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A POWERFUL NUCLEOPHILIC MICELLAR REAGENT.
SYNTHESIS AND PROPERTIES OF α-OXIMINO-KETONE-FUNCTIONALIZED SURFACTANTS

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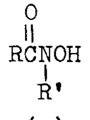
The search of new functional micellar reagents to provide more refined enzyme analogues has been recently rewarded by the report by Kunitake and his coworkers [1] of the properties of a catalytic system, comicelles of CTABr (cetyltrimethylammonium bromide) and the bifunctional reagent (Ia), of greater efficiency than that of α-chymotrypsin in promoting the hydrolysis of p-nitrophenyl acetate (PNPA). From literature data [1-4] and from our analysis (under common conditions [5]) of the catalytic properties of a number of functional reagents, long-chain hydroxamic acid derivatives [3] (I), oxime-functionalized [4] (II) and thiocholine-type [6] (III) surfactants are the most effective nucleophilic micellar catalysts in the hydrolysis of activated esters so far explored.

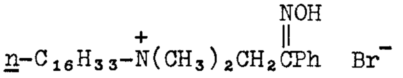
We now report the synthesis and kinetic properties of α-oximino-ketone-functionalized surfactants (IV) of substantially greater reactivity than that of any other functional surfactant and of α-chymotrypsin toward p-nitrophenyl esters.



$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{R'}}{\underset{|}{\mathrm{N}}}\mathrm{OH}$

(I)

a : R = 4-imidazolyl; R' = $n\text{-}C_{12}H_{25}$
b : R = $n\text{-}C_{13}H_{27}$; R' = CH_3

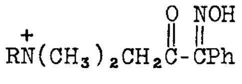


$n\text{-}C_{16}H_{33}\text{-}\overset{+}{N}(CH_3)_2CH_2\overset{\mathrm{NOH}}{\overset{\|}{C}}Ph\quad Br^-$

(II)

$n\text{-}C_{16}H_{33}\text{-}\overset{+}{N}(CH_3)_2CH_2CH_2SH\quad Br^-$

(III)



$R\overset{+}{N}(CH_3)_2CH_2\overset{\mathrm{O}}{\overset{\|}{C}}\text{-}\overset{\mathrm{NOH}}{\overset{\|}{C}}Ph$

(IV) X^-

a : R = $n\text{-}C_{12}H_{25}$; X = Cl
b : R = $n\text{-}C_{16}H_{33}$; X = Cl

Benzyl methyl ketone was converted to the corresponding *anti*-α-oximino derivative (V)[7] which was reacted with bromine (equivalent amount) affording (VI)[8]. Precaution had to be taken to halt the bromination reaction in due time (*ca.* 3 hr, reflux) to avoid decomposition of (VI). The reaction of the latter with the tertiary amine (equiv. amounts) yielded (IV) Br^- contaminated by small amounts of $R\overset{+}{N}(CH_3)_2H\ Br^-$ which could be removed by treatment of a MeOH solution of the crude product with Na_2CO_3 followed by rapid filtration, solvent evaporation and repeated washings with pentane. The residue was dissolved in 0.5 N HCl in MeOH, the solvent removed and the product repeatedly recrystallized[9] from CH_2Cl_2/ether

$$PhCH_2COCH_3 \xrightarrow[EtO^-,\ EtOH]{t\text{-}BuONO} \underset{(V)}{PhC(=NOH)COCH_3} \xrightarrow[AlCl_3,\ ether]{Br_2}$$

$$\underset{(VI)}{PhC(=NOH)COCH_2Br} \xrightarrow[ether]{RN(CH_3)_2} (IV)\ Br^- \xrightarrow[2.\ \ HCl]{1.\ \ Na_2CO_3} (IV)\ Cl^-$$

Compounds (IVa) are sparingly soluble in water at 25° [10^{-3} *M*; (IVa) : 2.5; (IVb) : *ca.* 1]. Their c.m.c. values at 25° [10^{-4} *M*; (IVa) : 1.3; (IVb) : 0.62] were obtained from conductivity measurements in pure H_2O and their apparent pK_a, 3.0 ± 0.2 in both cases, was determined spectrophotometrically (300 nm in the pH range 6 to 10) under the same conditions used for the kinetic measurements[5].

Hydrolyses of PNPA and PNPH (hexanoate) catalyzed by comicelles of (IV) and CTABr were followed at 400 nm and the apparent catalytic rate constants measured at pH 7.15 and 7.95 under pseudo-first-order condition ([ester]≪[IV]) are shown in the Table together with those[10] obtained for other micellar reagents under identical [but for (Ia) and the enzyme] conditions[5].

Surfactants (IV) are by 1.3 pK_a units more acidic substances than the corresponding oxime-functionalized derivative (III) and therefore more extensively ionized into oximate anions. It seems however that in spite of their being conjugate bases of stronger acids the oximate anions of (IV) are not weaker nucleophiles than those of (III) and this is likely to be due to their enhanced character of α-nucleophiles[12].

Saturation kinetics showing a very rapid " burst " and rather flat steady state tract were observed under conditions [ester]≫[IV]. The turnover rate, TABLE. Apparent catalytic rate constants, $\underline{k}_c$ (l/mol-sec), for the hydrolyses of PNPesters[a].

Catalyst	PNPA		PNPH	
pH:	7.15	7.95	7.15	7.95
(IVa)	920.	2570.	8.4×10^3	2.3×10^4 [b]
(III) R : $\underline{n}$-$C_{16}H_{33}$	10.	615.	-	-
(II) R : $\underline{n}$-$C_{16}H_{33}$	55.	325.	4.8×10^2	2.5×10^3
(Ib)	-	305.	4.4×10^2	2.6×10^3
(Ia)	-	930.[c]	-	-
α-chymotrypsin	-	560.[d]	-	-

[a] See note 5 for conditions; $[\text{ester}]_0 = 0.4 - 1.5 \times 10^{-5}$ $\underline{M}$. [b] Approximate value; [c] 30°, 3% EtOH, $\mu = 0.01$ (KCl), 0.01 $\underline{M}$ borate buffer, pH 8.0, [CTABr $= 1 \times 10^{-3}$ $\underline{M}$, $[\text{PNPA}]_0 = 1 \times 10^{-4}$ $\underline{M}$; see ref. 1. [d] 25.1°, 10% CH_3CN, 0.1 $\underline{M}$ phosphate buffer, pH 7.94; see ref. 11.

$\lesssim 2 \times 10^{-4} s^{-1}$ at pH 7.95, is low as expected for very effective monofunctional nucleophilic reagents. Further functionalization of surfactants structures (IV) aimed at improving their deacylation rate [1] may lead to an extremely efficient micellar catalyst.

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5. Conditions: comicelles [CTABr]:[Functional surfact.] = 7:1, TRIS buffer, $\mu = 0.1$ (KCl), 25°, 1% CH_3CN. The operational advantages and the (partly modified) treatment of raw kinetic data are those illustrated by: C. Gitler and A. Ochoa-Solano, *J. Amer. Chem. Soc.*, **90**, 5004 (1968).

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8. Recrystallized from benzene, it had: m.p. 141-142° and satisfactory elemental analysis. Nmr (δ, $CDCl_3$): 4.55 (s, 2H); 7.3 (s, 5H).

9. Mp's: 116-118° (IVa) and 142-144° (IVb). Satisfactory elemental analysis could be obtained after several recrystallizations for samples dried *in vacuo* over P_2O_5. Nmr (δ, $CDCl_3$): 7.3 (m, 5H); 5.5 (brd " s" , 2H, $\overset{+}{N}C\underline{H}_2CO$); 3.4 [brd m, 8H, $\overset{+}{N}(C\underline{H}_3)_2C\underline{H}_2$]; 1.2 [brd " s" , 20H (IVa) or 28H (IVb), $(C\underline{H}_2)_{n-2}$]; 0.9 (" t ", 3H).

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