Evaluation of Kinetic Parameters. k_1 is equal to the slopes of the plots of $1/\tau$ vs. [RR'NH], under the conditions where eq 6 holds. Extrapolation of the lines of slope k_1 (dashed lines in Figures 2 and 3) to zero amine concentration provides $k_{-1}a_{H^+}/K_a^{XH}$; thus k_{-1}/K_a^{XH} is obtained as the slope of a plot of $k_{-1}a_{H^+}/K_a^{XH}$ vs. a_{H^+}.

The "true" intercepts (extrapolation of actual data points to zero amine concentration) obey eq 9 which is a special case of eq 5 where [RR'NH] = 0.

$$\text{intercept} = \frac{k_{-1}k_{-3p}^{S}}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{9}$$

Inversion of eq 9 affords eq 10

$$(\text{intercept})^{-1} = \frac{1}{k_{-3p}^{S}} + \frac{k_{3p}^{OH}}{k_{-3p}^{S}k_{-1}}a_{OH^-} \tag{10}$$

which describes a straight line with intercept = $1/k_{-3p}$ and slope = $k_{3p}^{OH}/k_{-3p}^{S}k_{-1}$. Thus k_{-3p}^{S} and k_{3p}^{OH}/k_{-1} could be obtained from plots according to eq 10 in all cases except for the *n*-butylamine reaction where $1/k_{-3p}^{S}$ was indistinguishable from zero.

For the determination of k_{-3p}^{AH} we proceeded as follows. At very low amine concentrations and low pH the second term on the right-hand side of eq 5 is dominant because the equilibrium position favors TNB over X^-. For example in the piperidine reaction the ratio $[X^-]/[TNB]$, which is equal to $K_1K_a^{HX}$·$[RR'NH]/a_{H^+}$, is 1.32×10^{-2} at pH 10.83 and an amine concentration of 0.02 M, or 3.09×10^{-2} at pH 11.20 for the same amine concentration. Since at low amine concentrations we also have $k_{3p}^{A}[RR'NH] \ll k_{-1}$, eq 5 simplifies to eq 11[39]

$$\frac{1}{\tau} = \frac{k_{-1}(k_{-3p}^{S} + k_{-3p}^{AH}[RR'NH]a_{H^+}/K_a^{AH})}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{11}$$

Thus the initial slopes at low pH are given by

$$\text{slope} = \frac{k_{-1}k_{-3p}^{AH}a_{H^+}/K_a^{AH}}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{12}$$

from which k_{-3p}^{AH} can be calculated.

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Registry No. 1,3,5-Trinitrobenzene, 99-35-4; dimethyl sulfoxide, 67-68-5; piperidine, 110-89-4; pyrrolidine, 123-75-1; *n*-$BuNH_2$, 109-73-9; dimethylamine, 124-40-3; methylamine, 74-89-5.

(38) $K_1K_a^{XH}[RR'NH]/a_{H^+}$ is equivalent to the ratio of the first over the second term in eq 5.

(39) $[RR'NH]a_{H^+}/K_a^{AH}$ is equivalent to $[RR'NH_2^+]$.

Solvolytic Reactivity of 6-(Chloromethyl)benzo[*a*]pyrene and Selectivity of Trapping of the Arylmethyl Cation by Added Nucleophiles

Robert E. Royer,[1a] Guido H. Daub,* and David L. Vander Jagt*[1b]

Departments of Biochemistry and Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

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The rate of solvolysis of the chemical carcinogen 6-(chloromethyl)benzo[*a*]pyrene in aqueous organic solvents is first order and independent of the presence of added nucleophiles, as expected for a carbonium ion reaction. The solvolytic reactivity of this arylmethyl chloride is comparable to that of compounds, such a *p,p'*-dimethylbenzhydryl chloride, which are known to form relatively stable carbonium ions. Evidence for the formation of a relatively stable carbonium ion in the solvolysis of 6-(chloromethyl)benzo[*a*]pyrene was obtained from the activation parameters ($\Delta S^{\ddagger} = -4.6$ eu) and from the presence of a marked common-ion effect when the solvolysis proceeded in the presence of LiCl. The nucleophilicities of a number of nucleophiles were measured kinetically in the presence of LiCl by their abilities to inhibit the common-ion effect in the solvolysis reaction. The selectivity of trapping of the arylmethyl cation shows the following order: aniline > N_3^- > Cl^- > *N*-acetylcysteine ≃ pyridine > *n*-propylamine > hydroxide > diethylamine > water. This set of nucleophiles ranges in nucleophilic strength (k_{Nu}/k_{H_2O}) from 3 for diethylamine to 1.7×10^3 for aniline. The products of trapping from the solvolysis of 6-(chloromethyl)benzo[*a*]pyrene enriched in carbon-13 at the methyl carbon were analyzed by ^{13}C NMR. There is a good correlation of chemical shifts of carbon in 6-(substituted-methyl)benzo[*a*]pyrenes and 1-substituted alkanes.

Although exact details of the mechanisms whereby chemicals cause cell transformation are not known for any chemical carcinogen, a number of generalizations have emerged from the studies of many investigators. It is now thought that most chemical carcinogens are strong electrophiles either as encountered in the environment or after metabolic activation within the target organism. This concept, developed primarily by Miller and Miller,[3] helps explain the carcinogenic properties of a large number of chemicals which have seemingly unrelated structures. In addition, it is widely believed that a critical event in the process leading to cell transformation is the covalent modification of cellular DNA by the carcinogenic electrophiles.[4] However, there does not appear to be a direct correlation between carcinogenicity and extent of covalent modification, suggesting that specificity of attack of nucleophilic sites by the carcinogenic electrophiles may be critical. The properties of known carcinogenic electrophiles

(1) (a) Taken in part from the Ph.D. thesis of R.E.R., submitted to the Graduate School of the University of New Mexico in partial fulfillment of the requirements for the Ph.D. degree, 1977. (b) Author to whom correspondence should be addressed at the Department of Biochemistry, University of New Mexico School of Medicine, Albuquerque, N.M. 87131. (c) This work was supported by NIH Grant CA 16871 and by a Research Career Development Award (CA 70939) to D.L.V.J., both grants from the National Cancer Institute.

(2) Abbreviations: 6-CMBP, 6-(chloromethyl)benzo[*a*]pyrene; 9-CMA, 9-(chloromethyl)anthracene.

(3) E. C. Miller and J. A. Miller, *Annu. Rev. Biochem.*, **28**, 291 (1959); J. A. Miller, *Cancer Res.*, **30**, 559 (1970).

(4) P. Brookes, *Life Sci.*, **16**, 331 (1974).

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indicate that the possibilities for electrophile–nucleophile reactions should range from limiting S_N2 reactions with relatively unreactive electrophiles to limiting S_N1 reactions involving electrophiles which can form fairly stable carbonium ions.

This paper describes some studies of the electrophile 6-(chloromethyl)benzo[a]pyrene (6-CMBP[2]) which under solvolytic conditions can form a resonance-stabilized arylmethyl cation. We view this as a model for carcinogenic electrophiles which function through a limiting S_N1 mechanism. 6-CMBP is a carcinogen[5] and, therefore, is a realistic model electrophile. Specifically, we report here on the methodology used to measure the abilities of various nucleophiles to trap the arylmethyl cation generated under solvolysis conditions and on the use of ^{13}C NMR spectroscopy to examine the products of the trapping reactions. The accompanying paper describes the application of this methodology to studies of the selectivity of reactions of the carbonium ion from 6-CMBP with nucleosides, deoxynucleosides, and nucleotides.[6]

Experimental Section

Materials. Benzo[a]pyrene was synthesized according to published procedures, with a few exceptions. Succinoylation of pyrene was carried out as described by Cook and Hewett.[7] The ketone functional group of the resulting β-(1-pyrenoyl)propionic acid was reduced by using the Huang–Minlon modification of the Wolff–Kishner reduction as described by Norman and Waters.[8] Cyclization of γ-(1-pyrenyl)butyric acid was carried out as follows: γ-(1-pyrenyl)butyric acid (70.8 g, 0.26 mol) was placed in a polyethylene beaker, and cold hydrogen fluoride (710 mL) was added. The mixture was stirred periodically while the hydrogen fluoride evaporated. The crude product was washed thoroughly with 5% sodium bicarbonate solution and was dried. Recrystallization from benzene afforded 54.7 g (82%) of product; mp 169–170 °C (lit.[9] mp 168–171 °C). The product, 7-oxo-7,8,-9,10-tetrahydrobenzo[a]pyrene, was reduced to 7-hydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene with aluminum isopropoxide in isopropyl alcohol, and the resulting alcohol was dehydrated and dehydrogenated by heating with palladium on charcoal, as described by Bachmann et al.[9]

6-(Substituted-methyl)benzo[a]pyrenes, either natural abundance or enriched in the methyl group with carbon-13, were prepared by formylation of benzo[a]pyrene with *N*-methylformanilide or *N*-methylformanilide-*1*-^{13}C. The resulting aldehydes were reduced to the alcohols with aluminum isopropoxide in isopropyl alcohol, and the alcohols were converted into the labeled or unlabeled 6-(chloromethyl)benzo[a]pyrene by using thionyl chloride. Experimental details for these reactions have been published.[10] 9-(Chloromethyl)anthracene (9-CMA[2]) was prepared by reduction of 9-anthraldehyde with aluminum isopropoxide and isopropyl alcohol followed by conversion of the alcohol to 9-CMA with thionyl chloride.[11]

Reaction Kinetics. The acetone was reagent grade and was used without further purification. Dioxane was redistilled immediately before using. Aqueous acetone and aqueous dioxane solutions for the solvolysis studies were made up volume to volume. Aniline, *N*-propylamine, and diethylamine were redistilled immediately before using. Pyridine, sodium azide, and lithium chloride were reagent grade and were used as purchased.

Reaction rates for solvolysis of 6-CMBP in various aqueous organic solvents, with or without added nucleophiles, were determined from changes in optical density followed with a Gilford-modified Beckman DU spectrophotometer, temperature controlled with a circulating-water bath. Generally, 20 μL of a 5 mM stock solution of 6-CMBP was added to 3 mL of solvent in a 1-cm cuvette to initiate the reaction. This was done with continuous recording of the spectrophotometer output such that less than 5 s were required to initiate the reaction and to begin to monitor the progress of the reaction. Using this procedure we could reproducibly follow reactions with half-lives as short as 10 s. For most kinetic measurements, the reactions could be followed at 409 nm where 6-CMBP has higher absorptivity (ϵ 1.69×10^4 M^{-1} cm^{-1}) than the corresponding alcohol and most of the products formed by trapping the carbonium ion with various nucleophiles. Rate constants were determined from least-squares slopes of plots of log absorbance change vs. time, where the experimental data were collected over a period of at least 3 half-lives. Correlation coefficients for first-order reactions were generally >0.999; rate constants were reproducible to better than ±5%. Absorption spectra of the various compounds were recorded with a Cary 15 spectrophotometer. 9-CMA was studied similarly to 6-CMBP except the reactions were followed at 391 nm and starting concentrations of 9-CMA were 8.33×10^{-5} M rather than the 3.33×10^{-5} M used for 6-CMBP.

^{13}C NMR Data. ^{13}C NMR spectra were recorded either with a Varian XL-100 CW/FT (Nicolet TT100 FT System) or with a Varian CFT-20 spectrometer on FT mode with proton decoupling. Up to 100 000 pulses were used, depending upon the concentration of the sample. An easily distinguishable peak could be obtained from a 5-mL sample of 6-(hydroxymethyl-^{13}C)-benzo[a]pyrene (enriched to 90% ^{13}C in the hydroxymethyl carbon) at a concentration of 8×10^{-4} M, using 100 000 pulses. Me_2SO-d_6 was used as solvent for measurement of all of the ^{13}C NMR spectra except in the case of the pyridinium salt where D_2O was used. Chemical shift values generally were measured relative to the Me_2SO-d_6 and are reported relative to Me_4Si by using the relationship $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.6$.[12] However, the chemical shift of 6-(anilinomethyl-^{13}C)benzo[a]pyrene was measured relative to added dioxane by using the relationship $\delta(Me_4Si) = \delta(\text{dioxane}) + 66.2$,[13] and the chemical shift of 1-(benzo[a]pyrenyl-6-methyl-^{13}C)pyridinium chloride was measured relative to added methanol by using the relationship $\delta(Me_4Si) = \delta(MeOH) + 48.0$.[14]

Preparation of Samples for ^{13}C NMR Measurements. 6-(Substituted-methyl)benzo[a]pyrenes were prepared from carbon-13-enriched 6-CMBP (6-CMBP-^{13}C)[2] according to the following procedures.

6-[(*n*-Propylamino)methyl-^{13}C]benzo[*a*]pyrene. *n*-Propylamine (0.3 g, 5 mmol) was dissolved in 5 mL of 80% acetone, and 6-CMBP-^{13}C (7.5 mg, 25 μmol) in 5 mL of acetone was added with stirring. After 1 h, 1 mL of 0.1 M NaOH was added, and most of the acetone was removed on a rotary evaporator. The remaining mixture was centrifuged, the supernatant was removed, and the residue was taken up in Me_2SO-d_6. This same procedure was used to prepare **6-(anilinomethyl-^{13}C)benzo[*a*]pyrene** by replacing *n*-propylamine with aniline (0.1 mL, 1.1 mmol). Likewise, essentially the same procedure was used for trapping with sodium azide (33 mg, 0.51 mmol) to prepare **6-(azidomethyl-^{13}C)benzo[*a*]pyrene**, for trapping with *N*-acetylcysteine (0.17 g, 1 mmol) to prepare ***N*-acetyl-*S*-(benzo[*a*]pyrenyl-6-methyl-^{13}C)cysteine**, and for trapping with triethylamine (0.51 g, 5 mmol) to prepare **(benzo[*a*]pyrenyl-6-methyl-^{13}C)triethylammonium chloride**, except that NaOH was not added. For preparation of **1-(benzo[*a*]pyrenyl-6-methyl-^{13}C)pyridinium chloride**, 6-CMBP-^{13}C (7.5 mg, 25 μmol) was dissolved in 1 mL of pyridine. After 1 h, 1 mL of water was added, and then acetone was added until the product began to crystallize. The mixture was centrifuged, the supernatant was decanted, and the residue was dissolved in 5 mL of D_2O containing 20 μL of methanol as a ^{13}C NMR reference.

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Table I. Solvolytic Reactivity of 6-(Chloromethyl)benzo[a]pyrene and 9-(Chloromethyl)anthracene in Aqueous Organic Solvents

substrate	solvent	t, °C	[LiCl], mM	k,[a] s⁻¹	ΔH‡, kcal mol⁻¹	ΔS‡, eu
6-CMBP	80% acetone	25	0	9.40×10^{-3}	18.6	−4.6
		43	0	5.96×10^{-2}		
		25	1	4.2×10^{-3}		
		25	10	1.1×10^{-3}		
		25	50	4.3×10^{-4}		
		25	100	3.3×10^{-4}		
		25	250	1.4×10^{-4}		
		25	500	9.2×10^{-5}		
	50% acetone	25	500	9.7×10^{-3}		
	50% dioxide	25	500	1.0×10^{-2}		
9-CMA	80% acetone	25	0	2.96×10^{-4}	21.0	−3.6
		44	0	2.63×10^{-3}		
	50% acetone	25	0	5.0×10^{-2}		
		25	5	3.7×10^{-2}		
		25	10	3.0×10^{-2}		
		25	50	1.3×10^{-2}		
		25	100	8.1×10^{-3}		
		25	300	4.9×10^{-3}		
		25	500	3.4×10^{-3}		

[a] Rate constants generally reproducible to better than ±5%.

Results

Solvolytic Reactivity of 6-CMBP. The solvolysis of 6-CMBP in 80% acetone strictly follows first-order kinetics, as expected for a reaction proceeding by rate-determining carbonium ion formation. The activation parameters (Table I), especially $\Delta S^{\ddagger} = -4.6$ eu, are in agreement with the conclusion that the reaction produces a fairly stable carbonium ion. The reaction rate follows the simple expression of eq 1. Since the starting con-

$$-\mathrm{d[6\text{-}CMBP]}/dt = k[\mathrm{6\text{-}CMBP}] \quad (1)$$

centration of 6-CMBP is low (3.33×10^{-5} M), the amount of chloride which can form during the reaction is also low. The rate of an S_N1 reaction proceeding as in eq 2, with k_1 as the rate-determining step, should become slower as the concentration of X^- builds up during the reaction. This "common-ion effect" will become significant if k_{-1} is not too small. Then the rate equation takes the form of eq 3. A comprehensive scheme for an S_N1 process (eq 4)

$$\mathrm{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+ + X^-} \xrightarrow[k_2[\mathrm{H_2O}]]{} \mathrm{ROH + H^+ + X^-} \quad (2)$$

$$\frac{-\mathrm{d[RX]}}{dt} = \frac{k_1[\mathrm{RX}]}{\frac{k_{-1}[\mathrm{X^-}]}{k_2[\mathrm{H_2O}]} + 1} \quad (3)$$

$$\begin{array}{ccccc} \mathrm{RX} & \rightleftharpoons & \mathrm{R^+X^-} & \rightleftharpoons & \mathrm{R^+} \| \mathrm{X^-} \rightleftharpoons \mathrm{R^+ + X^-} \\ & & \downarrow & & \downarrow \quad \downarrow \\ & & \mathrm{ROH} & & \mathrm{ROH} \quad \mathrm{ROH} \end{array} \quad (4)$$

should include tight ion pairs, solvent-separated ion pairs, and free carbonium ions. Water or other nucleophiles conceivably can react at various points in the reaction scheme. Whether or not one observes a common-ion effect depends upon the amount of free carbonium ion which forms in the process. If essentially free ions, R^+ and X^-, are formed, the law of mass action dictates that addition of X^- should enhance the reverse reaction to form RX and therefore slow down the solvolysis rate. The common-ion effect can be a useful index of carbonium ion stability.

Table II. Solvolytic Reactivity of 6-CMBP and 9-CMA Compared with That of Some Other Reactive Alkyl Chlorides in 80% Acetone–20% Water at 25 °C

substrate	k, s⁻¹	rel rate
triphenylmethyl chloride	8.8[a]	936
p,p′-dimethylbenzhydryl chloride	2.7×10^{-2} [a]	2.9
α-(9-anthryl)ethyl chloride	1.6×10^{-2} [a]	1.7
6-CMBP	9.4×10^{-3}	1
9-CMA	2.9×10^{-4}	1/32
benzhydryl chloride	7.0×10^{-5} [b]	1/134
α-(2-naphthyl)ethyl chloride	4.8×10^{-6} [c]	1/1958
tert-butyl chloride	2.0×10^{-6} [d]	1/4700

[a] Estimated value: D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **93**, 4821 (1971). [b] O. T. Benfy, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2488 (1952). [c] E. Berliner and N. Shieh, *J. Am. Chem. Soc.*, **79**, 3849 (1957). [d] A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).

Table I shows the results of studies of the effects of chloride ion on the rate of solvolysis of 6-CMBP, as evaluated by eq 3. There is a marked common-ion effect; solvolysis of 6-CMBP in 80% acetone containing 500 mM LiCl is depressed 100-fold. The rate depression is owing mainly to the common-ion effect rather than to an ionic-strength effect. A number of salts were checked for their effects on the rate of solvolysis of 6-CMBP. Generally they increase the rate of solvolysis by a few percent. For example, 100 mM NaN_3 increases the rate of solvolysis by 37%. $NaClO_4$ behaves similarly.

For a comparison, the rate of solvolysis of 9-CMA also was determined (Table I). Although the rate of solvolysis of this arylmethyl halide is slower than that of 6-CMBP, 9-CMA has a similar entropy of activation (−3.6 eu) and also has a significant common-ion effect. Thus both 6-CMBP and 9-CMA appear to produce fairly stable carbonium ions such that the assumption that "free" ions are involved appears reasonable. Table II compares the solvolysis rates of a number of halides which are generally considered to react by limiting S_N1 mechanisms. 6-CMBP is comparable in reactivity to *p,p′*-dimethylbenzhydryl chloride.

Trapping of Carbonium Ions by Azide Ion. Generally, solvolytic reactions which proceed by limiting S_N1 mechanisms will show rates which are independent of the presence of added nucleophiles, except for possible ionic-strength effects. However, the product distribution will reflect the presence of a nucleophilic (Nu) which is present to compete with water for the carbonium ion (eq 5).

$$\mathrm{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+ + X^-} \begin{array}{l} \xrightarrow[k_2]{\mathrm{H_2O}} \mathrm{ROH} \\ \xrightarrow[k_{\mathrm{Nu}}]{\mathrm{Nu}} \mathrm{RNu} \end{array} \quad (5)$$

Commonly, the relative nucleophilicities of added nucleophiles can be determined from the product composition. The nucleophilicity of azide ion in trapping the carbonium ion from 6-CMBP was determined as follows: In the absence of azide, the solvolysis of 6-CMBP in 80% acetone, followed at 409 nm, allows one to monitor formation of alcohol (ϵ_{409} 7.2×10^3 M^{-1} cm^{-1}). In the presence of 50 mM sodium azide, no alcohol is detectable by TLC and only 6-(azidomethyl)benzo[a]pyrene is formed (ϵ_{409} 1.1×10^4 M^{-1} cm^{-1}). When the initial concentration of 6-CMBP is 3.3×10^{-5} M and sodium azide is 2.0×10^{-4} M, the final optical density after the solvolysis reaction is 0.29, leading to the calculation in eq 6. The concentration of

$$\mathrm{OD} = \epsilon_{\mathrm{ROH}}[\mathrm{ROH}] + \epsilon_{\mathrm{RN_3}}[\mathrm{RN_3}] \quad (6)$$

$$0.29 = 7.2 \times 10^3[\mathrm{ROH}] + 1.1 \times 10^4(3.3 \times 10^{-5} - [\mathrm{ROH}])$$

$$[\mathrm{ROH}] = 1.9 \times 10^{-5}\ \mathrm{M}$$

$$[\mathrm{RN_3}] = 1.4 \times 10^{-5}\ \mathrm{M}$$

water in 80% acetone is approximately 11 M. Therefore, the nucleophilicity of azide relative to water is

$$\frac{[\mathrm{RN_3}]}{[\mathrm{ROH}]} = \frac{k_{N_3^-}[N_3^-]}{k_2[H_2O]} = \frac{k_{N_3^-}(2.0 \times 10^{-4}\ \mathrm{M})}{k_2(11\ \mathrm{M})} = \frac{1.4 \times 10^{-5}\ \mathrm{M}}{1.9 \times 10^{-5}\ \mathrm{M}} \quad (7)$$

therefore

$$k_{N_3^-}/k_2 = 4.1 \times 10^4$$

This means that azide ion is 41 000 times better than H_2O as a nucleophile for trapping the carbonium ion generated by solvolysis of 6-CMBP. If we use the convention that rate constants for reactions of R^+ with solvent are in units of s^{-1} and that those for reactions of R^+ with other nucleophiles are in units of $M^{-1}\ s^{-1}$, then we define

$$\frac{k_{N_3^-}}{k_2[H_2O]} = \frac{k_{N_3^-}}{k_{H_2O}} = 3.7 \times 10^3 \quad (8)$$

Kinetic Measurement of Nucleophilicities. If solvolysis through an S_N1 process leads to a stable carbonium ion and shows a significant common-ion effect, as is seen with 6-CMBP, then eq 3 can be evaluated for $k_{-1}/(k_2[H_2O])$ which for 6-CMBP would give k_{Cl^-}/k_{H_2O} for the selectivity of trapping by chloride of this carbonium ion. Solvolysis of 6-CMBP in 80% acetone containing 1 mM LiCl shows a rate constant, $k_{obsd} = 4.27 \times 10^{-3}\ s^{-1}$ compared to $k_1 = 9.40 \times 10^{-3}\ s^{-1}$ in the absence of the common ion. Substituting into eq 3 gives $k_{Cl^-}/k_{H_2O} = 1.2 \times 10^3$, assuming that the low concentration of chloride used in this measurement does not alter the rate significantly owing to an ionic-strength effect but rather involves only the common-ion effect. This high selectivity of chloride for the carbonium ion means that the term $k_{-1}[X^-]/(k_2[H_2O]) \gg 1$ if $[X^-]$ is sizable. Therefore

$$\frac{-d[RX]}{dt} = k_{obsd}[RX] = \frac{k_1[RX]}{\frac{k_{-1}[X^-]}{k_2[H_2O]} + 1} \simeq \frac{\frac{k_1[RX]}{k_{-1}[X^-]}}{k_{H_2O}} = \frac{k_1 k_{H_2O}[RX]}{k_{-1}[X^-]} \quad (9)$$

If a nucleophile is present during the solvolysis of RX, in addition to the common ion, the nucleophile (Nu) should compete both with X^- and with water for R^+ and thereby lower the amount of internal return by the common ion. Thus, a competing nucleophile should appear to inhibit the common-ion effect. Steady-state treatment gives eq 10 as the expression for k_{obsd}'. If $k_{-1}[X^-] \gg k_{H_2O}$ and $k_{-1}[X]$

$$k_{obsd}' = \frac{k_1 k_2[H_2O] + k_1 k_{Nu}[Nu]}{k_{-1}[X^-] + k_2[H_2O] + k_{Nu}[Nu]} = \frac{k_1 k_{H_2O} + k_1 k_{Nu}[Nu]}{k_{-1}[X] + k_{H_2O} + k_{Nu}[Nu]} \quad (10)$$

$\gg k_{Nu}[Nu]$, expression 10 reduces to eq 11. This would

$$k_{obsd}' = \frac{k_1 k_{H_2O} + k_1 k_{Nu}[Nu]}{k_{-1}[X^-]} \quad (11)$$

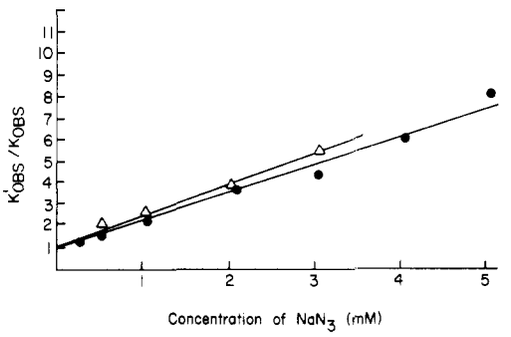

Figure 1. Effects of sodium azide on the solvolysis of 6-CMBP (●) and 9-CMA (△) in 50% acetone, 500 mM LiCl, plotted according to eq 12.

allow one to evaluate the nucleophilicites of a number of nucleophiles as follows (eq 12).

$$\frac{k_{obsd}'}{k_{obsd}} = \frac{\frac{k_1 k_{H_2O} + k_1 k_{Nu}[Nu]}{k_{-1}[X^-]}}{\frac{k_1 k_{H_2O}}{k_{-1}[X^-]}} = 1 + \frac{k_{Nu}[Nu]}{k_{H_2O}} \quad (12)$$

To test this, we evaluated the effects of sodium azide on the solvolysis of 6-CMBP in 50% acetone containing 500 mM LiCl. For this system, $k^{-1}[X^-]/(k_2[H_2O]) \simeq 240$ and thus the requirement that $k_{-1}[X^-] \gg k_{H_2O}$ is satisfied. Equation 11 was evaluated to test if $k_{-1}[X^-] \gg k_{Nu}[Nu]$ by examining for a linear relationship between k_{obsd}' and [Nu]. Figure 1 shows the effects of sodium azide on the common-ion effect, plotted according to eq 12. In the concentration range of 1–5 mM, k_{obsd}'/k_{obsd} vs. $[N_3^-]$ is linear. The slope, $k_{N_3^-}/k_{H_2O}$, is 1.42×10^3. This value would be 3.5×10^3 if the reaction were run in 80% acetone which agrees quite well with the value 3.7×10^3 determined above by looking at the product composition when only azide ion was present to trap the carbonium ion in competition with water. If eq 12 is applicable for a good nucleophile such as azide ion, this equation should be generally applicable to less powerful nucleophiles.

The nucleophilicities (k_{Nu}/k_{H_2O}) for a number of nucleophiles were measured by using this kinetic method of inhibition of the common-ion effect. The data are in Table III. The nucleophiles *n*-propylamine and hydroxide were tested both in 50% acetone and in 50% dioxane, both with 500 mM LiCl, in order to ensure that the possible reaction of these two nucleophiles with acetone did not perturb the results. The order of nucleophilicity is aniline > N_3^- > Cl^- > *N*-acetylcysteine ≃ pyridine > *n*-propylamine > OH^- > diethylamine > H_2O. Values of k_{Nu}/k_{H_2O} range from 1.7×10^3 for aniline to 3 for diethylamine.

Several nucleophiles were evaluated by using 9-CMA solvolysis, also in 50% acetone containing 500 mM LiCl (Table IV). Values of k_{Nu}/k_{H_2O} are smaller in this system although the same order exists as was found with 6-CMBP. This result suggests that the principle of reactivity–selectivity whereby more reactive reagents are less selective[15] is applicable to the trapping of these two carbonium ions. This is in marked contrast to recent studies by Ritchie involving highly stable cations which were shown to exhibit selectivities for nucleophiles which were independent of the cations.[16]

(15) For a review of the reactivity–selectivity principle see A. Pross, *Adv. Phys. Org. Chem.*, **14**, 69 (1977).
(16) C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170 (1975), and references therein.

Table III. Selectivity of Trapping of the Carbonium Ion Generated by Solvolysis of 6-CMBP[a]

nucleophile	concn, mM	k_{obsd},[b] s^{-1}	k_{Nu}/k_{H_2O}[c]
aniline	1	2.6×10^{-2}	1.7×10^{3}
sodium azide	1	2.2×10^{-2}	1.4×10^{3}
lithium chloride			4.8×10^{2}[d]
N-acetylcysteine	10	1.4×10^{-2}	40
pyridine	10	1.4×10^{-2}	40
n-propylamine	100	2.9×10^{-2}	20
sodium hydroxide	100	2.5×10^{-2}	16
diethylamine	100	1.3×10^{-2}	3
n-propylamine[e]	100	3.9×10^{-2}	29
sodium hydroxide[e]	100	3.0×10^{-2}	20

[a] Solvolysis in 50% acetone containing 500 mM LiCl at 25 °C. [b] Rate constants are reproducible to better than ±5%. [c] k_{Nu}/k_{H_2O} is the second-order rate constant for reaction of R^+ with Nu divided by the first-order constant for reaction of R^+ with H_2O as in eq 12. [d] Calculated from the common-ion effect at 1 mM LiCl (Table I) corrected to 50% acetone. [e] Run in 50% dioxane containing 500 mM LiCl at 25 °C.

Table IV. Selectivity of Trapping of the Carbonium Ion Generated by Solvolysis of 9-CMA[a]

nucleophile	concn, mM	k_{obsd},[b] s^{-1}	k_{Nu}/k_{H_2O}[c]
sodium azide	1	8.7×10^{-3}	1.6×10^{3}
lithium chloride			70[d]
N-acetylcysteine	10	4.3×10^{-3}	30
n-propylamine	100	4.9×10^{-3}	4
sodium hydroxide	100	5.5×10^{-3}	6
diethylamine	100	4.8×10^{-3}	4
triethylamine	100	3.6×10^{-3}	1

[a] Solvolysis in 50% acetone containing 500 mM LiCl at 25 °C. [b] ±5%. [c] See eq 12. [d] From Table I.

Table V. Chemical Shifts of the Labeled Arylmethyl Carbons in Some Derivatives of 6-(Methyl-^{13}C)benzo[*a*]pyrene

compd	chem shift[a]
6-(methyl-^{13}C)benzo[*a*]pyrene	14.3
6-(chloromethyl-^{13}C)benzo[*a*]pyrene	39.5
6-[(*n*-propylamino)methyl-^{13}C]benzo[*a*]pyrene	45.6
6-(hydroxymethyl-^{13}C)benzo[*a*]pyrene	55.8
N-acetyl-*S*-(benzo[*a*]pyrenyl-6-methyl-^{13}C)-cysteine	29.6
6-(anilinomethyl-^{13}C)benzo[*a*]pyrene	40.2
6-(azidomethyl-^{13}C)benzo[*a*]pyrene	46.5
1-(benzo[*a*]pyrenyl-6-methyl-^{13}C)-pyridinium chloride	55.2
(benzo[*a*]pyrenyl-6-methyl-^{13}C)-triethylammonium chloride	56.8

[a] Chemical shifts downfield from Me_4Si.

Carbon Chemical Shifts of 6-(Substituted-methyl)benzo[*a*]pyrenes. Several derivatives of 6-methylbenzo[*a*]pyrene enriched with carbon-13 in the methyl carbon were prepared either synthetically or by trapping of the carbonium ion produced by solvolysis of ^{13}C-enriched 6-CMBP. The chemical shifts of these products, relative to Me_4Si, are given in Table V. Table VI lists some reported or calculated chemical shifts for substituted methanes. Of interest to us is the question of a correlation of chemical shifts in these two systems. Figure 2 shows a correlation diagram for the carbon chemical shifts of substituted methanes plotted against those for derivatives of 6-methylbenzo[*a*]pyrene. A linear relationship exists, suggesting that reported chemical shifts which can be correlated with substituted methanes and other substituted alkanes also can be correlated with derivatives of 6-methylbenzo[*a*]pyrene.

Table VI. Chemical Shifts of the Methyl Carbons in Substituted Methanes Relative to Me_4Si

compd	chem shift	compd	chem shift
methane	−2.3[a]	methanol	48.0[d]
chloromethane	24.9[b]	dimethyl sulfide	19.5[e]
methylpropylamine	33.8[c]	*N*-methylaniline	30.2[f]

[a] D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964). [b] W. M. Litchman and D. M. Grant, *ibid.*, **90**, 1400 (1968). [c] Estimated to be equal to methylisobutylamine: L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, 1972. [d] E. Breitmaier, G. Haas, and W. Voelter, "Atlas of Carbon-13 NMR Data", Heyden and Son, Ltd, London, 1975. [e] H. Spiesecke and W. G. Schneider, *J. Phys. Chem.*, **35**, 722 (1961). [f] Reference *c*.

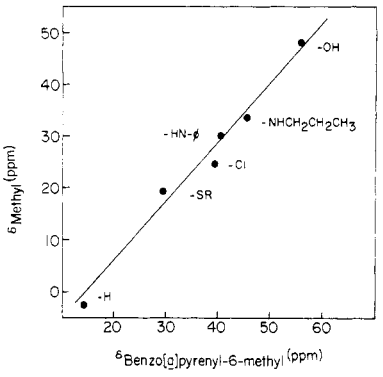

Figure 2. Correlation diagram of the carbon chemical shifts (parts per million downfield from Me_4Si) of substituted methanes and 6-(substituted-methyl)benzo[*a*]pyrenes.

Discussion

The observation of a strong common-ion effect in solvolytic reactions of alkyl halides has been used as an argument for the formation of relatively stable carbonium ions.[17] The observation of a common-ion effect will depend both upon the formation of an essentially free carbonium ion and upon the rate of the reverse reaction, $k_{-1}[X^-]$ in eq 5. The arylmethyl carbonium ion from 6-CMBP shows high reactivity toward chloride ion, resulting in a strong common-ion effect. The term $k_{-1}[Cl^-]$ at 500 mM concentration of lithium chloride is large enough to dominate the other terms in the denominator of eq 10, leading to a simple expression (eq 12) which is useful for obtaining a kinetic measurement of nucleophilicity.

Salts, other than chlorides, do not significantly alter the rate of solvolysis of 6-CMBP. For example, NaN_3 and $NaClO_4$ both show the same small effect on the solvolysis rate. Since N_3^- is a powerful nucleophile and ClO_4^- is a weak nucleophile, these similar small effects on the solvolysis rate must represent an ionic-strength effect. There is no indication that nucleophiles such as N_3^- are contributing to the rate of disappearance of 6-CMBP by an S_N2 process. The rate data suggest that the disappearance of 6-CMBP is strictly an S_N1 process. In addition, the fact that the nucleophilicity of N_3^- determined kinetically by the method of inhibition of the common-ion effect agrees very well with the value determined by analysis of the product composition allows one to conclude that the solvolysis of 6-CMBP proceeds mainly through an es-

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed., Cornell University Press, Ithaca, N.Y., 1969.

Table VII. Comparison of Selectivity (log $[k_{Nu}/k_{H_2O}]$) for the 6-CMBP- and 9-CMA-Derived Carbonium Ions with N_+ Values

nucleophile	log $[k_{Nu}/k_{H_2O}]$ (6-CMBP)	log $[k_{Nu}/k_{H_2O}]$ (9-CMA)	N_+[a]
aniline	3.23		4.10
azide	3.15	3.20	7.6
chloride	2.68	1.85	
N-acetylcysteine	1.60	1.48	
pyridine	1.60		5.00
n-propylamine	1.30	0.60	5.55
hydroxide	1.30	0.78	4.75
diethylamine	0.48	0.60	
triethylamine		0.0	
fluoride			>3.45
piperidine			6.11

[a] N_+ values, from ref 16, refer to log $[k_{Nu}/k_{H_2O}]$ for reactions in water.

sentially free carbonium ion rather than through ion pairs (eq 13). That is, if tight ion pairs or solvent-separated ion pairs are formed in addition to the free carbonium ion, there is no evidence that the added nucleophiles trap the carbonium ion except in its free form.

$$RX \rightleftharpoons R^+X^- \rightleftharpoons R^+||X^- \rightleftharpoons R^+ + X^- \xrightarrow{Nu} RNu \quad (13)$$

The selectivity values (k_{Nu}/k_{H_2O}) determined by trapping the carbonium ion from 6-CMBP with various nucleophiles are similar in order to those observed with 9-CMA and generally are larger (Tables III and IV). This observation is in agreement with the reactivity–selectivity principle.[15] The classic work of Swain and co-workers[18,19] on the nucleophilicities of various bases participating in S_N2 and S_N1 reactions showed that the order one observes in studies of S_N2 processes may be quite different from the order one observes in S_N1 processes. However, for both series, polarizability of the base appears to be an important factor. Sneen and co-workers[20] have investigated the selectivity of azide in reactions with carbonium ions and observed an apparent correlation between carbonium ion stability and selectivity for azide.

Recently Ritchie has described several stable cation systems whose reactivities with a wide range of nucleophiles appear to be independent of the cation.[16] These systems are correlated very well by the simple expression 14, where N_+ is a constant characteristic of a given nu-

$$\log k = \log k_0 + N_+ \quad (14)$$

cleophile, k is a rate constant for reaction of the cation with the nucleophile, and k_0 is a rate constant for reaction of the cation with water. Pross has discussed these results with reference to whether they represent a failure of the reactivity–selectivity principle and has suggested that the constant selectivity observed in the N_+ relationship results from the cancellation of two opposing effects; the strong solvation of a reactive electrophile would tend to increase selectivity while the reactant-like nature of the transition state for a reactive electrophile would tend to decrease selectivity.[21] The cation systems studied by Ritchie include aryldiazonium ions and triarylmethyl cations[16] which are much more stable than the carbonium ion from 6-CMBP, even though the carbonium ion from 6-CMBP also participates as a free carbonium ion in its reaction with nucleophiles. Table VII compares the selectivities observed with 6-CMBP and 9-CMA with N_+ values. The magnitudes and order differ considerably. Therefore, it appears reasonable to conclude that limiting S_N1 reactions which produce stable cations represent a broad range in reactivity–selectivity values, and the systems studied by Ritchie represent a limiting subgroup where the selectivity is constant. There are other studies which appear to violate the reactivity–selectivity principle.[22] Consequently, at present this principle is not as firm as it once appeared to be. Certainly caution should be used in trying to use this principle to draw conclusions about transition-state geometry.[23,24] Even in studies with closely related electrophiles, such as 6-CMBP and 9-CMA (Table VII), which appear to follow the reactivity–selectivity principle, the order of nucleophilicities does not appear to be predictable. Thus, for example, our results indicate aniline to be an unusually effective nucleophile compared to results observed by Ritchie[16] and by Swain.[19] The possibility of an association between aniline and the aromatic rings of the carbonium ions from 6-CMBP and 9-CMA is being considered although we have no evidence to support this idea.

The correlation diagram[25] in Figure 2 shows a good linear relationship between the carbon chemical shifts of substituted 6-methylbenzo[a]pyrenes and substituted methanes. It is well-known that chemical shift values predicted from substituent effects agree better with longer alkanes than with methanes or ethanes. The good correlation shown in Figure 2 allows one to expect that any chemical shifts which can be compared to those for substituted methanes will represent useful reference points for the substituted 6-methylbenzo[a]pyrenes. The use of this correlation to aid in the assignment of structures is developed more fully in the accompanying paper.

Registry No. 6-CMBP, 49852-84-8; 9-CMA, 24463-19-2; triphenylmethyl chloride, 76-83-5; *p,p'*-dimethylbenzhydryl chloride, 13389-70-3; α-(9-anthryl)ethyl chloride, 60302-14-9; benzhydryl chloride, 90-99-3; α-(2-naphthyl)ethyl chloride, 58464-06-5; *tert*-butyl chloride, 507-20-0; aniline, 62-53-3; sodium azide, 26628-22-8; lithium chloride, 7447-41-8; *N*-acetylcysteine, 616-91-1; pyridine, 110-86-1; *n*-propylamine, 107-10-8; sodium hydroxide, 1310-73-2; diethylamine, 109-89-7; triethylamine, 121-44-8; 6-(methyl-^{13}C)benzo[a]pyrene, 61655-09-2; 6-(chloromethyl-^{13}C)benzo[a]pyrene, 61655-10-5; [(6-propylamino)methyl-^{13}C]benzo[a]pyrene, 70682-16-5; 6-(hydroxymethyl-^{13}C)benzo[a]pyrene, 62084-24-6; *N*-acetyl-*S*-(benzo[a]pyrenyl-6-methyl-^{13}C)cysteine, 70682-17-6; 6-(anilinomethyl-^{13}C)benzo[a]pyrene, 70682-18-7; 6-(azidomethyl-^{13}C)benzo[a]pyrene, 70682-19-8; 1-(benzo[a]pyrenyl-6-methyl-^{13}C)pyridinium chloride, 70682-20-1; (benzo[a]pyrenyl-6-methyl-^{13}C)triethylammonium chloride, 70682-21-2; fluoride, 16984-48-8; piperidine, 110-89-4; benzo[a]pyrene, 50-32-8; β-(1-pyrenoyl)propionic acid, 7499-60-7; γ-(1-pyrenyl)butyric acid, 3443-45-6; 7-oxo-7,8,9,10-tetrahydrobenzo[a]pyrene, 3331-46-2; 7-hydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, 6272-55-5; *N*-methylformanilide, 93-61-8; *N*-methylformanilide-1-^{13}C, 61655-07-0; 6-formylbenzo[a]pyrene, 13312-42-0; 6-(formyl-^{13}C)benzo[a]pyrene, 61655-08-1; 6-(hydroxymethyl)benzo[a]pyrene, 21247-98-3; 9-anthraldehyde, 642-31-9; 9-(hydroxymethyl)anthracene, 1468-95-7.

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