Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 4927-4930, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00971-6

The Reactivity of a Surfactant-Bound Micellar Phosphotriester

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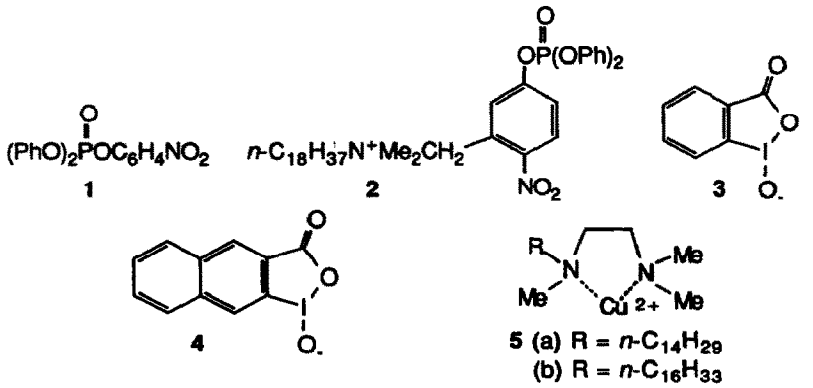
Abstract. The covalently bound substrate-surfactant-*p*-nitrophenyldiphenyl phosphate, **2**, is more reactive toward iodosocarboxylate and copper metallomicellar catalysts that the parent substrate, **1**, in aqueous cetyltrimethylammonium ion micelles.

The destruction of toxic phosphates and phosphonates continues to be an urgent problem, particularly with regard to the treaty-obligated demilitarization of stockpiled chemical weapons.[1] As alternatives to incineration, hydrolytic, and particularly catalytic methodologies, have been vigorously explored. In view of the recognized ability of cationic surfactant micelles to accelerate the cleavage of carboxylic esters, micelle-catalyzed hydrolyses of phosphate esters have been particularly well studied,[2] and *p*-nitrophenyldiphenyl phosphate (PNPDPP, **1**)[3] has become the unofficial "standard substrate," permitting comparisons of the efficacy of many different cleavage reagents.

Based on our prior studies of surfactant-bound carboxylate ester substrates,[4] we suspected that the substrate-functionalized phosphotriester surfactant **2** (C_{18}PNPDPP) might provide a more sensitive kinetic measure of cleavage reagent potency than the parent PNPDPP. Thus **2** should exhibit a higher affinity for surfactant aggregates, and should be more hydrolytically labile than **1** due to its cationic charge (see below). Moreover, the unusually low pK_a of the surfactant-functionalized *p*-nitrophenol leaving group of C_{18}PNPDPP should render it reactive to even weak nucleophiles.[5]

Among the many micelle-activated hydrolytic reagents tested against PNPDPP, the iodosocarboxylates[6] (typified by iodosobenzoate, **3**, and iodosonaphthoate, **4**) and certain metallomicelles[7] (especially Cu chelate **5a**[7c]), stand out as characterized by rapid cleavage of PNPDPP, catalytic turnover, and activity against fluorophosphonate nerve agents.[6d,7c] Here, we describe initial studies of the micellar cleavages of surfactant phosphate **2** by iodosocarboxylates **3** and **4**, and by the *N*-hexadecyl-*N*,*N*,*N*-trimethylethylene diamine cupric chelate, **5b**. Not only is C_{18}PNPDPP found to be more reactive toward micellar reagents **3**-**5** than the



normative substrate, PNPDPP, but the surfactant-bound phosphate is representative of a general strategy in which less reactive "independent" substrates (*e.g.*, esters, phosphonates, or phosphodiesters) could be similarly transposed to covalently bound-surfactant substrates in order to amplify the substrates' sensitivity toward prospective cleavage reagents.

C_{18}PNPDPP was synthesized from 3-methyl-4-nitrophenol by phosphorylation with diphenylchlorophosphate (Et_3N, Et_2O, 25°C, 4 h, 90%); bromination of the methyl group (NBS, CCl_4, Bz_2O_2, refl. 18 h, 88%); and quaternization of *N*-*n*-octadecyl-*N*,*N*-dimethylamine with the bromomethyltriarylphosphate (acetone, 25°C, 6 d, purified yield 27%). Surfactant substrate **2** was purified by chromatography on silica gel (20:1 CH_2Cl_2/MeOH + 2 drops of HCl; R_f ~ 0.3), and characterized by appropriate ^1H and ^{31}P NMR spectra,[8a] as well as an acceptable elemental analysis (monohydrate, C, H, N). Iodosobenzoate was commercially available, and iodosonaphthoate was at hand from a previous study.[6f] Chelate **5b** was prepared *in situ* from the appropriate ligand[9] and $Cu(NO_3)_2$.

Kinetic studies of the cleavages of **1** or **2** by **3**-**5** monitored the *p*-nitrophenoxide absorbance at 400 nm, using conventional or stopped-flow UV spectrometers as required.[10] Reactions were carried out in comicelles with cetyltrimethylammonium (CTA) chloride or bromide. Iodosocarboxylate cleavages of C_{18}PNPDPP are graphically represented in Figure 1, where the pseudo-first-order rate constants (k_ψ) are shown as a function of [CTACl] in the presence of a fixed quantity of (excess) iodosocarboxylate in pH 8.0, 0.01 M phosphate buffer and 0.01 M KCl. The maximum rate constants under "normal" stopped-flow conditions[10] occur at 5×10^{-4} M CTACl, and are $k_\psi = 0.66$ s^{-1} and 5.24 s^{-1} with **3** and **4**, respectively. When the **2** + **3** reaction is carried out with aqueous **3** alone (*i.e.*, not solubilized in micellar CTACl[10]), k_ψ^{max} increases to 1.73 s^{-1} at [CTACl] = 1.0×10^{-3} M. Clearly, compartmentalization of **2** and **3** in separate micellar solutions leads to a depressed rate constant, relative to direct addition of aqueous **3** to micellar **2** at the same final [CTACl]. In the absence of iodosocarboxylate, k_o for the cleavage of C_{18}PNPDPP at pH 8 in 5.4×10^{-3} M CTACl is 5.46×10^{-3} s^{-1}, so that the catalytic advantages (k_ψ^{max}/k_o) in micellar CTACl are about 120-317 for **3** and 960 for **4**. Kinetic data are collected in Table 1. All data were reproducible to ±10%.

Kinetics with the Cu catalyst **5b** were studied at pH 6.4 in comicellar CTABr; key results appear in Figure 2, where k_ψ values for the cleavages of substrates **2** or **1** are shown as a function of the [diamine ligand] in 1×10^{-3} M CTABr, with 1×10^{-3} M $Cu(NO_3)_2$ and 0.05 M morpholinoethanesulfonate buffer. Studies of k_ψ vs. [CTABr] and k_ψ vs. [$Cu(NO_3)_2$] show that (a) 2×10^{-5} M C_{18}PNPDPP is completely bound to CTABr at [CTABr] = 2.5×10^{-4} M,[8b] whereas 2×10^{-5} M PNPDPP requires ~8×10^{-4} M CTABr for maximal binding, and that (b) all ligand is bound to Cu at [ligand] = 5×10^{-4} M and [$Cu(NO_3)_2$] = 1×10^{-3} M.

The data in Figure 2 give k_ψ^{max} = 36.2×10^{-3} and 7.2×10^{-3} s^{-1} for cleavages of C_{18}PNPDPP and PNPDPP, respectively, at [**5b**] = 5×10^{-4} M in 1×10^{-3} M CTABr at pH 6.4. At this pH, k_ψ values in CTABr alone are 0.94×10^{-3} s^{-1} (**2**) and 0.10×10^{-3} s^{-1} (**1**), leading to catalytic advantages of ~38 and ~72, respectively, for Cu chelate **5b**. Again, kinetic data are collected in Table 1.

From the values of k_ψ^{max} (Table 1), it is clear that the cleavage rates of C_{18}PNPDPP are 5 (**5b**), 20 (**4**), or 27 (**3**) times faster than those of PNPDPP. A similar trend is evident from the k_{cat} data, where the **2**/**1** kinetic ratio rises to 16 with iodosonaphthoate catalyst **4**. Catalyst **4** also evokes the largest substrate sensitivity advantage in terms of (k_ψ^{max}/k_o), where the **2**/**1** ratio is a factor of 20.

Table 1. Kinetic Data for Phosphate Ester Cleavages at 25°C[a]

Catalyst	Substrate	pH	10^3[CTA(X)], M	$10^2 k_\psi^{max}$, s^{-1}	k_ψ^{max}/k_0[b]	k_{cat}, $M^{-1}s^{-1}$ c
3	1	8.0	1.0 (Cl)	6.4[d]	97.4[d]	759[e]
3[f]	2	8.0	0.5 (Cl)	66.	120.	5065
3[g]	2	8.0	1.0 (Cl)	173.	317.	3910
4	1	8.0	0.5 (Cl)	26.[e]	47.6	2950[e]
4	2	8.0	0.5 (Cl)	524.	960.	47200
5b	1	6.4	1.0 (Br)	0.72	72.	18[h]
5b	2	6.4	1.0 (Br)	3.6	38.	90[h]

[a]See text and figure captions for conditions. [b]Ratio of rate constants in micellar CTAX in presence and absence of the catalyst; see text for details. [c]k_ψ^{max}/[catalyst], corrected for 100% ionization of the catalyst at the operational pH, using pK_a values for the catalysts; see text. [d]Reference 6b. [e]Reference 6f. [f]"Normal" addition of 3.[10] [g]Iodosobenzoate was added to 2/CTACl.[10] [h]The apparent pK_a of 5b is ~5.8, determined kinetically from reactions of 5b with 2 as a function of pH.

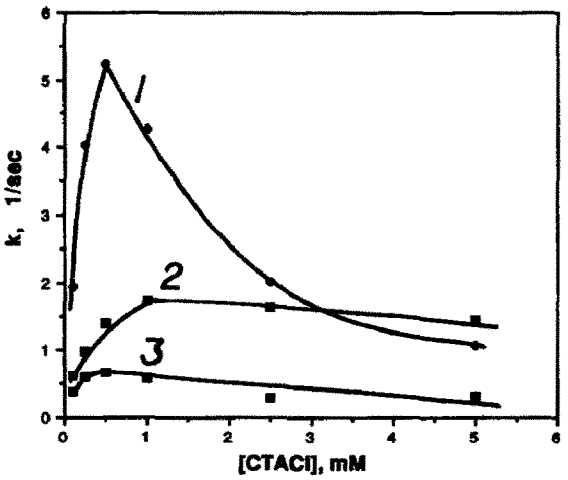


Figure 1. k_ψ for cleavages of C_{18}PNPDPP (2) by 3 or 4 as a function of [CTACl] at pH 8, with 3 added under "normal" (curve 3) or "modified" (curve 2) conditions, and 4 (curve 1) added under "normal" conditions.[10] For 2 + 3, [2] = 2.03×10^{-5} M, [3] = 1.52×10^{-4} M; for 2 + 4, [2] = 2.44×10^{-5} M; [4] = 1.25×10^{-4} M.

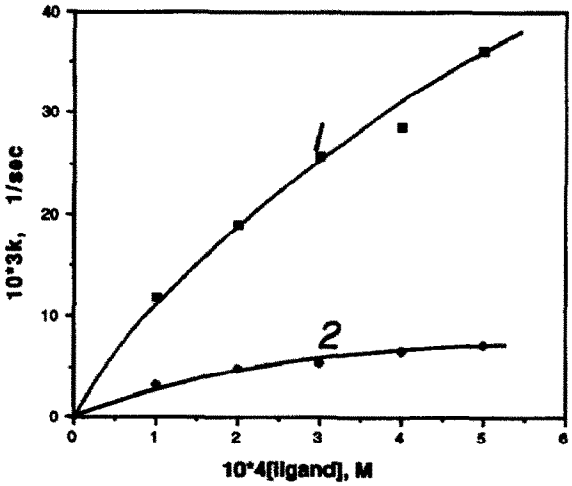


Figure 2. k_ψ for cleavages of C_{18}PNPDPP (curve 1) or PNPDPP (curve 2) by Cu chelate 5b as a function of [ligand] at pH 6.4, with [CTABr] = 1×10^{-3} M, [Cu(NO3)2] = 1×10^{-3} M, [2] = 2×10^{-5} M, [1] = 2×10^{-5} M.

The pK_a's of catalysts **3**, **4**, and **5b** are 7.2,[6a] 7.1,[6f] and 5.8,[11] respectively, exceeding that of the surfactant *p*-nitrophenoxide leaving group of **2**.[5] Accordingly, it may be that formation, rather than decomposition,[12] of a putative pentavalent phosphorous oxyanion[13] is the rate limiting step in the cleavage of **2**. In this case, the kinetic advantages of substrate C_{18}PNPDPP would largely derive from an enhanced reactivity of its phosphoryl group induced by the surfactant's cationic charge,[14] and from better binding to the CTA comicellar host. It remains to be seen whether similar (or perhaps greater) kinetic advantages are realized with other catalysts, or accrue to other classes of surfactant-bound phosphoester substrates.

Acknowledgments. We gratefully acknowledge financial support from the U.S. Army Research Office and the U.S. Army ERDEC (coordinated by Drs. H.D. Durst and Y-C. Yang), at Rutgers University, from the Ministry for University, Scientific, and Technical Research, at the Universitá di Padova, and from N.A.T.O. (R.A.M. and P.S.). We also thank Ms. C. Rodighiero for experimental assistance.

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8. (a) ^{31}P NMR at -17.5 ppm in $CDCl_3$, relative to external H_3PO_4. (b) The critical micelle concentration of **2** is 1.0×10^{-5} M (0.01 M aqueous KCl at pH 2.5) as determined by tensiometry.
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10. In "normal" stopped-flow experiments, a solution of **2** in aqueous CTACl (pH 4.0, 0.01 M KCl) was combined with an equal volume of **3** or **4** in CTACl and 20 mM PO_4 buffer at pH 8.0 (0.01 M KCl). In the case of **3**, where solubility permitted, iodosobenzoate in buffer alone (no CTACl) could be combined directly with a CTACl solution of **2**. This modification led to higher rate constants; see below.
11. This apparent pK_a, determined from a pH-rate constant profile of the cleavage of **2** by **5b** in micellar CTABr, is presumably related to a Cu-bound water molecule.[7c]
12. This would likely be the case in a comparable *p*-nitrophenyl ester cleavage: Jencks, W.P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, pp. 480*f*. Hupe, D.J.; Jencks, W.P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
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14. The electrostatic interaction between the cationic nitrogen and the phosphoryl group would both activate the lattter toward nucleophilic atack and stabilize the resulting phosphorous oxyanion, thus lowering the activation energy for nucleophile addition.

(*Received in USA* 24 *March* 1994; *revised* 10 *May* 1994; *accepted* 18 *May* 1994)