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Reactions of Carbocations with a Functionalized Hydrophobic Ammonium Ion

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At high pH (2-hydroxyethyl)tri-*n*-octylammonium bromide and mesylate 2 react readily with Malachite Green or Crystal Violet to give the corresponding ethers. Reaction is promoted by association of the carbocations with clusters of 2 and involves the nucleophilic zwitterion of 2. Reactions are considerably faster than those with OH^- or the cholinate zwitterion, but second-order rate constants in the clusters are lower than in micelles of (2-hydroxyethyl)dimethylhexadecylammonium bromide (1) by a factor of ca. 4.

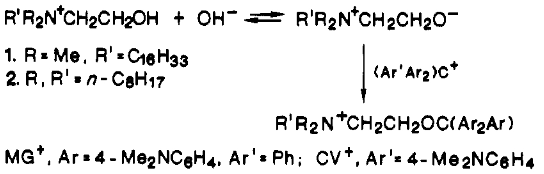
Micellar effects upon reactions of nucleophiles with performed carbocations have been extensively studied.[1–6] Anionic attack upon preformed carbocations, e.g., Malachite Green (MG) or Crystal Violet (CV), is assisted by cationic micelles. The unfavorable Coulombic interactions between the micelles and the carbocations, with their delocalized charge, are offset by hydrophobic attractions, so that reactants are brought together at the micellar surface.[4,5,7] Functional micelles of the hydroxyethyl surfactant I are also effective reagents toward carbocations at high pH (Scheme I) and attack of the zwitterion generates ether.[6]

Hydrophobic quaternary ammonium ions 3 interact with functionalized surfactants containing oxime or hydroxamate groups to give effective deacylating agents.[8] The

$$(C_8H_{17})_3N^+R$$
$$\mathbf{3},\ R = Me,\ Et$$

ammonium ions 3 do not micellize, although they are surface active, but they sharply speed nucleophilic displacements,[8] including dephosphorylation by areneimidazolide ions.[9] The reaction involves interaction between cation, imidazolide ion, and phosphate ester giving a reactive complex. This complex is probably a small hydrophobic cluster, and, as with micelles, the rate enhancement is due to reactants being brought into close proximity.

Scheme I



$$R'R_2N^+CH_2CH_2OH + OH^- \rightleftharpoons R'R_2N^+CH_2CH_2O^- \xrightarrow{(Ar'Ar_2)C^+} R'R_2N^+CH_2CH_2OC(Ar_2Ar)$$

The aim of our present work was to examine reactions of preformed carbocations with nonmicellizing hydroxyethyl derivatives 2. Coulombic repulsions disfavor binding of ions of like charge, but cationic micelles, which are large macroions, effectively bind MG^+ and CV^+ because of hydrophobic and dispersive attractions.[1–6] This might not be the case with tri-*n*-octylalkylammonium ions 2 which probably form small clusters,[8] so that carbocations may bind only weakly. At high pH the cholinate zwitterion reacts with MG^+ and is a suitable model for reactions of a monomeric hydroxyethyl derivative.[6]

At high pH the (hydroxyethyl)ammonium ions 2 are deprotonated and their alkoxide zwitterions are effective

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Table I. Second-Order Rate Constants for Fading of Malachite Green[a]

H_2O, wt %	100	90	80	70
k_2, M^{-1} s^{-1}	1.59	1.11	0.96	0.87

[a] At 25.0 °C with 0.01–0.08 M NaOH in H_2O/MeCN. For reaction of Crystal Violet in 80 wt % H_2O, k_2 = 0.80 M^{-1} s^{-1}.

nucleophiles toward phosphate esters and nitrochloroarenes.[11]

Experimental Section

Materials. The carbocations were commercial samples, and the preparation of the other materials has been described.[11] Reaction solvents were made up with redistilled CO_2 free water.

Products. The formation of ether rather than alcohol (Scheme I) was demonstrated by carrying out the reaction under kinetic conditions, except that [MG^+] was 6.5 × 10^{-4} M. The solvent was H_2O/MeCN (80:20, w/w) containing 0.02 M OH^- and 0.01 M **2** as its bromide salt. After 6 half-lives (ca. 30 s) excess $NaClO_4$ in H_2O/MeCN (80:20, w/w) was added, and the white precipitate of perchlorate salt was removed by filtration and washed (H_2O). The dried precipitate was dissolved in EtOH, and the solution was made slightly acidic with 10^{-3} M HCl to convert ether into carbocation. The color of MG^+ immediately appeared, and the solutions had λ_{max} at 616 nm.

As a control, the experiment was repeated by using tri-*n*-octylethylammonium mesylate instead of **2**. No color appeared on acidification of the precipitate, showing that coprecipitation of the alcohol was not a problem. The filtrate gave the characteristic color of MG^+ upon acidification, because reaction via solution of a nonfunctional ammonium ion gave a triarylmethanol.

Kinetics. Fading of MG^+ and CV^+ was followed spectrophotometrically at 616 and 590 nm, respectively.[2,4,12]

Substrate concentrations were 6.5 × 10^{-6} M, the solvent was H_2O/MeCN(80:20, w/w) because of solubility problems in H_2O, and the temperature was 25.0 °C. Reactions went to completion under our conditions. Both bromide and mesylate salts **2** were examined, but the bromide is only sparingly soluble so most work was done with the mesylate.

The slower reactions were followed in Gilford or Beckman spectrophotometers, and the faster in a Durrum stopped-flow spectrophotometer. The first order rate constants, k_ψ, are in reciprocal seconds.

Results and Discussion

Second-order rate constants (k_2) for reaction of the carbocations with OH^- in aqueous media are in Table I. The rate constants in water are in satisfactory agreement with literature values.[6,12] Addition of MeCN slows reaction although qualitative solvent theory predicts a rate increase and anionic nucleophilicities generally increase on addition of organic solvents to water. Ritchie has noted the possibility that OH^-, acting as a general base, catalyzes attack of a water molecule on a carbocation which is consistent with the solvent effect.[12]

Tri-*n*-octylalkylammonium salts are sparingly soluble in water, and even with very dilute **2** there was precipitation in the course of reaction, probably due to ether formation (Scheme I and Experimental Section). Reactions with **2** were therefore followed in H_2O/MeCN (80:20, w/w). Ether formation shows that the alkoxide moiety is the nucleophile rather than OH^- (Scheme I). This reaction is similar to that of cholinate zwitterion with MG^+.[6] However, reaction in solutions of **2** is faster than that with choline under similar conditions. For example in H_2O at 25.0 °C, k_ψ = 0.11 s^{-1} for reaction of MG^+ with 0.05 M choline and 0.0416 M NaOH,[6] whereas in H_2O/MeCN (80:20, w/w) $k_\psi \approx$ 1 s^{-1} for reaction with 0.04 M **2** and 0.05 M NaOH (Figure 1). The higher reactivity of the tri-*n*-octyl derivative **2** as compared with choline suggests that

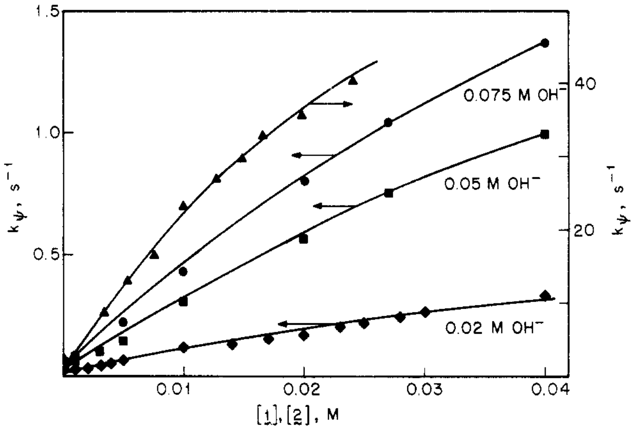

Figure 1. Reaction of Malachite Green with **2** (mesylate salt) in NaOH and H_2O/MeCN (80:20, w/w) (◆, ■, ●). Reaction of MG^+ with micelles of **1** in aqueous 0.042 M NaOH (▲). Lines are calculated (eq 1).

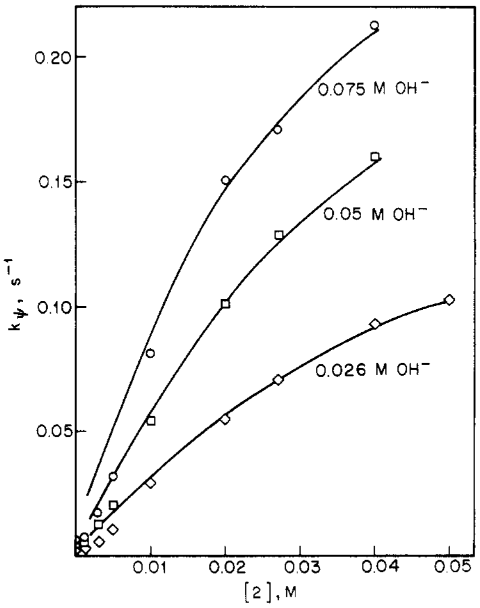

Figure 2. Reaction of Crystal Violet with **2** (mesylate salt) in NaOH and H_2O/MeCN (80:20 w/w) (◇, □, ○). Lines are calculated (eq 1).

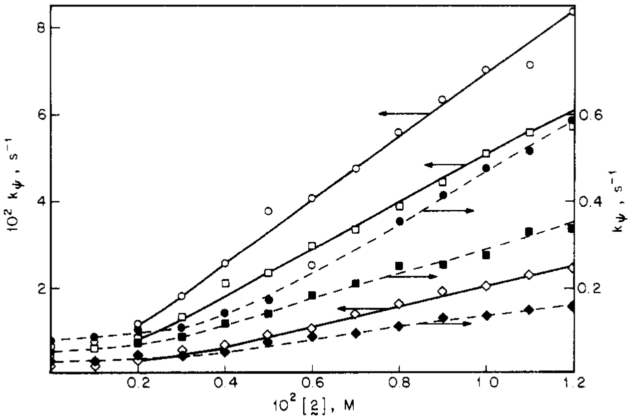

Figure 3. Reactions of Malachite Green (broken lines, solid points) and Crystal Violet (solid line, open points) with **2** (bromide salt): ○, ●, 0.075 M OH^-; □, ■, 0.05 M OH^-, ◇, ◆, 0.02 M OH^-.

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Table II. Binding and Rate Constants for Carbocation Reactions[a]

substr	[NaOH], M	K_s, M^{-1}	k'_M, s^{-1}	k_M,[b] s^{-1}
MG^+	0.020	10	1.1	26
MG^+	0.050	10	3.3	33
MG^+	0.075	12	4.0	29
CV^+	0.026	20	0.20	4
CV^+	0.050	25	0.30	3
CV^+	0.075	40	0.33	4
MG^{+c}	0.042	35	90	132

[a] At 25.0 °C in H_2O/MeCn (80:20, w/w) with **2**, unless specified. [b] Corrected for partial deprotonation with $pK_b = 0.34$ and 1.7 for **2** and **1**, respectively.[11a,17] [c] Reaction in water with 0.001–0.026 M *1*.[6]

hydrophobic interactions due to the bulky *n*-octyl groups are assisting reaction.

Rates increase with increasing [**2**] (Figures 1–3) and in solutions of the mesylate (Figures 1 and 2) tend toward, but do not reach, limiting values, with inflections at low concentrations of the ammonium ion. The rate increases, and the inflections in dilute **2** (Figures 1–3), are similar to those found for reactions of *p*-nitrophenyl diphenyl phosphate and 2,4-dinitrochloronaphthalene, but these hydrophobic substrates bind readily to clusters of **2**, and limiting values of k_ψ, corresponding to extensive substrate binding, were observed.[11a]

Only dilute bromide salt could be used and there was little curvature of the plots above 3×10^{-3} M salt (Figure 3). Counterions have large effects upon micellar-mediated bimolecular reactions of hydrophilic ions,[7] but values of k_ψ were insensitive to the nature of the counterion. Replacement of mesylate by bromide ion slows bimolecular reactions of anions in micelles because bromide ion binds strongly to the micelle and tends to exclude anionic reagents. It appears that hydrophilic anions do not bind strongly to clusters of nonmicellizing ammonium ions.

Variations of k_ψ with **2** at a given [NaOH] can be fitted reasonably well to eq 1, which is similar to the equations applied to many micellar-mediated reactions[7,13,14] where

$$k_\psi = \frac{k'_w + k'_M K_s[\mathbf{2}]}{1 + K_s[\mathbf{2}]} \qquad (1)$$

k'_w and k'_M are first-order rate constants of free and bound substrate and K_s is a binding constant of substrate toward **2**. The first-order rate constants, k'_w and k'_M will depend upon $[OH^-]$, but K_s is assumed to be independent of the state of aggregation of **2**.[11] This treatment was not applied to reactions in the bromide salt (Figure 3) because its low solubility restricted its concentration.

The fits of the data to eq 1, based on computer simulation, are shown in Figures 1 and 2 based on the parameters in Table II. Despite the approximations in eq 1 the fitting of observed to calculated rate constants is reasonably good for reactions in the mesylate salt of **2** (Figures 1 and 2), but there are deviations in dilute **2** because eq 1 does not account for the inflections. Multiple equlibrium models give better fits for reactions of strongly bound substrates,[15] but we do not have sufficient data to test them for reactions of the weakly bound carbocations, and we use eq 1 despite its limitations. The treatment assumes that K_s is independent of the concentration of ammonium ion, and this assumption is satisfactory for reactions in aqueous micelles because micellar structure does not change rapidly with [surfactant].[7,13] We do not know the state of aggregation of tri-*n*-octylalkylammonium ions, although Kunitake and co-workers have postulated formation of tetramers.[8]

Equation 1 was also applied to reaction of MG^+ with micellized (2-hydroxyethyl)dimethylhexadecylammonium bromide (**1**) (Figure 1). The fits in Figures 1 and 2 are reasonably good despite assumptions regarding binding of the carbocations to micelles of **1** (or clusters of **2**). Rate and equilibrium parameters calculated by using eq 1 are in Table II. Our assumption of constant K_s is reasonably satisfactory for MG^+, but K_s increases with $[OH^-]$ for the more hydrophobic CV^+ with its more delocalized charge. Various factors could be involved in the variation of K_s: (i) deprotonation of **2** will assist binding of the carbocations, (ii) added OH^- could increase the size of clusters of **2**, and (iii) OH^- could "salt-out" the carbocations from bulk solvent into the clusters. This "salting-out" has been postulated for micellar-mediated reactions in aqueous micelles.[16] Because of their larger size, micelles bind carbocations better than clusters of **2**, at a given ammonium ion concentration.

The first-order rate constants k'_M (eq 1) depend upon the extent of deprotonation of the hydroxyl group (Scheme I), and apparent dissociation constants $K_b$app (eq 2) have

$$[RO^-]/[ROH_T] = [OH^-]/([OH^-] + K_b\text{app}) \qquad (2)$$

$$R = (C_8H_{17})_3N^+CH_2CH_2 \text{ or } C_{16}H_{33}N^+Me_2CH_2CH_2$$

been estimated in other, similar, systems.[11,17] In our experiments with MG^+ and CV^+, we can neglect the contributions of reactions with OH^- or in water at higher concentration of **2** and write k'_M as in eq 3.

$$k'_M = k_M[RO^-]/[ROH] \qquad (3)$$

These assumptions, as applied to reactions of nonionic substrates, are discussed more fully in ref 11, and values of pK_b (apparent) are in Table II which also includes values of k'_M and k_M for reactions in the mesylate salt of **2** and in micelles of **1**.

The second-order rate constants k_M (eq 3) are calculated with the concentration of alkoxide ion as a mole ratio with respect to total amphiphile.[4] They therefore cannot be compared directly with second-order rate constants for reactions with OH^-, or the cholinate zwitterion, in water. For micelles the comparison can be made by estimating the molar volume element of reaction, and estimates range from 0.14 to 0.37 L.[4,7,18] The lower value has been used in analyzing kinetic data for micelles of the hydroxyethyl surfactant **1**,[11] and we use it here, so that

$$k_2^m = 0.14k_M \qquad (4)$$

For reaction of MG^+ in micelles of **1**, $k_2^m = 18.5\ M^{-1}\ s^{-1}$ which is not much larger than the second-order rate constant for reaction with cholinate zwitterion in water which is $4.7\ M^{-1}\ s^{-1}$,[19] based on $pK_a = 12.8$ in water.[20]

Therefore, as with many micellar-assisted bimolecular reactions, the rate increase is due largely to increased

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reactant concentration at the micellar surface. The relatively small difference between the second-order rate constants in water and in the functional micelles may be due to a relief of the Coulombic repulsions between the carbocation and the micellar cationic head groups in the transition state.

We have no estimate of the molar volume element of reaction in clusters of **2**, but k_M in these clusters is not much smaller than in micelles of **1** (Table II), despite differences in the solvents, so that the factors which control reactivity in micelles are at work in these hydrophobic clusters. Transition-state stabilization, or activation of the anionic nucleophile by cationic micelles or hydrophobic clusters, seems to be relatively unimportant, as compared with the concentration effect, as is general for micellar rate enhancements.[21] The overall reaction of MG^+ with **2** is faster than that with choline in H_2O by a factor of almost 10 (Figure 1 and ref 6), and the difference would probably have been greater if reaction with **2** could have been followed in H_2O instead of in $H_2O/MeCN$. Addition of an organic solvent slows reactions assisted by hydrophobic tri-*n*-octylalkylammonium ions, probably by reducing substrate binding to the clusters.[11]

The pseudophase model readily accommodates chemical reactivity in micelles and many of the physical properties of aqueous micelles, and it can be applied to reactions in solutions of hydrophobic ammonium ions and to reactions in a variety of "organized assemblies".[24,25]

Acknowledgment. Support of this work by the National Science Foundation (Organic Chemical Dynamics Program) is gratefully acknowledged.

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Stereochemistry of the Reaction of 7-Substituted Norbornadienes with Iron Carbonyls. 3. Reaction of $Fe(CO)_5$ with 7-(Benzoyloxy)norbornadiene

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Thermal reaction of 7-(benzoyloxy)norbornadiene with iron pentacarbonyl affords a cage dimer, 7,12-bis(benzoyloxy)heptacyclo[$6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}$]tetradecane (**1**, 29%), an anti,exo,trans,endo,anti (AXTNA) dimer ketone (**2**, 1%), a syn,endo,trans,endo,syn (SNTNS) dimer ketone (**3**, 2%), an anti,exo,trans,exo,anti (AXTXA) dimer ketone (**4**, 3%), and a novel cage dimer ketone (**5**, 0.4%). The structures of **2** and **3** were established via single-crystal X-ray structural analysis. The structures of **4** and **5** were gleaned via analysis of the proton and carbon-13 NMR spectra of these compounds. Thermal reaction of 7-[(*p*-methoxybenzoyl)oxy]norbornadiene (**6**) with $Fe(CO)_5$ afforded the corresponding cage dimer (**7**, 23%) and an anti,exo,trans,exo,anti (AXTXA) dimer ketone (**8**, 4%). The regiospecificity that has been noted previously in the case of $Fe(CO)_5$-promoted coupling of 7-*tert*-butoxynorbornadiene to carbon monoxide clearly is not a feature of the corresponding reactions reported herein.

As part of a continuing program that is involved with the study of the stereochemistry and mechanism of thermal reactions of iron pentacarbonyl with 7-substituted norbornadienes,[1-3] we have recently examined the reaction of $Fe(CO)_5$ with 7-(benzoyloxy)norbornadiene. In earlier work, we have exploited the $Fe(CO)_5$-promoted cyclodimerization of 7-substituted norbornadienes for the purpose of synthesizing novel, substituted heptacyclo[$6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}$]tetradecanes.[4-6] In addition, we have shown that the presence of a 7-Lewis base substituent in norbornadiene dramatically affects the stereochemical outcome of its $Fe(CO)_5$-promoted coupling to carbon monoxide.[2,3] The present study was undertaken in an effort to further delineate the role of the syn-7-Lewis base substituent in directing the course of this interesting coupling reaction.

In general, $Fe(CO)_5$-promoted coupling of 7-substituted norbornadienes to carbon monoxide is a highly stereospecific and regiospecific process. In the case of 7-*tert*-butoxynorbornadiene, while several products are formed

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