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Chiral sulphonated phosphines

II *. Influence of water on the enantioselectivity in the reduction of dehydro-aminoacids

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Abstract

For the reduction of dehydro aminoacids in various media with rhodium complexes containing chiral ligands, a linear correlation of log $\%S/\%R$ with the solvophobicity parameter S_p has been observed. The decrease in enantioselectivity in water is due to the high interfacial energy of this solvent.

Introduction

There have been several attempts to overcome the difficulty of separating reactants and products from transition-metal complexes in homogeneous catalyst systems. Two procedures have been used: (a) heterogenisation of the homogeneous catalyst by anchoring it to an inert support [2], and (b) use of a two-phase system consisting of water and a non-miscible organic phase [3,4]. In the latter procedure, the catalytically active species remains in the aqueous phase and can be readily recycled and this procedure is used industrially in the hydroformylation of propene in the presence of rhodium complexes associated with tris(triphenylphosphine *meta*-sulphonate) (t.p.p.t.s.) [5–7].

We recently reported the preparation and the use of chiral water-soluble phosphines; when used as ligands in rhodium complexes they allowed the enantioselec-

* For part I see ref. 1.

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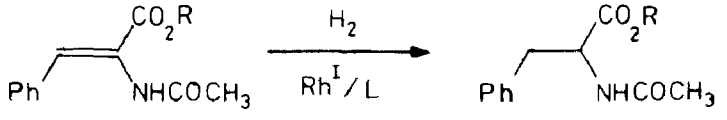
tive reduction of prochiral substrates in water [8–10] or better in a two-phase system [1,11]. However, some decrease in enantioselectivity was observed upon going from the organic phase (usually ethanol) to the aqueous phase, and we have undertaken some experiments to throw light on the reasons for this decrease in enantioselectivity, and in particular to see if it would be possible to correlate the enantioselectivity with the polarity or solvophobicity of the solvent.

Results and discussion

In the last ten years it has been shown that the course of the Diels–Alder cycloaddition can be remarkably influenced by the use of aqueous solvents [12–18]. Aldolisation also gave a selectivity in water opposite to that in an organic solvent [19]. More recently, Schneider et al. have found that for the Diels–Alder reaction there is a very good correlation between the log(*endo*/*exo*) values, and thus the reaction rate, and the solvophobicity parameter S_p of the solvent [20,21]. It thus seemed to us of interest to study the influence of the solvent in the enantioselective reduction of α-acetamido cinnamic acid **1a** and its methyl ester **1b** in the presence of rhodium complexes containing cyclobutanediop **3a**, tetrasulphonated cyclobutanediop **3b** or tetrasulphonated skewphos **4b** as ligand.

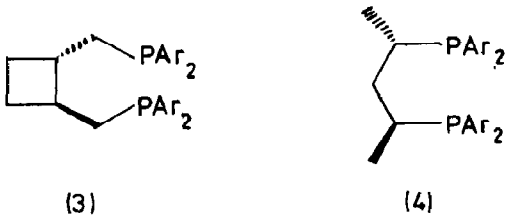
Braun [16] and Schneider [20,21] observed that for the Diels–Alder reaction there is a good linear correlation between log(*endo*/*exo*) or the stereoselectivity of the reaction and the solvophobicity parameter S_p [22] of the solvent used. In contrast, there was only a poor correlation with the polarity parameter $E_T(30)$ [23]. In the hydrogenation of dehydro-aminoacids, Halpern found that the enantioselectivity was determined by the difference in the rates of addition of hydrogen to the diastereoisomeric enamido complexes [24]. He showed that $\%S/\%R = k_2^{min}K_1^{min}/k_2^{max}K_1^{max}$ where k_2^{min} and k_2^{max} are the rate constants of the oxidative addition of hydrogen to the minor and the major enamido complex respectively, and K_1^{min} and K_1^{max} the equilibrium constants between the enamido complexes and the catalyst and the amino-acid precursor. To a first approximation, k_2^{min} and k_2^{max} are the more important factors in this relation. By analogy with the results for the Diels–Alder reaction, we thought that in the hydrogenation reaction the ratio $\%S/\%R$ (or $\%R/\%S$) might reflect the influence of the solvent on the rate of addition of hydrogen to these enamido complexes, and so examined the relationship between the values of log($\%S/\%R$) [or log($\%R/\%S$)] and the solvophobic parameter S_p and also the polarity parameter $E_T(30)$.



(1) (2)

(a) R = H

(b) R = CH_3



(3) (4)

(a) Ar = 

(b) Ar = 

The results obtained in the reduction of α-acetamidocinnamic acid **1a** with $[Rh(COD)(\mathbf{3a})]^+ ClO_4^-$ as the catalyst in various media, including pure solvents, are summarized in Table 1; the plots of values of $\log(\%S/\%R)$ against the solvophobicity parameter S_p or the solvent polarity $E_T(30)$ are shown in Fig. 1a and Fig. 1b. A linear correlation ($r = 0.923$) was obtained for the plot of $\log(\%S/\%R)$ vs. S_p values, which are based on changes in the free energy ΔG_S of the transfer of hydrocarbons from the gas phase into a given solvent [22]; only the value obtained in dioxane lies significantly away from the line. If data only for water–alcohol mixtures are used a better correlation is obtained ($r = 0.997$). A plot (not shown) of $\log(\%S/\%R)$ vs. the polarity parameter in methanol–water and ethanol–water mixtures is also very satisfactorily linear, but as noted previously [20], the effect of pure water is too large when compared with that of other polar but lipophilic

Table 1

Asymmetric hydrogenation of α-acetamido cinnamic acid **1a** catalyzed by $[Rh(COD)\mathbf{3a}]^+ ClO_4^-$ [a]

Solvent	S_p	E_T	e.e. (%) [b]	$\log(\%S/\%R)$
CH_3OH	0.1998	55.5	80	0.954
CH_3OH/H_2O (90/10)	0.2729		75.5	0.855
CH_3OH/H_2O (70/30)	0.4459		70	0.753
CH_3OH/H_2O (50/50)	0.6312		63.5	0.651
C_2H_5OH	0.1440	51.9	82	1.032
C_2H_5OH/H_2O (80/20)	0.2210		77	0.886
C_2H_5OH/H_2O (60/40)	0.3449		75	0.845
C_2H_5OH/H_2O (40/60)	0.5850		70	0.753
CH_2OH-CH_2OH	0.3763	56.3	70	0.753
dioxane	0.0794	36	72	0.788
dioxane/H_2O (60/40)	0.3899		67	0.704
dioxane/H_2O (40/60)	0.7548		65	0.673
N-Me acetamide		52	68.5	0.728
DMF	0.1384	43.8	77	0.886
Formamide	0.3863	56.6	70	0.753

[a] [substrate]/[Rh] = 50; [substrate] = 0.1 *M*; temperature: 25 °C; $p(H_2)$ 1.1 atm; chemical yields were quantitative. [b] Determined by polarimetry and by GLC with a chiral column.

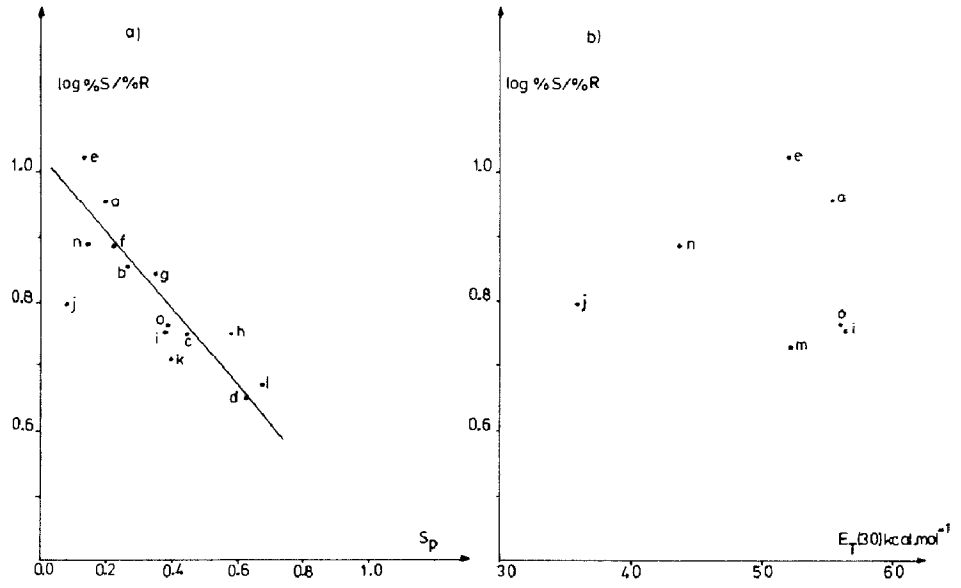


Fig. 1. (a) Log(%S/%R) vs. solvophobicity parameter S_p for the asymmetric hydrogenation of α-acetamido cinnamic acid **1a** catalyzed by [Rh(COD)**3a**]$^+$ ClO_4^- a–d: 100, 90, 70, 50% CH_3OH–H_2O(v/v); e–h: 100, 80, 60, 40% C_2H_5OH–H_2O(v/v); 1: CH_2OHCH_2OH; j–l: 100, 60, 40% dioxane–H_2O(v/v); m: *N*-Me acetamide; n: DMF; o: formamide. (b) Enantioselectivity as a function of solvent polarity E_T(30).

solvents. In fact, there is no correlation with the E_T(30) values in the case of pure solvents (Fig. 1b).

The results obtained for the reduction of α-acetamidocinnamic acid methyl ester **1b** in the presence of [Rh(COD)(**3a**)]$^+$ ClO_4 are summarized in Table 2. Plots of the values of log(%S/%R) against S_p and E_T(30) are shown in Fig. 2a and Fig. 2b respectively. Again there is a good correlation with the S_p values (Fig. 2a) (r = 0.923);

Table 2

Asymmetric hydrogenation or α-acetamido cinnamic acid methyl ester **1b** catalyzed by [Rh(COD) **3a**]$^+$ ClO_4^- [a]

Solvent	S_p	E_T	e.e. (%) [b]	log (%S/%R)
CH_3OH	0.1998	55.5	50	0.477
CH_3OH/H_2O (90/10)	0.2729		47	0.433
CH_3OH/H_2O (70/30)	0.4459		40	0.368
CH_3OH/H_2O (50/50)	0.6312		35	0.317
CH_3OH/H_2O (30/70)	0.8080		27	0.240
CH_2OH-CH_2OH	0.3763	56.3	38	0.347
dioxane	0.0794	36	47	0.443
dioxane/H_2O (60/40)	0.3899		42	0.389
dioxane/H_2O (40/60)	0.7548		37	0.337
N-Me acetamide		52.0	56	0.550
DMF	0.1384	43.8	63	0.644
Formamide	0.3863	56.6	41	0.378

[a] [substrate]/[Rh] = 50; [substrate] = 0.1 M; temperature: 25 °C; $p(H_2)$ 1.1 atm; chemical yields were quantitative. [b] Determined by polarimetry and GLC with a chiral column.

Table 3

Asymmetric hydrogenation of α-acetamido cinnamic acid **1a** catalyzed by [Rh(COD)Cl] + **3b** or **4b** [a]

Ligand	Solvent	S_p	E_T	e.e.% [b]	log (%S/%R)
3b	C_2H_5OH/H_2O (100/0)	0.1440	51.9	52	0.501
3b	C_2H_5OH/H_2O (75/25)	0.2500		46	0.432
3b	C_2H_5OH/H_2O (50/50)	0.4495		42	0.389
3b	C_2H_5OH/H_2O (25/75)	0.7600		36	0.327
3b	C_2H_5OH/H_2O (0/100)	1.0000	63.1	28	0.250
3b	*N*-Me acetamide		52	44 [c]	0.410
3b	Formamide	0.3863	56.6	16	0.140
4b	CH_3OH/H_2O (100/0)	0.1998	55.5	73	0.806
4b	CH_3OH/H_2O (85/15)	0.2729		70	0.753
4b	CH_3OH/H_2O (75/25)	0.4459		68	0.720
4b	CH_3OH/H_2O (50/50)	0.6312		63	0.643
4b	CH_3OH/H_2O (20/80)	0.8806		43	0.399
4b	CH_3OH/H_2O (0/100)	1.000	63.1	33	0.298

[a] [substrate]/[Rh] = 50; [substrate] = 0.1 *M*; temperature: 25° C; $p(H_2)$ 1.1 atm for **3b** and 15 atm. for **4b**: chemical yields were quantitative except otherwise indicated. [b] Determined by polarimetry and by GLC with a chiral column. [c] Chemical yield, 70%.

with only the result in dimethylformamide lies significantly above the correlation curve. In this case, there is no correlation with $E_T(30)$ values (Fig. 2b).

We also reduced α-acetamidocinnamic acid **1a** in various solvents or mixtures of solvents using [Rh(COD)Cl] + tetrasulphonated CBD **3b** or tetrasulphonated skewphos **4b** as the catalyst (Table 3). We find again a linear correlation between the log(%S/%R) and S_p values (Fig. 3).

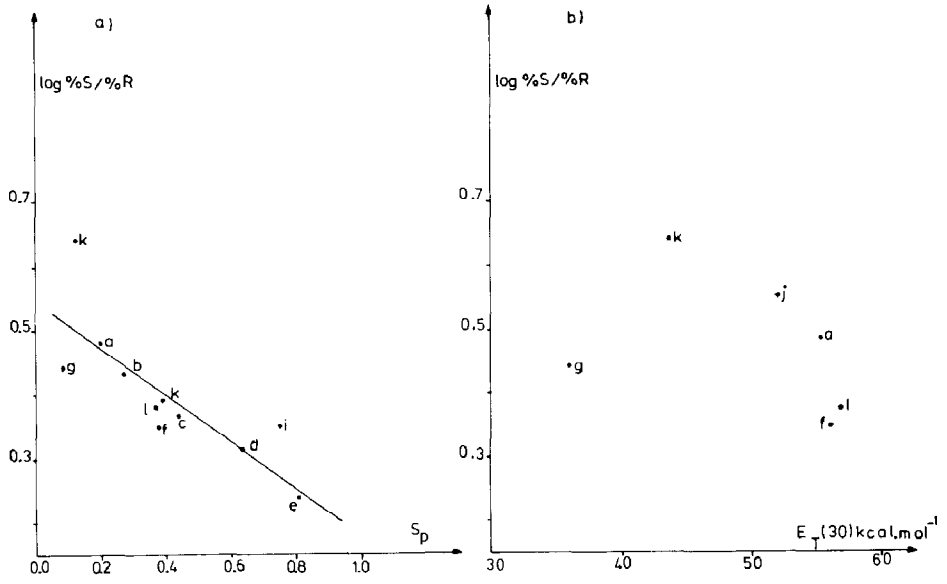


Fig. 2. (a) Log(%S/%R) vs. solvophobicity parameter S_p for the asymmetric hydrogenation of α-acetamido cinnamic acid methyl ester **1b** catalyzed by [Rh(COD)**3a**]$^+$ ClO_4^-. a–e: 100, 90, 70, 50, 30% CH_3OH–H_2O(v/v); f: CH_2OHCH_2OH; g–i: 100, 60, 40% dioxane–H_2O(v/v); j: *N*-Me acetamide; k: DMF; l: formamide. (b) Enantioselectivity vs. a function of solvent polarity $E_T(30)$.

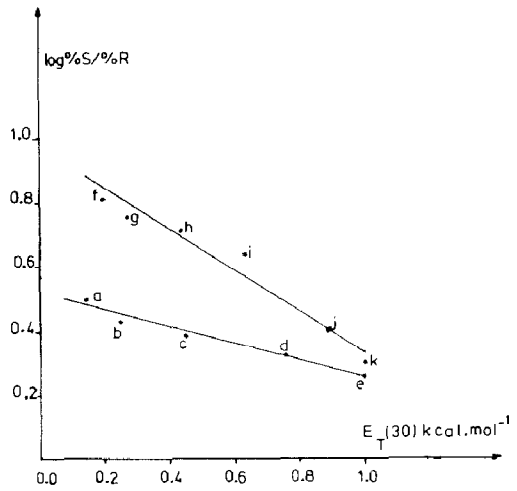


Fig. 3. Log(%S/%R) vs. solvophobicity parameter S_p for the asymmetric hydrogenation of α-acetamido cinnamic acid **1a** catalyzed by [Rh(COD)Cl] + **3b** in 100, 75, 50, 25, 0 % C_2H_5OH–H_2O(v/v) (a–e) or **4b** in 100, 85, 75, 50, 20, 0 % CH_3OH–H_2O(v/v) (f–k).

The results show clearly that there is a good correlation between log(%S/%R) and the solvophobicity parameter. As suggested for the Diels–Alder or the aldol reaction in water or solvent–water mixtures, the effects of water on selectivity may be related to its high cohesive energy and to the high energy needed to create a cavity in it as a consequence of its high interfacial energy; it is significant that water has the highest known value of the Hildebrandt parameter [25]. If this is the case then a reaction under kinetic control occurring in water should have the same stereoselectivity as one under pressure. It is known that an increase in pressure lowers the enantioselectivity in the reduction of α-aminoacid precursors when the ligands described in this study are used [26]; Ojima's group has shown that this decrease in enantioselectivity with increasing pressure is larger for 1,4-diphosphines such as Diop than for a 1,2-diphosphine such as Dipamp. We found the same behaviour using water or a two-phase system as the solvent , that is, a very large decrease for the 1,4-diphosphine and only a small one for the 1,2-diphosphine [1].

If solvophobic interactions seemed to play an important role, then in formamide, which is as highly structured as water, the enantioselectivity should be lower than that in *N*-methyl acetamide, which is less structured. Although the reduction is lower in the two solvents than in alcoholic media, and has to be performed at 30 °C in *N*-methylacetamide, we found lower enantioselectivities with formamide than with *N*-methyl acetamide as the solvent in the reduction of α-acetamidocinnamic acid with [Rh(COD)Cl] + (**3b**) as the catalyst (44% vs. 16% e.e.) and α-acetamido-cinnamic acid methyl ester with [Rh(COD)**3a**]$^+ClO_4^-$ as the catalyst (56% versus 41% e.e). However, in the case of the acid, with [Rh(COD)**3a**]$^+ClO_4^-$ as the catalyst, we found the same enantioselectivity, in both media.

Conclusion

We have observed a good correlation between the solvophobicity parameter of the solvent and the enantioselectivities obtained in the reduction of some prochiral

amino-acids precursors catalyzed by rhodium complexes associated with chiral diphosphines. Thus the most important factor seems to be the solvophobic parameter S_p and not the solvent polarity $E_T(30)$; the decrease in enantioselectivity in the reduction of these substrates in water or in a two phase system is probably due to the change of the solvophobic parameter. For the two-phase system this implies that the hydrogenation probably occurs in the aqueous phase and not at the interphase, and represents another example of inverse phase transfer catalysis [27,28], but more work is necessary to confirm this.

Experimental

All reactions involving rhodium complexes were carried out under argon. Solvents were distilled from appropriate drying agents [29] and stored under argon. (*S,S*)-Cyclobutanediop or (*S,S*)-1,2-bis(diphenylphosphinomethyl)cyclobutane (**3a**) was a gift from Rhône-Poulenc Recherches; (*S,S*)-BDPP or (*S,S*)-2,4-bis(diphenylphosphino)pentane (**4a**) was prepared as previously described [30]. The synthesis of the tetrasulphonated phosphines **3b** and **4b** was previously described [1]. Optical rotations were recorded with a Perkin–Elmer 241.

The hydrogenation experiments were conducted in the usual manner [1,8–11]. After reaction, the solvent was evaporated, the reaction products analyzed by ^1H NMR, and the e.e. determined by polarimetry and also by GLC analysis on the chiral phase Chirasil-Val after derivatization of the sample by a standard procedure [31].

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