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Note

Chiral sulphonated phosphines

IV[a]. High-performance liquid chromatographic separation of sulphonated phosphines

LOÏC LECOMTE and DENIS SINOU*
Laboratoire de Synthèse Asymétrique, Associé au CNRS, Université Lyon I, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cédex (France)
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There has been increasing interest during the last decade in the use of a two-phase system (water–organic solvent) in homogeneous organometallic catalysis where the catalyst is in the aqueous phase by the use of water-soluble ligands[1,2]. The water solubilization of phosphines is usually achieved by the introduction of a highly polar functional group such as an amine, carboxylic acid, hydroxide or sulphonate. Rhodium complexes of sulphonated phosphines are effective as catalysts in industry for hydroformylation[3,4] and in the synthesis of geranylacetone[5,6]. We have shown recently that asymmetric hydrogenation occurs in a two-phase system using chiral sulphonated phosphines[7–9], and that the enantioselectivity seems to depend on the degree of sulphonation of the chiral diphosphine. Hence it would be desirable to design a technique for the separation of these sulphonated phosphines, thus giving the composition of the sulphonated ligands used in hydrogenation.

As various aromatic sulphonic acids have been separated using reversed-phase ion-pair chromatography with a Hypersil SAS silica (C_1 or C_8) as the stationary phase, a quaternary ammonium salt (usually cetrimide) as the counter ion and water–propanol as the eluent[10–12], we thought that this technique, called "soap chromatography", would be the most appropriate in our case[13].

EXPERIMENTAL

Sulphonated phosphines (Fig. 1) were obtained as described previously[8]. Hexadecyltrimethylammonium bromide (cetrimide), tetrabutylammonium bromide (TBA), tetraethylammonium bromide (TEA) and tetramethylammonium bromide (TMA) were obtained from Fluka.

[a] For Part III, see ref. 9.

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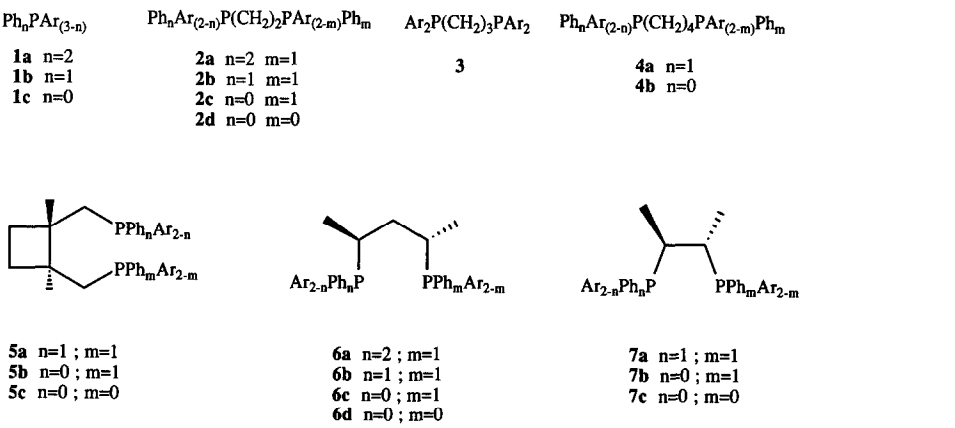

Fig. 1. Sulphonated phosphines. Ar = *m*-$C_6H_4SO_3Na$; Ph = C_6H_5.

High-performance liquid chromatography (HPLC) was performed on a Chromatem 380 instrument (Touzard and Matignon) with an SP 8200 single-wavelength (254 nm) detector. Separation was carried out on a 250 × 4.6 or a 150 × 4.6 mm I.D. stainless-steel column packed with 5-μm Hypersil SAS (C_1 or C_8) silica with a surface area of *ca.* 170 $m^2\ g^{-1}$. The precolumn was filled with pellicular silica. Water–*n*-propanol containing various amounts of the quaternary ammonium salt was used as the mobile phase, the flow-rate being 0.6 ml/min and the pressure about 10^3 p.s.i.

RESULTS AND DISCUSSION

In order to obtain some information on the conditions that allows the HPLC separation of the chiral sulphonated diphosphines, we made some preliminary studies on achiral sulphonated mono- and diphosphines and the corresponding oxides.

The influence of the cetrimide concentration on the capacity factor, k', of these achiral sulphonated phosphines and diphosphines **1**–**4**, and their oxides using water–*n*-propanol (5:2, v/v) as eluent is summarized in Table I. For the sulphonated phosphines derived from triphenylphosphine (**1a**–**c**) (entries 1–3), 1,2-bis(diphenylphosphino)ethane (**2a**–**d**) (entries 7–10) and 1,4-bis(diphenylphosphino)butane (**4a** and **b**) (entries 17 and 18), k' increased with increasing number of sulphonic groups in the molecule ($k'_{\mathbf{1a}} < k'_{\mathbf{1b}} < k'_{\mathbf{1c}}$, $k'_{\mathbf{2a}} < k'_{\mathbf{2b}} < k'_{\mathbf{2c}} < k'_{\mathbf{2d}}$ and $k'_{\mathbf{4a}} < k'_{\mathbf{4b}}$) for any concentration of cetrimide. For a given phosphine, a maximum k' was reached at a cetrimide concentration of about 6.8 m*M*. The same features were found for the corresponding oxides, the maximum k' being at a cetrimide concentration of about 14 m*M*. For the diphosphines having the same degree of sulphonation (**2c** and **4a**; **2d**, **3** and **4b**) and the corresponding phosphines oxides, k' increased with increasing hydrocarbon chain length between the two diphenylphosphino groups.

The sulphonated phosphines were generally eluted after the corresponding phosphine oxides. However, the reverse elution order was found for the tetrasulphonated diphosphines **2d**, **3** and **4b** for cetrimide concentrations up to 1.7 m*M*; the same behaviour was observed for the trisulphonated monophosphine **1c** at cetrimide concentrations up to 27 m*M*.

TABLE I

INFLUENCE OF CETRIMIDE CONCENTRATION ON THE CAPACITY FACTOR (k') IN THE SEPARATION OF THE SULPHONATED PHOSPHINES AND PHOSPHINES OXIDES **1–4**

Eluent, water–*n*-propanol (5:2); counter ion, cetrimide; column packing, 5-μm SAS (C_1) silica; flow-rate, 0.6 ml/min; pressure, 90 bar.

Entry No.	*Phosphine*	*k'*					
		[Cetrimide] (10^{-3} M)					
		1.69	*3.37*	*6.75*	*13.5*	*27*	*54*
1	**1a**	6.8	7.9	12.3	11.0	8.1	3.6
2	**1b**	7.5	10.6	21.0	17.6	9.6	4.5
3	**1c**	11.4	19.8	36.3	27.1	12.5	6.4
4	**1a** oxide	1.9	2.1	3.1	3.9	2.8	2.0
5	**1b** oxide	2.5	3.5	7.1	9.2	5.6	3.4
6	**1c** oxide	5.2	9.5	18.6	19.7	13.6	6.6
7	**2a**	4.3	6.8	11.0	11.0	6.8	3.9
8	**2b**	6.5	8.8	12.9	12.5	8.6	5.0
9	**2c**	11.1	14.0	18.9	18.1	10.9	6.6
10	**2d**	14.1	18.8	26.9	24.8	16.9	11.3
11	**2a** oxide	1.3	1.9	2.6	2.8	2.0	1.5
12	**2b** oxide	1.9	3.3	5.0	6.0	4.6	3.4
13	**2c** oxide	3.3	8.5	13.2	14.5	9.1	6.1
14	**2d** oxide	8.6	25.5	>40	>40	23.5	11.9
15	**3**	15.3	20.0	27.9	26.9	17.6	11.5
16	**3** oxide	9.1	27.8	>40.0	>40.0	24.0	12.0
17	**4a**	11.4	15.4	20.4	19.1	12.6	8.5
18	**4b**	16.0	21.6	30.9	28.9	18.8	12.0
19	**4a** oxide	3.5	9.3	13.5	14.8	11.0	7.8
20	**4b** oxide	9.3	29.5	>40.0	>40.0	25.3	12.8

TABLE II

INFLUENCE OF THE ALKYL CHAIN LENGTH OF THE TETRAALKYLAMMONIUM CATION ON THE CAPACITY FACTOR (k') IN THE SEPARATION OF SULPHONATED MONOPHOSPHINES **1**

Eluent, water–*n*-propanol (5:2); [counter ion], 0.027 *M*; column packing, 5-μm SAS (C_1) or 5-μm SAS (C_8) silica; flow-rate, 0.6 ml/min; pressure, 90 bar.

Column	*Counter ion*	*k'*		
		1a	***1b***	***1c***
C_1	TMA	0.86	0.10	0.02
	TEA	1.40	0.25	0.06
	TBA	3.6	1.6	1.0
	Cetrimide	8.1	9.6	12.5
C_8	TMA	1.90	0.12	0.01
	TEA	2.60	0.25	0.04
	TBA	4.20	0.88	0.46
	Cetrimide	7.80	10.90	16.50

The dependence of k' on the alkyl chain length of the counter ion was studied for the monophosphines **1a–c** using two columns (SAS C_1 and SAS C_8). The results in Table II show that the use of a counter ion with a shorter alkyl chain (tetrabutylammonium, tetraethylammonium or tetramethylammonium bromide) instead of cetrimide at the same mobile phase concentration reversed the elution order of the sulphonated phosphines, with **1c** now being eluted first and **1a** last. An increase in k' was also observed with increasing hydrophobicity of the counter ion, as reported previously[14,15].

We then studied the separation of chiral sulphonated diphosphines derived from (*S,S*)-1,2-bis[(diphenylphosphino)methyl]cyclobutane [(*S,S*)-cyclobutanediop], (*S,S*)-2,4-bis(diphenylphosphino)pentane [(*S,S*)-BDPP] and (*S,S*)-2,3-bis(diphenylphosphino)butane [(*S,S*)-Chiraphos]. The situation is more complex because the disulphonated and trisulphonated diphosphines are mixtures of two diastereoisomers, whereas the disulphonated diphosphines represent a mixture of three diastereoisomers. The results obtained with water–*n*-propanol (5:2) as the eluent and cetrimide (0.054 *M*) as the counter ion, which are summarized in Table III, show that for a given diphosphine or diphosphine oxide the retention time increases with increasing degree of sulphonation of the compound, following the behaviour of the achiral phosphines.

For (*S,S*)-BDPP, the monsulphonated diphosphine **6a** and the trisulphonated diphosphine **6c** gave two peaks in the ratio 50:50, corresponding, for each diphosphine, to the epimers at the phosphorus (*S,S,S*) and (*S,S,R*). The disulphonated (*S,S*)-BDPP **6b** exhibited three peaks in the ratio 25:50:25, corresponding to the three diastereoisomers at the phosphorus (*R,S,S,R*), (*R,S,S,S*) and (*S,S,S,S*). The same behaviour was found for the oxides of the sulphonated BDPP (Fig. 2).

For the (*S,S*)-cyclobutanediop, the oxide of the trisulphonated diphosphine **5b** also showed two peaks for the two epimers (*S,S,R*) and (*S,S,S*) at the phosphorus in the ratio 50:50, and the disulphonated diphosphine oxide **5a** three peaks for the three diastereoisomers at the two phosphorus (*R,S,S,R*), (*R,S,S,S*) and (*S,S,S,S*) in the

TABLE III

SEPARATION OF CHIRAL SULPHONATED PHOSPHINES AND THEIR OXIDES

Eluent, water–*n*-propanol (5:2); [cetrimide], 0.054 *M*; column packing, 5-μm SAS (C_1) silica; flow-rate, 0.6 ml/min; pressure, 90 bar.

Substrate	*k'*	
	Phosphine	*Phosphine oxide*
5a	5.4	3.5; 3.6; 4.3
5b	7.3	5.9; 6.5
5c	10.3	11.8
6a	3.3; 3.5	3.0; 3.4
6b	4.9; 5.2; 5.5	3.8; 4.2; 4.5
6c	7.2; 8.2	6.7; 7.6
6d	10.8	12.2
7a	5.2	3.4
7b	7.8	7.1
7c	11.8	13.8

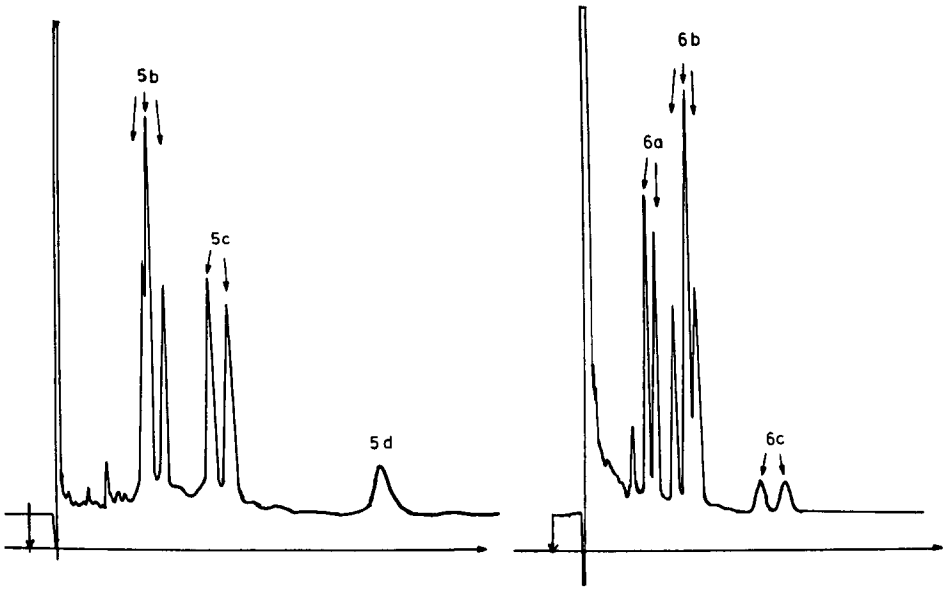

Fig. 2. Chromatogram of the di-, tri- and tetrasulphonated (*S,S*)-cyclobutanediop oxides (left) and of the mono-, di- and trisulphonated (*S,S*)-BDPP oxides (right). Eluent, water–*n*-propanol (5:2); [cetrimide], 0.054 *M*; column packing, 5-μm SAS (C_1) silica; flow-rate, 0.6 ml/min; pressure, 90 bar.

TABLE IV

INFLUENCE OF THE ALKYL CHAIN LENGTH OF THE TETRAALKYLAMMONIUM CATION ON THE CAPACITY FACTOR (*k'*) FOR MONO-, DI-, TRI- AND TETRASULPHONATED (*S,S*)-BDPP **6a–d**

Eluent, water–*n*-propanol (5:2) containing the counter ion; column packing, 5-μm SAS silica; flow-rate, 0.6 ml/min; pressure, 90 bar.

Column	*Ligand*	*k'*			
		Counter ion			
		TEA (0.027 M)	*TBA (0.027 M)*	*Cetrimide (0.027 M)*	*Cetrimide (0.054 M)*
C_1	**6a**: isomer 1	4.8	12.2	4.9	3.3
	isomer 2	3.7	9.1	5.2	3.5
	6b: isomer 1	0.9	6.6	7.9	4.9
	isomer 2	0.8	4.8	8.6	5.2
	isomer 3	0.6	4.0	9.3	5.5
	6c: isomer 1	0.3	2.9	12.0	7.2
	isomer 2	0.15	2.3	13.8	8.2
	6d	0.04	1.9	16.9	10.8
C_8	**6a**: isomer 1	4.4	23.3	9.6	4.6
	isomer 2	4.0	18.5	11.1	4.9
	6b: isomer 1	1.7	4.9	14.6	8.8
	isomer 2	1.2	3.8	16.5	9.6
	isomer 3	0.7	2.9	18.4	10.3
	6c: isomer 1	0.9	1.5	22.9	14.0
	isomer 2	0.09	1.0	24.9	16.5
	6d	0.02	0.6	30.5	20.8

ratio 25:50:25 (Fig. 2). However, the separation was not so good for the sulphonated (*S*,*S*)-cyclobutanediop **5a–c**.

For the sulphonated (*S*,*S*)-Chiraphos **7a–c** and their oxides, no separation of the diastereoisomers at the phosphorus was observed.

Using water–*n*-propanol (5:2) as the eluent, the influence of some parameters was studied in more detail for the sulphonated diphosphines **6a–d** derived from (*S*,*S*)-BDPP (Table IV). As found previously for the achiral diphosphines, k' increased when the cetrimide concentration decreased from 0.054 to 0.027 *M*. The use of counter ions with shorter alkyl chains, such as TEA and TBA, reversed the elution order of the sulphonated phosphines; for a given diphosphine, k' was higher with TBA than TEA.

CONCLUSION

Sulphonated diphosphines and their oxides were separated by ion-pair chromatography using an 5-μm Hypersil SAS C_1 column. The mobile phase was water–*n*-propanol (5:2) containing cetrimide (0.054 *M*); tetraethyl- or tetrabutylammonium bromide could also be used. The method allows a very easy and efficient determination of the composition of the mixtures obtained from the sulphonation of these phosphines, particularly for the chiral diphosphines used in asymmetric catalysis.

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