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Asymmetric Resolution in Ester Reduction by $NaBH_4$ at the Interface of Aqueous Aggregates of Amino Acid, Peptide, and Chiral-Counterion-Based Cationic Surfactants

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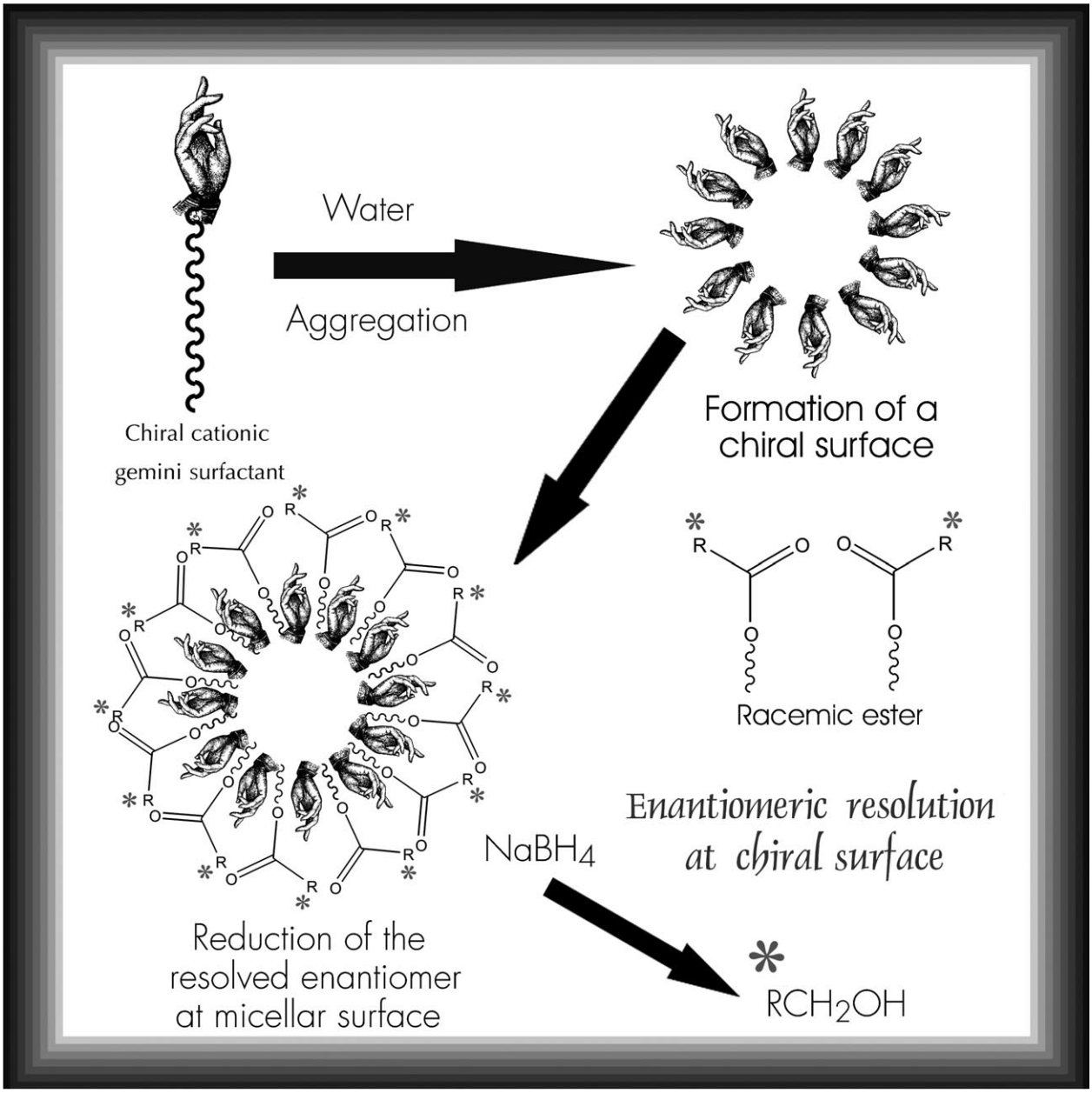

Abstract: This study provides insight into the physicochemical aspects of aqueous aggregates that comprise amino acid, peptide, and chiral-counterion-based cationic surfactants and their correlation with the proficiency of asymmetric resolution in ester reduction. The effects of the structural differences in the naturally occurring amino acid based and synthetic chiral-counterion-containing gemini surfactants on the surface properties as well as on other microstructural parameters were studied and correlated to the varied head groups of the surfactants. The supramolecular chirality induced from the head-group region of chiral amphiphiles in aqueous self-aggregates is evident from circular dichroism, scanning electron microscopy, and transmission electron microscopy studies. This large-scale chirality at the interface of self-aggregates was exploited towards asymmetric resolution in ester reduction by $NaBH_4$. An enantiomeric excess of 53% ((*R*)-2-phenylpropan-1-ol) was found in the case of the *n*-hexyl ester of 2-phenylpropionic acid as substrate in the aqueous aggregate of *N*,*N*′-dihexadecyl-*N*,*N*,*N*′,*N*′-tetramethyl-*N*,*N*′-ethanediyldiammonium diquinate. Thus, a simple and environmentally benign pathway for asymmetric resolution in ester reduction by sodium borohydride alone is reported, which utilizes the varied spatial asymmetry at the interface of aqueous aggregates of cationic chiral amphiphiles.

Keywords: aggregation · amphiphiles · asymmetric resolution · chirality · microstructural parameters

Introduction

One of the major challenges in organic synthesis is the development of environmentally benign chemical processes as better alternatives to the use of conventional volatile organic solvents. To this end, the construction of supramolecular structures by the self-assembly of surfactant molecules have been utilized in several chemical processes,[1,2] owing primarily to their potential biocompatibility as well as their ability to compartmentalize biomolecules.[3] Importantly, besides being the green alternative to traditional methods of executing organic reactions, aqueous aggregates also offer the possibility of enantioselection through the use of suitable chiral surfactants.[1,4] The demand toward the preparation of enantiomerically pure compounds, which are of increasing importance in pharmaceuticals and agrochemicals, is indeed ever growing.[5]

Recently, we reported the asymmetric reduction of prochiral ketones in aqueous solutions of amino acid based cationic surfactants, which exploited the supramolecular chirality of the aggregates.[2c] By utilizing the intrinsic solubilizing characteristics of self-assemblies, we preliminarily developed a simple method to reduce esters with just sodium borohydride under ambient conditions in aqueous self-aggregates of cationic surfactants without any external modifications.[2a] $NaBH_4$ usually fails to reduce esters under ambient conditions; it can do so only under conditions of high temperature, high equivalence of $NaBH_4$, presence of co-reagent or different reductant counterion, or other polar functional groups in the structure of esters.[6] In cationic aqueous aggregates, the close proximity of the reacting molecules at the interface enhances their interfacial concentration relative to the stoichiometric concentration,[1] thereby increasing the probability of collisions between reactants and lowering the energy of activation, thus leading to facile ester reduction at the interface.

Chirality in the microdomain of organized assemblies is induced by the surfactant.[7] Thus, different types of L-amino acid and peptide-based (**1**–**7**) and chiral gemini (**8**–**10**) surfactants (Scheme 1) were synthesized. Here the supramolecular chirality in the anisotropic microdomain of organized structure was tuned rationally by changing the head-group geometry or by the incorporation of a chiral counterion at the polar head group of the surfactant. The supramolecular chirality induced from the head-group region of chiral amphiphiles **1**–**10** in aqueous self-aggregates is evident from circular dichroism (CD), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) studies. As part of our continuing endeavor to explore novel uses of these chiral self-assemblies as reaction media, we report herein an investigation with a series of different chiral self-organized aggregates of the above surfactants as hosts for efficient asymmetric resolution in the reduction of esters I–V (Scheme 2) by $NaBH_4$ alone. This is done with a view to

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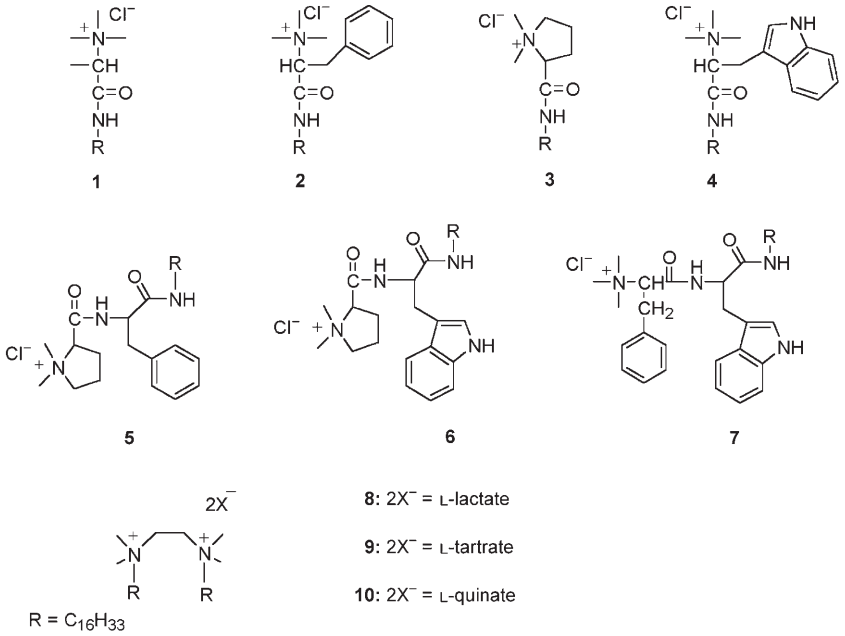
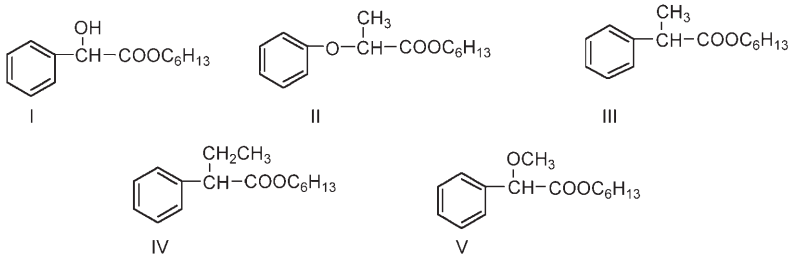


Scheme 1. Schematic representation of the structure of L-amino acid based (**1–4**), peptide-based (**5–7**), and chiral-counterion-based (L-lactate, L-tartrate, and D-quinate; **8–10**) gemini surfactants.



Scheme 2. Schematic representation of the structure of esters I–V.

obtain newer insight into the physicochemical aspects and derive any possible correlation between the molecular structure of surfactants and different microheterogeneous parameters of anisotropic chiral microdomains.

To the best of our knowledge, asymmetric resolution in ester reduction by $NaBH_4$ resulted for the first time in an optical yield of 53% (*R*)-2-phenylpropan-1-ol when the *n*-hexyl ester of 2-phenylpropionic acid (III) was used as substrate in an aqueous aggregate of **10**.

Results and Discussion

Herein we tried to gain insight into the physicochemical properties of the self-organized aggregates based on synthesized amino acid, peptide, and chiral gemini surfactants **1–10** (Scheme 3) and correlate these properties with asymmetric resolution in the reduction of esters by $NaBH_4$ alone. The large-scale chirality at the micellar interface due to the varied architecture of the surfactant head was determined by experiment. The influence of this manifested chirality on physicochemical properties of the corresponding aggregates and in asymmetric resolution in ester reduction is delineated below.

Self-Aggregation in Aqueous Solution: Surface-Tension Method

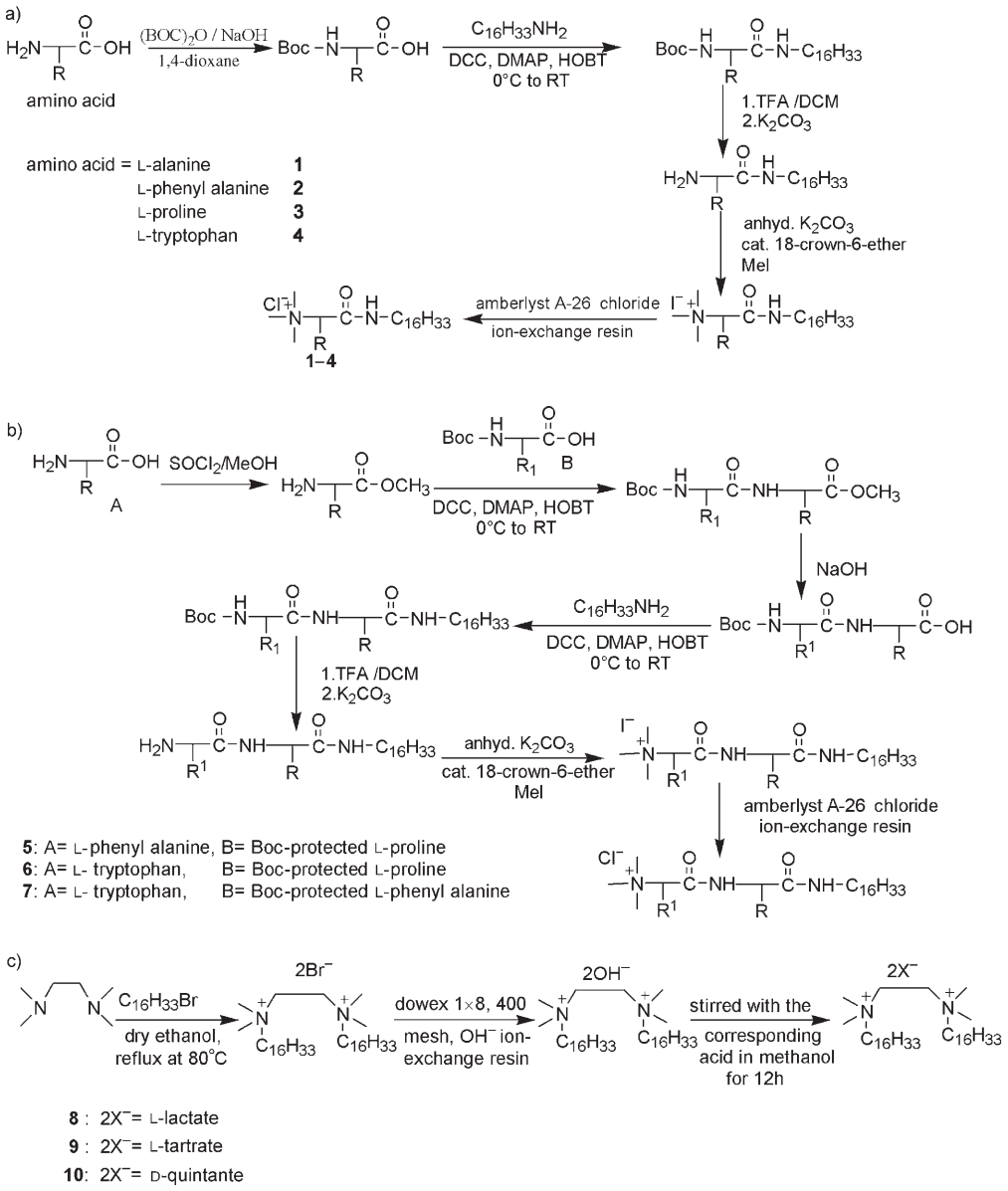
The critical micellar concentrations (CMCs) at the air–water interface for **5–10** were obtained from the break in the plots of surface tension (γ) versus concentration of surfactants (see Supporting Information; the CMCs of **1–4** are reported in our previous work[2c]) and found to decrease with an increase in head-group size and minimum surface area per molecule (A_{min}), in concurrence with the literature (Table 1).[8] The A_{min} value of the surfactants at the air–water interface was determined by using the Gibbs adsorption isotherm (Equations (1) and (2)):

$$\Gamma_{max} = \frac{1}{4.606RT} \lim_{C \to C_{CMC}} \frac{d\pi}{d \log C} \quad (1)$$

$$A_{min} = \frac{10^{18}}{N\Gamma_{max}} \quad (2)$$

where π is the surface pressure calculated from the equation $\pi = \gamma_{water} - \gamma_{solution}$, Γ_{max} is the maximum surface excess concentration, T is the absolute temperature, $R = 8.314\ J\,mol^{-1}\,K^{-1}$, and N is the Avogadro number. Γ_{max} is calculated from the slope in the π versus log[surfactant] curve by using pre-CMC tensiometric data.

The CMC values for surfactants **5–7** are lower than those for **1–4** as the A_{min} values of the former are greater than for the latter.[8] The CMCs for surfactants **8–10** are much higher than those of **5–7**, presumably due to their highly hydrophilic counterions as well as increased charge density,[9] and slightly lower than those of **1–4**, thus indicating a larger head-group area. The A_{min} values provide information about the space that every molecule needs to be accommodated at the air–water interface. It can be inferred from the A_{min} data that as the head group becomes bigger for the peptide as well as gemini surfactants, it occupies more space, the maximum amount being for **10**.



Scheme 3. Schematic representation of the synthetic procedures for surfactants **1**–**10**. a) Synthetic scheme for **1**–**4**. b) Synthetic scheme for **5**–**7**. c) Synthetic scheme for **8**–**10**. Boc = *tert*-butoxycarbonyl, DCC = *N*,*N*-dicyclohexylcarbodiimide, DCM = dichloromethane, DMAP = 4-*N*,*N*-dimethylaminopyridine, HOBT = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid.

Fluorescence Study

The CMCs of surfactants **5**–**10** as well as the micropolarity of the micellar microenvironment was determined by a steady-state fluorescence study with pyrene[10] as a probe (1×10^{-7} M). Pyrene exhibits a characteristic steady-state fluorescence emission spectrum consisting of three prominent vibronic bands. The nature and intensity of these fine-structured bands in the pyrene fluorescence are dependent on the polarity of the environment.[10a,11] The intensity ratio of the first to the third band (I_1/I_3) was taken as a measure of the polarity of the microenvironment. On micellization, pyrene molecules in water are preferentially located in the hydrophobic region, causing an abrupt change in I_1/I_3.[12] The CMC values obtained (Table 1) from the variation in I_1/I_3 with surfactant concentration (see Supporting Information) are in agreement with those obtained from the surface-tension measurements. Micropolarity (I_1/I_3) was found to vary from 0.74 in a hydrophobic solvent such as *n*-hexane to 1.37 in water, the most-hydrophilic solvent. These results in general indicate that the micelles prepared with **1**–**10** are mostly hydrated, as the value of I_1/I_3 ranges from 1.02–1.28 (Table 1); in particular, **5**–**10** are more hydrated than **1**–**4**.

Circular Dichroism

The bulk asymmetry in a chiral assembly is largely affected by noncovalent molecular packing of individual compo-

Table 1. Critical micellar concentration (CMC), surface area per head group (A_{min}), and micropolarity (I_1/I_3) values for surfactants **1**–**10**.

Surfactant	CMC [M][a,b] (tensiometry)	CMC [M][a,b] (fluorescence)	A_{min} [nm^2]	I_1/I_3[c]
1	4.3×10^{-4}	4.8×10^{-4}	0.69 ± 0.02	1.02
2	2.1×10^{-4}	2.5×10^{-4}	1.13 ± 0.01	1.08
3	1.8×10^{-4}	1.9×10^{-4}	1.16 ± 0.03	1.15
4	1.3×10^{-4}	1.5×10^{-4}	1.26 ± 0.03	1.13
5	2.1×10^{-5}	2.2×10^{-5}	2.17 ± 0.03	1.19
6	2.2×10^{-5}	1.5×10^{-5}	2.60 ± 0.03	1.18
7	1.2×10^{-5}	1.3×10^{-5}	3.37 ± 0.02	1.18
8	1.5×10^{-4}	1.5×10^{-4}	8.63 ± 0.03	1.28
9	1.2×10^{-4}	1.2×10^{-4}	6.59 ± 0.03	1.19
10	1.1×10^{-4}	1.8×10^{-4}	8.73 ± 0.03	1.22

[a] CMC of surfactants **1**–**4** were obtained from the literature.[2c] [b] The accuracy in measurements of the CMC of surfactants in duplicate experiments was within $\pm2\%$. [c] Intensity ratio due to first and third vibronic peak of pyrene steady-state fluorescence indicates the micropolarity at the micellar interface.

nents.[13,14] The chiral molecular interactions presumably form a network of repetitive molecular units resulting in a supramolecular chiral surface.[7c] To ascertain the presence of supramolecular chirality in self-assemblies, CD spectra of **5**–**10** (those of **1**–**4** were reported earlier[2c]) were recorded both in aqueous solution above the CMC and in water/methanol (1:1 *v*/*v*). In the presence of an organic protic solvent such as methanol, which provides a simple means to disintegrated self-assembly, the peak magnitude is expected to decrease due to the unordered arrangement of the amide planes in the absence of supramolecular chirality. Among the peptide-based surfactants **5**–**7**, apart from **5** the differences in the CD spectra between the aggregated and nonaggregated forms (Figure 1) were not as distinct as was observed in the case of single amino acid based surfactants **1**–**4**.[2c] Unexpectedly, almost no difference was observed in the CD spectra between the aggregated and nonaggregated forms of surfactants **8**–**10** (see Supporting Information). The nature of the CD spectra of the aggregated forms of different surfactants was found not to alter with variation in the concentration of surfactants apart from an increase in the intensities of the peak with a rise in concentration. However, some notable enantioselectivity was found in aqueous aggregates of **8**–**10** for esters I and III, which may be due to the existence of manifested supramolecular chirality (see below).

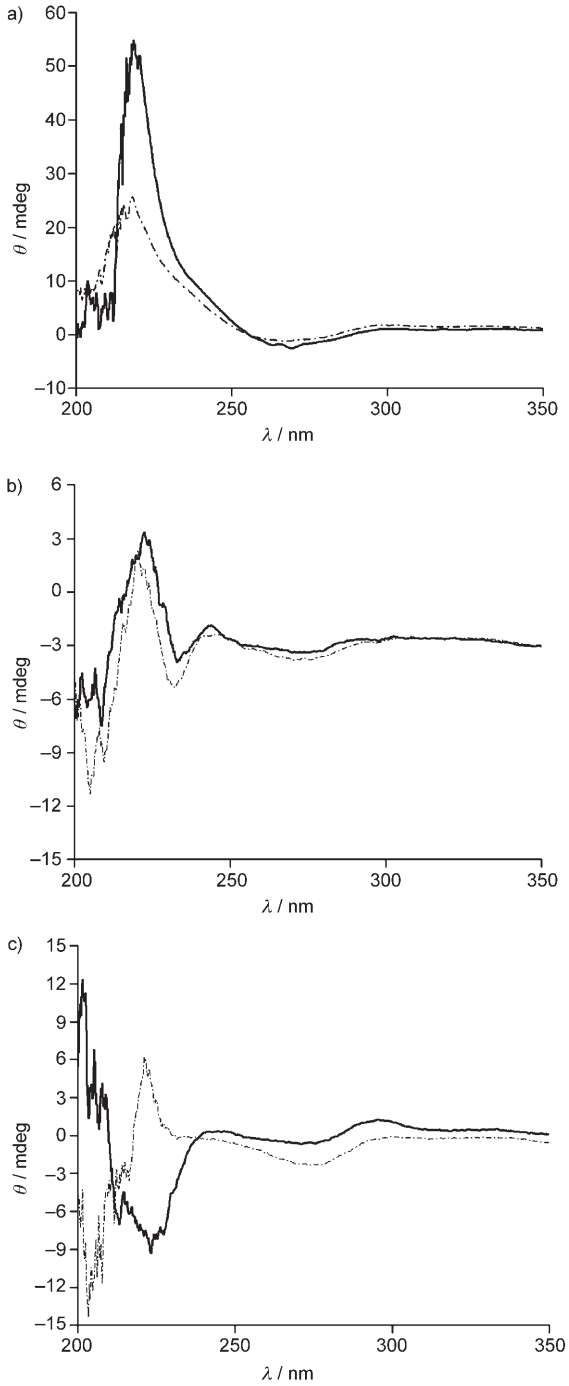


Figure 1. CD spectra for a) **5**, b) **6**, and c) **7** recorded in water (——) as well as in aqueous methanol (1:1 *v*/*v*) (–•–•). Concentration of **5**–**7**= 1×10^{-4} M.

Scanning Electron and Transmission Electron Microscopy

The unexpected results of the CD spectra for aggregated and nonaggregated forms of **8**–**10**, along with literature data in which the chirality of gemini surfactants were mainly described through SEM/TEM studies,[15] invoked us to carry out the electron microscopy studies. SEM images of the aggregated forms of **8**–**10** (Figure 2a–c) show thin fibrous morphology several micrometers in length in the three samples. Furthermore, the TEM images of the aggregated forms of **8**–**10** (Figure 3a–c) also reveal coiled structures comprising twisted ribbons, which entangle to form long helical fibers. This is generated from short and rigid covalent connections that enforce proximity between charged head groups that would otherwise repel, thus resulting in a spontaneous curvature of the water–surfactant interface and thereby inducing helicity. It is known that the twisted ribbons are stable for gemini surfactants with hydrocarbon chains ranging from 14 to 16 carbon atoms and primarily dictates the chirality.[15]

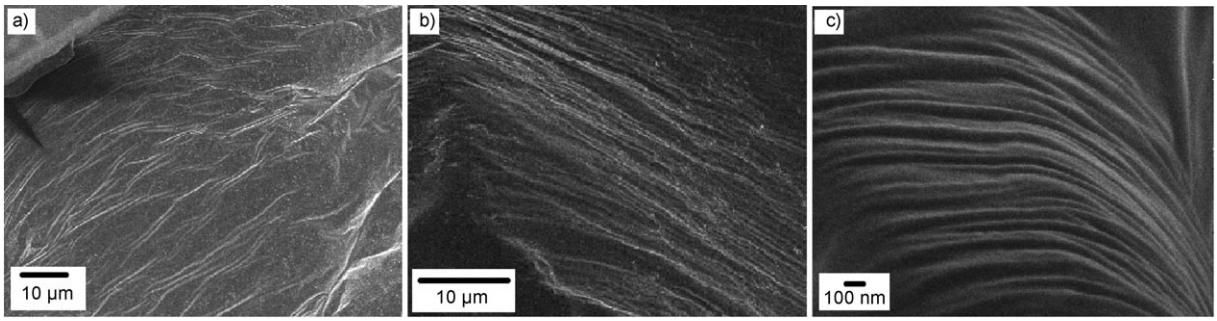


Figure 2. Field emission SEM (FESEM) images of dried samples of aqueous solutions (10 mM) of a) **8**, b) **9**, and c) **10**.

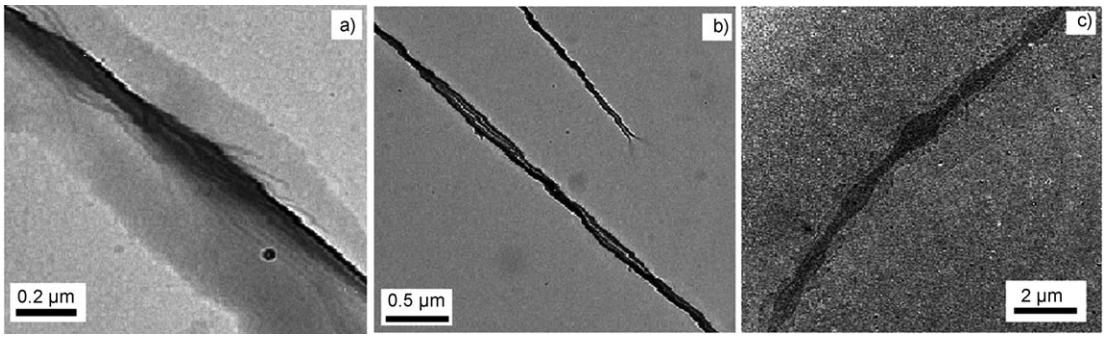


Figure 3. TEM images of dried samples of aqueous solutions (10 mM) of a) **8**, b) **9**, and c) **10**.

Asymmetric Resolution in Ester Reduction by $NaBH_4$

As mentioned above, to carry out asymmetric resolution in ester reduction, a series of ester molecules (Scheme 2) were reduced by $NaBH_4$ alone in aqueous solutions of the chiral cationic surfactants (Scheme 1) to exploit the proximity of the reactants. Initially we employed $NaBH_4$ reduction at room temperature for ester I (0.5 mM) in cationic aggregates of **1** (5 mM). The observed enantiomeric excess (*ee*) was very low (3.0%; Table 2, entry 1). Asymmetric resolution in the reduction of esters II–V was then carried out in the aqueous aggregates of **1**, but no considerable change in *ee* was noticed. This is consistent with the CD spectra of **1** (see reference [2c]), in which no significant difference was observed between the aggregated and nonaggregated forms. This may again be correlated with the lower spatial asymmetry of the polar head group of **1**, as obtained through the effective pair potential approach.[2c,16] Next, asymmetric resolution in the reduction of esters I–V was carried out in aqueous aggregates of **2**–**4**, in which the conformational flexibility was likely to be reduced by the incorporation of rigid head groups. Increased spatial asymmetry of the polar head is expected to improve the extent of manifested chirality at the interface. In accordance with our expectation, *ee* increased to 29% with surfactant **4** (Table 2, entry 3). This influence of supramolecular chirality was found to be maximum for substrates III and IV (Table 2, entries 3 and 4), for which hydrophobicity may play a dominant role by allowing the substrate molecules to remain tightly bound to the micellar interface. As a consequence, these two substrates can exploit the chirality to the utmost.

Table 2. $NaBH_4$ reduction of esters in the aqueous chiral aggregates at room temperature.

Entry	Ester	Enantiomeric excess [%][a]									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1	I	3	7	3	11	23	9	7	39	39	13
2	II	3	5	9	9	5	3	7	18	7	1
3	III	2	23	23	29	29	17	17	12	17	47 (53)[b]
4	IV	10	24	26	27	27	16	11	16	11	38
5	V	0.5	1.5	0.5	4	1	1	2	4	2	4.5

[a] Alcohols with *R* enantiomer in excess were from the reduction of esters I–III except in the case of **10**, alcohols with *S* enantiomer in excess were from esters I, IV, and V. [b] Reduction was carried out at 4 °C.

With the aim of further increasing the manifested chirality at the interface, multichiral groups were introduced at the polar head of surfactants **5**–**7**. This was done with the view that a possibly larger steric constraint will be placed at the interfacial region as the aromatic part of one amino acid is further extended by peptide coupling with another amino acid. To investigate the role of varying spatial asymmetry in dictating the stereoselectivity, asymmetric resolution in the reduction of esters was performed in these aqueous aggregates under similar experimental conditions. To our surprise, the *ee* was not improved over the monochiral surfactants **2**–**4**, except for amphiphile **5**, which gave 23, 29, and 27% *ee* with esters I, III, and IV, respectively (Table 2). The *ee* observed in dipeptide surfactants were either comparable or

less than those observed in monochiral ones. This result can be attributed to the concept proposed by Nandi and Vollhardt[17] that "the energy of interaction is expected to be favorable over a broader orientational space due to the availability of more degrees of freedom" in the case of multichiral amphiphiles. Thus, a higher degree of freedom in multichiral surfactants probably results in loss of large-scale chirality. This was an attempt to explain why, in contrast to our expectations, the enantioselection in the case of the multichiral amphiphiles is not enhanced relative to the monochiral. However, this hypothesis is entirely derived from the concept addressed in reference [17]. Importantly, at this point it seems that the asymmetric resolution is primarily substrate- and surfactant-structure-dependent.

The chiral centers of the surfactants **1**–**7**, which we used in asymmetric resolution, are within the polar-head-group architecture. Herein, we endeavored to manifest supramolecular chirality in the anisotropic microdomain of organized structure by the incorporation of chiral counterions at the polar head of the surfactants. Therefore, three cationic gemini surfactants **8**–**10** with chiral counterions L-lactate, L-tartrate, and D-quinate (Scheme 1) were synthesized; attention was paid to their unique property of forming more-orderly bound[18] aggregates, which may in turn lead to enhanced chirality at the interface. Aqueous aggregates of these three cationic gemini surfactants (10 mM) were utilized in the asymmetric resolution of the reduction of esters I–V (1 mM). Interestingly, the optical yield improved remarkably in the case of ester I (39, 39, and 23%, respectively, for **8**–**10**), which was otherwise insignificant for all the other amphiphiles except **5**. This increase in *ee* reached a maximum, 47.0%, in case of **10** with ester III (Table 2, entry 3). Considerable enantioselectivity was found only with ester I for surfactants **8** and **9** and with esters III and IV for surfactant **10**; the generalized dependence of enantioselection with helicity as evident from SEM and TEM studies (Figures 2 and 3) was not observed with all esters. Again, the substrate and surfactant structures seem to influence the enantioselection. Moreover, cetyltrimethylammonium surfactants with the same chiral counterions L-lactate, L-tartrate, and D-quinate did not show any *ee* in the reduction of esters by $NaBH_4$, although the comparison between gemini and conventional single-chain surfactants is not straightforward, as they represent two completely different classes of surfactants.

To increase the optical yield further, we decided to carry out the ester reduction at a low temperature (4°C), as the rotational disorder of the molecules is known to decrease rapidly with a decline in temperature, leading to a decrease in free rotation about their long axis. As a result, the intermolecular interaction becomes more sensitive to the presence of any asymmetry about their short axis and, hence, effectively asymmetric to the neighboring molecules. Orientation-dependant interactions due to the chiral structure of the molecule therefore become important.[19] Thus, asymmetric resolution during the reduction of esters was carried out under the experimental conditions under which the highest *ee* was obtained at room temperature, that is, with ester III in an aqueous aggregate of **10** at 4°C. The *ee* was found to improve slightly to 53% (*R*)-2-phenylpropan-1-ol, the highest ever found in ester reduction by $NaBH_4$ within aqueous aggregates of chiral surfactants.

Conclusion

In summary, we report a simple and stereoselective way of asymmetric resolution during the reduction of esters in a series of self-organized aggregates comprising amino acid, peptide-based, and gemini chiral surfactants by $NaBH_4$ alone. The large-scale chirality at the micellar interface and its correlation with the asymmetric resolution in ester reduction was attempted. The results indicate that there is no straightforward way of telling to what extent the induced helicity influences the enantioselection, which was found to be dependent primarily on substrate and surfactant structure. However, the general purpose of this method lies in the synthesis of optically pure chemicals in an easy and environmentally benign fashion, thereby paving the way for promising future applications.

Experimental Section

Materials

HPLC-grade solvents were purchased from Qualigens and Merck, India. Silica gel of 60–120 mesh from SRL, India was used for column chromatography, and TLC was performed on Merck precoated silica gel 60-F_{254} plates. Amberlyst A-26 chloride ion-exchange resin was obtained from BDH, UK. All other reagents and solvents were purchased from SRL, India. ^{1}H NMR spectra were recorded on a 300 MHz (Bruker) spectrometer. Mass spectrometric data of surfactants were acquired by ESI at 25–70 eV in a Q-tof-Micro Quadruple mass spectrophotometer (Micromass). FESEM and TEM images were taken with JEOL-6700F and JEM-2010M microscopes, respectively. Emission spectra were recorded on a Perkin-Elmer LS 55 luminescence spectrometer. CD experiments were performed on a JASCO J-600C spectropolarimeter. Optical rotations of all the amphiphiles were measured with a Perkin-Elmer LC 341 polarimeter. HPLC was performed with a SHIMADZU LC-10 AT series liquid chromatograph.

Surface-Tension Measurements and Critical Micellar Concentration

The CMC of the surfactants were measured with a Jencon (India) tensiometer by applying the Du Noüy ring method at (25±0.1)°C in water. The CMC values (Table 1) were determined by plotting surface tension (γ) versus concentration of the surfactant (see Supporting Information). The accuracy of the measurements in duplicate experiments were within ±2%.

Fluorometry

Pyrene is extensively used as a fluorescence probe to investigate the formation of hydrophobic microdomains by surfactants in aqueous solution. The steady-state fluorescence spectrum of pyrene shows a strong dependence of polarity on the micellar microenvironment. The excitation wavelength was fixed at 335 nm, and emission spectra were recorded from 360 to 600 nm. Measurements for all surfactants were carried out at 25°C. At the same temperature, the emissions due to pyrene in water and *n*-hexane were also measured. The pyrene concentration was maintained at 1×10^{-7} M. Estimated CMC (see Supporting Information) and micropolarity values obtained in the fluorescence study are given in Table 1.

Circular Dichroism

CD spectra were recorded for both the aggregated and nonaggregated states at 25 °C with a spectropolarimeter. The concentration range used for recording the CD spectra, which was adjusted by optical-density measurements at 220–230 nm, were around 1×10^{-4} M for surfactants **5**–**7** (Figure 1) and in the range of 5×10^{-3} M for **8**-**10** (see Supporting Information). CD spectra for **1**–**4** were reported earlier.[2c] Each CD spectral scan was repeated thrice to ensure reproducibility.

Scanning Electron and Transmission Electron Microscopy

SEM samples were prepared by depositing a drop of the aqueous solution (10 mM) of the sample on a cover slip, which was air-dried for two days then vacuum-dried for a few hours. TEM samples were prepared by depositing the aqueous solution (10 mM) onto a carbon-coated copper grid. It was then air-dried for two days and vacuum-dried for a few hours.

Syntheses

The schematic procedures for all the surfactants are provided in Scheme 3. The detailed synthetic procedure for **1**–**4** is available in our previous report.[2c]

5–**7**: Boc-protected L-amino acids (10 mmol) were coupled with methyl esters of the corresponding L-amino acids to prepare peptides (11 mmol) with DCC (11 mmol) as the coupling reagent in the presence of DMAP (11 mmol) and HOBT (11 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature. The Boc-protected peptides obtained (9 mmol) were dissolved in the required amount of methanol and subjected to hydrolysis by adding aqueous NaOH (1 N, 20 mL) at room temperature. After 2 h of stirring, the solvents were removed with a rotary evaporator, and the aqueous portion was extracted with diethyl ether to remove the unreacted methyl ester. The aqueous portion was then acidified with HCl (1 N) and extracted with ethyl acetate. The ethyl acetate extract was then washed repeatedly with water to remove any traces of acid and concentrated. The Boc-protected peptides (8 mmol) were then coupled with *N*-hexadecylamine (8.8 mmol) with DCC (8.8 mmol) as the coupling reagent in the presence of DMAP (8.8 mmol) and HOBT (8.8 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature. The Boc-protected amides obtained (8 mmol) were then subjected to deprotection by TFA (32 mmol) in dry DCM at room temperature. After 2 h of stirring, the solvents were removed with a rotary evaporator, and the mixture was extracted with ethyl acetate. The ethyl acetate portion was washed thoroughly with aqueous sodium carbonate (10%) followed by brine until neutral. The organic extracts were dried over anhydrous sodium sulfate and concentrated to give the corresponding amines. The amines produced (7 mmol) were quarternized with excess iodomethane, anhydrous potassium carbonate (7.7 mmol for **5** and **6**, 15.4 mmol for **7**) and a catalytic amount of 18-crown-6-ether in dry *N*,*N*-dimethylformamide (DMF) for 1.5 h at room temperature. The reaction mixture was extracted with ethyl acetate and washed with aqueous sodium thiosulfate and brine. The concentrated ethyl acetate extracts were subjected to crystallization in methanol/diethyl ether to give the solid quarternized iodides, which were subjected to ion exchange on an amberlyst A-26 chloride ion-exchange resin column to yield the desired pure surfactant. Yields were in the range of 65–70%.

8–**10**: These surfactants were prepared by an ion-exchange method. *N*,*N*-tetramethylethylenediamine (12 mmol) and 1-bromohexadecane (26.4 mmol) were dissolved in dry ethanol (30 mL) and heated at reflux (≈80 °C) for 48 h. The product was crystallized with chloroform/ethyl acetate. Next, the bromide counterions of the surfactant were replaced by hydroxide ions by dissolving the surfactant in methanol with a basic ion-exchange resin (dowex 1×8, 400 mesh, Lancaster) and stirring the mixture for 2–3 h at room temperature. This process was repeated four or five times to ensure complete ion exchange. The corresponding (L-lactic, L-tartaric, D-quinic) acid (24.2, 12.1, and 24.2 mmol, respectively) was then added to the hydroxide-containing surfactant in methanol, and the mixture was stirred for 12 h at room temperature. The methanol portion was then concentrated and twice subjected to crystallization with methanol/diethyl ether. As surfactants **8**–**10** are highly hygroscopic, it was not possible to remove all the water. Yields were in the range of 85–90%.

Pure alcohols: The racemic pure alcohols of the corresponding esters (Scheme 2, I–V) were synthesized by using the cetyltrimethylammonium bromide (CTAB)–micellar-assisted $NaBH_4$ reduction of the corresponding *n*-hexyl esters.[2a] The characterization data of the alcohols are available in the Supporting Information.

Specific Rotation

The specific rotations of the synthesized amphiphiles at room temperature are as follows: $[\alpha]_D=-20.9$ ($c=1.03$, MeOH) for **1**; $[\alpha]_D=+15.1$ ($c=1.1$, $CHCl_3$) for **2**; $[\alpha]_D=-23.8$ ($c=0.76$, MeOH) for **3**; $[\alpha]_D=-29.3$ ($c=1.7$, $CHCl_3$) for **4**; $[\alpha]_D=+1$ ($c=1.0$, MeOH) for **5**; $[\alpha]_{D=}-15$ ($c=1.0$, MeOH) for **6**; $[\alpha]_D=-5$ ($c=1.3$, MeOH) for **7**; $[\alpha]_D=-6$ ($c=2.0$, MeOH) for **8**; $[\alpha]_D=-10$ ($c=1.0$, MeOH) for **9**; $[\alpha]_D=-19$ ($c=1.6$, MeOH) for **10**.

^{1}H NMR Spectroscopic, Mass Spectrometric, and Elemental Analysis Data

5: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.19$–7.44 (m, 5H), 5.09–5.26 (m, 1H), 4.87–4.96 (m, 1H), 3.39–3.54 (m, 2H), 3.19–3.29 (m, 2H), 3.06 (s, 3H), 2.46 (s, 3H), 2.19–2.35 (m, 4H), 1.44–1.65 (m, 4H), 1.18–1.32 (br, 26H), 0.87 ppm (t, 3H); MS (ESI): *m*/*z* calcd: 514.80; found: 514.27 $[M]^+$; elemental analysis: calcd (%) for $C_{32}H_{56}N_3O_2Cl$: C 69.85, H 10.26, N 7.64; found: C 69.55, H 10.11, N 7.56.

6: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.03$–7.72 (m, 5H), 5.10–5.26 (br, 1H), 4.92–5.01 (m, 1H), 3.14–3.49 (m, 4H), 2.76 (s, 3H), 2.32–2.35 (m, 2H), 2.18 (s, 3H), 1.93–2.13 (m, 4H), 1.32–1.53 (m, 2H), 1.18–1.25 (br, 26H), 0.87 ppm (t, 3H); MS (ESI): *m*/*z* calcd: 553.44 $[M-Cl]$; found: 553.42 $[M]^+$; elemental analysis: calcd (%) for $C_{34}H_{57}N_4O_2Cl$: C 69.3, H 9.75, N 9.51; found: C 69.5, H 9.55, N 9.33.

7: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.48$–7.67 (m, 4H), 7.04–7.41 (m, 6H), 5.08 (m, 1H), 4.87 (m, 1H), 3.51–3.87 (m, 4H), 3.48 (s, 3H), 3.35 (s, 6H), 2.86–2.91 (m, 2H), 1.89–1.96 (m, 2H), 1.16–1.33 (br, 26H), 0.88 ppm (t, 3H); MS (ESI): *m*/*z* calcd: 617.47 $[M-Cl]$; found: 617.48 $[M]^+$; elemental analysis: calcd (%) for $C_{39}H_{61}N_4O_2Cl$: C 71.69, H 9.41, N 8.57; found: C 71.59, H 9.29, N 8.39.

8: ^{1}H NMR (300 MHz, D_2O): $\delta=4.03$–4.10 (m, 2H), 3.64–3.69 (m, 2H), 3.55–3.64 (m, 2H), 3.24–3.31 (m, 4H), 3.06 (s, 6H), 2.83 (s, 6H), 1.68 (br, 4H), 1.23–1.35 (m, 6H), 1.11–1.17 (br, 52H), 0.76 ppm (t, 6H); MS (ESI): *m*/*z* calcd: 566.76 $[M-C_{16}H_{34}]^+$; found: 341.12; elemental analysis: calcd (%) for $C_{44}H_{92}N_2O_6$: C 70.92, H 12.44, N 3.76; found: C 70.82, H 12.38, N 3.64.

9: ^{1}H NMR (300 MHz, D_2O): $\delta=4.58$ (s, 2H), 3.64–3.71 (m, 4H), 3.3 (m, 2H), 3.06 (s, 6H), 2.89 (s, 6H), 2.75 (m, 2H), 1.68 (br, 4H), 1.18 (br, 52H), 0.77 ppm (t, 6H); MS (ESI): *m*/*z* calcd: 566.76 $[M-C_{16}H_{34}]^+$; found: 341.12; elemental analysis: calcd (%) for $C_{42}H_{86}N_2O_6$: C 70.54, H 12.12, N 3.92; found: C 70.63, H 12.22, N 3.84.

10: ^{1}H NMR (300 MHz, D_2O): $\delta=4.04$–4.05 (m, 2H), 3.88–3.97 (m, 2H), 3.67–3.70 (m, 2H), 3.54–3.59 (m, 2H), 3.43–3.47 (m, 2H), 3.27–3.32 (m, 2H), 3.16–3.18 (m, 2H), 3.08 (s, 6H), 2.85 (s, 6H), 1.75–2.02 (m, 8H), 1.69 (br, 4H), 1.19–1.26 (br, 52H), 0.78 ppm (t, 6H); MS (ESI): *m*/*z* calcd: 566.76 $[M-C_{16}H_{34}]^+$; found: 341.12; elemental analysis: calcd (%) for $C_{52}H_{104}N_2O_{12}$: C 65.79, H 11.04, N 2.95; found: C 65.62, H 10.96, N 3.05.

Micelle-Mediated Reduction of Esters With $NaBH_4$

In a typical experiment, the required amount of ester I or II dissolved in HPLC-grade acetonitrile was added to an aqueous micellar solution (1 mL, 5 mM for **1**–**7**, 10 mM for **8**–**10**) of the respective surfactant to reach a substrate concentration of 0.5 (for **1**–**7**) or 1 mM (for **8**–**10**). The esters were added at 10% with respect to the concentration of the surfactant so that the structure of the aggregates would not be affected. After 10 min of stirring, 5 or 10 μL of an aqueous solution of $NaBH_4$ (15.2 mg in 1 mL) was added to the reaction mixture to attain the $NaBH_4$ concentration of 2 or 4 mM, respectively, and the mixture was stirred at room temperature for 6 h. An aqueous solution of sodium perchlorate (1.1 equiv with respect to surfactant concentration) was added to the re-

action mixture to precipitate the surfactant through counterion exchange. The reaction mixture was then extracted with ethyl acetate (2 mL), and 1 mL of the organic portion was placed in a microcentrifuge tube and evaporated to dryness by controlled flow of nitrogen. *n*-Hexane/isopropanol (95:5 *v*/*v*, 200 μL) was added to the microcentrifuge tube, and the mixture was centrifuged for 3 min. The supernatant liquid was then injected into an HPLC column (CHIRALCEL OD-H, 4.6 mm × 250 mm, Daicel Chemical Industries, Ltd.).

A 20-μL sample loop was used for the injection of the product mixtures. Detailed information of the HPLC data are given in the Supporting Information.

For esters III–V, whose alcohols did not separate through this HPLC column, large-scale reactions (50 mL) were performed with the same mole ratio as mentioned above. In a typical experiment, the required amount of ester dissolved in HPLC-grade acetonitrile was added to an aqueous micellar solution (50 mL, 5 mM for **1**–**7**, 10 mM for **8**–**10**) of the respective surfactant to reach a substrate concentration of 0.5 (for **1**–**7**) or 1 mM (for **8**–**10**). After 10 min of stirring, 250 or 500 μL of an aqueous solution of $NaBH_4$ (15.2 mg in 1 mL) was added to the reaction mixture to attain the $NaBH_4$ concentration of 2 or 4 mM, respectively, and the mixture was stirred at room temperature for 6 h. Sodium perchlorate (1.1 equiv with respect surfactant concentration) was added to the reaction mixture to precipitate the surfactant through counterion exchange. Full workup with ethyl acetate followed, and the material was concentrated and purified by column chromatography. The specific rotation of the corresponding alcohol was then measured, and the enantioselectivity was obtained with respect to the specific rotation of the pure enantiomer in the literature.[20] The chemical yield of the alcohols (conversion of esters) was generally in the range of 50–70%. The characterization data of the alcohols are available in the Supporting Information.

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