Dependence of Enantioselectivity on the Distribution of a Chiral Hydrogenation Catalyst between an Aqueous and a Micellar Phase: Investigations Using Pulsed Field Gradient Spin Echo NMR Spectroscopy

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Abstract: The enantioselectivity obtained from rhodium complex catalyzed hydrogenations conducted in water can often be increased considerably by the addition of amphiphiles. At present the reasons for this increase in selectivity are not fully understood. The application of pulsed field gradient spin echo NMR (PGSE-NMR) spectroscopy to determine the average diffusion coefficients of the catalysts in both known and novel examples of asymmetric hydrogenation shows definitively that the increase in enantioselectivity is coupled with an aggregation of the catalyst to the micelles. This aggregation or solubilization of the catalyst in the micelles leads to the formation of a new colloidal phase in the aqueous solution. This phase has stronger hydrophobic properties, and thus the hydrogenation is more comparable to those conducted in a hydrophobic or less polar organic solvent. In the case of anionic amphiphiles, which form amphiphilic salts with the cationic catalyst, the embedment of the catalyst complex into the micelle is generally complete. The whole hydrogenation then takes place exclusively inside the micelles, leading to high enantioselectivity. If the catalyst is not completely embedded into the micelle, for example in the cases of nonionic or cationic surfactant solutions, the solubility of the substrate plays an important role. For soluble substrates the hydrogenation of the substrate occurs predominately in the aqueous phase itself, leading to very poor enantioselectivities. In these cases, only the use of a large excess of amphiphile, far above the critical micelle concentration (cmc), will lead to higher enantioselectivities due to a shift of the equilibrium towards the micellar bonded forms of catalyst and substrate. In contrast, poorly soluble substrates exhibit a high tendency to be incorporated into micelles, which leads to much higher enantioselectivities if the cmc of the surfactant is small enough. Changes in the cmc of amphiphiles caused by their aggregation with catalysts could also be estimated. The variation in selectivity observed for the catalysts containing seven-membered, flexible chelate rings is apparently due to changes in their conformation in the less polar micellar medium, and this effect is also seen in organic solvents. As expected, catalysts containing smaller chelate rings show this effect to a considerably lower extent since they are conformationally more rigid.

Keywords: amino acids · asymmetric catalysis · diffusion · hydrogenation · micelles · NMR spectroscopy

Introduction

Asymmetric hydrogenation of dehydroamino acid derivatives using chiral rhodium(I) complex catalysts in water commonly results in enantioselectivities that are lower than those of the same hydrogenations conducted in an organic solvent.[1–4] This disadvantage can be overcome by the addition of amphiphilic substances, even in polymerized form, as was shown by Oehme et al.[5–9] The ability of added surfactants to increase the selectivity depends on the type of catalyst employed, and in particular on the ligand. Chelates with ring sizes of at least seven are influenced to a larger extent by the addition of amphiphiles (Table 1). It seems plausible that the conformational flexibility of the ligand in the chelate structure is a prerequisite for this effect.[10] Large increases in enantioselectivity (83 to 98 % *ee*) are possible,[7] or even a change in the preferred product enantiomer.[4, 11] In a recent example the enantioselectivity increased from almost zero to 80 % *ee*.[11]

Early on researchers investigated whether this phenomenon really depends on the micelle- or vesicle-forming ability of the amphiphile and where the catalytically active species is located. Osborn et al.[12] found that sodium bis(2-ethylhexyl)sulfosuccinate (AOT) similarly increased the enantioselectivity of imine hydrogenations in organic solvents. This was not coupled with the reverse micellar structure of AOT, and a

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reliable method for the determination of the catalyst's location became of interest. In experiments with chiral amphiphiles in water Oehme et al.[13] advanced interesting arguments concerning the location of achiral catalysts in the region between the chiral head groups and the hydrophobic tails of micelles formed by the amphiphiles.[14] However, no quantitative statement was possible about the part of the catalyst agglomerated to the micelles. Such investigations are very important since the supramolecular behavior of amphiphiles may change distinctly in the presence of catalysts or substrates as well as under the reaction conditions.

The NMR pulsed gradient spin echo (PGSE) method is a powerful tool for investigating aggregation processes in complex surfactant systems.[15–17] The PGSE technique enables the selective and quantitative measurement of the self-diffusion coefficients (D) of individual components in complex mixtures. This approach has been widely used to study the diffusion characteristics of different biological[18] and chemical systems.[19] The technique has also been shown to be very effective for the investigation of micellization and solubilization phenomena[20] and was recently applied to determine molecular diffusion and thus the size of species in organometallic reactions.[21]

The translational mobility of a compound in solution is reduced considerably when it becomes incorporated in some way into a micelle. Diffusion of the micelle and compound together has the effect that the diffusion coefficient (D) is reversed proportionally to the size of the aggregated species (as expressed quantitatively in the Stokes–Einstein equation [Eq. (1)], in which r is the radius of the particle and η is the viscosity).

$$D = k_b T/(6\pi\eta r) \quad (1)$$

The observed self-diffusion coefficient (D) of a compound is a time-averaged value. Therefore, if the diffusion constants of the pure micelles (D_{mic}) and of the "free" species (D_{free}) are determined separately, the part (p) of the species agglomerated to the micelles can be determined from the observed average diffusion constant (D_{obs}) of the species in the mixture [Eq. (2)].

$$D_{obs} = pD_{mic} + (1-p)D_{free} \quad (2a)$$

$$p = (D_{obs} - D_{free})/(D_{mic} - D_{free}) \quad (2b)$$

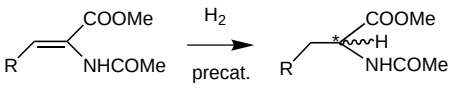
This is valid under the condition that D_{mic} of the pure micelles does not undergo large changes due to inclusion of low molecular weight compounds and is only an approximation for the applied large catalyst complexes.

Abstract in German: *Die Enantioselektivität chiraler kationischer Rhodium-Phosphin-Katalysatoren bei Hydrierungen in Wasser als Lösungsmittel läßt sich häufig durch Zusatz von Amphiphilen erheblich steigern. Dabei sind die ursächlichen Zusammenhänge oft noch weitgehend unklar. Durch Anwendung der PGSE NMR-Technik zur Bestimmung der mittleren Diffusionskoeffizienten von Katalysatoren auf bekannte und neue Beispiele asymmetrischer Hydrierungen ließ sich eindeutig klären, daß die Selektivitätszunahme an eine Aggregation der Katalysatoren mit den Micellen gebunden ist. Diese Aggregation bzw. Solubilisierung des Katalysators in Micellen bedeutet die Bildung einer neuen hydrophoben kolloidalen Phase und ist somit vergleichbar mit der Hydrierung in einem hydrophoben oder weniger polaren organischen Lösungsmittel. Sie kann, wie im Falle anionischer Amphiphile, die mit dem Katalysator-Kation amphiphile Komplexsalze bilden, vollständig sein. Die gesamte Hydrierung findet dann ausschließlich im Micellverband statt. Bei nur teilweise micellarer Bindung der Katalysatoren, die sich halbquantitativ bestimmen läßt, spielt die Substratlöslichkeit noch eine große Rolle. Für gut wasserlösliche Substrate können die verbleibenden Anteile an wenig selektiver Homogenhydrierung in der rein wäßrigen Phase oft erst durch einen erheblichen Tensidüberschuß weit oberhalb der „Kritischen Micellkonzentration" (cmc) zurückgedrängt werden, was durch eine Verschiebung der Gleichgewichte hin zu den micellar gebundenen Formen von Katalysator und Substrat verursacht wird. Das steht im Gegensatz zu Befunden mit wenig wasserlöslichen Substraten, die wegen ihrer erhöhten Tendenz zur Einbindung in Micellen einen steileren Anstieg der Enantioselektivität mit Erhöhung der Amphiphilenkonzentration zeigen. Änderungen der cmc von Amphiphilen durch die Gegenwart von Katalysatoren lassen sich ebenfalls bestimmen. Die eigentliche Ursache für die Wandelbarkeit der Selektivität unserer Katalysatoren mit flexiblem Chelat-Siebenring ist offensichtlich in der Möglichkeit zur Änderung ihrer Konformation durch das weniger polare Medium Micelle zu sehen, wie sie auch in organischen Lösungsmitteln gefunden wird. Folgerichtig zeigen Katalysatoren, die infolge engerer Chelatringe weitgehend konformativ starr sind, nur wesentlich geringere Effekte.*

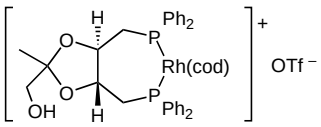
Results and Discussion

We applied mainly rhodium(I) chelates of (*R,R*)-4,5-bis(diphenylphosphinomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (abbreviated HO-diop) because as a catalyst in water it led to a particularly distinct increase in selectivity after addition of amphiphiles.[11] We prepared [Rh(HO-diop)(cod)]OTf (cod = cyclooctadiene, OTf = trifluoromethanesulfonate) as a precatalyst for the hydrogenation of methyl 2-acetamidoacrylate (aMe) and methyl (*Z*)-2-acetamidocinnamate (AMe) (Scheme 1). We usually applied the trifluoromethanesulfonate complex instead of the less water-soluble tetrafluoroborate [Rh(HO-diop)(cod)]BF_4[22] since the solubility of the catalyst is particularly important at low amphiphile concentrations. Unless otherwise noted the D values were measured under hydrogenation conditions.

As already stated, the formation of micelles is thought to be essential for the enhancement of enantioselectivity.[4–11] In describing the principal properties of surfactants we must differentiate between nonionic, anionic, and cationic surfactants as well as between different hydrophobic strengths (length of the carbon chain), which is related to the critical micelle concentration (cmc). All of these properties control the aggregation or micellization behavior in the system.



precat. = [Rh(HO-diop)(cod)]OTf



Substrate	R	Enantioselectivity in water
aMe	H	8.1 %*ee* (*S*); *er* = 0.85 (*R*/*S*)
AMe	Ph	1.9 %*ee* (*R*); *er* = 1.04 (*R*/*S*)

Scheme 1. Asymmetric hydrogenation of methyl 2-acetamidoacrylate (aMe) and (*Z*)-2-acetamidocinnamate (AMe) in water.

We began our investigations using the nonionic 1-*O*-octyl β-D-glucopyranoside (OGP). Owing to its relatively high cmc of approximately 0.018 mol L^{-1} in water,[23] NMR measurements are possible at concentrations both above and below the cmc. Under the reaction conditions the *D* value for OGP decreased sharply above its cmc, indicating no influence of the catalyst and the substrate on the cmc of OGP (see Figure 1). Up to this

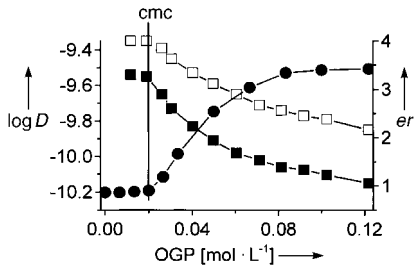


Figure 1. Influence of increasing amounts of the amphiphile OGP on the diffusion coefficients (*D*; ■ = catalyst, □ = OGP) and the enantiomeric ratio (*er* = *R*/*S* = ●) in the hydrogenation of aMe. Conditions: [Rh(HO-diop)(cod)]OTf (3×10^{-3} mol L^{-1}), aMe (66.7×10^{-3} mol L^{-1}) in D_2O, 0.1 MPa H_2, 25 °C. The *er* value was determined separately.

concentration of OGP, neither the *D* values of the catalyst nor the enantiomeric ratio (*er*) of the hydrogenated product varied significantly. Above the cmc of OGP, the observed connection between the *D* value of OGP, the *D* value of the catalyst, and the determined *er* of the hydrogenation product clearly indicate the influence of micelle formation on the enantioselectivity. This effect can be explained as follows. At concentrations of OGP above its cmc, more and more micelles are formed, giving a lower average *D* value for the amphiphile. At the same time the proportion of the catalyst agglomerated to the micelle increases, which is, in turn, indicated by a lower *D* value of the catalyst. Compared with pure water, micelles provide a less polar environment for the agglomerated catalyst, and an increase of ion pairing may be the consequence, which would also result in a decrease of the catalyst's diffusion coefficient *D*.[21b, c] The higher *er* (*R*/*S*) value for the hydrogenation products when the reaction is performed in an organic solvent[22] instead of water is consistent with the same tendency when the catalyst is agglomerated with the micelles. The higher the concentration of the amphiphile, the larger the proportion of the catalyst influenced by the micelles.

Anionic amphiphiles such as sodium dodecylsulfate (SDS) lead to a more complicated situation. The precatalyst precipitates as the dodecylsulfate complex salt [Rh(HO-diop)(cod)]DS already below the cmc of SDS in pure water (0.0081 mol L^{-1}[24]).[11] With increasing amounts of SDS this precipitate redissolves in the micellar dispersion as shown by the constant low diffusion coefficient ($\log D = -10.1$), indicating complete embedment of the catalyst into the SDS micelles (Figure 2). Measure-

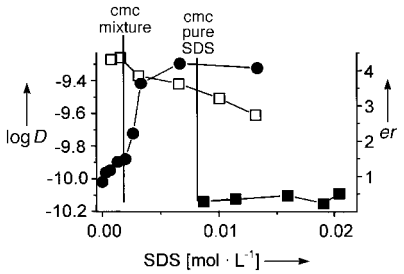


Figure 2. Influence of increasing amounts of the amphiphile SDS on diffusion coefficients (*D*; ■ = catalyst, □ = SDS) and the enantiomeric ratio (*er* = *R*/*S* = ●) in the hydrogenation of aMe. Conditions: Precatalyst [Rh(HO-diop)(cod)]BF_4 (2.5×10^{-3} mol L^{-1}, aMe (66.7×10^{-3} mol L^{-1}) in D_2O under 0.1 MPa argon. The enantioselectivity was determined separately with [Rh(HO-diop)(cod)]BF_4 (0.67×10^{-3} mol L^{-1})under 0.1 MPa H_2, 25 °C.

ment of the diffusion coefficient of the catalyst is impossible below 0.007 mol L^{-1} SDS due to the catalyst's very low solubility and consequent limited incorporation into the colloid.

Although the curves describing the average diffusion coefficient (*D*) of the catalyst with the nonionic (OGP, Figure 1) and anionic (SDS, Figure 2) amphiphiles differ, in both cases the increase in enantioselectivity is connected to the aggregation of the catalyst by amphiphiles having a relatively high cmc. Therefore, we conducted similar experiments using a surfactant with a very low cmc and very high surface activity—the nonionic amphiphile tetradecyldimethylphosphine oxide ($C_{14}H_{29}Me_2PO$, cmc = 3.9×10^{-5} mol L^{-1}[25]). As can be seen in Figure 3, the *D* value of the

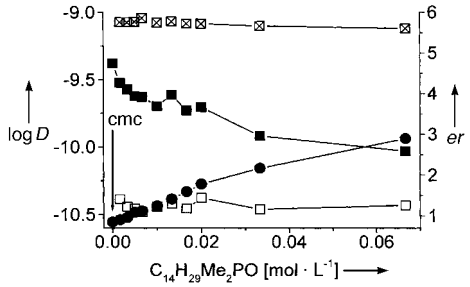


Figure 3. Influence of increasing amounts of $C_{14}H_{29}Me_2PO$ on the diffusion coefficients (*D*; ⊠ = aMe, ■ = catalyst, □ = $C_{14}H_{29}Me_2PO$) and the enantiomeric ratio (*er* = *R*/*S* = ●) in the hydrogenation of aMe. Conditions: [Rh(HO-diop)(cod)]OTf (2.5×10^{-3} mol L^{-1}), aMe (66.7×10^{-3} mol L^{-1}) in D_2O, 0.1 MPa H_2, 25 °C. The enantioselectivity was determined directly from the NMR tubes under hydrogen.

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phosphine oxide indicates complete micellization at all concentrations in the experimental range (higher than 0.001 mol L^{-1}). The enantioselectivity of the aMe hydrogenation, nevertheless, increased only gradually with increasing amounts of added amphiphile. The catalyst's degree of inclusion into the aggregates is indicated by its decreasing diffusion coefficient (D). Although at low concentration (0.0017 mol L^{-1}) practically all of the phosphine oxide exists in micellar association, the level of micelles present in the reaction mixture is evidently still insufficient to allow incorporation of much of the catalyst by aggregation. Thus, in general, and in particular for the highly water-soluble substrate methyl α-acetamidoacrylate (aMe), the overwhelming part of the hydrogenation occurs on the large amount of homogeneously dissolved complex in the aqueous phase. This leads to a very low enantioselectivity (5.1 % *ee (S)*, $er = 0.90$), which is indeed similar to that found for the control reaction in the absence of an amphiphile. When the same concentration of amphiphile is used for the reaction of the less water-soluble substrate methyl (Z)-2-acetamido-cinnamate (AMe) the proportion of hydrogenation by the even somewhat smaller amount of micelle-bound catalyst confirmable at this point seems to be much higher (35.8 % *ee (R)*, $er = 2.11$). This can be explained at least in part by the increased amount of the less polar aromatic substrate embedded in the micellar agglomerate and only to some extent by the generally higher enantioselectivity found for this substrate in other solvents. This follows from comparison of the diffusion coefficients (D) for both substrates shown in Figure 3 and Figure 4.

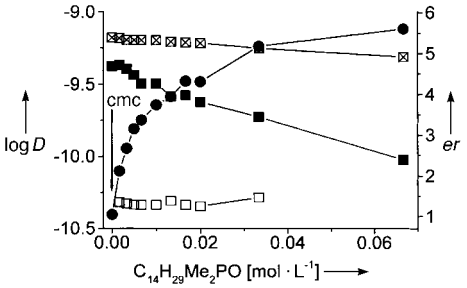


Figure 4. Influence of increasing amounts of $C_{14}H_{29}Me_2PO$ on diffusion coefficients (D; ⊠ = AMe, ■ = catalyst, □ = $C_{14}H_{29}Me_2PO$) and the enantiomeric ratio ($er = R/S =$ ●) in the hydrogenation of AMe. Conditions: see legend of Figure 3.

Most of the AMe substrate is present as a suspension in the reaction mixture due to its very low solubility. Since only a very small amount of the AMe substrate is present in the aqueous phase, very little unselective, purely homogeneous hydrogenation can take place. Therefore the proportion of hydrogenation effected by the micelle-bound catalyst becomes much larger with increasing phosphine oxide concentration than in the case of the more polar and therefore fully water-soluble aMe. This is due to the increasing inclusion of the AMe substrate into the micelles. The result is a curve with a much higher gradient for the enantiomeric ratio (er) of the aromatic hydrogenation product even though the relatively polar catalyst cannot compete as well is not solubilized as well as the more hydrophobic substrate AMe in micelles (Figure 4). This is indicated by a measurable smaller decrease of the diffusion coefficients (D) for the polar catalyst in the presence of the hydrophobic substrate AMe compared to that with the more hydrophilic aMe, which is of course particularly distinct at low concentrations of the amphiphile.

The different behavior of the two substrates can be clearly seen from Figure 5, where the enantioselectivity er is given as a function of the proportion (p) of micelle-embedded catalyst.

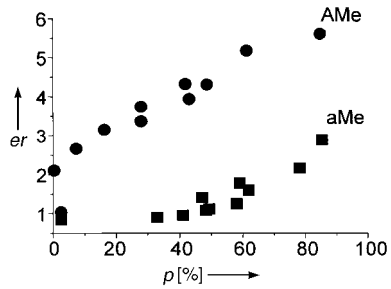


Figure 5. Influence of the part (p) of the catalyst agglomerated to the micelles formed by $C_{14}H_{29}Me_2PO$ on the er of the hydrogenated products ($D_{free} = 4.30 \times 10^{-10}$ $m^2 s^{-1}$, $D_{mic} = 0.350 \times 10^{-10}$ $m^2 s^{-1}$).

The clear induction period up to $p = 40$ % for the reaction of the water-soluble substrate aMe indicates that micellar-based catalysis competes with purely homogeneous hydrogenation only when more than 40 % of the catalyst is in the agglomerated form.

Similar curves with a somewhat lower increase in the er, particularly for AMe, were found for decyldimethylphosphine oxide, which is less hydrophobic and has lower surface activity (cmc = 0.0041 mol L^{-1})[25] (see Figure 6). Logically, for this

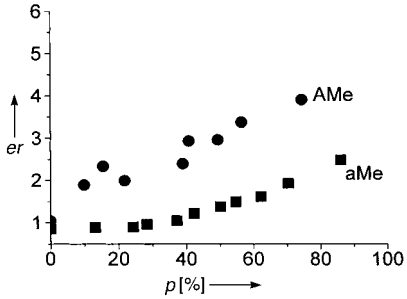


Figure 6. Influence of the agglomerated part (p) of the catalyst embedded in micelles formed by $C_{10}H_{21}Me_2PO$ on the er of the hydrogenated products ($D_{free} = 4.3 \times 10^{-10}$ $m^2 s^{-1}$, $D_{mic} = 0.348 \times 10^{-10}$ $m^2 s^{-1}$).

amphiphile with lower micelle-forming tendency we need a higher concentration for hydrogenation in the micellar phase. However, even at the same p value for the complex ($p > 60$ %) the enantioselectivity of the embedded catalyst is less than that obtained for the tetradecyldimethylphosphine oxide, apparently due to differences in the environment polarity of the two micelle types.

Cationic amphiphiles such as hexadecyltrimethylammonium hydrogensulfate (cmc = 4.0×10^{-4} mol L^{-1})[34] show remarkably high activity in hydrogenation experiments.[6] A steep selectivity increase is found for the hydrogenation of AMe in the presence of this strongly surface-active amphi-

phile. An *er* value of 5.5 was obtained at an amphiphile concentration of 0.07 mol L^{-1}, whereas separate measurements at this point with the water-soluble aMe showed only a low *er* value of 2.5 (see Figure 7). This indicates that the catalyst is relatively strongly bound (solubilized) to the micelles, which is similar to the behavior of nonionic surfactants with strong surface activity (see Figure 3 and Figure 4). This is confirmed by experiments with hexadecyltrimethylammonium tosylate, which also shows a large effect on the enantioselectivity (for AMe: *er* = 3.6 at 0.033 mol L^{-1}).

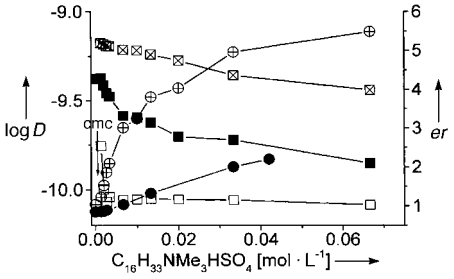
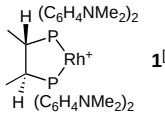
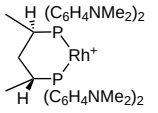
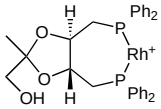
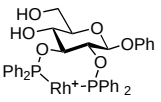


Figure 7. Influence of increasing amounts of $C_{16}H_{33}NMe_3HSO_4$ on diffusion coefficients (D; ⊠ = AMe, ■ = catalyst, □ = $C_{16}H_{33}NMe_3HSO_4$) and the enantiomeric ratio in the hydrogenations of both AMe and aMe (*er* = *R*/*S*; ⊕ = AMe, ● = aMe). Conditions: [Rh(HO-diop)(cod)]OTf (2.5×10^{-3} mol L^{-1}), substrate (66.7×10^{-3} mol L^{-1}) in D_2O, 0.1 MPa H_2, 25 °C. The enantioselectivity was estimated directly from the NMR tubes under hydrogen.

The basic question about the origin of the increase in selectivity, however, remains. We know that if the catalyst has a flexible chelate ring, the surrounding solvent molecules have an enormous influence on the enantioselectivity that the catalyst can deliver.[10, 22, 26] We believe that the medium acts on the equilibria of the catalytic species distinguished by conformation[27] and thereby controls the subsequent *Re*/*Si* equilibria of the intermediate catalyst–substrate complexes. The ratio of these *Re* and *Si* complexes and the frequently very large difference in their further reactivity with hydrogen[28] could kinetically determine the enantiomeric ratio of the products. If this is the correct explanation for the solvent dependence of the enantioselectivity and for the action of added amphiphiles, then one would expect the effects to be minimized with catalysts more rigid than our flexible seven-membered [Rh(HO-diop)]$^+$ chelate. Indeed one can see from Table 1 that conformationally less flexible catalysts containing a five- or six-membered ring show low *relative enantioselectivities* $Q_{a/b}$[4] in the presence of the amphiphile sodium dodecylsulfate (SDS). Only one example reaches $Q_{a/b} = 1.6$; the average value of $\bar{Q}_{a/b}$ is 1.0 ± 0.3. In contrast, this average increases to $\bar{Q}_{a/b} = 5.5 \pm 1.4$ in the experiments with the seven-membered ring catalysts, with the lowest single value of $Q_{a/b} = 3.3$. This result for the anionic amphiphile is particularly meaningful because SDS binds the cationic complexes quantitatively, and hence the substrate solubility does not influence the extent of the increase in selectivity.[7, 11] Only the substrate in contact with the embedded catalyst may be hydrogenated. There is no dissolved catalyst for less selective, homogeneous hydrogenation of the substrate dissolved in water.

We have, however, seen a similar outcome with neutral amphiphiles such as Triton X100. Also this amphiphile does not affect the enantioselectivity of catalysts bearing small

Table 1. Importance of the flexibility of the catalysts' chelate rings and the extent of enantioselectivity change caused by the presence of the amphiphile sodium dodecylsulfate (SDS, 0.1 mmol) in hydrogenations in water.[a]

Catalyst	Number of ring members	Substrate[d]	*t*/2 [min] without SDS	*t*/2 [min] with SDS	Enantioselectivity [% *ee*] without SDS	Enantioselectivity [% *ee*] with SDS	$Q_{a/b} = er_a/er_b$[e]
 **1**[b]	5	AMe	70	5	3.9(*R*)	2.4(*R*)	1.0
		aH	790	8	6.5(*R*)	30.5(*R*)	1.6
		AMe	> 2600	175	17.6(*R*)	2.6(*R*)	0.7
 **2**[b]	6	aMe	5	2	0.7(*S*)	10.2(*R*)	0.8
		aH	11	3	38.4(*S*)	37.5(*S*)	1.0
		AMe	69	4	31.1(*S*)	10.2(*S*)	0.7
$Q_{a/b} = 1.0 \pm 0.3$							
 **3**	7	aMe	3	2	8.1(*S*)	61.6(*R*)	5.0
		aH	13	3	24.9(*R*)	68.8(*R*)	3.3
		AMe	7	4	1.9(*R*)	76.5(*R*)	7.5
 **4**[c]	7	aMe	32	3	76.8(*S*)	95.1(*S*)	5.2
		aH	87	4	78.6(*S*)	95.9(*S*)	5.7
		AMe	390	6	83.4(*S*)	97.2(*S*)	6.4
$Q_{a/b} = 5.5 \pm 1.4$							

[a] Reaction conditions: 1 mmol substrate, 0.01 mmol catalyst as a cod-containing BF_4 salt, 0.1 mmol SDS, 15 mL H_2O, 25 °C, 0.1 MPa. [b] We thank I. Toth and B. E. Hanson for the gift of these tetrafluoroborate complexes.[29] [c] The experimental values were taken from an earlier publication.[7] [d] aH = 2-acetamidoacrylic acid; aMe is the corresponding methyl ester; AMe = methyl (*Z*)-2-acetamidocinnamate. [e] er_a = enantiomer ratio for the reaction with SDS, er_b = enantiomer ratio for the reaction without SDS.

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Table 2. Hydrogenation with [Rh(HO-diop)(cod)]BF_4 as precatalyst in presence of Triton X100.[a,b]

Substrate	Solubility [%][c]	Without amphiphile			With amphiphile				$Q_{a/b}$ =
		t/2 [min]	% *ee*	er_b (*R*/*S*)	Amphiphile [mmol]	*t/2* [min]	% *ee* (*R*)	er_a (*R*/*S*)	er_a/er_b
aMe	100	3.4	8.1(*S*)	0.85	0.1	1.7	26.3	1.71	2.0
					1.5	1.4	53.9	3.34	3.9
aH	40	12.5	24.9(*R*)	1.66	0.1	3.1	57.0	3.65	2.2
					1.5	2.6	72.7	6.32	3.8
AMe	22	6.7	1.9(*R*)	1.04	0.1	5.3	68.6	5.37	5.2
					0.25	3.5	70.0	5.67	5.5
AH	11	8.8	34.4(*R*)	2.05	0.1	4.5	85.4	12.7	6.2
					1.5	3.5	86.6	13.9	6.8

[a] Reaction conditions as in Table 1. [b] Abbreviations as in Table 1; AH = (*Z*)-2-acetamidocinnamic acid. [c] Solubility of 1 mmol substrate in 15 mL water.

rings for all three substrates tested (aMe, aH, AMe, $\bar{Q}_{a/b} = 1.0 \pm 0.04$), but has a remarkable effect with the seven-membered ring chelate derived from our HO-diop ($Q_{a/b}$ between 2 and 7 dependent on the substrate solubility, see Table 2). Increasing the amount of this amphiphile from 0.1 to 1.5 mmol has a distinct effect on the selectivity only for fairly soluble substrates. This is caused by a reduction in the proportion of purely homogeneous hydrogenation caused by the stepwise increase of the micellar uptake of the substrate. Thus, we observe a doubling of the enantiomeric ratio for the fully water-soluble aMe when a large amount of Triton X100 is added (1.5 mmol compared to 0.1 mmol). However, such a large increase in the micelle concentration has an almost negligible effect on the hydrogenation of (*Z*)-2-acetamidocinnamic acid (AH), the substrate with the lowest water solubility.

The generality of these results is fairly restricted. Nearly insoluble and thus kinetically almost unreactive substrates such as (*Z*)-2-benzamidocinnamic acid and its methyl ester, which have a solubility of less than 2% under the reaction conditions, show a minor increase in enantioselectivity in the presence of Triton X100. However, in such cases quantitative hydrogenation is either impossible or requires an extremely long time (several days). We assume that the strongly hydrophobic substrate and the less hydrophobic complex of the catalyst compete in micellar solubilization. This decreases the part of the embedded catalyst able to hydrogenate the micellar-solubilized substrate. This is in contrast to hydrogenations conducted in the presence of SDS, in which such nearly insoluble substrates cannot displace the ionic-bonded catalyst from the micellar phase. Therefore even sparingly soluble substrates contact more of the quantitatively embedded catalyst and are hydrogenated exclusively in the micellar phase with high enantioselectivity in moderate times.[7, 11]

Experimental Section

NMR PGSE experiments: The theoretical and practical aspects of the PGSE NMR experiments have recently been reviewed.[30] The major practical difficulty in acquiring undistorted high-resolution spectra results from eddy current effects. Several approaches have been developed to improve the resolution of the diffusion-ordered two-dimensional NMR spectra (DOSY). The best accuracy and resolution has been achieved by incorporating bipolar gradient pulses[31] into the longitudinal eddy current delay (LED) pulse sequence.[32] The measurements were performed on Bruker ARX400 spectrometer equipped with a Bruker gradient unit (10 A) and a 5-mm inverse *z* gradient probe head with actively shielded gradient coils. In all NMR experiments the probe temperature was maintained at 300 K by the standard Bruker temperature control unit. The bipolar LED sequence (LEDbp)[31] was selected to obtain Fourier-transformed spectra without line-shape distortions. A total of 64 different gradient strengths from $g = 0.016$ to 0.471 T m^{-1} were used with eddy-current delay $T_e = 50$ ms, duration of the gradient pulses $\delta/2 = 1$ ms, Stejskal–Tanner diffusion delay $\Delta = 100$ ms and pulse separation $\tau = 0.2$ ms. After Fourier transformation, phasing, and polynomial baseline correction the inverse Laplace transform (ilt) from the DOSY software package [33] was used to determine the diffusion coefficients. For very weak catalyst signals the diffusion coefficients *D* were calculated from the slope-normalized signal intensities ($\ln I_g/I_0$) as a function of the gradient strength (g^2) as given by Equation (3).

$$\ln I_g/I_0 = -\gamma^2 g^2 \delta^2 (\Delta - \delta/3 - \tau/2) D \quad (3)$$

Preparation: [Rh(HO-diop)(cod)]BF_4[22] and [Rh(HO-diop)(cod)]-$C_{12}H_{25}OSO_3$[11] were prepared as previously reported.
[Rh(HO-diop)(cod)]OTf: A solution of 165 mg (0.98 mmol) $NH_4OSO_2CF_3$ in THF (3 mL) was added to a solution of [Rh(HO-diop)(cod)]BF_4 (800 mg, 0.98 mmol) in THF (5 mL). The precipitated NH_4BF_4 was filtered off and the filtrate reduced to half its volume. The desired complex was precipitated by addition of ether (20 mL) and then dried in vacuum. Yield 770 mg (90%).

The amphiphiles used were all commercially available. We prepared only the phosphine oxides[25] and these were purified by the method of Lunkenheimer et al.[35]

Hydrogenation of dehydroamino acid derivatives: Hydrogenation experiments were performed as reported earlier.[5, 10] The water was carefully removed from product solutions containing amphiphiles by using a rotary evaporator, and the residue was redissolved in methanol suitable for gas chromatographic or HPLC investigation.

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