Effect of Micelles on Cyclization Reactions: The Use of *N*-Hexadecyl-2-chloropyridinium Iodide as an Amphiphilic Carboxyl-Activating Agent in Lactonization and Lactamization

I. Rico,* K. Halvorsen, C. Dubrule, and A. Lattes

Laboratoire des IMRCP, UA CNRS 470, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cédex, France

Received March 17, 1993 (Revised Manuscript Received September 27, 1993)*

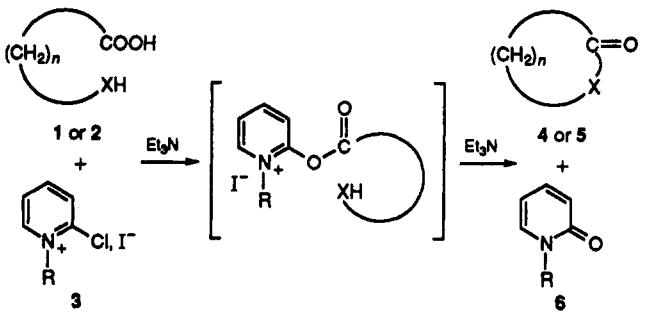
Lactonization and lactamization with a novel carboxyl-activating agent, *N*-hexadecyl-2-chloropyridinium iodide (C_{16}PyCl,I), were investigated. The organization of this agent in micelles in the reaction medium facilitates cyclization giving rise to a micellar effect. Under these conditions, the corresponding lactam is produced from the ω-amino acid 12-aminododecanoic acid in good yield (double that obtained with the Mukaiyama reagent, *N*-methyl-2-chloropyridinium iodide C_1PyCl,I). On the other hand, the yield of lactone from 16-hydroxyhexadecanoic acid was the same with either carboxyl-activating agent. These results were accounted for in terms of substrate-dependent micellar effects. Because of solubility effects, the ω-amino acids and ω-hydroxy acids are not localized in comparable ways *vis á vis* the interface and, thus, have different reactivities. Moreover, hydrolysis of the reagents, C_{16}PyCl,I and C_1PyCl,I, was also detected. The interference of this reaction with the cyclization process was also found to depend on a micellar effect with C_{16}PyCl,I that is not observed with C_1PyCl,I.

Introduction

The preparation of compounds with medium and large rings is of considerable interest in view of the number of naturally occuring compounds with 7–20-membered rings, specially lactones and lactams.[1] The formation of these rings is entropically unfavorable and intermolecular dimerization or polymerization processes cannot always be circumbented, even with high-dilution techniques. Therefore the carboxyl groups of ω-hydroxy acids and ω-amino acids need to be activated in order to prepare the corresponding lactones and lactams. For example, Mukaiyama described the use of *N*-methyl-2-chloropyridinium iodide (C_1PyCl,I) as a carboxyl activating agent.[2]

Previous studies of cyclization reactions in micellar environments include lactonization in reverse micelles[3] and more recently cyclization of *o*-(ω-bromoalkoxy)-phenoxides in aqueous direct micelles.[4] Jaeger *et al.*[3] attempted to use reverse micelles of Aerosol OT (AOT) or didodecyldimethylammonium bromide (DDAB) to favor lactonization of 15-hydroxypentadecanoic acid but were unsuccessful. In contrast, Lennox *et al.* observed enhanced cyclization rates due to the looping of the substrate at the interface of the micelle, an effect similar to a "2D template" effect.[4b]

We tried to use this effect for both lactonization and lactamization by using *N*-hexadecyl-2-chloropyridinium (C_{16}PyCl,I) instead of *N*-methyl-2-chloropyridinium iodide. Then we explored the possibility of creating a micellar effect by means of molecular aggregation of C_{16}-PyCl,I in the reaction mixture and looping of either the ω-amino acid or the ω-hydroxy acid at the interface of the micelle. *It is noteworthy that we used N-hexadecyl-2-chloropyridinium iodide both as a constituent of the micelles and as a reagent: we have frequently applied this principle of "molecular economy" to other reactions in organized systems.*[5] Thus, we compared the action of C_{16}PyCl,I with that of C_1PyCl,I for lactamization or lactonization as described in the following reaction:



1,4: XH = OH; *n* = 15
2,5: XH = NH_2; *n* = 11
3a (C_1PyCl, I), **6a:** R = CH_3; **3b** (C_{16} PyCl, I), **6b:** R = $C_{16}H_{33}$

Results

1. Synthesis of *N*-Hexadecyl-2-chloropyridinium Iodide (C_{16}PyCl,I). Al Lohedan *et al.* described the preparation of *N*-alkyl-2-bromopyridinium iodide by direct alkylation of 2-bromopyridine by the alkyl iodide.[6] The authors did not report the concentrations of starting compounds and only indicated that the stoichiometric reaction was carried out under reflux in acetonitrile for 4 days. When this method was applied to 2-chloropyridine and hexadecyl iodide, we found that the yields of *N*-hexadecyl-2-chloropyridinium iodide were less than 10%, regardless of the concentrations of starting materials and reaction durations. These low yields are due to the presence of chlorine in the α-position to the nitrogen, which

* Abstract published in *Advance ACS Abstracts,* December 15, 1993.

(1) Paterson, I.; Mansouri, M. M.; *Tetrahedron* **1985**, *41*, 3569 and refs herein.
(2) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707.
(3) Jaeger, D. A.; Ippoliti, J. T. *J. Org. Chem.* **1981**, *46*, 4964.
(4) (a) Cerricelli, G.; Luchetti, L.; Mancini, G.; Muzzioli, M. N.; Germani, R.; Ponti, P. D.; Spreti, N.; Savelli, G.; Bunton, C. A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 2, 1801. (b) Wei, I.; Lucas, A.; Yue, J.; Lennox, R. B. *Langmuir* **1991**, *7*, 1336.
(5) (a) Lattes, A.; Rico, I. *Pour la Science* **1992**, *173*, 44. (b) Gautier, M.; Rico, I.; Lattes, A. *J. Org. Chem.* **1990**, *55*, 1500.
(6) Al Lohedan, H. A.; Bunton, C. A.; Romsted, L. S. *J. Org. Chem.* **1982**, *47*, 3528.

0022-3263/94/1959-0415$04.50/0

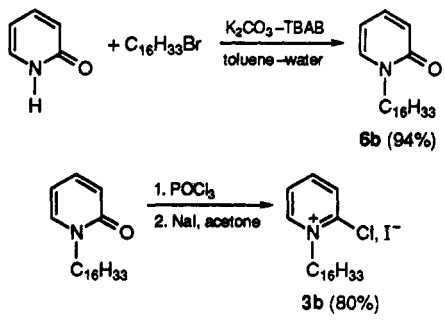
Table 1.[a,b] Physicochemical Parameters Pertaining to Polarity and Structure of Various Solvents[10-12]

solvents	ϵ_r	μ (10^{-30} C m)	E^N_T	ced (J cm^{-3})	δ (J cm^{-3})$^{1/2}$
1,2-dichloroethane	10.4	6.1	0.327	416	20
water	78.3	5.9	1.000	2302	48
formamide (F)	109	11.2	0.799	1575	39
DMF	36.7	10.8	0.404	582	24
dichloromethane	8.9	5.2	0.309	414	-
chloroform	4.8	3.8	0.259	362	19
benzene	2.3	0.0	0.11	357	18

[a] Parameters relating to polarity: ϵ_r (electrical permitivity at 25 °C), μ (dipole moment in C m, 1 Debye = $3.336.10^{-30}$ C m), E^N_T (normalized polarity parameters derived from the transition energy at 25 °C of the charge-transfer band at long wavelength for a standard pyridinium *N*-phenate betaine[10]). [b] Parameters relating to cohesion of the solvent: ced (cohesion energy density) = $\Delta U_{vap}/V$, δ (Hildebrand's solubility parameter).

reduces the nucleophilic character of pyridine: the pK_a of the conjugate acid of 2-chloropyridine is 0.72 versus 5.20 for the conjugate acid of the nonsubstituted pyridine.[7]

In view of the difficulty of direct alkylation, we developed a new two-step procedure illustrated in the following reaction scheme:



The first stage is a phase-transfer reaction in giving a 94% yield of *N*-hexadecyl-2-pyridone (**6b**). These conditions prevent O-alkylation of the 2-hydroxypyridine, which tends to predominate under normal alkylation conditions. The second stage is a one-pot process, in which the *N*-hexadecylpyridone (**6b**) is chlorinated and the chloride ion is replaced by iodide, that affords *N*-hexadecyl-2-chloropyridinium iodide (**3b**) in 80% yield.

2. Physicochemical Study of *N*-Hexadecyl-2-chloropyridinium Iodide (C_{16}PyCl,I). Experiments were designed to establish the existence of aggregates of C_{16}PyCl,I and to determine whether direct or inverse aggregates are formed by this agent in the solvent usually used for the cyclization reaction with the classical Mukaiyama reagent: 1,2-dichloroethane.[2]

2-1. Direct or Inverse Micelles? Table 1 provides information on the polarity and the cohesion of 1,2-dichloroethane. Table 1 also lists physical parameters of (i) water, formamide (F), and DMF which belong to a family of solvents that are sufficiently polar and structured to enable formation of direct micelles (DMF is the limit case)[8] and (ii) benzene, chloroform, and dichloromethane, which, because of their low polarity, lead to formation of inverse micelles.[9] The cohesion energy density and polarity of 1,2-dichloroethane are similar to those of dichloromethane. Inverse micelles of cationic surfactants

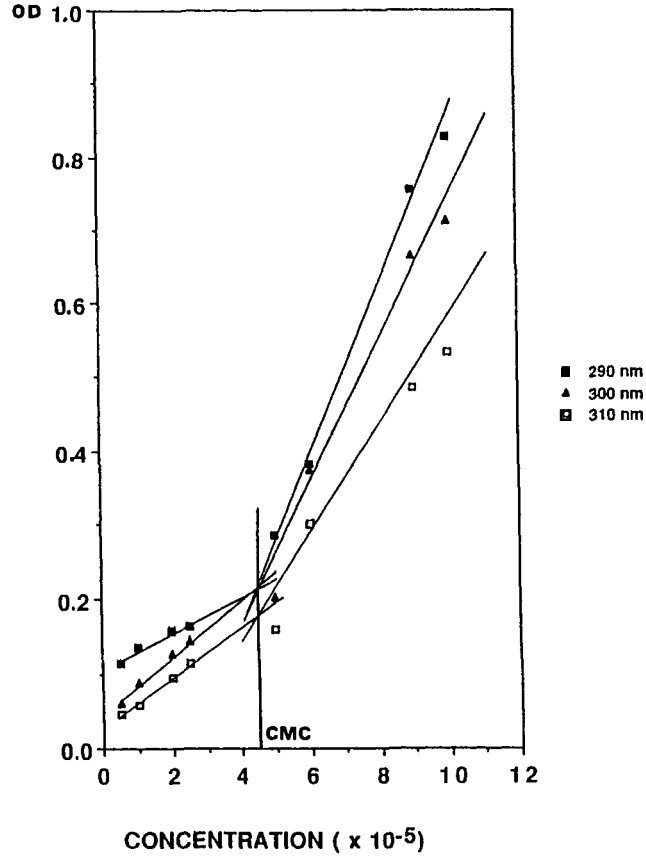


Figure 1. Plot of absorbance OD against concentration (M) of C_{16}PyCl,I in 1,2-dichloroethane at 25 °C.

such as the alkylammonium propionates have been shown to form in dichloromethane. The critical micellar concentrations (CMC) were found to be around 10^{-2} M at 25 °C for C_6 to C_{10} alkyl chains with aggregation numbers of 6–7.[13,14] *Thus, inverse micelles would be expected in 1,2-dichlorethane.*

2-2. Micellization of C_{16}PyCl,I in 1,2-dichlorethane.

(a) Critical Micellar Concentrations (CMC). The CMC of C_{16}PyCl,I was determined by UV spectrophotometry, which was used in a previous study to determine the CMC values of unsubstituted *N*-alkylpyridinium halides (C_nPy,X) in water[15] and in organic solvents such as benzene or chloroform.[16] Measurements were made in the region of the charge-transfer band. This intense and spread out band is due to formation of a complex between I^- and the pyridinium ring. The CMC of the surfactant is determined from the change in slope of the plot of absorbance against substrate concentration. This change reflects the stronger association of I^- with the micelle than with the monomer prior to micellization. This method was used for C_{16}PyCl,I at wavelengths within the relevant charge-transfer bands (λ = 290, 300, and 310 nm in 1,2-dichloroethane). The results obtained at 25 °C are illustrated in Figure 1. In 1,2-dichloroethane, the change in slope was observed around 4.5×10^{-5} M. This value

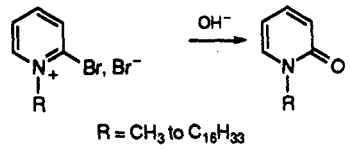
(7) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley Interscience: New York, 1985.
(8) Auvray, X.; Perche, T.; Petipas, C.; Anthore, R.; Marti, M. J.; Rico, I.; Lattes, A. *Langmuir* **1992**, *8*, 2671.
(9) Eicke, H. F. *Top. Curr. Chem.* **1980**, *87*, 85.
(10) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988; pp 408–410.
(11) Dack, M. R. J. *Aust. J. Chem.* **1975**, *28*, 1643.
(12) Dack, M. R. J. *Chem. Soc. Rev.* **1975**, *4*, 211.
(13) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic Press: New York, 1975; pp 320–325.
(14) El Seoud, O. A.; Fendler, E. J.; Fendler, J. H.; Medary, R. T. *J. Phys. Chem.* **1973**, *77*, 1876.
(15) Mukerjee, P.; Ray, A. *J. Phys. Chem.* **1966**, *46*, 1316.
(16) Muto, S.; Meguro, K. *Bull. Soc. Chem. Jpn.* **1973**, *46*, 1316.

is much lower than the CMC values (10^{-2} M) observed for the alkylammonium propionates in dichloromethane.[13,14] However, the CMC values of *N*-alkylpyridinium salts are generally much lower than those of surfactants lacking this type of aromatic ring in the polar head. Thus, at 25 °C, the CMC of *N*-dodecylpyridinium iodide is 7.10^{-5} M in benzene, whereas that of dodecylammonium propionate is 2.10^{-3} M in the same solvent.[13] The pyridinium ring thus contributes to the hydrophobicity of the molecule. It is noteworthy that a charge-transfer band is also observed at concentrations below the CMC. This charge-transfer band at low concentration is indicative of the existence of ion pairs of the activation agent in 1,2-dichloroethane, a relatively weak dissociating solvent (ϵ_r = 10.4 at 25 °C). More detailed studies of the size and aggregation number of such micelles in 1,2-dichloroethane by quasielastic light scattering are in progress. Preliminary results indicate the presence of small aggregates.[17]

All these results show that C_{16}PyCl,I forms micelles in 1,2-dichloroethane at very low concentrations. Therefore, micellar effects could be produced in a very large range of concentrations during cyclization processes.

(b) Incorporation of Water into Micelles. Inverse micelles in some cases can solubilize water,[2] whereas direct micelles solubilize hydrocarbon. To confirm the nature of the micelles, we examined the solubilization of water in micelles of C_{16}PyCl,I in 1,2-dichloroethane and found that water could not be solubilized in the inverse micelles of this surfactant. This result is not surprising since a lot of surfactants do not solubilize water in inverse micelles without a cosurfactant. Since the cyclization takes place in a medium containing both 1,2-dichloroethane and triethylamine, we examined solubilization in the presence of triethylamine (which can act as a cosurfactant) in the same proportions as those used in the cyclization reaction. In this medium the activating agent was found to hydrolyze progressively in this medium giving rise to 1-hexadecyl-2-pyridone (**6b**) (detected by capillary column GPC). Since this hydrolysis may compete with the cyclization reaction, we studied this hydrolysis reaction. For comparative purposes, the Mukaiyama reagent was also investigated under the same conditions.

2–3. Hydrolysis of C_{16}PyCl,I and C_1PyCl,I. The hydrolysis of analogous molecules in water has been reported by Bunton *et al.* who examined the following reaction under alkaline conditions:[6]



R = CH_3 to $C_{16}H_{33}$

These authors found that for R = Me and Et, hydrolysis in water was inhibited by the presence of cationic micelles of cetyltrimethylammonium bromide (CTAB). This inhibition was accounted for by weak binding of the short-chain pyridinium salts to the micelles and by the predominance of the hydrolysis reaction in the continuous aqueous phase. In contrast to the short-chain derivatives, the long-chain derivatives (R = $C_{12}H_{25}$, $C_{14}H_{29}$, and $C_{16}H_{33}$) localize at the interface of the micellar interface, and hydrolysis is thereby speeded up by a local concentration effect of both the hydrolyzable substrate and HO^- ions.

(17) Lachaise, J.; Marion, G.; Graciaa, A.; Rico, I.; Lattes, A., unpublished.

Table 2. Yields (%) of *N*-Alkyl-2-pyridone (determined by capillary column GPC) after Hydrolysis of Activation Agents C_1 PyCll and C_{16}PyCll in 1,2-dichloroethane for 24 h

	without argon		with argon	
solvent	C_1PyCl,I	C_{16}PyCl,I	C_1PyCl,I	C_{16}PyCl,I
1,2-dichloroethane (0.028 M)	20	71	0	25

In view of these results, we examined the hydrolysis reaction of the activating agents C_{16}PyCl,I and C_1PyCl,I without the addition of water and under the reflux conditions used in the cyclization reaction. Assay of the water content by the Karl Fischer method showed an initial water content of 0.02% in 1,2-dichloroethane. The hydrolysis was carried out both with and without dry argon and was followed by assay of the *N*-alkyl-2-pyridone by capillary column GPC (see Experimental Section). The same concentrations of activating agents used for the cyclization reaction were used for the hydrolyses: (i) 0.028 M in 1,2-dichloroethane (concentration used for macrolactamization) and (ii) excess triethylamine (see Experimental Section).

The results are listed in Table 2, and several comments can be made on these results. Both activating agents were hydrolyzed, especially in the absence of dry argon. *It is noteworthy that this hydrolysis reaction has not previously been described in cyclization reactions using the Mukaiyama reagent (C_1PyCl,I).* The fact that C_1PyCl,I was much less hydrolyzed than C_{16}PyCl,I can be attributed to a micellar catalytic effect for the long-chain derivative C_{16}PyCl,I, in contrast with C_1PyCl,I. In the inert argon atmosphere, the low water content of the medium (around 0.01 M or 0.02%) can account for the lack of hydrolysis of C_1PyCl,I, whereas the enhanced hydrolysis of the long-chain derivative can be explained by micellar catalysis. In this situation, the mixture (water + triethylamine) and the HO^- ions have a greater affinity for the polar micellar core than for the apolar continuous phase. The HO^- ions are thus highly concentrated within the micelle, thereby enhancing hydrolysis (see Figure 2).

3. Lactonization and Lactamization Activated by C_1PyCl,I or C_{16}PyCl,I. Since both reagents are sensitive to traces of water, we compared the cyclization reactions in the presence and absence of an atmosphere of dry argon. Lactonization of 16-hydroxydecanoic acid (1) was carried out in 1,2-dichloroethane according to the method of Mukaiyama *et al.*[2] In an attempt to avoid high dilution conditions, we employed a 5-fold higher substrate concentration ([substrate] = 0.028 M) than that described by Mukaiyama. Reagents were also added dropwise over a period of 10 min rather than by the conventional slow addition. Identical conditions were used for both C_1PyCl,I or C_{16}PyCl,I. The results are listed in Table 3.

Lactamization of 12-aminododecanoic acid (2) was also carried out according to the procedure of Mukaiyama *et al.*[2] in 1,2-dichloroethane at the same substrate concentration (0.028 M). Although the starting ω-amino acid is only weakly soluble in 1,2-dichloroethane, the lactam is quite soluble in this solvent. The reaction was thus studied in this solvent, and the reagents were added in one batch rather than dropwise. Yields of macrocyclic derivatives were determined by GPC (see Experimental Section). The results are listed in Table 4.

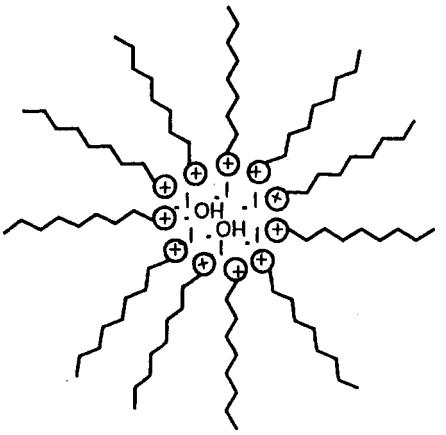


Figure 2. Hydrolysis of $C_{16}PyCl,I$ in 1,2 dichloroethane.

The following comments can be made on the reuslts in Tables 3 and 4.

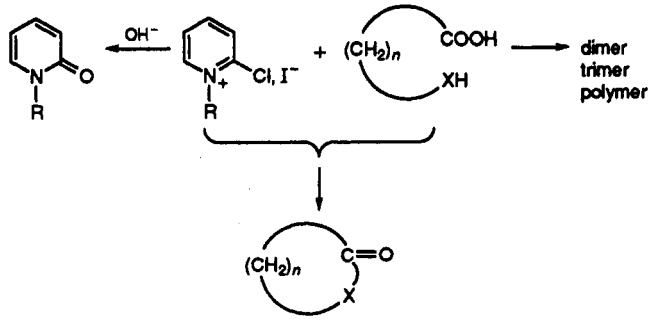
(i) Lactonization. In agreement with the results on hydrolysis of the activating agents, yields were higher in the presence of an atmosphere of dry argon (Table 3, entries 1 and 2 versus 3 and 4). Also in line with the results on hydrolysis, the competing reaction appeared to most reduce the yield for $C_{16}PyCl,I$ (entry 2 versus 4). As reported previously by Jaeger,[2] it appears that there was little micellar effect since yields were similar for both activating agents.

(ii) Lactamization. Stoichiometry had little effect on the yields of macrolactam (Table 4, entries 1 and 2 versus 3 and 4) but the presence of dry argon had a marked effect for $C_{16}PyCl,I$ (entries 2 and 6). This effect demonstrates the importance of competition between hydrolysis of the activating agent and the cyclization reaction in the micellar medium in 1,2-dichloroethane. Furthermore, if we compare our results to those obtained by Vilarrasa *et al.*[19,20] in their systematic study of cyclization of ω-amino acids, the yield obtained with $C_{16}PyCl,I$ is much higher than those previously reported.

These results indicate the operation of a micellar effect for lactamization but not for lactonization.

Discussion and Conclusion

(i) The mechanism can be schematized as follows:



In this scheme, the hydrolysis reaction can be limited by carrying out the reaction under an atmosphere of dry argon.

(18) Politi, M. J.; Chaimovich, M. *J. Phys. Org. Chem.* **1991**, *4*, 207.
(19) Bartra, M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 5132.
(20) Bartra, M.; Bou, V.; Garcia, J.; Urpi, F.; Vilarrasa, J. *J. Chem. Soc. Chem. Commun.* **1988**, 270.

Table 3. Lactonization of $HOC_{15}H_{31}CO_2H$ (S) Activated by C_1PyCl,I or $C_{16}PyCl,I$ at 80 °C without High Dilution, [S] = 0.028 M in 1,2-Dichloroethane

		cyclization conditions		yield of
entry	activating agent (A)	argon	ratio (A/S)	lactone (%)
1	C_1PyCl,I	−	2/1	37
2	$C_{16}PyCl,I$	−	2/1	23
3	C_1PyCl,I	+	2/1	41
4	$C_{16}PyCl,I$	+	2/1	36

Table 4. Lactamization of $NH_2C_{11}H_{23}CO_2H$ (S) Activated by C_1PyCl,I or $C_{16}PyCl,I$ at 80 °C without High Dilution, [S] = 0.028 M in 1,2-Dichloroethane

		cyclization conditions		yield of
entry	activating agent (A)	argon	ratio (A/S)	lactam (%)
1	C_1PyCl,I	−	1/1	20
2	$C_{16}PyCl,I$	−	1/1	35
3	C_1PyCl,I	−	2/1	24
4	$C_{16}PyCl,I$	−	2/1	32
5	C_1PyCl,I	+	1/1	24
6	$C_{16}PyCl,I$	+	1/1	54 (50)*

* All yields were determined by GPC except the value shown in parentheses, which is the isolated yield of product (see Experimental Section). The agreement between the two values is good.

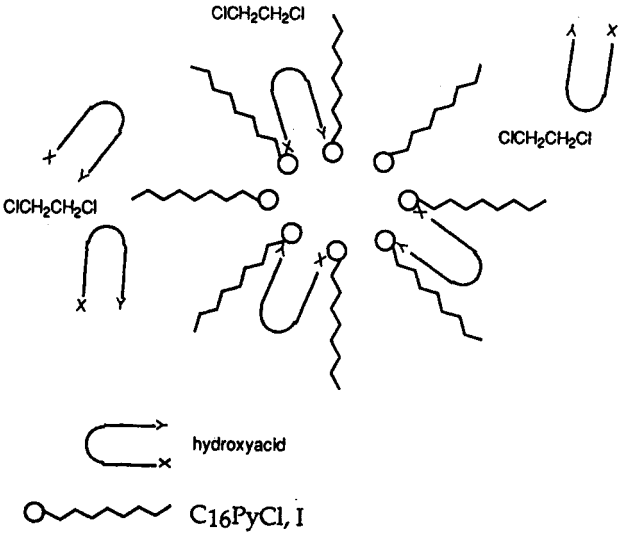


Figure 3. Cyclization of an ω-hydroxy acid that is completely soluble in the continuous phase.

(ii) The observed difference in yield between lactonization and lactamization with $C_{16}PyCl,I$ as activating agent was accounted for by differences in solubility of the substrate in the continuous medium. The efficiency of the cyclization appeared to be inversely related to the solubility of the substrate in the solvent. If the substrate is completely soluble in the organic solvent, polymerization will tend to occur before the substrate has had time to react at the interface. On the other hand, if the substrate is poorly soluble in the organic solvent, it will be solubilized at the interface where cyclization will take place. The differences in yields between these two substrates can be accounted for by the high solubility of the ω-hydroxy acids and the poor solubility of the ω-amino acids in 1,2-dichloroethane. The two situations are illustrated in Figures 3 and 4.

These results are in total agreement with previous studies on cyclization reactions in micellar media. Indeed, in the work of Jaeger,[3] the ω-hydroxy acid is solubilized in the organic continuous phase. Moreover, the hydrophilic carbodiimide activating agent is localized in the polar

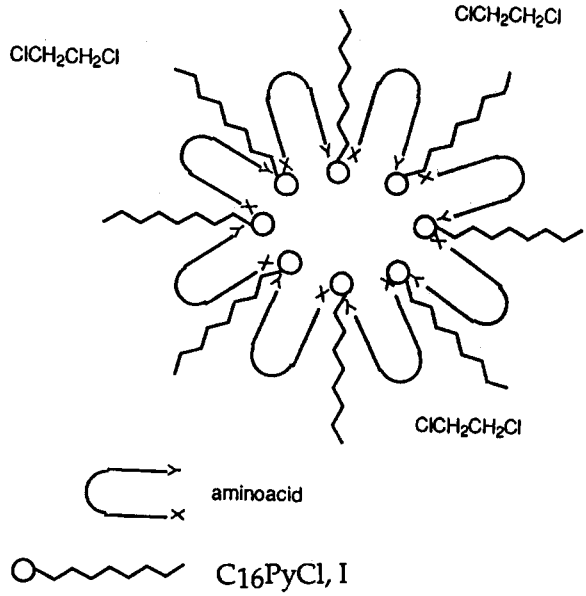


Figure 4. Cyclization of an ω-amino acid that is poorly soluble in the continuous phase.

core of the micelle, and the yields of cyclization are low. In contrast, in the work of Lennox,[4b] the organic substrate is not at all soluble in the aqueous continuous phase and so is completely localized at the interface of the micelle. In this case, micellar environment enhances the cyclization reaction.

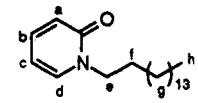
(iii) The value of a microstructured medium for preparation of lactams was demonstrated: the organization of the medium derived from the structure of the activating agent, *N*-hexadecyl-2-chloropyridinium iodide (C_{16}PyCl,I), a long-chain modified Mukaiyama reagent, was an added benefit. By using this new activating agent and by curbing the hydrolysis reaction we doubled the yield of lactam normally obtained with the Mukaiyama reagent. The reaction could also be carried out at high substrate concentration (0.028 M), avoiding both high dilution conditions and modification of the starting ω-amino acid. Moreover, it is noteworthy that the concentrations used in the cyclization reactions are much higher than the CMC of C_{16}PyCl,I, and a micellar effect during all the cyclization processes results.

Since cyclization takes place at the interface, and polymerization occurs essentially in the continuous phase, the solubility of the substrate in the solvent (continuous phase) is of particular importance. This method would be especially suited to cyclization of peptides, which are poorly soluble in organic solvents.

Experimental Section

Reagents and solvents were purchased from Aldrich and were used as supplied. Solvents were kept over molecular sieves (4 Å). Merck silica gel (0.040–0.060 nm) was employed for column chromatography. Water content was determined by the Karl Fischer method on a Mettler DL18 instrument. The UV spectra were recorded on a Hewlett-Packard 8452A diode-array spectrophotometer. The gas-phase chromatographic analyses were carried out on a Delsi Di 200 chromatograph equipped with a DB-1 type SE30 capillary column (25 m × 0.32 mm) and a flame ionization detector. The peaks were integrated with a Shimadzu C-R4A instrument.

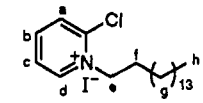
1. Synthesis of *N*-Hexadecyl-2-chloropyridinium iodide. (i) Synthesis of *N*-hexadecyl-2-pyridone (6b). A mixture of 2-hydroxypyridine (4.85 g, 50 mmol) and 1-bromohexadecane (23.60 g, 75 mmol, 1.5 equiv) was refluxed for 1 h in a mixture of 2.2 mL of water and 400 mL of toluene in the presence of K_2CO_3 (13.8 g, 100 mmol, 2 equiv) and tetrabutylammonium bromide (1.63 g, 5 mmol, 0.1 equiv). The reaction mixture was filtered, evaporated, and purified by column chromatography (500 g, hexane/AcOEt, 30/70) to afford 15 g of *N*-hexadecylpyridone (**6b**) (94%):



6b

mp = 44 °C; TLC (silica, hexane/AcOEt 30/70) R_f = 0.30; ^{1}H NMR ($CDCl_3$, ppm) 0.85 (t, 3H, J = 6.5 Hz, h), 1.25 (m, 26H, g), 1.72 (m, 2H, f), 3.88 (t, 2H, J = 7.4 Hz, e), 6.15 (td, 1H, J = 6.7, 1.2 Hz, c), 6.56 (dd, 1H, J = 9.0, 1.2 Hz, a), 7.26 (m , 2H, b + d); MS *m/e* 319 (M+). Anal. Calcd for $C_{21}H_{37}NO$: C, 78.94; H, 11.67; N, 4.38. Found: C, 78.85; H, 11.56; N, 4.34.

(ii). Synthesis of *N*-Hexadecyl-2-chloropyridinium Iodide (3b). Compound **6b** (4.25 g, 13.3 mmol) and phosphorus oxychloride (17.40 g, 113 mmol, 8.5 equiv) were heated together at 100 °C for 2 h. The excess $POCl_3$ was evaporated, and the residue was dissolved in 14 mL of acetone. This acetone solution was added dropwise to a solution of NaI (3.60 g, 24 mmol, 1.8 equiv) in 16 mL of acetone. The yellow precipitate was filtered, washed with ether (2 × 25 mL), and then dissolved in dichloromethane (200 mL). The organic phase was washed with water (30 mL) and a saturated solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The yellow precipitate was recrystallized from EtOH (100 mL). Drying in an oven afforded 4.96 g of *N*-hexadecyl-2-chloropyridinium iodide (**3b**) (80%):



3b

mp = 114 °C; ^{1}H NMR ($CDCl_3$, ppm) 0.85 (t, 3H, J = 6.5 Hz, h), 1.3 (m, 26H, g), 2.02 (m, 2H, f), 4.99 (t, 2H, J = 8.7 Hz, e), 8.16 (dd, 1H, J = 8.1, 1.4 Hz, a or d), 8.24 (td, 1H, J = 6.2, 1.4 Hz, b or c), 8.72 (td, 1H, J = 8.1, 1.7 Hz, b or c), 9.88 (dd, 1H, J = 6.2, 1.7 Hz, a or d); MS (*m/z*) FAB, cat^+ = 338; $2cat^+ + I^-$ = 803; cat^+ + glycerol = 430. Anal. Calcd for $C_{21}H_{37}ClNI$: C, 54.14; H, 8.01; N, 3.01; Cl, 7.61; I, 27.24. Found: C, 54.24; H, 7.83, N, 3.07; Cl, 7.39; I, 27.38.

2. Hydrolysis of C_1PyCl,I and C_{16}PyCl,I. *N*-Hexadecyl-2-chloropyridinium iodide (930 mg, 2 mmol or 465 mg, 1 mmol) or 2-chloro-1-methylpyridinium iodide (510 mg, 2 mmol or 205 mg, 1 mmol) were placed in 18 mL of 1,2-dichloroethane at 80 °C in the presence of triethylamine (404 mg, 4 mmol or 808 mg, 8 mmol) for 24 h, with or without a stream of dry argon. The yields in *N*-alkylpyridones were determined by GPC with the following chromatographic conditions.

C_{16}PyCl,I: $T_{inj} = T_{det}$ = 280 °C; temperature program 180–210 °C, 3 °C/min, 210 °C for 3 min, 210–265 °C, 20 °C/min, 265 °C for 6 min; retention time (min), products are methyl stearate (11.4) 1-hexadecyl-2-pyridone (19.3).

C_1PyCl,I: $T_{inj} = T_{det}$ = 280 °C; temperature program 60–165 °C, 30 °C/min, 165 °C for 4 min, 165–250 °C, 15 °C/min; retention time (min), products are 1-methyl-2-pyridone (4.0), methyl stearate (13.8).

Yields were determined as follows: 100 μL of a solution of methyl stearage (standard, 0.028 M) was added to 100 μL of reaction mixture, and the mixture was then injected into the capillary column. The yields were calculated from the ratio of the surface areas from calibration curves established with pure *N*-alkylpyridones and methyl stearate.

3. Lactonization. A solution of 16-hydroxyhexadecanoic acid (277 mg, 1 mmol) and triethylamine (808 mg, 8 mmol) in 16 mL of 1,2-dichloroethane was added dropwise over 10 min to a solution of *N*-alkyl-2-chloropyridinium iodide in 20 mL of 1,2-dichloroethane at 80 °C. The reaction, followed by GPC, goes to

completion within 24 h. Yields were determined as described above by GPC using calibration curves established with the hexadecanolide and methyl stearate as standards.

The chromatographic conditions were as follows: $T_{inj} = T_{det}$ = 280 °C; temperature program 180–225 °C, 3 °C/min, 225–265 °C, 20 °C/min, 265 °C for 5 min; retention time (min), products are hexadecanolide (7.0), methyl stearate (12.0), 1-hexadecyl-2-pyridone (20.9).

4. Lactamization. A solution of 12-aminododecanoic acid (220 mg, 1 mmol) and triethylamine (808 mg, 8 mmol) in 16 mL of 1,2-dichloroethane was added in one batch to a solution of *N*-alkyl-2-chloropyridinium iodide in 20 mL of 1,2-dichloroethane at 70 °C. The reaction, followed by GPC, goes to completion within 24 h. The yields were determined by GPC as described above from calibration curves established with the azacyclotridecanone and methyl stearage as standards. The chromatographic conditions were as follows: $T_{inj} = T_{det}$ = 280 °C; temperature program 140–220 °C, °C/min, 220–265 °C, 20 °C/min, 265 °C for 5 min; retention time (min), products are azacycotridecanone (5.9), methyl stearate (11.8), 1-hexadecyl-2-pyridone (17.1).

Lactam (**5**) was isolated after evaporation of solvent and washing with toluene to remove any remaining *n*-hexadecylpyridone. Azacyclotridecanone (**5**) was isolated in 50% yield after column chromatography of the residue (CH_2Cl_2/MeOH 98/2) and was identified by ^1H NMR and mass spectrometry by comparison with the commercial compound.