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Evidence of Enhanced Reactivity of DAAP Nucleophiles toward Dephosphorylation and Deacylation Reactions in Cationic Gemini Micellar Media

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Abstract: 4,4′-(Dialkylamino)pyridine (DAAP)-based compounds **1**−**4** catalytically cleave hydrophobic organophosphate and carboxylate esters in various host micellar aggregates at mildly alkaline pH. The role of the micellar reaction medium in such esterolytic reactions has been carefully examined in this work. The cationic gemini surfactant based micellar aggregates provide more than 1 order of magnitude better reaction medium for the above reactions than their conventional single-chain, single-charge, cationic cetyl trimethylammonium bromide (CTABr) micelles. The catalytic turnover behavior of DAAP nucleophiles in the presence of excess substrates is also retained in gemini micellar media.

Realization of a "green" chemical process in solution involves appropriate choice of a safe, nontoxic, and inexpensive solvent.[1] Despite solubility limitations, water remains the most obvious choice for this purpose. However, the use of water as a medium for promoting organic reactions has been rather neglected in the development of organic reactions and synthesis, although it is the solvent in which almost all biochemical processes take place.[2]

When the chemistry involves conversion of large stockpiles of toxic molecules into nontoxic end products (decontamination), the use of aqueous media is even more appropriate.[3] For instance, many chemical warfare and persistent agents (Chart S1, Supporting Information), such as paraoxon, parathion, VX, or sarin, etc., are hydrophobic phosphorus(V) esters, and their decontamination often involves dephosphorylation or hydrolysis.[4] Phosphotriesters and their derivatives are toxic to both target and nontargeted organisms. Paraoxon and parathion are most often responsible for the poisoning of agricultural workers. Remediation of such contamination is therefore an urgent goal. However,the extreme toxicity of such compounds often mandates that most laboratory research employ simulants instead of the actual compounds. Since these esters or their standard simulant, *p*-nitrophenyl diphenyl phosphate (PNPDPP),[5] are not water-soluble, aqueous solutions of surfactants (micelles or other aggregates) are generally employed as a reaction medium for the cleavage of such organophosphate esters.[6] In such a medium, organic reactants are partitioned into the surfactant aggregates by electrostatic and hydrophobic interactions, and the observed rate accelerations are largely due to the increased localization of the reactants and also of the typical physiochemical properties of micellar environment, which are significantly different from those of the bulk solvents.[6] Chemical means of achieving efficient destruction of such toxic organophosphate esters remains an active area of much research, with attention focused recently on peroxides,[7] iodosoarene carboxylates,[8] and metallomicelles[9] employed in cetyltrimethylammonium (CTA) surfactant micelles as a medium.

Recently, syntheses of surfactants of several other molecular architectures have been reported which upon solubilization in water form different types of micelles.[10] Among the new synthetic surfactants, gemini surfactants appear quite attractive as hosts, in that the aqueous solutions of such systems often display unique properties that can result in improved performance.[11] However, most papers on gemini surfactants have focused on the investigation of their specific aggregation properties, with a very few studies on reaction rates.[12]

Unlike CTA, which possesses a single hydrocarbon chain connected to one polar cationic $-NMe_3^+$ headgroup, a gemini surfactant of the type, 16-*m*-16 (Chart 1), is composed of a hydrophobic, polymethylene spacer

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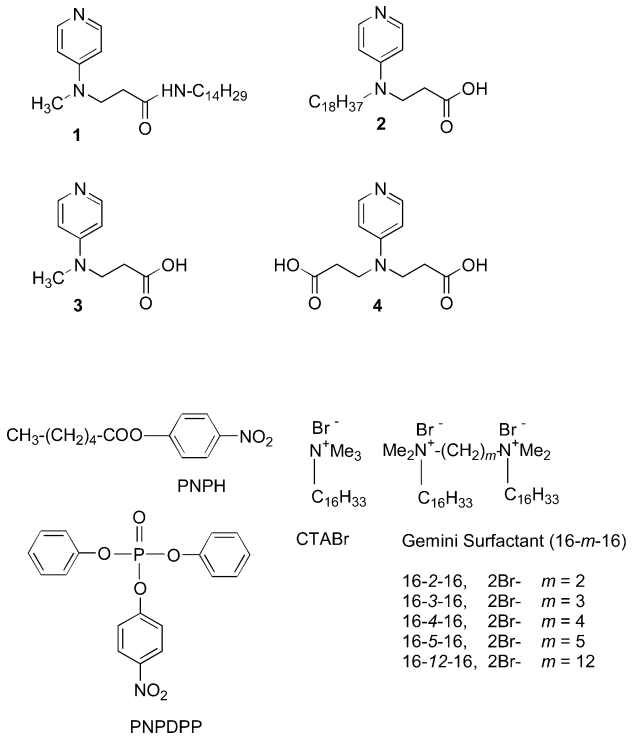
CHART 1. Catalysts, Substrates, and Surfactants Used in This Investigation



$-(CH_2)_m-$ that is attached to the two cationic $-NMe_2^+$ headgroups. Previously, it has been shown that the spacer chain length significantly influences the aggregation properties of these surfactants in water.[13] Since the 16-*m*-16 surfactants are "dimeric" forms of CTA, when one uses them as medium for performing hydrolytic reactions, several questions of fundamental importance arise. How general is phosphotriester hydrolysis in cationic gemini micelles by nucleophiles used in CTA micelles? What is the kinetic range of some of these reactions in gemini micellar media? Does variation in the spacer chain length of host gemini surfactants influence the rates of such esterolytic reactions? In this paper, we report on the kinetic advantages in using gemini micelles as the reaction medium.

To appropriately probe the above questions, we have chosen the well-known hydrophobic, reactive phosphotriester PNPDPP[5] and also a carboxylate ester substrate, *p*-nitrophenyl hexanoate (PNPH) (Chart 1). We selected several 4,4′-(dialkylamino)pyridine (DAAP) based compounds (Chart 1), which are known to be highly potent reagents because they possess "supernucleophilic" DAAP function,[14,15] and then compared their abilities to cleave both types of substrates, PNPDPP and PNPH, in aqueous CTA micelles against that in the corresponding cationic gemini surfactant (16-*m*-16) micelles.

Accordingly, the time course of the hydrolysis of PNPDPP and PNPH under pseudo-first-order conditions by each of **1**−**4** in micellar CTABr at pH 8.2 was first examined at 25 °C spectrophotometrically by following the release of the *p*-nitrophenoxide ion at 400 nm. Inspection of Table 1 reveals that compounds **1** and **2** are the most reactive nucleophiles toward both types of substrates. In CTABr micellar solution at pH 8.2, **1** and **2** accelerate the hydrolysis of PNPDPP by factors of 170 and 415, respectively, relative to rates of hydrolysis by OH^- in micellar CTABr at pH 8.2. These nucleophiles also display 56-fold and 234-fold greater reactivity over OH^- against PNPH in CTABr micellar solution at pH 8.2, respectively. The potentiation of the rates by other two nucleophiles, **3** and **4**, for both the deacylation and dephosphorylation reactions is, however, modest in CTABr micelles under identical conditions (Table 1).

To investigate the effect of host surfactant structure on the rate constants, we then followed the above reactions using each of **1**−**4** in gemini micellar solution of 16-*m*-16 at pH 8.2 and at 25 °C by using conditions similar to those which we used under CTABr micelles. The corresponding pseudo-first-order rate constants for the cleavage reactions of PNPDPP and PNPH mediated by nucleophiles **1**−**4** as a function of the concentration of 16-*m*-16 surfactant micellar aggregates were determined. A representative pseudo-first-order rate constant vs [16-*4*-16] profile for the dephosphorylation mediated by **2** in gemini micelles is shown in Figure 1, wherein a pronounced maximum in the rate constant for the hydrolysis is clearly seen at [16-*4*-16] = 1.5 mM. At this concentration of host, 16-*4*-16 provides >12-fold and >17-

TABLE 1. Rate Constants for the Cleavage of PNPDPP and PNPH by 1−4 in Various Host Micellar Media[a]

		$10^2\ k_\psi$, $(s^{-1})^b$							
		PNPDPP				PNPH			
entry	nucleophile	16-*4*-16	k_{rel}^c	CTABr	k_{rel}^d	16-*4*-16	k_{rel}^c	CTABr	k_{rel}^d
1	OH^-	0.006	1	0.002	1	0.014	1	0.005	1
2	**1**	4.3	717	0.34	170	9.7	693	0.28	56
3	**2**	8.52	1420	0.83	415	18.8	1343	1.17	234
4	**3**	0.5	83	0.04	20	1.22	87	0.11	22
5	**4**	0.4	67	0.02	10	0.81	58	0.07	14

[a] Conditions: 0.05 M (tris-maleate) buffer, pH 8.2, $\mu = 0.1$ (KBr), 25 °C, [substrate] = 2.5×10^{-5} M. In the case of [CTABr] = 2.5×10^{-3} M, [catalyst] = 2.5×10^{-4} M and [16-*4*-16] = 1.5×10^{-3} M, [catalyst] = 2.5×10^{-4} M. [b] Reactions were performed in triplicate with ±3% or better reproducibility in k_{obs}. [c] $k_{16-4-16}/k_{OH}$. [d] k_{CTABr}/k_{OH}.

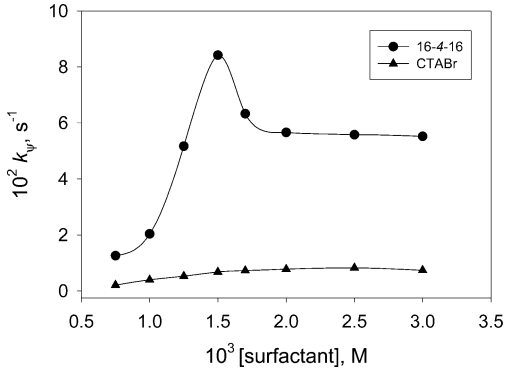


FIGURE 1. Pseudo-first-order rate constants for the cleavage of 2.5×10^{-5} M PNPDPP by 2.5×10^{-4} M of **2** as a function of host surfactant concentration at pH 8.2: (●) 16-*4*-16, (▲) CTABr.

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fold kinetic advantages over CTABr in the hydrolysis of PNPDPP and PNPH respectively induced by **2**.

Inspection of Table 1 reveals that **1** and **2** continue to be the most reactive nucleophiles toward both types of substrates in gemini micellar 16-*4*-16 solutions also. The data of Table 1 further indicate that the hydrolysis rates in 16-*4*-16 micelles were significantly enhanced over CTA micelles. In micellar solution of 16-*4*-16 at pH 8.2, **2** accelerates the hydrolysis of PNPDPP and PNPH, respectively, by factors of at least 1420 and 1343, respectively, relative to the hydroxide ion. In contrast, **1** in 16-*4*-16 micelles enhanced the rates of hydrolysis of PNPDPP and PNPH respectively by factors of 717 and 693 over OH^- ion in the same micellar media. Clearly the nucleophile, **2** associate with either type of micellar media rather "intimately" via both electrostatic and hydrophobic interactions respectively through its pendant $-CH_2CH_2-COO^-$ subunit and long *n*-octadecyl chain. This kind of efficient binding of the other nucleophiles **1**, **3**, and **4** with micellar pseudophase is not possible as none of them can associate with host surfactant micelles via both kinds of interactions.

What could be the reason for the better reaction rates in gemini 16-*m*-16 micelles? The reactive forms of **1**−**4** are free unprotonated forms of the respective 4,4′-(dialkylamino)pyridine moieties. It is therefore important to know whether such rate enhancements in gemini micelles were caused due to the differences in pH at the respective "Stern layer" regions of 16-*m*-16 and CTA micelles. To shed light on this, the pseudo-first-order rate constants for substrate cleavages at 25 °C were determined at different pH's between 6.5 and 9.0. Respective pH−rate constant profiles for the esterolytic cleavages of PNPH and PNPDPP by each of **1**−**4** gave the apparent pK_a values. The plot of log k_ψ vs pH appears in Figure S1 (Supporting Information), which shows the discontinuities at pH ∼7.55, a value taken as the systemic pK_a for **2** in CTABr micelles. In the same figure, the plot of log k_ψ vs pH obtained for **2** in 16-*4*-16 micelles is also shown. Clearly, the pK_a value for **2** determined in 16-*4*-16 micelles is hardly different from that obtained in CTA micelles. Hence, these results suggest that there may not be any significant difference in local pH at the interfaces of either type of host micelles, where reaction between the substrate and the nucleophile most likely take place. Hence, the kinetic benefits witnessed in the hydrolytic reactivity of these nucleophiles in the cationic gemini 16-*4*-16 micellar medium might reflect activation of the anionic nucleophile such as **2** in particular by ion-pairing to the dual cationic parts of a single 16-*4*-16 surfactant molecule in the micelle.

To understand the differential behavior of two comicellar systems, we performed a series of kinetic experiments by keeping the concentration of the host cosurfactant (CTABr or 16-*4*-16) constant while gradually increasing the catalyst concentration. For these studies we employed two potent catalysts, **1** and **2**, and increased their concentration from 1.25×10^{-4} to 6×10^{-4} M. The relevant kinetic data have been presented in Table S1 (Supporting Information). For the cleavage of PNPDPP, the rate constants increased until the catalyst concentration reached 3.75×10^{-4} M in both types of comicelles for both the catalysts. However, the gains in the rate constants were not proportional to the concentration of the catalyst. Beyond 5×10^{-4} M catalyst concentration, either type of catalysts could not be solubilized in CTABr micelles, and the resulting solution precipitated. Even though the rates did not increase further in gemini micelles upon solubilization of even 6×10^{-4} M of catalysts, the resulting solution did not turn turbid even after storage over several days. Importantly however, the observed rate constants were at least 1 order of magnitude larger in gemini comicelles than in CTABr comicelles for both **1** and **2** at every catalyst concentration examined. These results indicate that both catalysts bind more efficiently with the gemini micelles.

TABLE 2. Kinetic and Thermodynamic Parameters for the Cleavage of PNPDPP by Comicelles of 1−4 with Either CTABr or Gemini (16-*4*-16) Surfactants[a]

	16-*4*-16			CTABr		
catalyst	$10^2\ k_{lim}$, s^{-1}	K_b, M^{-1}	$10^2\ k_2$, $M^{-1}\ s^{-1}$	$10^2\ k_{lim}$, s^{-1}	K_b, M^{-1}	$10^2\ k_2$, $M^{-1}\ s^{-1}$
1	4.94	2650	23.40	0.43	1245	2.09
2	9.31	3370	41.02	0.92	1738	4.16
3	0.67	2157	17.60	0.05	852	1.37
4	0.34	2100	10.89	0.03	830	0.92

[a] Kinetic runs were performed at pH 8.2, 0.05 M tris-maleate buffer using solutions containing increasing amounts of catalyst and CTABr with molar ratios of 1:15, 1:10, and 1:5 or catalyst and 16-*4*-16 with molar ratios of 1:10, 1:6, and 1:3 using PNPDPP as substrate. The parameters k_{lim} and k_2 were calculated by fitting in Michaelis−Menten equation. See the text for details.

An alternative analysis of the rate data at pH 8.2 for the catalysts, **1**−**4** was obtained in both types of comicelles. For this, kinetic studies were performed with solutions containing increasing amount of catalyst and cosurfactants, while keeping the catalyst/CTABr or catalyst/16-*4*-16 ratio constant, using PNPDPP as substrate. The corresponding rate-concentration profiles show the saturation behavior (Figure S2, Supporting Information). Analysis of the curves by fitting the k_ψ vs [catalyst] data using the Michaelis−Menten type equation[6c] allows the estimation of (i) the rate constants k_{lim} expected for the substrate being fully bound to the aggregates and (ii) the apparent binding constants (K_b) for PNPDPP in different comicelles. Selected data are given in Table 2.

The second-order rate constants for these reactions in micellar pseudophase, k_2, were calculated[6c] using the equation $k_2 = k_{lim}V_M[D^t]_m/[D^f]_m(1 + [H^+]/K_a)$, where $[D^t]_m$ is the total concentration of the micellized surfactant, $[D^f]_m$ is the concentration of the catalyst, and K_a is the dissociation constant for the catalyst at pH 8.2 in which reactions were performed. We have used a V_M value of 0.37 L mol^{-1} for CTABr micelles[6c] and 0.597 L mol^{-1} for 16-*4*-16, $2Br^-$ micelles.[16] The term $[D^t]_m/[D^f]_m$ takes into account the dilution of the reactive amphiphilic catalyst in the CTABr or gemini surfactant comicelles, and the term $(1 + [H^+]/K_a)$ denotes the fraction of the dissociated catalyst at pH 8.2. Comparison of k_2 values in Table 2 confirms significantly enhanced reactivity of the DAAP catalysts in gemini 16-*4*-16 comicelles over that in CTABr micellar aggregates for the cleavage of PNPDPP.

Data in Table 2 reveal that the affinity constants (K_b) for the substrate are larger with 16-*4*-16 gemini micelles

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compared to that with CTABr. The apparent second-order rate constants are also higher in the gemini micellar aggregates. Taken together, these results clearly suggest that the binding constants for both catalysts and substrates are larger for the 16-*4*-16 micelles compared to that in CTABr micelles.

Using the most potent nucleophile among the present series, the kinetic studies were performed for the cleavage reactions of PNPDPP and PNPH by **2** in various host micelles made of gemini surfactants possessing different spacer chain lengths, 16-*m*-16, $m = 2$, 3, 4, 5, and 12. Figure S3 (Supporting Information) reveals that the gemini micelles invariably provide significantly better kinetic benefit over CTA micelles irrespective of the *m*-value. The micelles prepared from 16-*4*-16 ($m = 4$) offer the most effective medium for carrying out these reactions. When the spacer length was extended to $m = 12$, the reactivity toward either type of ester hydrolysis was considerably lowered. Nevertheless, the observed rates for the hydrolysis of both PNPDPP and PNPH were significantly greater in gemini 16-*12*-16 micelles than in CTA micelles.

In a mixture of water and single-chain surfactant like CTA, the system tries to minimize its free energy by forming micellar aggregates in which the apolar n-$C_{16}H_{33}$ chains are brought together to minimize the contact with water.[17a] The polar $-NMe_3^+$ headgroups are positioned at the interface with water and away from each other as a result of electrostatic repulsions. In a corresponding gemini surfactant such as 16-*m*-16, the two cationic headgroups are covalently linked by a $-(CH_2)_m-$ spacer. Consequently, a compromise for the location of the spacer is necessary depending on the length and on the extent of repulsion between two $-NMe_2^+$ headgroups.[17b] When the spacer length is shorter than the "equilibrium" distance between two headgroups, the spacer ($m < 4$) remains fully extended to minimize the repulsion between the headgroups. This situation leads to a significant unfavorable contact of the spacer with water. To avoid such a situation the packing of gemini surfactants are such that at $m \leq 3$, the micellar aggregates of 16-*m*-16 adopt wormlike thread shapes.[13] It is possible that while such types of micelles (16-*3*-16) still provide better reaction medium than CTA for the esterolysis reactions presented herein, this spacer length and micellar shape are not optimum for the best reactivity. Such an optimum is reached at $m = 4$, where micellar structures are not threadlike. In cases where the spacer is longer than the "equilibrium" distance between two cationic headgroups, the spacer ($m > 4$) tends to loop inside micellar core to minimize its contact with water depending on the *m*-value. Increased looping of the spacer will also "separate" substrate and reagent at the "Stern layer" region and thereby mitigate the efficiency of the reaction.

To test whether catalysts such as **2** exhibit catalytic turnover behavior in both types of micellar media, kinetic runs in the presence of excess substrates were performed. At pH 8.2 and 25 °C using $[\mathbf{2}] = 1.25 \times 10^{-5}$ M, and $[CTABr] = 1 \times 10^{-3}$ M, we observed a quantitative release of *p*-nitrophenoxide with evidence of "burst" kinetics using up to a 10-fold excess of either PNPH or PNPDPP over catalyst. The same behavior was virtually reproduced in 16-*4*-16 micelles, except that the turnover was even more rapid in gemini micelles (not shown).

It may be concluded that the dicationic gemini surfactant micelles provide remarkably better environment for nucleophile assisted dephosphorylation or deacylation reactions than in the corresponding monocationic CTA micelles. The most rapid hydrolysis, observed for PNPDPP with reagent **2**, involves excess **2** in gemini micelles of 16-*4*-16 at pH 8.2 where $k_\psi = 8.52 \times 10^{-2}$ s^{-1}. Under these conditions, the hydroxide ion mediated hydrolysis rate for the corresponding reaction is only 6×10^{-5} s^{-1}. This kinetic benefits associated with geminis may be due to the fact that the spacer chain at the headgroup level decreases the extent of water penetration at the micellar surface.[18] Best results were obtained with16-*4*-16. Dephosphorylation or deacylation reactions are generally facilitated by a decrease in the water content of the reaction environment. In cases where the spacer is longer than the "equilibrium" distance between two cationic headgroups within the gemini, the spacer ($m > 4$) tends to loop inside micellar core to minimize its contact with water. Increased looping of the spacer also "separates" substrate and reagent at the Stern layer region and thereby mitigates the efficiency of the reaction. Can we expand the kinetic benefits of such reactions even further by appropriate modification of the host surfactant architecture? Would geminis offer the optimal activation or an alternative surfactant backbone may be better? Work is underway in our laboratory to answer these questions.

Experimental Section

Descriptions of analytical instruments have been reported.[9a] All buffers were made in Millipore water. All chemicals were purchased from best known commercially sources. Solvents were dried and freshly distilled as required. PNPDPP was synthesized and purified according to a literature procedure.[19]

Synthesis. Compounds **1**−**4** were synthesized using procedures described earlier.[15] Gemini surfactants, 16-*m*-16, were synthesized using procedures reported previously.[13]

Kinetic Measurements. Kenetic measurements were carried out and the rate constants were obtained as described earlier.[9a]

Acknowledgment. This work was supported by the Department of Science and Technology, India. V.P.K. thanks CSIR for a senior research fellowship.

Supporting Information Available: G-series nerve agents (Chart S1). Plots of k_ψ vs pH profiles for the cleavage of PNPDPP in comicelles of **2** with either CTABr or 16-*4*-16 (Figure S1). Kinetic cleavage experiment by using solutions containing increasing amounts catalyst and 16-*4*-16 or CTABr comicelles (Figure S2). Effect of spacer chain length on the cleavage of PNPDPP and PNPH by the comicelles of **1** and **2** with gemini surfactants (Figure S3). Effect of catalyst concentration on the cleavage of PNPDPP by the comicelles of **1** or **2** with either CTABr or Gemini (16-*4*-16) surfactants (Table S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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