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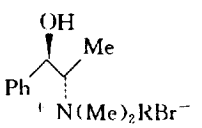
The Asymmetric Induction and Catalysis of Chiral Reverse Micelle: Asymmetric Reduction of Prochiral Ketones

Yongmin Zhang* and Peipei Sun

Department of Chemistry, Hangzhou University, Hangzhou, 310028. **P. R. China**

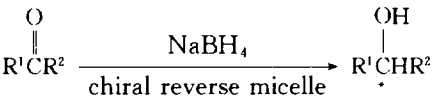
Abstract: Within chiral reverse micelles formed from chiral surfactants, prochiral ketones can be reduced with $NaBH_4$ to optically active alcohols. The enantioselectivity of the reaction is affected by the structures of both surfactant and substrate, and also related to the composition of the microenvironment. The presence of some sugars can effectively increase the enantiomeric excess of the products.

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 form in apolar solvents also show catalytic activity in organic reactions, and have received extensive attention in recent years[2]. In contrast with aqueous micelle, reverse micelles are the 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 media. Since these " water pools" which are similar to the polar part of enzyme are the active centres of the whole system[3], it is anticipated that while the reactions take place in a chiral reverse micelle, stereoselectivity of the reactions might be effected. But to our knowledge, no asymmetric induction in a chiral reverse micelle has been reported. Here we wish to report an asymmetric reduction of prochiral ketones in a chiral reverse micelles. Several chiral quaternary ammonium salts were synthesized from (-)-(1S, 2R)-ephedrine for our work[4].



Ⅰ: $R=C_2H_5$, Ⅱ: $R=n\text{-}C_8H_{17}$ Ⅲ: $R=n\text{-}C_{12}H_{25}$ Ⅳ: $R=n\text{-}C_{16}H_{33}$

The reverse micelles which were produced by certain compositions of surfactants Ⅱ - Ⅳ and water in benzene-hexanol solutions provided the asymmetric microenvironments for the reduction of ketones by sodium borohydride.



Scheme 1

a. $R^1=C_6H_5$ $R^2=CH_3$; b. $R^1=C_6H_5$ $R^2=C_2H_5$; c. $R^1=C_6H_5$ $R^2=n\text{-}C_3H_7$; d. $R^1=C_6H_5$ $R^2=i\text{-}C_3H_7$ e. $R^1=C_6H_5$ $R^2=t\text{-}C_4H_9$; f. $R^1=CH_3$ $R^2=C_2H_5$; g. $R^1=\alpha$-naphthyl $R^2=CH_3$

The results are shown in Table 1[5]. Optically active alcohols were obtained, and all the enriched enantiomers of products have(R)-configurations. The asymmetric induction of reverse micellar system to the reduction is quite complicated, and the microenvironment of the components strongly depends on their relative proportions. For example, while the ratios of surfactants to water are less than 1 : 7, the homogeneous systems would not be easy to form, and the inductive effect would be apparently lowered. The presence of n-hexanol was essential for the formation and stabilization of the systems, but the effect of ethanol and n-butanol is not abvious. Similar to aqueous micelles, the asymmetric induction of reverse micelle to the reduction reaction also depends on "the chain length effect". In our experiments, when the surfactant with a dodecyl group was adopted, the highest enantioselectivity was obtained. Evidently the micelles with different carbon chains have different natures, such as size, polarity and dispersity, etc, and the ability to combine substrate is also different. So it would have a range for the chain length in which the best efficiency can be reached. Table 1 also shows that with the same chiral micellar system, higher enantiomeric excess was generally achieved by the increase of carbon chain length of substrate. This can also be naturally attributed to hydrophobic-lipophilic interactions between the substrate and the micelle.

Table 1. Reduction of Ketones in Chiral Reverse Micellar Systems

Entry	Product	Surfactant Ⅰ			Surfactant Ⅱ			Surfactant Ⅳ		
		Yield[a] (%)	$[\alpha]_D^{25}$[b]	E. e[c] (%)	Yield[a] (%)	$[\alpha]_D^{25}$[b]	E. e[c] (%)	Yield[a] (%)	$[\alpha]_D^{25}$[b]	E. e[c] (%)
1	2a	82	+1.88	3.8	79	+3.32	6.8	75	+2.88	5.9
2	2b	84	+3.16	7.9	82	+4.28	10.7	88	+3.92	9.8
3	2c	73	+4.80	11.0	78	+6.23	14.3	81	+5.32	12.2
4	2d	76	+5.91	12.4	88	+7.10	14.9	90	+5.38	11.3
5	2e	78	+4.83	15.8	84	+7.19	23.5	82	+5.26	17.2
6	2f	88	+0.28	2.0	85	+0.56	4.0	85	+0.54	3.9
7	2g	72	+4.61	6.2	77	+8.40	11.3	71	+6.55	8.8

a) Isolated yields by column chromatography. b) For the determination of rotations, benzene is used as solvent to **2a**-**2c**, diethyl ether to **2d**, and acetone to **2e**, and ethanol to **2f**, **2g**. c) Obtained from $[\alpha]_D^{25}/[\alpha]_{D,max}^{25}$.

The maximum absorption of the reverse micelle of Ⅲ is at 275.2 nm in the UV spectra, and it would have a bathochromic shift to 282.4 nm when propiophenone was bound. But the change of maximum absorption in the ephedrine system was not found when ketone and sodium borohydride were added (275.5nm). The following fact can also confirm that the binding of micelle to substrate, instead of the complexing of ephedrine to boron, plays a leading role in catalysis and asymmetric induction. Under the same conditions, when quaternary ammonium salt Ⅰ was used to replace the surfactant (Ⅱ-Ⅳ), the reaction gave very low enantiomeric excesses (e.e 0-2.6%). When ephedrine was adopted, however, the racemic products were generated, and the chemical yields are not greater than 50%.

The presence of some sugars can enhance the enantioselectivity. Table 2 lists the affection of D-fructose and D-glucose to the reaction. It is clear that chiral surfactant and sugar in reverse micellar system work synergistically to effect the enantioselective reduction.

Table 2. Reduction of Ketones in Reverse Micelle in Presence of Sugar[a)]

Entry	Product	Yield(%)	$[\alpha]_D^{25}$	E.e(%)
1	**2**a	82	+4.00	8.2
2	**2**b	77	+4.97	12.4
3	**2**c	78	+7.32	16.8
4	**2**c[b)]	72	+6.80	15.6
5	**2**d	85	+8.35	17.5
6	**2**e	80	+8.14	26.6
7	**2**g	73	+10.80	14.5
8	**2**g[b)]	70	+9.58	12.9

a) Micelle formed from surfactant Ⅲ. Others see the notes of Table **1**. b) D-Glucose was added. D-Fructose was added in others. The concentration of sugar is 0.06M.

As the simplest analogue of enzyme, chiral reverse micelles, as well as aqueous micelles, show catalytic activity and asymmetric induction. This model is not the same as the usual phase transfer type catalysis. Relative report has also confirmed this mechanism[6]. More in-depth studies are having been carried out.

Acknowledgements

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4. The chiral quaternary ammonium salts I - IV were prepared from ephedrine. See: Fan, W. ; Zhou, Q. ; Shen, J. ; Lu, P. ; Zhang, Y. *Acta chimica Sinica 45*, 287, **1987**. I : m. p. 72-73℃, $[\alpha]_D^{20}$ -14.5 (ethanol); **I** : m. p. 83-84℃, $[\alpha]_D^{20}$ -12.7 (ethanol); **II** : m. p. 88-89℃, $[\alpha]_D^{20}$ -11.3 (ethanol); IV : m. p. 112-113℃, $[\alpha]_D^{20}$ -9.1 (ethanol). The structures of them were identified by ^{1}H NMR and IR.

5. General procedure of the preparation of reverse micellar solution and asymmetric reduction of ketones: 0.18 ml water was added dropwise in 10 ml benzene-hexanol (5 : 1, v/v), then 1.5 mmol surfactant was added under rigorous stirring. The solution was sonicated for 5 min in commercial ultrasonic cleaning bath (25KHz) or rigorous stirred for 40 min at 30℃, to form a homogeneous system. Then 5 mmol carbonyl compound and 6 mmol sodium borohydride were added. The reaction mixture was stirred at 20℃ for 4 h, to give the product.

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