Functional Micellar Catalysis. Part 7.[1] Cleavage of Activated Enantiomeric Substrates by Chiral Functional Surfactant Systems

Roberto Fornasier and Umberto Tonellato*
Centro 'Meccanismi di Reazioni Organiche' del C.N.R., Istituto di Chimica Organica, Universita di Padova, 35131 Padova, Italy

The cleavage of enantiomeric *p*-nitrophenyl derivatives of the *N*-methyl-*N*-1-[hydroxy(phenyl)methyl]-ethylcarbamate (**3**), the 1-methylheptyl carbonate (**4**) and the α-methoxyphenylacetate (**5**) in the presence of homomicelles of *N*-hexadecyl-*N*-methylephedrinium bromide (**1**) and co-micelles composed of *N*$^{\alpha}$-myristoyl-L-histidine (**2**) and hexadecyltrimethylammonium bromide or (**1**) was investigated. Rate effects ranging from inhibition to large enhancements and enantioselectivities ranging from 1.0 to 3.3 were observed.

In the last few years, considerable attention has been devoted to micellar control of the stereochemistry of organic reactions.[2-8] In particular, efforts have been focused upon enantioselective esterolysis of chiral substrates in micelles of chiral surfactants[2,6] or diastereoselective reactions between nucleophilic surfactants and di- or tri-peptide esters.[7] Following early reports of modest experimental success[8,9] [such as a *ca.* 10% difference in reactivity between the two enantiomers of *p*-nitrophenyl α-methoxyphenylacetate solubilized in (−)-*N*-n-decyl-*N*-methylephedrinium bromide micelles[9]], remarkable enantioselectivities have been recorded in the deacylation of *p*-nitrophenyl esters of amino-acid derivatives with cationic co-micelles containing histidine derivatives[3b,5,6] or in the cleavage of diastereoisomeric dipeptide derivatives by a micellar thiocholine-type surfactant.[7d]

$PhCH(OH)CH(Me)\overset{+}{N}(Me)_2C_{16}H_{33}Br^-$
(**1**) CMEB

(+) 1*S*,2R
(−) 1*R*,2*S*

$ImCH_2CH(CO_2H)NHCOC_{13}H_{27}$
(**2**) MyrHis

$PhCH(OH)CH(Me)N(Me)CO_2PNP$
(**3**) PNPE

(+) 1*R*,2*S*
(−) 1*S*,2*R*

$C_6H_{13}CH(Me)OCO_2PNP$
(**4**) PNPO

(+) *S*
(−) *R*

$PhCH(OMe)CO_2PNP$
(**5**) PNPM
(+) *S*
(−) *R*

Im = imidazol-4-yl

PNP = *p*-nitrophenyl

Published data are still fragmentary and only in a few cases has a rationale been offered.[6,7] In an effort to gain some insight into the factors governing micellar stereochemistry we have investigated and here report the kinetic effects of micelles of the enantiomers of (**1**) (CMEB) and of co-micelles containing L-myristoylhistidine (**2**) (MyrHis) on the cleavage of the enantiomers of carbamate (**3**) (PNPE), of carbonate (**4**) (PNPO), and of ester (**5**) (PNPM), mostly in pH 8.8—9.5 aqueous borate buffers. Surfactant (**1**) is structurally related to choline-type surfactants which have been shown[10,11] to react with activated esters *via* acylation of their hydroxy function and MyrHis (**2**) is well known[11,12] to react using the imidazole ring as the nucleophilic site.

Results and Discussion

Surfactants (**1**) and carbamates (**3**) were obtained from (+)- and (−)-ephedrine, carbonates (**4**) from the enantiomers of octan-2-ol, and ester (**5**) from the enantiomers of mandelic acid following described[8,13] or standard synthetic procedures. The enantiomers of CMEB (**1**) are slightly soluble in water (up to 5—6 × 10^{-4}M at 25 °C, pH 9.5 borate buffer) and dissolve better than the racemic compound. Their critical micelle concentration (c.m.c.) is *ca.* 3 × 10^{-5}M as determined by surface tension measurements; slightly larger values (4—5 × 10^{-5}M) were evaluated from kinetic measurements and were virtually identical for enantiomeric surfactants and substrates. L-MyrHis (**2**) was used as component of co-micelles with cetyltrimethylammonium bromide (CTAB) or with CMEB.

Rate measurements were made for 0.02M-borate buffers at pH 9.5 and pH 8.8 in the case of PNPM, with the condition[14] [surfactant] ≫ [substrate], with added 1% v/v CH_3CN, at 25 °C. We were aware of ageing effects, as reported by Hindman and Jacobus[15] and by Moss and Sunshine,[8] and we also found substantial effects, particularly in the case of CMEB. Rate data were, therefore, collected for fresh solutions and the same stock solutions of surfactants were used for each pair of enantiomeric substrates.

The rate profiles (at least six kinetic runs each; see Figure) were obtained from the observed pseudo-first-order rate constants k_ψ for the appearance of *p*-nitrophenol. The kinetic parameters k_c, the second-order apparent catalytic rate constant, and K_s, the association constant of the substrate to the

Table 1. Apparent catalytic rate constants[a] (k_c/l mol^{-1} s^{-1}) and association constants (10^3K_s/l mol^{-1}) for the cleavage of enantiomeric substrates (3)—(5) at pH 9.5 (PNPE and PNPO) and pH 8.8 (PNPM)

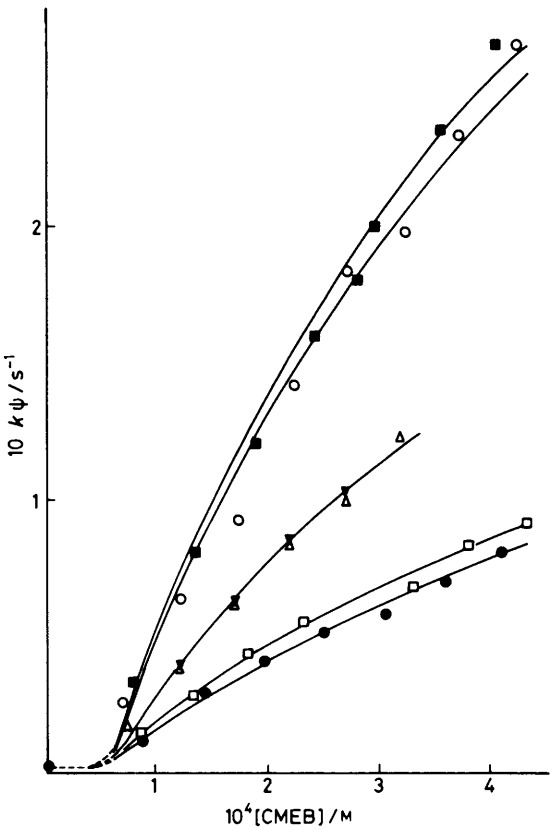
Micellar system	PNPE (3)				PNPO (4)				PNPM (5)			
	(+)		(−)		(+)		(−)		(+)		(−)	
	k_c	K_s	k_c	K_s	k_c	K_s	k_c	K_s	k_c	K_s	k_c	K_s
(+)-CMEB	6.0	0.7	5.0	0.7	46	7.1	38	7.3	380	1.8	1 180	1.95
(−)-CMEB	4.8	0.7	5.9	0.7	39	7.4	47	7.3	1 220	1.8	360	1.8
CMEB	5.7	0.7	5.6	0.7	67	8.1	70	8.8	690	1.85	680	1.8
CTAB	(4.5)	1.7	(4.6)	1.7	(2)	15			(190)	6.7	(210)	7.0
CTAB–MyrHis[b]	(3.8)[d]	2.0	(4.0)[d]	2.0	420	20	360	20	7 800	8.7	8 650	8.1
(+)-CMEB–MyrHis[c]	(3.5)	0.6	(3.4)	0.6	108	26	201	31	730	2.1	1 150	1.9
(−)-CMEB–MyrHis[c]	(3.4)	0.6	(3.5)	0.6	200	28	230	29	1 250	2.0	810	2.1

[a] Values in parentheses: see text. [b] CTAB:MyrHis = 8.5:1. [c] CMEB:MyrHis = 7:1. [d] (2.3) [(+)-PNPE] and (2.4) [(−)-PNPE] for CTAB:MyrHis = 3.6:1.

Table 2. Enantioselectivities, $k_c^{(+)}/k_c^{(-)}$ ($k_c^{(-)}/k_c^{(+)}$), for substrates (3)—(5) in the presence of chiral surfactant systems.

Substrate	(+)-CMEB	(−)-CMEB	MyrHis–CTAB[a]	MyrHis–(+)-CMEB[b]	MyrHis–(−)-CMEB[b]
PNPE[c]	1.2	(1.2)	1.0	*ca.* 1.0	*ca.* 1.0
PNPO[c]	1.2	(1.2)	1.15	1.85	(1.15)
PNPM[d]	(3.1)	3.3	(1.1)	1.55	(1.54)

[a] CTAB:MyrHis = 8.5:1. [b] CMEB:MyrHis = 7:1. [c] pH 9.5. [d] pH 8.8.



Rate–concentration profiles for the cleavage of PNPM in the presence of CMEB. Symbols (the rotatory sign of CMEB precedes that of PNPM): ■ (−), (+); ○ (+), (−); □ (+), (+); ● (−), (−); ▼ (±), (+); △ (±), (−). Lines were calculated using the rate equation in the Experimental section and the kinetic parameters of Table 1

micellized surfactants, were evaluated following a described[14] model and procedure (see also Experimental section). Experimental scatter of rate and c.m.c. data, and the rather limited range of concentrations explored in the case of CMEB micelles (see Figure) or co-micelles, point to a rather large error affecting particularly (partly by choice in the computation procedures) the K_s values.

The k_c and K_s values are reported in Table 1. The k_c values shown in parentheses refer to CTAB or other surfactant systems which, by all the evidence (see below), do not react as functional micelles; the k_c values for co-micelles CMEB–MyrHis have been evaluated as if they were homomicelles.

As summarized in Table 2 the enantioselectivity observed ranges from total absence to a factor of 3.3 in the cleavage of PNPM in homomicelles of CMEB. As already pointed out, small rate differences should be regarded with caution but, at least in the case of micellar CMEB, the data reported in the Tables are presented with a good degree of confidence. In fact, we have investigated the activity of the two enantiomeric surfactants for each pair of enantiomeric substrates and found similar (within expected errors) kinetic effects.

The cleavage of carbamate PNPE is normally accelerated by non-functional CTAB micelles ($k_{\psi max.}:k_o$ *ca.* 30). It is, however, surprisingly insensitive to imidazole-functionalized micelles. Thus, addition of MyrHis to micellar CTAB or CMEB results in a decrease of the apparent rate of cleavage of PNPE. We also proved that PNPE is virtually insensitive to other imidazole-functionalized surfactants such as $C_{16}H_{33}\overset{+}{N}(Me)_2CH_2Im$ Cl^-, a potent esterolytic agent toward *p*-nitrophenyl acetate or hexanoate.[11,16] The inhibitory effect of MyrHis which increases as the MyrHis:CTABr ratio increases (see Table 1) may well be due[17] to partial neutralization of the positive charge of the cationic micelles by the carboxylate group of the histidine residue (lesser concentration of the reactive OH^- counter-ions at the micellar surface) assuming complete inertness of the imidazole ring. Literature data[18] indicate that the alkaline hydrolysis of *N*-disubstituted carbamates is very sensitive to the size of the nitrogen-substituents. We infer that steric hindrance to nucleophilic attack at the carbonyl group by the bulky imidazole ring is a quite reasonable explanation for the effects observed with co-micelles containing MyrHis (as well as other imidazole-functionalized surfactants). In this case no en-

antioselectivity is observed. On the other hand, CMEB homomicelles are better catalysts than those of CTAB in the cleavage of PNPE and this indicates that the ephedrinium surfactant reacts, at least partially, *via* nucleophilic attack of the (dissociated[10,11]) hydroxy-function which has lesser steric requirements than the imidazole moiety. In the case of CMEB, PNPE enantioselectivity, although by a small factor, is observed. When MyrHis is added to CMEB, inhibition and no enantioselectivity is observed, due, presumably, to the same electrostatic factors invoked in the case of MyrHis–CTAB co-micelles.

At variance with that of PNPE, the cleavage of both carbonate PNPO and ester PNPM is very sensitive to functional micelles. Large rate enhancements were recorded in the presence of CMEB micelles and co-micelles containing MyrHis and in each case enantioselectivities were observed.

The large enantioselectivity (3.1—3.3) observed in the case of the enantiomers of PNPM in the presence of CMEB homomicelles came to us as a surprise in view of the very small (*ca.* 10%, see above) kinetic differences reported by Bunton and his co-workers[9] for the same substrates and micellar (−)-*N*-dodecyl-*N*-methylephedrinium bromide in pH 9.0 borate buffer. Such a dramatic change on going from a dodecyl to a hexadecyl moiety in the surfactant's structure is unprecedented and merits further study which is in progress. Furthermore, in the above cited study,[9] racemic PNPM was found to react considerably slower than each enantiomer in the presence of the (−)-ephedrinium surfactant. We found, instead, that the appearance of *p*-nitrophenol from racemic PNPM in the presence of (+)-CMEB did not follow simple first-order kinetics but was apparently the combined result of two kinetically first-order processes with different rate constants, the slower one being similar to that measured for the slower (*S*)-PNPM enantiomer.

Racemic CMEB micelles are not enantioselective, as expected. However, while in the cleavage of PNPM and PNPE average kinetic effects were observed (as shown in the Figure for PNPM) the racemic surfactant's micelles were more effective in the cleavage of PNPO than those of each enantiomer of CMEB. Possibly, the interactions between these enantiomers, which lead to a racemic compound in the solid state (see Experimental section), are also effective in the micellar aggregate and a racemate–substrate interaction may lead to a more effective reaction path than enantiomer–substrate interaction in the case of PNPO.

Although a blend of positive and negative results offers a rather complicated picture, this work presents the following indications. Chiral surfactants which react as nucleophilic agents appear to be required for substantial stereoselectivity: as with non-functionalized,[8] functionalized but inert chiral surfactants (*e.g.* MyrHis and PNPE) are also not enantioselective. Furthermore, the proximity of the chiral centres and active sites improves the degree of enantiomeric discrimination (larger factors in the cleavage of PNPM than in those of PNPO and PNPE). Finally, as pointed out in other studies,[6–8] enantioselectivity is not the consequence of micellar discrimination between the enantiomers (the K_s values are similar) but the result of differences in the free energies of diastereoisomeric transition states.

Experimental

Cetyltrimethylammonium bromide (CTAB) and the enantiomers of ephedrine, octan-2-ol, and mandelic acid were commercial products. N^{α}-Myristoylhistidine (**2**) was obtained according to Gitler and Solano,[12a] (−)-*N*-methylephedrine $[\alpha]_D^{25}$ −24.2° (*c* 0.01 in EtOH) was obtained from (−)-(1*R*,2*S*)-ephedrine and the dextrotatory enantiomer, $[\alpha]_D^{25}$ +24.5° (*c* 0.01 in EtOH), from (+)-ephedrine as described.[19] (+)-(*S*)-*p*-Nitrophenyl α-methoxyphenylacetate, PNPM (**5**), and its enantiomer were obtained from (+)-(*S*)- and (−)-(*R*)-mandelic acid, following the procedure described by Moss and Sunshine.[8] (+)-(1*S*,2*R*)-*N*-Hexadecyl-*N*-methylephedrinium bromide (**1**), $[\alpha]_D^{25}$ +10.9° (*c* 0.01 in EtOH), m.p. 115—116 °C (lit.,[13] 116—117 °C) was obtained by quaternization with hexadecyl bromide of (+)-*N*-methylephedrine while the levorotatory isomer, $[\alpha]_D^{25}$ −10.8° (*c* 0.01 in EtOH), m.p. 114—116 °C, was similarly obtained from (−)-*N*-methylephedrine. A 1:1 mixture of enantiomeric CMEB form a racemic compound as clearly revealed by the characteristic m.p. curve, with a 25 °C higher m.p. and a 42 °C higher transition to liquid crystals than that of each enantiomer.

(+)-(1R,2S)-p-*Nitrophenyl* N-*Methyl*-N-1-[*hydroxy*-(*phenyl*)*methyl*]*ethylcarbamate* (**3**) (*PNPE*).—A solution of *p*-nitrophenyl chloroformate (0.63 g, 3.1 mmol) in dichloromethane was added to a solution of (−)-*N*-methylephedrine (1.03 g, 6.2 mmol) in the same solvent. The reaction mixture was stirred at room temperature for 10 h and then the precipitated ephedrinium salt was filtered off. The solution was evaporated to dryness and the residue chromatographed on a silica gel column using a 95:5 chloroform–methanol mixture as eluant. The oily product was crystallized from n-hexane to give the *product* (0.47 g, 46%), m.p. 98—100 °C (Found: C, 61.3; H, 5.2; N, 8.35. $C_{17}H_{18}N_2O_5$ requires C, 61.8; H, 5.45; N, 8.5%); $[\alpha]_D^{25}$ +9.9° (*c* 0.01 in EtOH); δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, d), 2.9 (4 H, m), 3.9—4.8 (2 H, m), and 6.5—8.2 (9 H, m).

The (−)-(1S,2R)-*isomer* was similarly obtained from (+)-*N*-methylephedrine, m.p. 98—99.5 °C, $[\alpha]_D^{25}$ +9.8° (*c* 0.01 in EtOH).

(+)-(S)-p-*Nitrophenyl* 1-*Methylheptyl Carbonate* (**4**) (*PNPO*).—(−)-(*S*)-Octan-2-ol (0.32 g, 2.4 mmol) and pyridine (0.24 ml, 3 mmol) were added slowly and under stirring to a solution of *p*-nitrophenyl chloroformate (0.53 g, 2.6 mmol) in chloroform (5 ml). After 12 h at room temperature under stirring, the mixture was evaporated to dryness. Chromatography on a silica gel column using a 1:1 mixture of ether and light petroleum gave a viscous *oil* (0.34 g, 45%) (Found: C, 61.3; H, 7.2; N, 4.95. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.15; N, 4.75%); $[\alpha]_D^{25}$ +5.1° (*c* 0.03 in $CHCl_3$); δ_H (60 MHz; $CDCl_3$) 1.4 (16 H, m), 4.9 (1 H, q), and 7.2—8.3 (4 H, m).

The (−)-(R)-*isomer* was obtained from (+)-(*R*)-octan-2-ol following the same procedure, $[\alpha]_D^{25}$ −5.05° (*c* 0.028 in $CHCl_3$).

Kinetic Measurements.—The general procedure has been described.[20] The appearance of *p*-nitrophenol was monitored at 410 nm using a Varian Cary 219 or a Carlo Erba Spectracomp 601 instrument equipped with thermostatted cell holder and magnetic stirrer. The observed rate constants were related, in the case of homomicelles, by the equation $k_\psi = (k_o + k_c[D]_m)/(1 + K_s[D]_m)$, to the k_c and K_s parameters defined above, to $[D]_m$, the concentration of the micellar surfactant(s), and to k_o, the k_ψ value measured in the absence of micelles. The k_c and K_s parameters have been evaluated from linear correlations between the reciprocal values of the corrected k_ψ constants and $[D]_m$ as described.[14]

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