4-methyl group in 2,4-dimethylpyridine is observed to be only about a factor of 2 (entry 3). Including a 4-methyl substituent only increases the rate by a factor of 1.4 for the 2,6-dimethyl-substituted case (entry 7). The data clearly show that the steric interactions of groups in the 2- and 6-positions has an attenuating effect upon the polar substituent effect at the 4-position.

Inverse Kinetic Isotope Effects. Substitution of the 10-H by D in $PAH^{\bullet+}$ is accompanied by inverse kinetic isotope effects during reactions with nitrogen-centered nucleophiles.[14] The kinetic isotope effects are due to the hybridization change, sp^2 to sp^3,[15] that takes place during nucleophilic attack on the cation radical. In fact, this represents a very definitive mechanistic probe for these reactions. The observation of the inverse secondary isotope effect is a strong indication that the mechanism of the reaction involves a rate-determining attack of the nitrogen-centered nucleophile at the 10-position of the cation radical.

This very effectively rules out the electron-transfer mechanism, equations 2 and 3, for these reactions. In all cases in this study where we have tested for an inverse kinetic isotope effect, we have found values ranging from 0.7 to 0.8. For the alkyl- and phenyl-substituted pyridines, the data are summarized in the last column of Table IV.

The electron-transfer mechanism (eqs 2 and 3) was suggested[6] as a possibility for the reaction of $PAH^{\bullet+}$ and piperidine. In this case, we cannot rule this mechanism out on the basis of oxidation potentials. We have been able to measure an approximate inverse kinetic isotope effect ($k_H/k_D \approx 0.85$) for this reaction. The kinetics were studied by using the prepeak method as described earlier.[10,11] The uncertainty in the absolute value of the inverse kinetic isotope effect is due to the fact that rate constants measured with this nucleophile have been observed to be sweep-rate dependent,[2] indicating an error due to the interference of charge-transfer kinetics. On the other hand, repeated measurements alternating between solutions containing PAH and PAD revealed that the apparent rate constant was always greater for the reactions of $PAD^{\bullet+}$. Therefore, the magnitude but not the existence of the inverse kinetic isotope effect is subject to experimental error. On this basis, we conclude that the reaction of $PAH^{\bullet+}$ with piperidine takes place by the same mechanism as observed for the other nitrogen-centered nucleophiles and that electron transfer (2) is not involved.

The data reported here show that all of the reactions of anthracene and 9-substituted anthracene cation radicals are rapid,

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providing that the nitrogen center is not sterically hindered by 2- or 2,6-substituents. The reactivity of $AH^{\bullet+}$ is slightly greater than that of $PAH^{\bullet+}$. The most important factor in this difference in reactivity is probably the statistical factor of 2, arising from the fact that there are two equivalent unsubstituted positions available for reaction with $AH^{\bullet+}$, one of which is substituted in $PAH^{\bullet+}$.

Our Results in Relation to the Configuration Mixing Model Predictions. It has recently been pointed out[6] that the products of many of the basic reactions of organic chemistry are singly excited with respect to the reactants. In these cases, the reaction coordinate can be formulated as a single electron shift (SES) leading from reactant configuration to product configuration. This treatment gives rise to curve-crossing models in which reactant configurations are converted to product configurations in the neighborhood of the intersections by avoided crossings. For the case of the cation radical–nucleophile reaction (11), a single electron shift[5] cannot result in bond formation since no unpaired electrons remain on Ar–H to pair with that on $N^{\bullet+}$. Thus, in

$$\text{Ar–H}^{\bullet+}\text{N} \xrightarrow{\text{SES}} \text{Ar–H/N}^{\bullet+} \qquad (11)$$

$$\text{Gap(Add)} = I_{\text{N:}}{}^{*}(\text{s}) - A_{\text{E}}{}^{*}(\text{s}) + \Delta E_{\text{ST}}(\pi\pi^{*}) \qquad (12)$$

this case it is necessary to include $\Delta E_{ST}(\pi\pi^*)$ in the initial gap (12), which corresponds to the singlet–triplet excitation energy of Ar–H. It has been proposed that reactions with initial gaps less than 60 kcal/mol should be rapid (second-order rate constants greater than 10^6 M^{-1} s^{-1}) while those with initial gaps greater than 100 kcal/mol are expected to be slow.[6] It was pointed out that the data reported[2] for the reaction of 9-$PAH^{\bullet+}$ with pyridine represent a dilemma since the reactions are very rapid, even though the initial gap was estimated to be of the order of 112 kcal/mol.

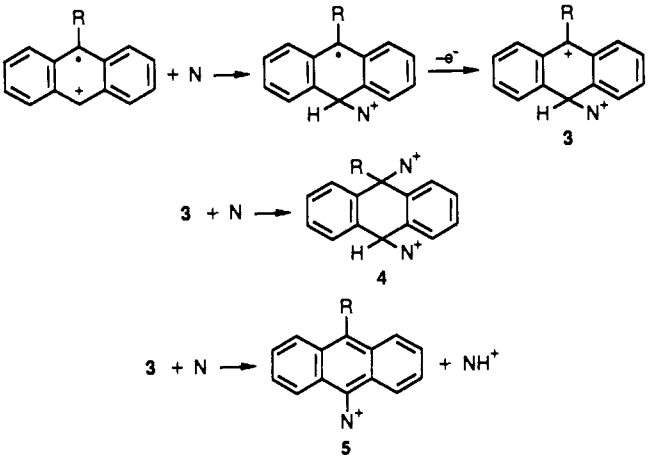
We have recently reexamined the formulation of CM model initial gaps for combination reactions involving bond formation within donor–acceptor complexes and found that eq 12 is incomplete.[16] The derivation of the CM model initial gap for the cation radical–nucleophile combination reaction is shown in Scheme I. The $RT \ln K^{*}_{ST}/K^{\circ}_{DA}$ term in 18 corresponds to the ratio of equilibrium constants for the association of excited-state (K^{*}_{ST}) and ground-state (K°_{DA}) reactants. The problem that arises in attempting to estimate the reaction barrier from the initial gap is that this term generally cannot be evaluated. The lack of data on the magnitude of $RT \ln K^{*}_{ST}/K^{\circ}_{DA}$ clearly negates use of the simple CM model treatment to calculate reaction barriers for cation radical–nucleophile combination reactions. In the absence of $RT \ln K^{\circ}_{ST}/K^{\circ}_{DA}$ data, it would appear to be prudent to restrict the use of the model in discussions of cation radical reactivity to qualitative trends. For example, the model correctly predicts that a carbenium ion will be more reactive toward nucleophiles than a cation radical with the same electron affinity.[6] The latter prediction arises from the singlet–triplet excitation term in 18 that does not appear in the initial gap for the carbenium ion reaction.

Products of the Reactions of Nitrogen-Centered Nucleophiles with Cation Radicals Derived from Anthracenes. The oxidative addition of a nitrogen-centered nucleophile to a neutral anthracene molecule involves the loss of two electrons and the consumption of two molecules of nucleophile. After the initial nucleophilic attack (Scheme II) followed by a homogeneous electron transfer, the resulting carbocation **3** can partition between two product-forming reactions. The intermediate carbocations **3** formed in the reaction of anthracene[18] and 9,10-diphenylanthracene[19] cation radicals with pyridine undergo a combination reaction with the nucleophile to give the adducts **4**, while **3** formed from 9-phenylanthracene either form the adduct **4** or undergo an acid–base reaction with the nitrogen-centered nucleophile to give the product of substitution **5**.[20] We observe very similar behavior with substituted pyridines; $AH^{\bullet+}$ and $DPA^{\bullet+}$ react to give adducts **4** while 9-substituted anthracene cation radicals yield the substitution products **5**.[21] Details of the product studies of these reactions will be published elsewhere.[21]

Scheme I

process	free energy	
$\text{N:/Ar–H}^{\bullet+} \rightarrow \text{N:} + \text{Ar–H}^{\bullet+}$	$RT \ln K^{\circ}_{DA}$	(13)
$\text{N} \rightarrow \text{N}^{\bullet+} + \text{e}^{-}$	$I_{D}{}^{*}(\text{s})$	(14)
$\text{Ar–H}^{\bullet+} + \text{e}^{-} \rightarrow \text{Ar–H}$	$-A_{A}{}^{*}(\text{s})$	(15)
$\text{N}^{\bullet+} + \text{Ar–H} \rightarrow \text{N}^{\bullet+} + {}^{3*}\text{Ar–H}$	$\Delta E_{ST}(\pi\pi^{*})$	(16)
$\text{N}^{\bullet+} + {}^{3*}\text{Ar–H} \rightarrow \text{N}^{\bullet+}/{}^{3*}\text{Ar–H}$	$-RT \ln K^{*}_{ST}$	(17)
$\text{N:/Ar–H}^{\bullet+} + \text{N}^{\bullet+}/{}^{3*}\text{Ar–H}$	$(I_{D} - A_{A})^{*}(\text{s}) + \Delta E_{ST}(\pi\pi^{*}) - RT \ln K^{*}_{ST}/K^{\circ}_{DA}$	(18)

Scheme II



Conclusions. The rapid reactions of anthracene and substituted anthracene cation radicals with nitrogen-centered nucleophiles take place by the direct attack of the nucleophile on the 9- or 10-position of the anthracene nucleus. An electron-transfer mechanism was ruled out by showing that the energetics of the initial electron transfer between substrate and nucleophile is predicted from energetic considerations to be several orders of magnitude slower than the observed reaction rates. The reactions are accompanied by inverse secondary deuterium kinetic isotope effects when the position undergoing attack is substituted with deuterium. This observation strongly supports attack by the nucleophile as the rate-determining step. The steric effect exerted by substituents in the 2- and 2,6-positions of the pyridine ring has a much greater influence on the reaction rates than the weak polar substituent effect observed for 4-substituted pyridines. Arrhenius activation energies were observed to be small and sometimes negative, implying that the bond-forming reaction involves an initial reversible π-complex formation followed by rearrangement to the σ-complex.

Experimental Section

Materials. Reagent grade acetonitrile was distilled from P_2O_5 before it was passed through a column of active neutral alumina to remove water and protic impurities. Dichloromethane, after passing through active neutral alumina, was used without further purification. Tetrabutylammonium hexafluorophosphate (Aldrich) was recrystallized from dichloromethane–ether before use. 9-Phenylanthracene (Aldrich) and 9-cyanoanthracene (Aldrich) were used as received. 9-Nitroanthracene was prepared according to a published procedure.[22] 9-Phenylanthracene-*10-d* was prepared by $LiAlD_4$ reduction of 9-bromo-10-phenylanthracene, obtained by bromination of 9-phenylanthracene. Anthracene-*9,10-*d_2 was prepared from 9,10-dibromoanthracene by halogen–lithium exchange at −78 °C with butyllithium under a nitrogen atmosphere followed by quenching with D_2O. All pyridines were purified

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the same day prior to use by using standard techniques.

Instrumentation and Data-Handling Procedures. Cyclic and linear-sweep voltammetry were performed on a JAS Instrument Systems J-1600-B potentiostat driven by a Hewlett-Packard 3314A function generator. After passing a sample through a Stanford Research Systems Model SR640 dual-channel low-pass filter, the data were recorded on a Nicolet Model 310 digital oscilloscope with 12-bit resolution. The oscilloscope and function generator were controlled by an IBM AT compatible personal computer via an IEEE interface. The current-potential curves were collected at selected trigger intervals to reduce periodic noise,[23] and 20 curves were averaged before treatment with a frequency domain low-pass digital filter and numerical differentiation.

Cyclic Voltammetry Measurements. A standard three-electrode one-compartment cell was used for all kinetic measurements. Positive feedback IR compensation was used to minimize the effects of uncompensated solution resistance. Reference electrodes were $Ag/AgNO_3$ (0.01 M) in acetonitrile constructed in the manner described by Moe.[24] The working electrodes, 0.2-0.8-mm Pt, were prepared by sealing wire in glass and polishing to a planar surface as described previously.[25] The working electrodes were cleaned before each series of measurements with a fine polishing powder (Struers, OP-Alumina Suspension) and wiped with a soft cloth. The cell was immersed in a water bath controlled to 25 ± 0.2 °C.

Kinetic Measurements. Rate constants were obtained by comparing derivative cyclic voltammetry[26] data to theoretical data obtained by digital simulation.[27] The reactions were studied under second-order conditions with use of solutions containing substrate (1.0 mM) and nucleophile (2.0 mM). Rate constants were evaluated at several different sweep rates (ν), giving a range of values for the derivative peak ratio (R'_1)[26] by using eq 19 in which the constant depends upon R'_1. For example, when R'_1 is 0.500, the constant is equal to 79.2 when the substrate concentration is 1.0 mM.

$$\log k(\mathrm{M/s}) = (\text{constant})(F/RT)\nu \qquad (19)$$

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1α,25-Dihydroxyprevitamin D_3: Synthesis of the 9,14,19,19,19-Pentadeuterio Derivative and a Kinetic Study of Its [1,7]-Sigmatropic Shift to 1α,25-Dihydroxyvitamin D_3[1]

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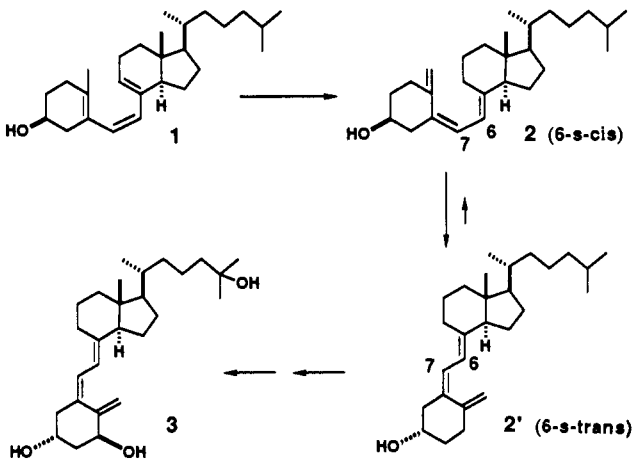
Abstract: The hormonally active steroid 1α,25-dihydroxyvitamin D_3 (**3**) exists in equilibrium with its previtamin form **5**. In an attempt to further understand the significance of this previtamin and previtamin D's in general, the pentadeuterio analogue of **5** was synthesized. Accordingly, 9,14,19,19,19-pentadeuterio-1α,25-dihydroxyprevitamin D_3 (**6**) was prepared from the readily available, optically active synthons (*S*)-(+)-carvone (**10**) and the Inhoffen-Lythgoe diol (**9**). A general method was developed to regioselectively deuteriate β-methyl-α,β-unsaturated aldehydes via their Schiff bases and was used in the synthesis to convert aldehyde **16a** to its deuteriated analogue **16b**. Thermolysis of **6** afforded 9,9,14,19,19-pentadeuterio-1α,25-dihydroxyvitamin D_3 (**24**). A kinetic investigation of the [1,7]-sigmatropic hydrogen (deuterium) shifts which convert previtamins **5** and **6** to vitamins **3** and **24**, respectively, revealed that at 25 °C the process proceeds with a relatively normal primary kinetic isotope effect, k_H/k_D, of 5.5.

Introduction

It is now well-established that a key step in the primary metabolic pathway leading to the physiologically active form of vitamin D, namely 1α,25-dihydroxyvitamin D_3 (**3**),[2] is the transformation of previtamin D_3 (**1**) to vitamin D_3 (**2** and **2'**) (Scheme I). This metabolic conversion, at least formally a [1,7]-sigmatropic hydrogen shift, has been well-studied in solution.

Scheme I



The intermediacy of the previtamin D_2 in the conversion of provitamin D_2 (ergosterol) to vitamin D_2 was first demonstrated

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