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Investigation of the influence of carbohydrate amphiphiles on the complex catalysed asymmetric hydrogenation of (*Z*)-methyl α-acetamidocinnamate in water

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Abstract

A series of carbohydrate amphiphiles has been tested in the asymmetric hydrogenation of (*Z*)-methyl α-acetamidocinnamate using water as medium. Dependent on the chain length and the hydrophilicity of the head group an enhancement of activity and enantioselectivity of the $[Rh(COD)_2]BF_4$ + BPPM catalyst system could be observed. Sometimes the enantioselectivity exceeds that in methanol. The method used here is convenient and environmentally friendly because carbohydrates as amphiphiles are biologically degradable in water. Selected carbohydrate amphiphiles are able to transfer chirality onto the included substrate in a low manner (up to 6% ee). In these cases hydrogen bondings in the head group seem to be responsible for the effect of chiral induction.

Keywords: Carbohydrate amphiphiles; (*Z*)-Methyl α-acetamidocinnamate; Enantioselectivity; Hydrogenation; Chiral induction

1. Introduction

Since the pioneering work by Kagan and co-workers [1] the asymmetric hydrogenation of amino acid precursors has been developed to a standard method, resulting in high activities and enantioselectivities. Traditionally, organic solvents are used, especially methanol [2], but more recently water has become an important alternative [3]. The addition of small amounts of different micelle forming amphiphiles to the substrate and the catalytic system $[Rh(COD)_2]BF_4$ + BPPM in water led to activities and enantioselectivities comparable with those in methanol [4].

To investigate the mechanism between micelle, catalyst and substrate we were interested in the application of chiral amphiphiles to indicate any chiral amplification or induction.

The well-known properties of carbohydrate amphiphiles as lyotropic liquid crystals [5] and the investigation of their aggregation behaviour and ability to solubilise membrane proteins [6] encouraged us to use this type of compounds in our micellar system.

In this paper we want to report about the influence of carbohydrate amphiphiles on the hydrogenation of (*Z*)-methyl α-acetamidocinnamate catalysed by chiral and nonchiral

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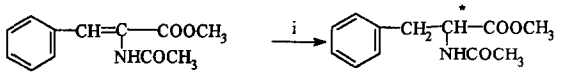
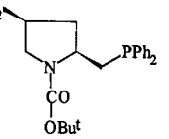


i : [L_2*Rh(cod)]$^+$ BF_4^- (cat.), amphiphile, water, H_2, (0,1 MPa)

L_2 : BPPM = PPh_2 (chiral)



(2S, 4S)-1-tert.Butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine

BDPB = $(C_6H_5)_2P—CH_2—CH_2—CH_2—CH_2—P(C_6H_5)_2$ (achiral)
1,4-Bis(diphenylphosphino)butane

Scheme 1.

rhodium(I)-phosphine complexes in water (Scheme 1).

Chiral induction by chiral micelles is well-known for different reactions e.g. ester saponification [7], hydrogenation of ketones [8], oximercuration [9], etc. The enantioselectivities obtained are low, as a rule 1–30%, and in a rare exception high (57–96%).

Part of the discussion will also be the role of hydrophilic–lipophilic balance (HLB) [10] in carbohydrate amphiphiles and the influence of the alkyl chain length on the ability to form micelles.

2. Experimental

2.1. Materials

Most detergents were purchased from commercial sources and used as obtained.

Tetradecyl-β-D-maltoside, dodecyl-α- and dodecyl-β-D-maltoside, dodecyl-β-D-glucopyranoside, decyl-β-D-maltopyranoside, decyl-α- and decyl-β-D-glucopyranoside were obtained from Sigma GmbH, octyl-α- and octyl-β-D-glucopyranoside from Fluka. The diphosphine ligand BPPM [11] was supplied by Merck. The phosphine bis(diphenylphosphino)butane was also commercially available (Fluka).

Tetradecyl-α-D-maltoside and hexadecyl-β-D-maltoside were prepared as described in [12]. Lactobionic acid was obtained from Aldrich.

All of the alkylated carbohydrates show liquid crystalline behaviour in water (lyotropic behaviour) and waterfree (thermotropic behaviour).

Table 1
Hydrogenation of (Z)-methyl α-acetamidocinnamate (AC) in water, effect of carbohydrate amphiphiles

Entry	Amphiphile	cmc	$[Rh(COD)_2]BF_4$ + BPPM		[Rh(BPPM)(COD)]-BF_4		Rh(BPPM)(COD)]-ClO_4	
			$t/2$ min	% ee *R*	$t/2$ min	% ee *R*	$t/2$ min	% ee *R*
1	Without in CH_3OH		2	90				
2	Without in H_2O		90	78				
3	Tetradecyl-α-D-maltoside ($TD_\alpha M$)	2.2×10^{-5} [12]	7	95	6	96	5	96
4	Tetradecyl-β-D-maltoside ($TD_\beta M$)	1.5×10^{-5} [12]	6	94	6	96	4	96
5	Dodecyl-α-D-maltoside ($DD_\alpha M$)		9	93	6	95	7	94
6	Dodecyl-β-D-maltoside ($DD_\beta M$)	1.0×10^{-4} [14]	9	93	5	94	7	93
7	Decyl-β-D-maltopyranoside ($D_\beta MP$)		8	94	5	94	7	94
8	Dodecyl-α-D-glucopyranoside ($DD_\alpha GP$)		23	82	15	83	42	82
9	Dodecyl-β-D-glucopyranoside ($DD_\beta GP$)	0.2×10^{-3} [15]	23	82	16	82	45	81
10	Decyl-α-D-glucopyranoside ($D_\alpha GP$)		43	82	12	83	38	81
11	Decyl-β-D-glucopyranoside ($D_\beta GP$)	2.2×10^{-3} [15]	8	94	5	94	4	96
12	Octyl-α-D-glucopyranoside ($O_\alpha GP$)	1.0×10^{-2} [16]	22	81	12	81	55	79
13	Octyl-β-D-glucopyranoside ($O_\beta GP$)	2.4×10^{-2} [16]	23	81	13	81	60	80
14	Lactobionic acid dodecylamide (LD)		16	90	5	90	11	92
15	Lactobionic acid tetradecylamide (LT)		20	85	12	84	25	84
16	Lactobionic acid hexadecylamide (LH)		21	81	15	81	41	82

Reaction conditions: 25°C; 0.1 MPa H_2; 15 ml H_2O; 1 mmol AC; 0.01 mmol $[Rh(COD)_2]BF_4$ + 0.011 mmol BPPM or $[Rh(BPPM)(COD)]^+X^-$ ($X^- = BF_4^-$, ClO_4^-) Rh:amphiphile = 1:20.

The transition temperatures of the pyranosides are given in [5].

(*Z*)-methyl α-acetamidocinnamate was prepared in accordance to [4].

2.1.1. Synthesis of the 1,5-lactone of lactobionic acid [13]

Lactobionic acid (45.1 g, 0.126 mol) was dissolved in 100 ml of 2-methoxyethanol at 120°C bath temperature. Upon adding 50 ml of toluene a colourless paste was formed. The mixture of solvents was removed using the rotavapor and the procedure was repeated twice. The remaining syrup was used without purification for the reaction with the alkylamine.

2.1.2. Synthesis of lactobionic alkylamides LD, LT, LH (see Table 1) (Preparation in analogy to [17])

Lactobionic-1,5-lactone (5 g, 14 mmol) was emulsified in 30 ml of methanol. A solution of the amine (14 mmol) was added at room temperature and stirred for 24 h, during which a colourless slurry was formed. After the addition of 20 ml of methanol the product was obtained by filtration. After drying in vacuum the products were recrystallised in 125 ml of hot methanol.

Yields: LD: 79%, LT: 70%, LH: 69%

Analytical data:

LD: $C_{24}H_{47}NO_{11}$ (525.66): calc. C 54.83 H 9.01 N 2.66; found: C 54.78 H 8.58 N 2.71; optical rotation: $[\alpha]_D^{26.5} = +28.85$ (c = 1.02, MeOH)

LT: $C_{26}H_{51}NO_{11}$ (553.71): calc. C 56.40 H 9.28 N 2.53; found: C 56.50 H 9.40 N 2.58; optical rotation: $[\alpha]_D^{26} = +20.97$ (c = 0.51, DMF)

LH: $C_{28}H_{55}NO_{11}$ (581.76): calc. C 57.80 H 9.93 N 2.41; found: C 57.79 H 9.66 N 2.48; optical rotation: $[\alpha]_D^{25.2} = +16.41$ (c = 0.53, DMF)

^{1}H-NMR (similar for all three compounds): LH (DMSO d_6, in ppm): 0.85 (t, 3H, CH_3), 1.21 (m, 6H, CH_2), 1.41 (m, 2H, β CH_2), 3.08 (m, 2H, α-CH_2) all sugar protons 3.3–5.1, 7.53 (t, 1H, NH)

The lactobionic amides show thermotropic smectic A phases in a range of more than 100°C. They decompose after reaching the isotropic phase.

Phase transition: LD: Cr 128 S_A 240 dec.
LT: Cr 126 S_A 252 dec.
LH: Cr 128 S_A 259 dec.

2.1.3. Complexes [Rh(COD)(phosphine)]BF_4 (or ClO_4) were prepared according to [Rh(COD)(BPPM)]ClO_4 in [18]

Analytical data:

[Rh(COD)(BPPM)]BF_4 (851.53): calc. C 59.24 H 5.80 N 1.64 P 7.28 Rh 12.08;

found: C 58.76 H 6.02 N 1.87 P 7.40 Rh 11.50

[Rh(COD)(BPPM)]ClO_4 (864.14): calc. C 58.37 H 5.72 N 1.62 P 7.17 Rh 11.91;

found: C 57.35 H 5.80 N 1.62 P 6.65 Rh 11.67

[Rh(COD)(BDPP)]BF_4 (724.38): calc. C 59.69 H 5.56; found: C 59.64 H 5.42

2.2. Hydrogenation

Hydrogenation was performed under normal pressure and at 25°C. A suspension of 1 mmol (*Z*)-methyl α-acetamidocinnamate, 0.01 mmol [Rh(COD)$_2$]BF_4, 0.011 mmol of ligand (phosphine) (or 0.01 mmol [Rh(COD)(phosphine)]X) and 0.2 mmol surfactant in 15 ml of deaerated water was stirred for 15 min under argon in a hydrogenation flask. Then, stirring was stopped, the argon replaced by hydrogen at atmospheric pressure, and the hydrogenation started by stirring. The reaction was followed volumetrically. The time necessary to consume half of the theoretical amount of hydrogen (halftime) was taken as a measure for the activity. After finishing the experiment, the mixture was extracted with 5 ml of chloroform. The enantiomeric excess of the product was determined by GLC on a Hewlett Packard chromatograph 5880 A fitted

with a 10 m capillary column XE-60-L-*N*-tert-butyl-valinamide (FID, split 1:60, 150°C). The standard deviation in ee was found to be $\pm 1\%$.

3. Results and discussion

Our results are summarised in Table 1. In comparison to methanol there is a significant decrease in activity and enantioselectivity in water caused by the low solubility of the catalytic system and specific properties of the medium water.

All carbohydrate amphiphiles used increase activity and enantioselectivity in the hydrogenation of (*Z*)-methyl α-acetamidocinnamate in comparison to the value found for pure water.

As shown in Table 1, there are clear differences dependent on the structure of amphiphiles. The influence seems to be connected with the ability to form micelles and to solubilise substrate and complex, which are both slightly soluble in water. Three different properties of the carbohydrate amphiphiles are to take in account: firstly the cmc, representing the ability to form micelles, secondly the HLB (hydrophilic lipophilic balance) as measure of the solubility in water and nonpolar phases and thirdly hydrogen bonds in the carbohydrate part responsible for a stabilization of the micelles on the outer side and probably for the chiral recognition. Data of cmc's are given in Table 1. The term HLB, first suggested by Clayton [19] can be quantified by increment addition. The interplay of all properties seems to be complicate. As we could show in an earlier paper [4] the enhancement of activity and enantioselectivity depends on the cmc of the surfactant. One more argument for a reaction in micellar assemblies is the use of polymerised micelles [20]. In this case the effect could be indicated on much lower concentrations because of the stabilization of the amphiphile-assemblies. Comparable solubilizations are known to be important in biological and chemical processes [21]. The distribution of the reactants within the micelles should be responsible for the enhancement of the reaction rate [19]. In our case only 10 to 20 mol% of the surfactant are necessary with respect to the substrate.

Three types of carbohydrate amphiphiles were tested with the different hydrophilic head groups maltose, glucose and lactobionic acid. In the case of the maltosides we found optimal activity and selectivity by extending the chain from decyl to dodecyl and tetradecyl. In our experience this is connected with a facilitation of micelle formation [22].

Obviously, the behaviour of glucopyranosides is quite different because of the lower hydrophilicity of the head group: These compounds gave as a rule low activities and low enantioselectivities (see entries 8–10 and 12–13) except decyl-β-D-glucopyranoside with an excellent halftime of 4 min and an enantioselectivity of 96% ee (entry 11). The effectivity of decyl-β-D-glucopyranoside is unexpected and we suppose an optimal cooperation between cmc, HLB and hydrogen bonds leading to a high concentration of micelles and a relatively high chiral induction. The change from the β- to the α-anomer (entries 10 and 11) gave a significant loss of activity and enantioselectivity probably due to a new orientation of the hydrogen bridges.

Even the lactobionic acid amphiphiles show a maximum effect in the case of dodecyl derivatives with a halftime of 5 min and 90% ee, whereas tetradecyl and hexadecyl derivatives gave only low activities and enantioselectivities.

The optically active catalyst with BPPM as ligand was used in three variants: Prepared in situ from $[Rh(COD)_2]BF_4$ or as crystalline complexes $[Rh(BPPM)(COD)]BF_4$ and $[Rh(BPPM)(COD)]ClO_4$. In comparison to the in situ formed catalyst the tetrafluoroborate complex gave with maltose-, glucose- and lactobionic acid derivatives slightly enhanced activities, but the perchlorate complex showed a different behaviour dependent on the amphiphile. With tetradecyl-α- and tetradecyl-β-D-maltoside and with decyl-β-D-glucoside the best ac-

tivities could be achieved and with the less active glucopyranosides and lactobionic derivatives the results were sometimes poorer than with the tetrafluoroborate complex.

We were also interested in testing the chiral induction by means of carbohydrate amphiphiles using an achiral rhodium(I) complex for hydrogenations. As summarised in Table 2 carbohydrate amphiphiles could not only activate the hydrogenation but also induce chirality on a low level. Tetradecyl- and dodecyl-β-D-maltoside show the highest induction with an enantiomeric excess of 6% ee.

All other amphiphiles gave less or no induction. Requirements for a transfer of chirality seem to be a chiral suprastructure due to hydrogen bonds between the carbohydrate head group on the surface of the micelle [23] and the fixation of the catalytic system near chiral centres. Possibly, the β-anomers are favoured in comparison to the α-anomers [16]. We suppose as a conclusion of the chiral induction that the catalyst substrate system is situated between the head group and the hydrophobic tail. Fig. 1 shows a schematic picture of the embedded catalyst–substrate complex within a chiral micelle. The model of micelle is taken from a proposal made by Menger and Mounier [24].

The contact to the head group should be responsible for the chiral induction and the contact to the hydrophobic part explains the high activity.

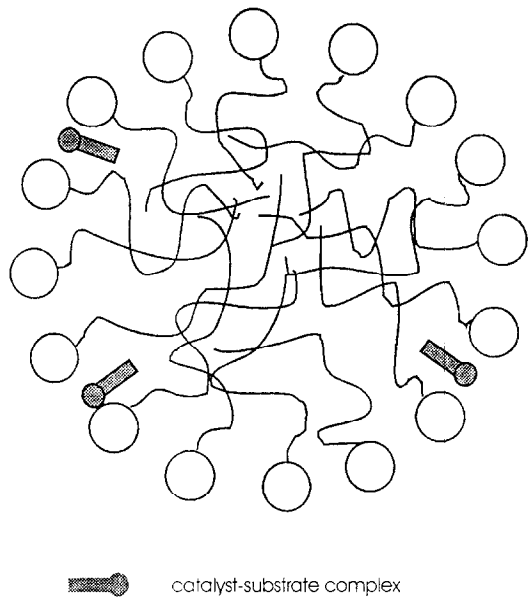


Fig. 1. Speculative picture of a micelle with embedded catalyst–substrate complex. The relationship of the molecule sizes is arbitrary.

Hinze et al. [25] described an enhancement of separation in micellar HPLC with mixed micelles (SDS + carbohydrate amphiphiles), but the mechanism of chiral recognition seems to be different, because we could not find a similar effect in our system. Addition of Tween 40 or SDS and also an change of the temperature

Table 2
Experiments for chiral induction. Hydrogenation of (Z)-methyl α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BDPB or $[Rh(BDPB)(COD)]BF_4$. Effect of carbohydrate amphiphiles

Entry	Amphiphile	$[Rh(COD)_2]BF_4$ + BDPB		$[Rh(BDPB)(COD)\ BF_4$	
		$t/2$ min	% ee *R*	$t/2$ min	% ee *R*
1	$HD_\beta M$	55	5	27	4
2	$TD_\alpha M$	39	3	9	3
3	$TD_\beta M$	40	6	9	3
4	$DD_\alpha M$	27	2	12	3
5	$DD_\beta M$	23	6	6	5
6	$D_\beta MP$	28	4	9	5
7	$DD_\alpha GP$	175	racemate		
8	$DD_\beta GP$	100	racemate		
9	$D_\alpha GP$	200	racemate	no reaction	
10	$D_\beta GP$	25	3	9	4
11	$O_\beta GP$	300	racemate		

Reaction conditions see Table 1. BDPB = $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$.

from 25 to 40°C increased the activity and decreased the chiral induction.

4. Conclusions

A series of carbohydrate amphiphiles enhances activity and enantioselectivity of the asymmetric hydrogenation in water. With a rhodium(I) BPPM complex as optically active precatalyst and (*Z*)-methyl α-acetamidocinnamate as substrate halftimes of 5 min and enantioselectivities up to 96% ee could be observed. A comparison of carbohydrate amphiphiles with alkylchains of different lengths has shown that micelle forming properties, hydrophilic–lipophilic balance (HLB) and the structure caused by hydrogen bonding in the head group may be responsible for the effect. In some cases a low but reproducible induction of chirality could be observed owing to the chiral structure of the micelle by use of a nonchiral rhodium complex as catalyst. Some mechanistic implications are possible on the base of observations.

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