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A COMPARISON OF HYDROXYL- AND IMIDAZOLE-FUNCTIONALIZED MICELLAR CATALYSTS IN ESTER HYDROLYSES

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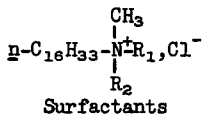
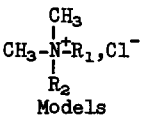
Interest in micellar catalysts, particularly as enzyme models, continues to burgeon.[3] Surfactants bearing "simple" head groups generally foster modest rate enhancements,[3] and little stereoselectivity with chiral reactants.[4] But hydroxyl-[5] and imidazole-functionalized[6] surfactants (chymotrypsin[7] "analogs") afford larger rate enhancements[5,6] and greater stereoselectivity[6h,i,8] in the catalysis of hydrolytic reactions. There has been little effort to order and interrelate the growing body of kinetic data; comparisons of catalyst effectiveness are difficult because substrates, chain lengths, counterions, and conditions vary. A comparison of the chymotrypsin analogs, under mild and constant reaction conditions, was needed, and is presented here.

Surfactants[9] and related model compounds[10] are described by Table I. The hydrolyses of



Surfactants (S series)



Models (M series)

TABLE I

Surfactant or Model	R_1	R_2
I	CH_3	CH_3
II	CH_3	CH_2CH_2OH
III	$CH_2C_6H_5$	CH_2CH_2OH
IV	CH_3	CH_2Im[a]
V	CH_2CH_2OH	CH_2Im[a]

[a] Im = 4-imidazolyl

p-nitrophenyl acetate (PNPA) and p-nitrophenyl hexanoate (PNPH), catalyzed by I-S - V-S, at 25±0.3° and pH 8 in 0.01 M[11] and 0.4 M phosphate buffers, were followed spectrophotometrically at 400 nm (liberation of p-nitrophenoxide) using Beckman DB or Durram D-110 stopped-flow spectrometers. The substrate concentration was 2×10^{-5} M, and surfactant was present in excess. Pseudo-first-order kinetics were observed.[12] The surfactant concentration was varied from run to run, so that rate constant-[surfactant] profiles were obtained. These yielded the k_{ψ}^{max} values which appear in Table II. Table III displays the k_{ψ}^{max} values relative to the hydrolytic rate constants observed in buffer alone.

In 0.01 M buffer, the effectiveness[13] order of the monofunctional surfactants toward PNPA is IV>III>II>I; in terms of k_{ψ}^{max}, IV:II:I ~ 1200:12:1. Toward the more hydrophobic PNPH, imidazole-surfactant IV is 1500 times more effective than non-functionalized I. These observations parallel previous findings,[5b,c,d,6g] but quantify the very large rate enhancements obtainable with IV, at relatively low pH, and the marked superiority of the imidazole-surfactant, IV over the choline-

Table II. $10^5 k_{\psi}^{max}$ (sec^{-1}) for Hydrolyses of PNPA and PNPH Catalyzed by Surfactant Micelles and Corresponding Model Compounds.[a]

Catalyst[b]	0.01 M Buffer				0.4 M Buffer			
	Surfactant[c]		Model		Surfactant[c]		Model	
	PNPA	PNPH	PNPA	PNPH	PNPA	PNPH	PNPA	PNPH
none	1.8	2.1			8.1	2.7		
I	16. [1.8]	27. [0.18]	2.1	1.7				
II	190. [1.4]				200. [2.3]	130. [0.8]	14.	30
III	450. [0.7]							
IV	20,000. [4.0]	43,000. [0.25]	13.	5.5	11,000. [3.0]	17,000. [1.0]	37.	23
V	13,000. [2.8]	21,000. [0.13]	9.6	2.9	7,500. [3.0]	15,000. [0.5]	93.	28
IV+II[d]					5,600. [2.5]	7,000. [2.5]		
Imid[e]			1,400.	220.			1,700.	290

[a] See text for conditions. [b] See Table I for structures of surfactants and models. [c] Numbers in brackets [ ] are concentrations (M x 100) at which k_{ψ}^{max} was determined; k_{ψ} values for corresponding model compounds were obtained at similar concentrations. [d] An equimolar solution of IV+II was used; optimal catalysis was obtained with a solution which was 2.5×10^{-2} M in each surfactant. [e] Imidazole alone. Concentrations were 3×10^{-2}, 6×10^{-3}, 3×10^{-2}, and 6×10^{-3} M, respectively.

Table III. k_{ψ}^{max} Relative to k_{ψ} in the Absence of Catalyst.[a]

[Buffer]	Substrate	Catalyst					
		None	I	II	III	IV	V
0.01 M	PNPA	1.0	8.9	110	250	11,000	7,200
0.01 M	PNPH	1.0	13			20,000	10,000
0.4 M	PNPA	1.0		25		1,400	930
0.4 M	PNPH	1.0		48		6,300	5,600

[a] Data is rounded to 2 significant figures.

surfactant, II. Similar trends are seen in the more concentrated buffer, but k_{ψ}^{max} values are generally lower, and relative rate scales are compressed.

Alternative suggestions to account for the greater effectiveness of II over I include: (a) the OH functions as a general acid, activating the substrate toward nucleophilic attack by H-bonding to its carbonyl oxygen;[5b,d] (b) the OH is partially converted to the far more nucleophilic alkoxide, which is responsible for the catalytic enhancement;[5a,c,e,g] (c) the activity of external OH^- is greater in the Stern layer of the choline-surfactant micelles.[5f] Mechanism (b) is strongly supported by the recent work of Martinek et. al.[5g] Our observations that bifunctional surfactant V is a poorer catalyst than monofunctional IV in all situations, and that a 1:1 co-micelle of II and IV is less effective than IV alone, speaks against general acid catalysis by II (mechanism a). Were it operative, such catalysis should be cooperative with nucleophilic catalysis by imidazole-surfactants, and should afford rate enhancements, rather than retardations, when both -OH and -Im functions are present.

Recent work of the Moscow group[6d-f] indicates that the anion is the catalytic form of the imidazole moiety in cationic surfactant micelles. Our observations support this view. Although imidazole itself is a good catalyst for the hydrolysis of PNPA or PNPH[7] (cf., Table II), the acylation step involves a dipolar transition state with positive charge development on the imidazole.[7] Such a step would be inhibited if the imidazole moiety were bonded to a cation. Indeed, IV-M and V-M are considerably poorer catalysts than imidazole toward PNPA or PNPH (Table II). Were imidazole solely in its neutral form in micelles of IV-S and V-S, then its catalytic effectiveness would be inferior even to that of IV-M or V-M.[14] The great effectiveness of the imidazole-surfactant micelles therefore requires that the imidazole anion, and not the neutral imidazole moiety, be the catalytic center in micellar IV and V.

Relative to IV-M, the enhanced effectiveness of IV-S can be attributed to binding of the substrates by the micelles; enhanced acidity of the imidazole moiety of IV-S in the micelle's positive field and consequent partial deprotonation to the highly nucleophilic imidazole anion, and stabilization of the transition state for the attack of the anion on PNPA or PNPH.[15] Assessment of the relative weights of these factors, and a comparable partition of the enhancement fostered by II-S (relative to II-M), await further work; such an analysis has been presented for the benzimidazole-CTABr system.[6f]

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(1) Fellow of the Alfred P. Sloan Foundation.

(2) Allied Chemical Company Fellow, 1974-5.

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(9) Surfactants III-S, IV-S, and V-S gave satisfactory elemental analyses and nmr spectra. Their cmc's, determined by surface tension measurements,[4] were: III-S, 1.2 x 10^{-4} M (H_2O, 25°); IV-S, 7.9 x 10^{-5} M (0.01 M phosphate buffer, pH 8, 25°); V-S, 6.8 x 10^{-5} M (0.01 M phosphate buffer, pH 8, 25°).

(10) Model compounds IV-M and V-M were prepared from 4-chloromethylimidazole and trimethylamine or N,N-dimethylethanolamine, respectively. They had definitive nmr spectra, but satisfactory elemental analyses could not be obtained due to their extreme hygroscopicity.

(11) Solutions of IV-S or V-S (~10^{-2} M) in 0.01 M buffer required adjustments of ~+0.3 pH units to restore pH 8.0. This was done by adding NaOH at the pH meter immediately prior to use.

(12) Individual rate constants were obtained from absorbance or transmittance data by standard computational methods: K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, 1964, pp. 313-315, 558-565.

(13) "Effectiveness" refers to comparative values of k_{ψ}^{max}.

(14) Reactions of ester substrates with neutral nucleophiles are little affected by ionic surfactants of any charge type.[3c] Moreover, acylation of neutral benzimidazole or of N-methylbenzimidazole is inhibited in a cationic micelle because the development of the dipolar transition state from the neutral reactants is less favorable in the less polar micellar medium than in aqueous solution.[6f] Application to the case at hand seems clear.

(15) The negative charge on the anionic imidazole moiety would be dispersed in the transition state for attack on an ester. Charge dispersal would be favored in the micellar medium.