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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of α-amino acids in chiral reverse micelles

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Abstract

Through alkylation of ethyl 2-phthalimidoacetate in chiral reverse micelles formed from chiral surfactants, followed by hydrazinolysis and hydrolysis of the resulting products, optically active α-amino acids were synthesized. The highest enantioselectivity was 59.5%. Meanwhile, we have found that the asymmetric induction depends on the reaction temperature, the alkyl chain length of surfactant and the strucure of the surfactants.

1. Introduction

Chiral aqueous micelles have aroused much interest since they may be used as the simplest analogues to mimic the stereochemistry of enzymatic reactions.[1] Reverse micelles which formed in apolar solvents also show catalytic activity in organic reactions, and have received extensive attention in recent years.[2] In contrast to aqueous micelles, reverse micelles are a homogeneous system constituted from those aggregates or 'water pools' in which the polar head groups of the surfactant molecules are directed towards the interior of water, and the lipophilic chains are exposed to the apolar medium. Since these 'water pools' which are similar to the polar part of an enzyme are the active centres of the whole system,[3] it is anticipated that if the reaction takes place in a chiral reverse micelle, stereoselectivity of the reaction might be achieved. Here we wish to report the enantioselective synthesis of α-amino acids by hydrazinolysis and hydrolysis of chiral 2-phthalimido-esters formed in chiral reverse micelles. For our work, chiral surfactants I and II were synthesized from (−)-(1*S*,2*R*)-ephedrine[4] and III was obtained from (+)-(8*R*,9*S*)-cinchonine.[5]

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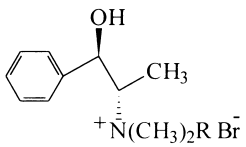
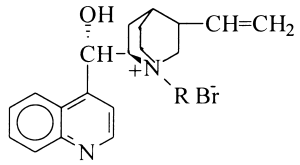
Table 1
The influence of reaction temperature[a)]

Product	Temperature(℃)	Yield (%)	$[\alpha]^{25}_{D}$ [b)]	e.e.%[c)]
4a	30	40.5	+2.5	17.2
	40	45.8	+3.2	22.1
	50	46.2	+2.3	15.9

a) Surfactant is I. b) 6N HCl is used as solvent.
c) Obtained from $[\alpha]^{25}_{D}/[\alpha]^{25}_{D.max}$, $[\alpha]^{25}_{D.max}$ are cited from the literature[6].



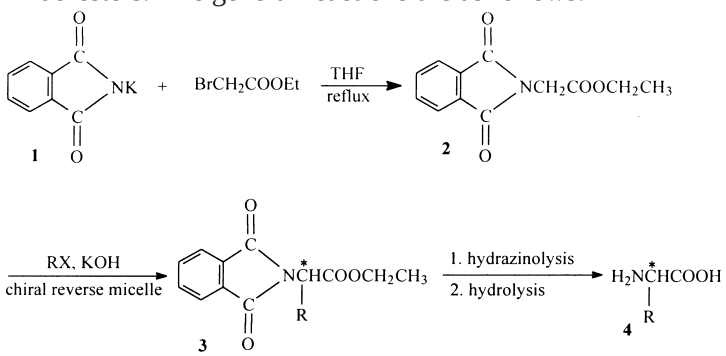
I: R=$C_{12}H_{25}$-n
II: R=$C_{16}H_{33}$-n



III: R=$C_{12}H_{25}$-n

2. Results and discussion

The reverse micelles which were produced by certain compositions of I–III and H_2O in dichloromethane:n-hexanol solutions provided asymmetric microenvironments for enantioselective synthesis of 2-phthalimido-esters. The general reaetions are as follows:



RX: a) CH_3I b) $CH_3CH_2CH_2I$ c) i-C_3H_7Br d) $PhCH_2Br$

The influence of reaction temperature was investigated and the results are listed in Table 1 from where it can be seen that temperature influenced the enantiomeric excess and a relatively higher e.e. was obtained at 40°C.

We then studied these reactions when various RX and surfactants were employed. The results shown in Table 2 clearly demonstrate that enantioselectivity was achieved in all chiral reverse micelles employed. The micelle formed from III provided better enantioselectivity than I and II. It might be explained that the polar head group of III has higher rigidity. At the same time, when the surfactant is I or II, all the enriched enantiomers of α-amino acids have the same absolute configuration of *S*. However, when surfactant III is employed, the absolute configuration is *R*. From this, we could draw the conclusion that there is a relationship of configuration between chiral surfactant and product. Similar to aqueous micelles, the asymmetric induction of reverse micelle also depends on 'the chain length effect'. In our experiments, the reverse micelle formed from the surfactant with shorter alkyl chain I provided better

Table 2
Synthesis of enantioselective α-amino acids

Product	Surfactant	Total Yield (%)[a]	M. P.(℃)	$[\alpha]^{25}_{D}$	e.e.%[e]	Absolute Configuration[f]
4a	I	45.8	293	+3.2[b]	22.1	S
	II	40.5	291	+2.4[b]	16.5	S
	III	42.2	295	-4.1[c]	28.7	R
4b	I	42.3	305	+6.4[d]	26.4	S
	II	48.5	305	+5.2[d]	21.5	S
	III	45.8	306	-8.0[d]	33.5	R
4c	I	54.5	295	+9.8[b]	35.7	S
	II	46.7	294	+8.4[b]	30.5	S
	III	50.3	292	-11.2[b]	40.9	R
4d	I	57.5	270	-2.3[d]	50.8	S
	II	60.3	269	-1.9[d]	42.6	S
	III	59.1	270	+2.7[d]	59.5	R

a) Based on compound **2**. b) 6N HCl is used as solvent. c) 1N HCl is used as solvent.
d) 5N HCl is used as solvent. e) Obtained from $[\alpha]^{25}_{D}/[\alpha]^{25}_{D,max}$, $[\alpha]^{25}_{D,max}$ are cited from the literature[6,7].
f) Absolute configurations depend on the literature[6,7].

enantioselectivity than the longer chain analogue II. Evidently the micelles with different carbon chains have different natures, such as size, polarity and dispersity, etc, and the ability to combine with the substrate is also different. There could be a range of chain length for which the best efficiency can be reached. The presence of n-hexanol was essential for the formation and stabilization of the systems.

3. Experimental

Melting points were not corrected. The IR was recorded on Perkin–Elmer 683 spectrometer. The ^{1}H NMR spectra were recorded on a JEOL JUM-PMX 60 SI (60 MHz) spectrometer. The optical rotations were obtained from a WZZ-1 automatic rotation detector (Shanghai).

3.1. General procedure

3.1.1. Preparation of ethyl 2-phthalimidoacetate ***2***[8]

In a 100 ml round-bottomed flask, 2.7 g (40 mmol) ethyl bromoacetate was dissolved in 50 ml dried THF, 3.7 g (20 mmol) potassium phthalimide was added, and the reaction mixture was stirred at 70°C for 5 h, cooled, and THF was then evaporated. Then 60 ml $CHCl_3$ was added and filtered after vigorous stirring. The filtrate was washed with a 0.4% NaOH solution (30 ml), a 3% HCl solution (2×80 ml) and H_2O (2×50 ml). The organic layer was dried over anhydrous Na_2SO_4 overnight. Then $CHCl_3$ was evaporated and the crude product was purified by column chromatography on silica gel with cyclohexane–ethyl acetate (9:1) as an eluent.

Yield: 55%; m.p. 109–110°C; δ_H ($CDCl_3$) 1.3 (3H, t, *J*=7 Hz), 4.15 (2H, q, *J*=7 Hz), 4.48 (2H, s), 7.57–8.17 (4H, m) ppm; ν_{max}/cm^{-1} 1780, 1745, 1720.

*3.1.2. The alkylation of ethyl 2-phthalimidoacetate **2** in chiral reverse micelles*

H_2O (0.50 ml) was added dropwise in 20 ml dichloromethane:n-hexanol (5:1, v/v), then surfactant (0.001 mol) was added under stirring. The solution was vigorously stirred for 40 min at 30°C to form a homogeneous system. Then 0.504 g (0.009 mol) KOH was added. After being stirred for 15 min, a mixture of 1.40 g (0.006 mol) ethyl 2-phthalimidoacetate and RX (0.006 mol) in 5 ml CH_2Cl_2 was added. The mixture was stirred at 40°C for 20 h, then filtered. The filtrate was dried over anhyd. Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on silica gel with acetone–petroleum benzine (1:5, v/v) as an eluent.

3a: m.p. 116°C; δ_H ($CDCl_3$) 1.15–1.60 (6H, m), 4.12 (2H, q, *J*=7 Hz), 4.59 (1H, q, *J*=5 Hz), 7.58–8.14 (4H, m) ppm; ν_{max}/cm^{-1} 1780, 1745, 1715.

3b: m.p. 124°C; δ_H ($CDCl_3$) 1.05–1.60 (10H, m), 4.12 (2H, q, *J*=7 Hz), 4.59 (1H, t, *J*=4.9 Hz), 7.55–8.14 (4H, m) ppm; ν_{max}/cm^{-1} 1780, 1745, 1720.

3c: m.p. 114°C; δ_H ($CDCl_3$) 1.09–1.62 (10H, m), 4.12 (2H, q, *J*=7 Hz), 4.58 (1H, d, *J*=5 Hz), 7.57–8.14 (4H, m) ppm; ν_{max}/cm^{-1} 1780, 1745, 1720.

3d: m.p. 91°C; δ_H ($CDCl_3$) 1.28 (3H, t, *J*=7 Hz), 2.70 (2H, d, *J*=5 Hz), 4.10 (2H, q, *J*=7 Hz), 4.60 (1H, t, *J*=5 Hz), 7.12–8.17 (9H, m) ppm; ν_{max}/cm^{-1} 1780, 1750, 1720.

*3.1.3. Preparation of α-amino acids **4** by the hydrazinolysis and hydrolysis of 2-phthalimido-esters **3**[8]*

In a 25 ml round-bottomed flask, 2 mmol 2-phthalimido-ester was dissolved in 10 ml anhyd. ethanol, 85% hydrazine hydrate (0.16 g, 2.8 mmol) was added subsequently and the mixture was refluxed for 1 h, cooled, then ethanol was evaporated. H_2O (6 ml) and conc. HCl (4 ml) were added, and the mixture was refluxed for 2 h, cooled and filtered. The filtrate was evaporated, 10 ml H_2O was then added and evaporated to dryness. This operation was repeated several times. Then 10 ml anhyd. ethanol was added and refluxed for 20 min, filtered and the filtrate was adjusted to pH=7 by piperidine. The mixture was then cooled and filtered. The white solid was collected and washed with anhyd. ethanol, then gave the product **4**. The IR and ^1H NMR spectra of the products **4** were identical with Sadtler Spectroscopy.

Acknowledgements

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