Tetrahedron Vol. 49, No. 30, pp. 6605-6612, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

Influence of Different Types of Amphiphiles on the Rhodium(I) Complex-Catalyzed Asymmetric Hydrogenation of (Z)-Methyl-α-acetamidocinnamate in Aqueous Medium

Ingrid Grassert, E. Paetzold, G. Oehme*

Institut für Organische Katalyseforschung an der Universität Rostock e.V.,
Buchbinderstraße 5-6, O-2500 Rostock, Germany

(*Received in Germany* 19 *February* 1993)

Abstract: The homogeneous asymmetric hydrogenation of (Z)-methyl-α-acetamidocinnamate catalyzed by the system $[Rh(COD)_2]BF_4$ + 1.1 BPPM could be effected in water as medium in the presence of micelle-forming amphiphiles. Both activity and enantioselectivity were enhanced significantly and have been compared with results obtained in methanol as solvent. The effect was found with nonionic, zwitterionic and anionic surfactants and depends on the critical micelle concentration. Cationic surfactants like hexadecylalkyl ammonium salts act according to the anion as inhibitor (e.g. bromide), or promotor (e.g. hydrogensulfate). The principle of enhancing activity and stereoselectivity in complex-catalyzed hydrogenation due to micelles seems to be a phenomenon of general importance.

INTRODUCTION

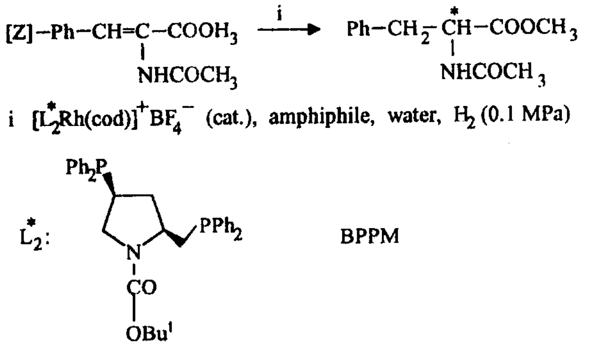
The homogeneous asymmetric hydrogenation of amino acid precursors by means of optically active rhodium(I) phosphine or phosphinite complexes as catalysts has been developed as an important reaction in the laboratory and on a technical scale.[1] The reaction occurs in organic solvents of high polarity because of the solubility of the catalyst and the substrate. One of the favoured solvents is methanol, whereas water gave only low activities and strongly decreased enantioselectivities.[2] The reason may be low solubility and lack of hydrophobicity; a connection between reactivity and hydrophobicity has been proposed in enzyme chemistry.[3] A possibility for simulation of enzyme-like conditions would be the transfer of the reaction system into micelles or vesicles, that means into amphiphilic colloidal phases.[4]

In a first communication, we showed, that the anionic surfactant sodium dodecylsulfate (SDS) and the neutral surfactant Triton X 100 both lead to encouraging effects.[5] Measurements with SDS have been done in 14 parts of water to 1 part of methanol (v/v). It is well known from stereoselective solvolytic reactions in micelles that the compositions of surfactants can influence the stereoselectivity significantly.[6]

Reactions with charged species often depend on the positive or negative charge of ionic amphiphiles.[7] This report will describe new investigations with nonionic, zwitterionic, anionic, cationic, and mixed surfactants in asymmetric hydrogenation.

RESULTS AND DISCUSSION

The basis reaction is shown in Scheme 1: (Z)-methyl-(α)-acetamidocinnamate has been hydrogenated in the presence of an optically active rhodium(I) phosphine complex to methyl N-acetyl phenylalaninate with high enantiomeric excess.



Scheme 1.

The asymmetric ligand L_2^* was in all cases (2S,4S)-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine (BPPM) described by Achiwa[8] and the catalyst was formed in an in situ system $[Rh(COD)_2]BF_4$ + 1.1 BPPM) or prepared as a crystalline complex. It is well known that the complex with BPPM leads to high enantiomeric excesses in alcohols as solvents and also shows high activities.[9] On the other hand water is a poor solvent for catalyst and substrate and leads to low activities and low enantioselectivities. Table 1 summarizes data for the hydrogenation in the presence of different kinds of neutral surfactants.

Table 1. Hydrogenation of (Z)-methyl-α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BPPM. Effect of neutral surfactants (Brij compounds). Reaction conditions: 25 °C; 0.1 MPa H_2; 15 ml H_2O; 1 mmol (Z)-methyl-α-acetamidocinnamate; 0.01 mmol $[Rh(COD)_2]BF_4$; 0.011 mmol BPPM, in situ preparation of catalyst. Without surfactant addition in water: t/2=90 min, % ee=78 (R), without surfactant addition in methanol: t/2=2 min, % ee=90 (R).

Entry	Rh : Brij	Brij 56		Brij 58		Brij 76		Brij 78	
	(mol/mol)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)
1	1 : 2	16	91	19	93	16	90	18	89
2	1 : 5	9	93	9	94	16	92	16	93
3	1 : 10	10	94	10	93	12	94	14	93
4	1 : 20	7	95	9	95	7	95	10	92
5	1 : 50	13	93	10	94	17	93	15	92
6	1 :100	15	94						
7a)	1 : 20			4	96				

Brij 56	decaoxyethylene-hexadecyl ether	$HO(CH_2CH_2O)_{10}$-$C_{16}H_{33}$
Brij 58	eicosaoxyethylene-hexadecyl ether	$HO(CH_2CH_2O)_{20}$-$C_{16}H_{33}$
Brij 76	decaoxyethylene-octadecyl ether	$HO(CH_2CH_2O)_{10}$-$C_{18}H_{37}$
Brij 78	eicosaoxyethylene-octadecyl ether	$HO(CH_2CH_2O)_{20}$-$C_{18}H_{37}$
a)	crystalline complex $[Rh(COD)BPPM]BF_4$	

Four polyoxyethylene ethers (Brij) have been used with varying alkyl and polyoxyethylene chains. It has been shown that the addition of a relatively small amount of amphiphile significantly influences rate and selectivity of the reaction. The ratio 1:2 (entry 1) gave the most important alteration in halftime (t/2) and enantioselectivity (% ee). An optimum for practical use seems to be the ratio 1:20 (entry 4), that means the concentration of Brij is 20% of the substrate concentration. Use of the purified rhodium-BPPM complex yielded slightly better results than the in situ preparation. The enantioselectivity of 96% ee (entry 7) exceeds the results observed in methanol. All surfactants of the Brij type gave in principle the same effect with only small variations. It is well known that the critical micelle concentrations (cmc's) of polyether surfactants are relatively low (Scheme 2) and we have to assume an intact micelle formation in all examples.

The same requirements are given for Tweens, inexpensive surfactants derived from sorbitol, with long chain acyl groups as hydrophobic parts and polyoxyethylene chains (5 to 7 units) as hydrophilic head groups. Tweens 20, 40, 60 and 80, respectively, have a suitable hydrophilic-hydrophobic balance (one hydrophilic and one hydrophobic group). Tween 65 and Tween 85 have three hydrophobic substituents and seem to be not dispersable in water. The same behaviour has been observed with Span 20 (sorbitan monolaurate).

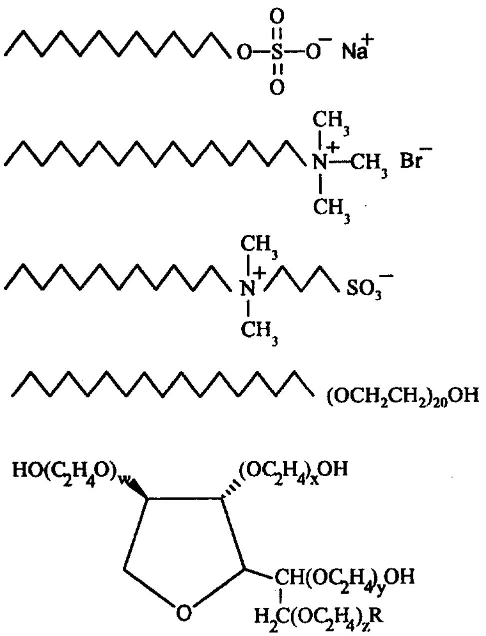
Results with the well balanced Tween types are shown in Table 2.

Table 2. Hydrogenation of (Z)-methyl-α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BPPM. Effect of neutral surfactants (Tween compounds). Reaction conditions see Table 1.

Entry	Rh:Tween	Tween 20		Tween 40		Tween 60		Tween 80	
	(mol/mol)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)
1	1 : 1	35	87	60	88	40	87	40	87
2	1 : 2	20	89	30	87	11	90	25	93
3	1 : 5	9	90	9	93	8	92	11	94
4	1 : 10	7	92	7	94	11	93	9	94
5	1 : 20	6	93	5	95	4	94	7	94
6	1 : 50	5	93	5	96	4	93	4	94
7	1 :100	4	93	5	94	5	94	5	95

Tween 20	polyoxyethylenesorbitan monolaurate
Tween 40	polyoxyethylenesorbitan monopalmitate
Tween 60	polyoxyethylenesorbitan monostearate
Tween 80	polyoxyethylenesorbitan monooleate

Increase in activity and enantioselectivity occurs at very low concentrations (entries 1 and 2). The central building block of all Tweens is chiral and optically active but we were unable to detect any chiral induction by use of nonchiral rhodium complexes. Tween 40 or Tween 80 can be recommended as micellar media for practical use.



	cmc (mol/l)	Ref.
(SDS)	8.1×10^{-3}	10
(CTAB)	9.2×10^{-4}	10
(DDAPs)	1.2×10^{-3}	10
(Brij 58)	7.7×10^{-5}	10
(Tween 20) R is $C_{11}H_{23}COO$	5.9×10^{-5}	11
(Tween 80) R is $C_{17}H_{33}COO$ (Sum of w, x, y, z is 20)	1.0×10^{-5}	12

Scheme 2. Selected cmc's at 25°C

Table 3. Hydrogenation of (Z)-methyl-α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BPPM. Effect of zwitterionic surfactants (sulfobetaines). Reaction conditions see Table 1.

Entry	Rh:Betaine	DeDAPs		DDAPs		HDAPs		ODAPs	
	(mol/mol)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)
1	1 : 2	45	82	45	84	12	90	6	91
2	1 : 5	45	82	10	91	8	91	4	90
3	1 : 10	40	82	7	93	7	93	8	92
4	1 : 20	40	83	5	93	6	94	8	92
5	1 : 50	7	92	4	93	5	94	6	92
6	1 :100	3	94	3	95	4	95	5	94

DeDAPs	N-decyl-N,N-dimethyl-3-ammonio-1-propanesulfonate
DDAPs	N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate
HDAPs	N-hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate
ODAPs	N-octadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate

Selected results with a series of zwitterionic amphiphiles are given in Table 3.

These sulfobetaines are similar in head group (derived from an amine by reaction with propanesultone) but different in the length of the hydrophobic alkyl chains (C_{10}, C_{12}, C_{16}, C_{18}). Discrepancies were observed at low concentrations of surfactants (entry 1, 2 and with decreasing tendency in entry 3, 4). The data are presented in Fig. 1a and 1b.

The relationship between activity and relative concentration of the amphiphile is shown in Fig. 1a and the relationship between enantioselectivity and relative concentration of the amphiphile is shown in Fig. 1b. The halftime decreases (activity increases) and the enantioselectivity increases significantly in a similar concentration range except for the decyl compound, which shows the activity and selectivity jump at much higher concentrations. We suggest as reason a connection with the critical micelle concentrations (cmc's).

Scheme 2 contains selected cmc's taken from the literature. Cmc's from ionic and zwitterionic amphiphiles are clearly higher than from nonionic amphiphiles. The cmc of dodecyl-dimethyl-ammonio-propanesulfonate is noted in Fig. 1 and shows that the change of activity and enantioselectivity is maximal near the cmc. It is well

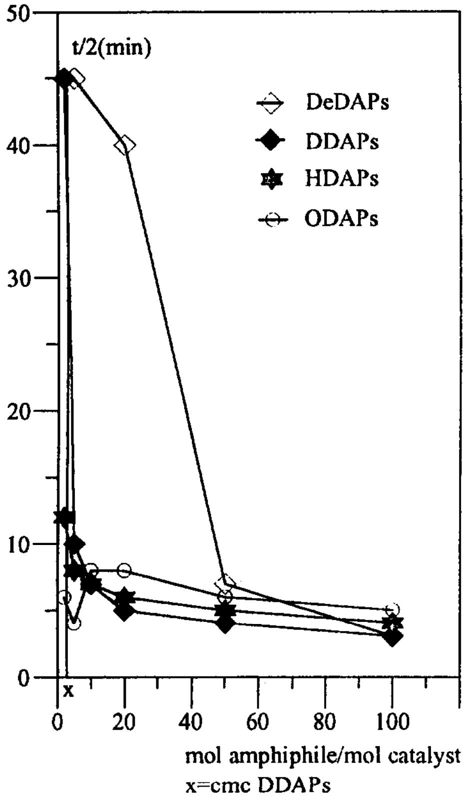


Fig.1a: Influence of surfactants on the halftime of asymmetric hydrogenation
Substrate:(Z)-$PhCH=C(COOMe)NHCOCH_3$
Cat.:$[Rh(COD)_2]BF_4$+ BPPM

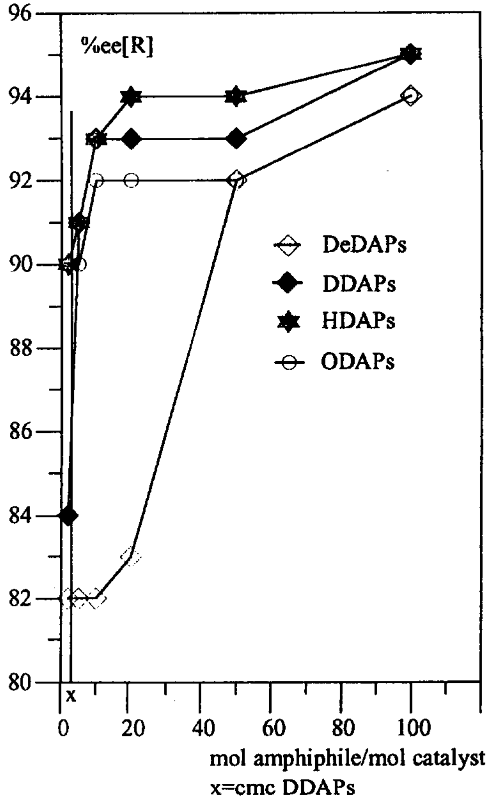


Fig.1b: Influence of surfactants on the enantioselectivity of asymmetric hydrogenation
Substrate:(Z)-$PhCH=C(COOMe)NHCOCH_3$
Cat.:$[Rh(COD)_2]BF_4$+ BPPM

known that the formation of micelles depends on the structure of the amphiphile, and the hydrophobic-hydrophilic balance is optimal for a chain length of C_{12} up to C_{18}. Probably the cmc of decyl-dimethyl-ammonio-propanesulfonate is much higher and explains the exception.

Finally, in Table 4 results are summarized for anionic (sodium dodecylsulfate, SDS) and cationic (cetyl-ethyl-dimethylammonium bromide, CEDA Br; cetyl-ethyl-dimethylammonium tetrafluoroborate, CEDA BF_4; and cetyl-trimethyl-ammonium hydrogensulfate, CTA HSO_4) amphiphiles. Recently we reported, that SDS promoted hydrogenation in a mixture of water with a little methanol as medium.[5] The same effect was found in pure water (see Table 4).

Table 4. Hydrogenation of (Z)-methyl-α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BPPM. Effect of ionic surfactants. Reaction conditions see Table 1.

Entry	Rh:surfactant	Anionic surfactant		Cationic surfactant			
		SDS		CTA HSO_4		1 CTA HSO_4 +1NaOH	
	(mol/mol)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)	t/2 (min)	% ee (R)
1	1 : 2	80	62	no reaction			
2	1 : 5	70	73	10	90		
3	1 : 8	10	88				
4	1 : 10	6	93	5	94	5	93
5	1 : 20	6	94	5	94	4	94
6	1 : 50	3	94	5	94		
7	1 : 100	2	94	5	94		

CTA HSO_4: $C_{16}H_{33}(CH_3)_3N\ HSO_4$

In accordance with the cmc's (see Scheme 2) the concentration of the surfactants has to be slightly higher than for nonionic and zwitterionic amphiphiles. Cationic amphiphiles are significantly influenced by the anion. Whereas CTA HSO_4 acts in the hydrogenation of (Z)-methyl-α-acetamidocinnamate in water like SDS, CEDA Br inhibits the reaction because the bromide occupies a free coordination side in the rhodium catalyst. Careful replacement of the bromide by tetrafluoroborate also gave inactive surfactant probably because the cationic rhodium catalyst cannot interact with the cationic micelle. Some activation was observed on addition of SDS.

The reason for the different behaviour of the tetrafluoroborate and hydrogensulfate is not yet clear. It could be that the hydrogen of hydrogensulfate is dissociated to give a quasi anionic micelle. Addition of an equimolar amount of sodium hydroxide gave no significant change in activity.

Interesting phenomena have been observed in mixtures of surfactants, e. g. small amounts of SDS in micelles of CTA HSO_4 led to an enhancement in stereoselectivity.

CONCLUSIONS

Different types of micelle-forming amphiphiles promote activity and enantioselectivity in asymmetric hydrogenation of (Z)-methyl-α-acetamidocinnamate in aqueous medium. The quality of results is comparable with hydrogenation products in methanol. The effect of surfactants seems to be connected with the formation of micelles because in all cases positive effects are observed above the cmc.

The optimal concentration of surfactants used lies ten to twentyfold higher than the concentration of the catalyst and is substoichiometric with respect to the substrate.

The practical procedure is very simple but the problem of finding a practical recycling method for the catalytic system has not yet been solved. Nonionic surfactants like Brij and Tween seem to be favoured for preparative use (see Scheme 2). Mixed surfactant systems are also promising.

EXPERIMENTAL

The enantiomeric excess (% ee) was determined by glc on a Hewlett-Packard chromatograph 5880 A fitted with a 10 m capillary column XE-60-L-valine-tert. butylamide (FID, split 1:60, 150 °C). The standard deviation in ee was found to be ± 1%. All detergents and BPPM were purchased from commercial sources and used as obtained. Brij compounds were from Fluka Chemika-Bio-Chemika, Tween compounds, sulfobetaines and hexadecyl-dimethyl-ethylammonium bromide from Sigma GmbH, BPPM from the Fa. Merck. $[Rh(COD)_2]BF_4$ and (Z)-methyl-α-acetamidocinnamate were prepared by known methods.[13,14]

Hydrogenation: Hydrogenation was performed under normal pressure and at 25 °C. Solvent, surfactant, rhodium complex and phosphine were placed in a deaerated hydrogenation flask and stirred for 15 min. The reaction was followed by a volumetric measurement at 25 °C ± 0.5 °C. When the reaction was complete, the mixture was extracted with chloroform (5 ml) and in this extract the enantioselectivity controlled by glc.
Usually the addition of detergents produces a transparent dispersion in water.

Brij compounds are poorly soluble in water. In these cases Brij and substrate were warmed with water to about 90 °C until the solution was homogeneous. During the cooling to 25 °C a fine colourless precipitate was formed. The catalyst was added to the reaction mixture at 25 °C and after addition of hydrogen the solution became transparent.

$[C_{16}H_{33}C_2H_5(CH_3)_2N]BF_4$ (CEDA BF_4): $[C_{16}H_{33}C_2H_5(CH_3)_2N]Br$ (7.6 g, 0.02 mol) was dissolved in methylene chloride (20 ml). A saturated solution of $NaBF_4$ (30 ml) was added to this solution and the mixture was stirred. After exchange of anions in a two phase reaction the methylene chloride phase was evaporated, the residue dissolved in methanol (10 ml) and a solution of $AgBF_4$ (100 mg, Fluka) in methanol (5 ml) added. After filtration the methanol was removed under vacuum, and the substance recrystallized from methanol, dried in vacuum to give 3.4 g of a colourless product.
Anal. calcd. for $C_{20}H_{44}BF_4N$ (385.38): C 62.33 H 11.51 N 3.64; found: C 62.2 H 11.6 N 3.7, no halogen could be detected.

Acknowledgements. We thank Ing. Karin Kortus for the gaschromatographic determination of the enantiomeric excess. This work has been supported by the Fonds der Chemischen Industrie.

REFERENCES

1. Kagan, H. B. *Bull. Soc. Chim.* Fr. **1988**, 846-853; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, 45, 6901-6939.
2. Lecomte, L.; Sinou, D.; Bakos, J.; Toth, J.; Heil, B. *J. Organomet. Chem.* **1989**, 370, 277-284.
3. Schellenberger, A., Ed., *Enzymkatalyse*, Springer-Verlag: Berlin 1989, Chapter 4.
4. Kunitake, T.; Shinkai, S. *Adv. Phys. Org. Chem.* **1980**, 17, 435-487; Bunton, C. A., Savelli, G. *Adv. Phys. Org. Chem.* **1986**, 22, 213-309.

5. Oehme, G.; Paetzold, E.; Selke, R. *J. Mol. Catal.* **1992**, 71, L1-L5 (in this paper unpublished results are mentioned submitted by Kagan, H. B. and Samuel, O.).
6. Ueoka, R.; Matsumoto, Y.; Ihara, Y. *Chem. Lett.* **1984**, 1807-1810; Weijnen, J. G. H.; Kondijs, A.; Engbersen, J. F. J. *J. Org. Chem.* **1992**, 57, 7258-7265.
7. Romsted, L. S. in *Surfactants in Solution*, Mittal, K. L., Lindman, B., Eds., Plenum Press, New York 1984, Vol. 2, p. 1015-1068; Bunton, C. A. *Surfactant Sci. Ser.* **1991**, 38, 13-47.
8. Achiwa, K. *J. Am. Chem. Soc.* **1976**, 98, 8265-8266.
9. Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, 45, 4728-4739.
10. Fendler, J. H. *Membrane Mimetic Chemistry*, Wiley-Interscience, New York 1982, p. 9.
11. Lichtenberg, D.; Robsen, R. J.; Dennis, E. A. *Biochim. Biophys. Acta* **1983**, 737, 285-304.
12. Burgess, J.; Pelizzetti, E. *Progr. React. Kinet.* **1992**, 17, 1-170 (see p. 30); Helenius, A.; Mc Caslin, D. R.; Fries, E.; Tanford, C. in *Methods in Enzymology*, Academic Press, New York 1979, Vol. LVI, p. 734.
13. Nagy-Magos, Z.; Vastag, S.; Heil, B.; Marko, L. *Transition Met. Chem.* **1978**, 3, 123-124.
14. Selke, R. *J. Organomet. Chem.* **1989**, 370, 241-248 in connection with Cook, A. H.; Harris, G.: Heilbron, J. *J. Chem. Soc.* **1948**, 1060-1065 and Herbst, R. M.; Shemin, D. S. *Org. Synth. Coll.* Vol. 2, Wiley, New York 1943, 1-3.