Selector Screening for Enantioseparation of DL-α-Methyl Phenylglycine Amide by Liquid–Liquid Extraction

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ABSTRACT Enantioseparation through liquid extraction technology is an emerging field, e.g., enantioseparations of amino acids (and derivatives thereof), amino alcohols, amines, and carboxylic acids have been reported. Often, when a new selector is developed, the versatility of substrate scope is investigated. From an industrial point of view, the problem is typically approached the other way around, and for a target racemate, a selector needs to be found in order to accomplish the desired enantioseparation. This study presents such a screening approach for the separation of the enantiomers of DL-α-methyl phenylglycine amide (DL-α-MPGA), a model amide racemate with high industrial relevance. Chiral selectors that were reported for other classes of racemates were investigated, i.e., several macrocyclic selectors and Pd-BINAP complexes. It appeared very challenging to obtain both high extraction yields and good enantioselectivity for most selectors, but Pd-BINAP-based selectors performed well, with enantioselectivities up to 7.4 with an extraction yield of the desired enantiomer of 95.8%. These high enantioselectivities were obtained using dichloromethane as solvent. Using less volatile chlorobenzene or 1-chloropentane, reasonable selectivities of up to 1.7 were measured, making these the best alternative solvents for dichloromethane. *Chirality 00:000–000, 2014*.

KEY WORDS: enantioselective liquid–liquid extraction; amides; crown ethers; calixarenes; heterocycles; Pd-BINAP

INTRODUCTION

Over the past three decades the development and application of enantioseparation technology has become of major importance for the pharmaceutical industry.[1–4] Active pharmaceutical ingredients and key intermediates should be enantiomerically pure due to differences in the pharmacological effects of enantiomers.[2] Although routes through chiral feedstock,[5] asymmetrical catalysis,[6] and dynamic kinetic resolution[7] are sometimes available and favorable for their theoretical 100% yield, obtaining enantiopure compounds is industrially mainly done by the separation of enantiomers, usually through crystallization techniques.[2,8,9] Crystallization, however, is not always possible,[10] and alternatives are needed. On a laboratory scale, many alternative technologies are available, but most techniques are difficult to scale-up, or not economic at commercial scale.[3] Simulated Moving Bed chromatography[11–13] is an example of a scale-up strategy for laboratory chiral separation technologies. The efficiencies compared to the original laboratory separations have been highly improved; nevertheless, the solvent use and expensive stationary phases remain limiting factors for application on an industrial production scale.

Alternative approaches such as horizontal reactive distillation,[14] enantioselective liquid–liquid extraction (ELLE),[15] the closely related chiral liquid membrane (CLM),[16,17] membrane-assisted ELLE systems,[18] or centrifugal partitioning chromatography technologies (CPC)[19] may be applied for the enantioseparation of racemates. These technologies have been demonstrated to be scalable, and the development of new chiral selectors for ELLE and CLM technology is ongoing. Over the years, efficient selectors have been developed and applied for enantioseparation of amino acids and derivatives thereof,[20–31] amino alcohols and amines,[32–35] and carboxylic acids.[36–39] A review of enantioselective liquid–liquid extraction recently appeared.[3]

One of the drawbacks of the ELLE technology is that a moderate selectivity (typically >1.5)[40] is required to avoid an excessive number of stages. Many selectors used in stationary phases in chromatography are thus not suitable for the traditional liquid–liquid extraction approach. Approaches to overcome this limitation in versatility include the application of biphasic recognition to increase the selectivity of the system,[35,36,38] or to use thin-layer extraction[41,42] to enable large numbers of stages while keeping the equipment size small. Several hybrid processes have been published, trying to advance benefits from multiple unit operations in a single operation or in a sequence of operations. E.g., in cases where preferential crystallization is possible from enantioenriched solutions, hybrid processing may be a solution to improve processing efficiency, e.g., by enriching racemic solutions to moderate enantiomeric excess through a CLM process, followed by preferential crystallization,[43] or involving chiral nanoparticles in the extraction process.[44] Another, rather generically applicable hybrid approach, is to apply the ELLE concept in a chromatographic mode. This can be done by impregnating the extract phase (the chiral selectors in a

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solvent) in the pores of a resin to increase the capacity of a fixed bed chromatographic process.[45] For such a hybrid process (extraction and chromatography), the maximum number of economically realistic stages is much higher than in extraction. Therefore, we estimate that the selectivity constraint of 1.5 for ELLE[40] may be reduced to about 1.2–1.3.

Whether applied in ELLE, CLM, or any of the novel hybrids, the first stage in the development of a new chiral separation process remains finding a suitable chiral selector. Although many selectors have been reported for amino acids, amino alcohols and amines, and carboxylic acids,[3] enantioseparation of amide containing racemates is a specific challenge. Whereas in the literature often the use of a single selector or a class of selectors (also known as hosts) for a range of substrates is investigated, industrial challenges would typically call for a selector screening for a specific racemate. We report here a screening study for the ELLE of DL-α-methyl phenylglycine amide (DL-α-MPGA), an industrially relevant amino acid amide. Based on the literature on ELLE for amino acid derivatives and chiral HPLC,[46] we decided to study macrocyclic chiral hosts from the crown ether, calix[4]arenes and heterocycle classes, as well as binol derivatives such as binol phosphoric acids and Pd-BINAP. The model racemate DL-α-MPGA as well as all chiral selectors used in this study are displayed in Figure 1.

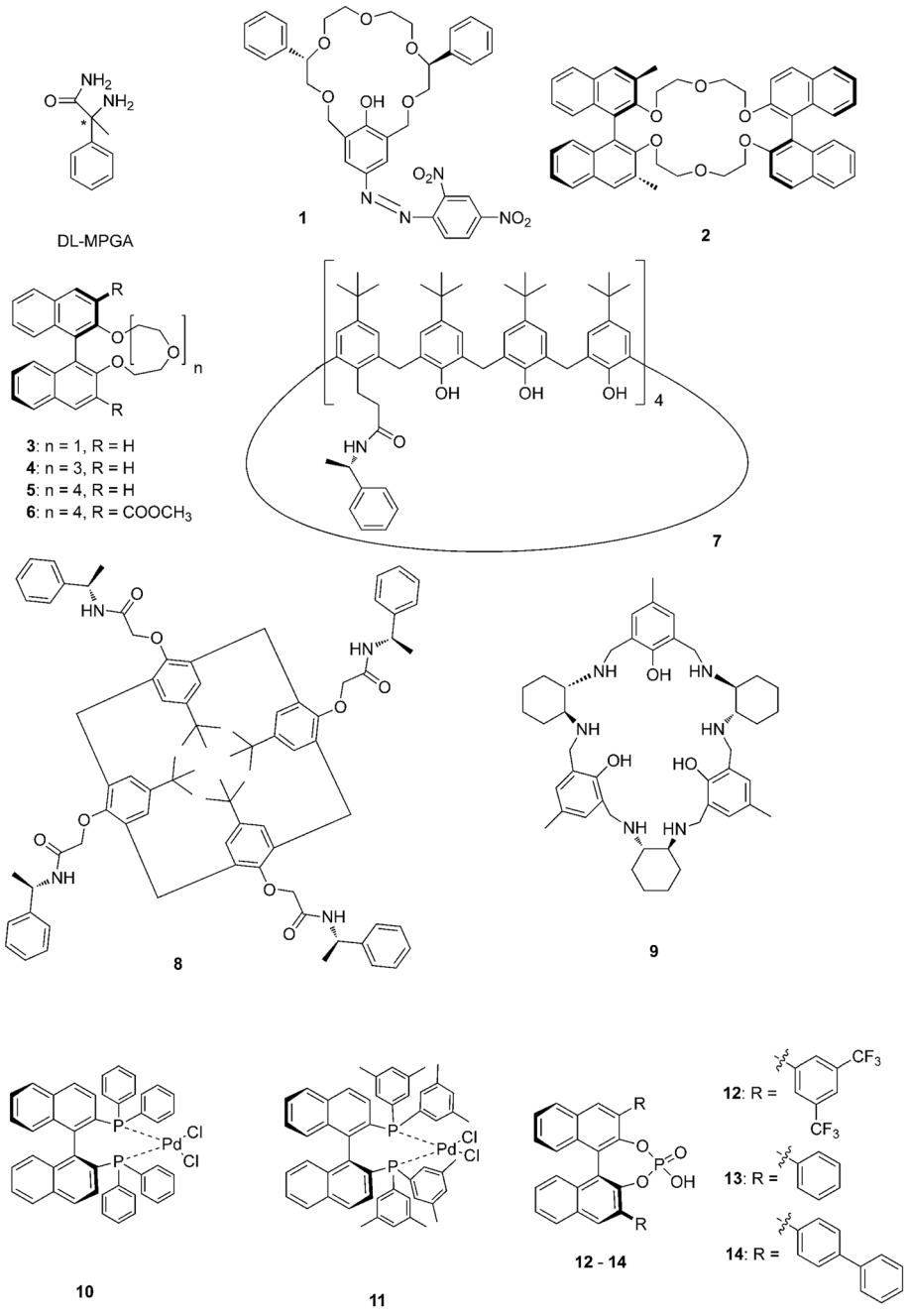

Fig. 1. Structures of DL-α-MPGA and the chiral selectors that were applied in this study.

MATERIALS AND METHODS

Definitions and Extraction Mechanisms

In the ELLE literature, two types of mechanisms have been reported, the interfacial ligand exchange mechanism, and the homogeneous ligand addition mechanism.[29,47–49] The most important difference between the two mechanisms is when the homogeneous ligand addition mechanism applies. In that case the enantiomers physically distribute towards the organic phase in which they form a complex with the chiral host. Because the solubility of ionic species into apolar solvents is typically low, distributions of ionizable (through protonation or deprotonation) enantiomers into the organic phase can be manipulated by changing the pH. The enantiomers of DL-α-MPGA are bases and may be protonated. The protonation equilibrium is by definition the same for both enantiomers and the relation for the K_b is given in Eq. 1.

$$K_b = \frac{[MPGAH^+] + [OH^-]}{[MPGA]} \tag{1}$$

The distributions of the enantiomers are affected by the solubility of the neutral α-MPGA in the applied organic solvent, by the availability of the neutral form (i.e., the applied pH during the extraction), and by the interaction between the host and the enantiomers. The distribution coefficients are defined as:

$$D_D = \frac{[D-\alpha-MPGA]_{org,tot}}{[D-\alpha-MPGA]_{aq,tot}} \tag{2a}$$

$$D_L = \frac{[L-\alpha-MPGA]_{org,tot}}{[L-\alpha-MPGA]_{aq,tot}} \tag{2b}$$

In Eqs. 2a and 2b, the subscripts *tot* indicate all forms in which the solutes can possibly exist in that phase, i.e., in the aqueous phase the α-MPGA enantiomers may be present in the neutral form and in the protonated form, while in the organic phase, the neutral α-MPGA might be present as well as complexes of the α-MPGA enantiomers with a chiral host. The operational enantioselectivity, α_{op} is defined as the ratio of the two distribution coefficients:

$$\alpha_{op} = \frac{D_L}{D_D} \tag{3}$$

Another measure for the extraction efficiency is the yield, which is defined as the fraction of the enantiomers that is extracted to the organic phase:

$$Y_D = \frac{\left([D-\alpha-MPGA]_{aq,tot,in} - [D-\alpha-MPGA]_{aq,tot}\right)}{[D-\alpha-MPGA]_{aq,tot,in}} \tag{4a}$$

$$Y_L = \frac{\left([L-\alpha-MPGA]_{aq,tot,in} - [L-\alpha-MPGA]_{aq,tot}\right)}{[L-\alpha-MPGA]_{aq,tot,in}} \tag{4b}$$

Materials

DL-α-MPGA was provided by DSM (Geleen, The Netherlands). $PdCl_2$((*S*)-xylyl-BINAP) was obtained from Strem Chemicals (Bisscheim, France). $PdCl_2$((*S*)-BINAP) was prepared in situ using $PdCl_2$ and *(S)*-BINAP. All other chiral selectors were custom synthesized at Syncom (Groningen, The Netherlands) using known procedures. All solvents were of analytical grade and used as supplied.

pK_b – Determination and Validation

To determine the pK_b, pure water and 3 mM HCl solution in varying proportions ranging from 0–5 mL were added to aliquots of 1–3 mL of a 3.3 mM aqueous DL-α-MPGA solution. After mixing several minutes the pH was measured. Validation of the pK_b was done by contacting 2 mM aqueous DL-α-MPGA solutions with a set pH ranging from 5–11.5 with 1,2-dichloroethane (DCE) and with octanol (phase ratio 1 mL organic phase / 1 mL aqueous phase) in the absence of any chiral selector.

Equilibrium Enantioselective Liquid–Liquid Extraction Experiments

ELLE experiments were carried out in jacketed 50 mL glass vessels connected to a Julabo F-32 thermostat bath to control the temperature, or in 20 mL glass vials in a thermostated shaking bath (in all experiments the temperature was 25 °C). Two mM aqueous DL-α-MPGA solutions were mixed with organic phase solutions of the chiral selectors (extractants). The initial concentration of DL-α-MPGA was 2 mM, and extractant concentrations ranging from 1 to 5 mM were applied. After magnetically stirring at 600 rpm for at least 2 h (or alternatively, shaken overnight at 150 min^{-1}), the phases were allowed to settle. Samples were taken from the aqueous phase to measure the pH and to determine the concentration of DL-α-MPGA by high-performance liquid chromatography (HPLC). The concentration of DL-α-MPGA in the organic phase was determined by mass balance. Experiments to determine physical partitioning ratios were carried out without a host present.

Analytical Method

The concentrations of the individual enantiomers of DL-α-MPGA in the aqueous phase were determined with an accuracy of ±3% by chiral HPLC analysis making use of either a Varian (Palo Alto, CA) Pro Star HPLC setup or an Agilent (Palo Alto, CA) 1100 series, equipped with a Chiralpak IB (+) chiral column (250 X 4.6 mm ID). Detection was done at 220 nm using an UV detector. The flow rate of the eluent, a 90:10 v:v mixture of 100 mM KPF_6 in water: acetonitrile, was 0.6 mL/min, the injection volume was 20 μL. The column was kept at 20 °C using a thermostated column oven.

RESULTS AND DISCUSSION

Estimation of pK_b and Physical Partitioning

In order to understand the effect of pH on the extraction behavior of DL-α-MPGA, the pK_b was determined by measuring the pH of DL-α-MPGA solutions and DL-α-MPGA solutions to which HCl was added. By measuring the pH, the concentrations of $[H^+]$ and $[OH^-]$ are known, and $[Cl^-]$ was given by the added amount of HCl, from which the last unknown, the $[MPGAH^+]$, could be calculated as well as the ratio of $[MPGAH^+]$ / [MPGA]. Fitting Eq. 1 to the experimental data resulted in $pK_b = 6.90$ (and, hence, $pK_a = 7.10$). The physical distribution as a function of the pH was expected to exhibit an s-curve with negligible distribution at low pH and attaining the maximum distribution at $pH > pK_a$. The maximum distribution coefficients (D_{max}) were determined experimentally to be 0.84 for octanol, and 0.41 for DCE. In Figure 2a the parity plot is shown for the fitting of the pK_b, and in Figure 2b the validation is displayed, showing $D_{DL}/D_{DL,max}$ for both solvents octanol and DCE.

From Figure 2 it can be concluded that the measured pH and the calculated pH for $pK_b = 6.90$ are in good agreement. From the validation experiments it can also be concluded that the neutral form of MPGA is partitioning over the two phases, whereas the protonated $MPGAH^+$ does not. The transition from negligible partitioning at low pH to the maximum value at high pH corresponds very well with the calculated fraction of MPGA that is in the neutral form.

Screening Chiral Selectors for the Enantioselective Extraction of DL-α-MPGA

The chiral selectors that were studied for the enantioseparation of DL-α-MPGA can be classified as macrocyclic hosts and binol derivatives. The selectors **1** to **9** are macrocylic hosts, **10**, **11,** and **12** are binol derivatives.

Because high selectivities were observed in the past for chiral separations of amino acid derivatives using crown ethers as host,[23–25,33] a series of chiral crown ethers (structures **1**

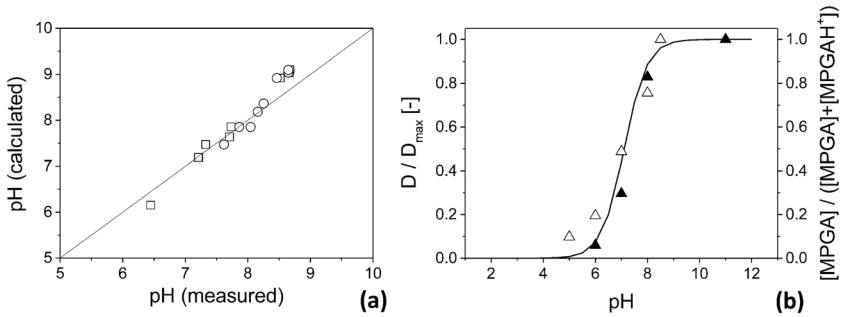

Fig. 2. (a) Parity plot of measured and calculated pH in the pK_b-estimation; circles and squares correspond to two different series of measurements. **(b)** Validation experiments comparing the measured distributions with the maximum distribution at high pH (all α-MPGA in the neutral form). Line: calculated fraction of α-MPGA in the neutral form, open symbols: using DCE as solvent, closed symbols: using octanol as solvent.

through **6** in Fig. 1) were studied for the enantioseparation of DL-α-MPGA. Furthermore, some calix[4]arenes and a heterocycle were studied (selectors **7–9**), as they are known for their use in stationary phases in chiral HPLC.[46] Because macrocycles, and in particular crown ethers, are not only able to extract neutral species, but can also form complexes with ion pairs with the cations inside the cavity,[50] next to the effect of the organic solvent, also the effect of the pH on the extraction was studied. An overview of the ELLE results obtained with the investigated hosts is presented in Table 1.

In experiments 1–4 (host **1**), 11, 12, 15, 16 (host **3**), 18–21 (host **5**), 26–28 (host **9**), the effect of the organic solvent was investigated at pH 8.8. Under these conditions MPGA is predominantly in the neutral form (the pK_b was determined by acid-base titration at 6.90). The general trend in the distribution for both enantiomers is octanol > DCE > 3-pentanone > toluene. However, for none of the solvents was a reasonably high selectivity observed, except for some cases where the distribution coefficient was very low (e.g., in experiment 10). Experimental selectivities obtained at very low distributions should be valued with caution due to the experimental inaccuracy, which has a large effect on the calculated selectivity under these conditions.

Experiments 3, 5, 6 with host **1** in 3-pentanone were performed to study the effect of the pH. If there was a host–guest interaction, the distribution of the DL-α-MPGA would improve as compared to the physical distribution in the absence of the host. The physical distribution in 3-pentanone at pH 8.8 was determined to be 0.5, and it can be concluded that the pH-dependent distribution in the presence of host **1** approaches a maximum value that resembles the physical distribution. It can thus be concluded that host **1** is not a suitable host for DL-α-MPGA. The trend in experiments 13–15 is identical, hence also host **3** in 3-pentanone appears not to complex with DL-α-MPGA. In the case of host **2** in toluene, it can be observed that the distribution at pH 5–7 exceeds the physical distribution (which is 0.04), and is much higher than the distribution at pH 8.8. It thus appears that there is a host–guest complexation between protonated amine functionality in α-MPGA and host **2**; however, there is hardly any selectivity, and the distribution is still rather low. Considering both the variations in solvent and in pH, unfortunately it must be concluded that for α-MPGA none of the hosts **1–9** show enough enantioselectivity at reasonable distribution ratios to be applied in a liquid–liquid-based enantioseparating process.

When applying the standard conditions (5 mM host in solvent, 2 mM aqueous DL-α-MPGA, $V_{aq}/V_{org} = 1$, T = 25 °C) for hosts **10** and **11**, it was found that the distribution coefficients were so high that the aqueous phase concentrations dropped below the detection limit of the HPLC. Therefore, the extraction conditions were modified so that the experiments could be analyzed. Experiments 29 and 30 show very high selectivities of 7.4 and 6.2, indicating that both $PdCl_2$-(*S*)-BINAP and $PdCl_2$-xylyl-(*S*)-BINAP are suitable hosts for ELLE of DL-α-MPGA. This finding shows once more the

TABLE 1. ELLE selector screening results

Experiment	Host	Solvent	pH	D_L	D_D	α_{op}
1	**1**	Octanol	8.8	0.80	0.77	1.0
2	**1**	DCE	8.8	0.40	0.41	1.0[a]
3	**1**	3-pentanone	8.8	0.48	0.51	1.1[a]
4	**1**	Toluene	8.8	0.16	0.14	1.1
5	**1**	3-pentanone	7.0	0.12	0.12	1.0
6	**1**	3-pentanone	5.0	0.16	0.14	1.1
7	**2**	Toluene	3.0	0.11	0.10	1.1
8	**2**	Toluene	5.0	0.17	0.17	1.0
9	**2**	Toluene	7.0	0.15	0.16	1.1[a]
10	**2**	Toluene	8.8	0.04	0.02	2.0
11	**3**	Octanol	8.8	0.74	0.75	1.0[a]
12	**3**	DCE	8.8	0.53	0.57	1.1[a]
13	**3**	3-pentanone	5.0	0.09	0.11	1.2[a]
14	**3**	3-pentanone	7.0	0.16	0.19	1.2[a]
15	**3**	3-pentanone	8.8	0.43	0.47	1.1[a]
16	**3**	Toluene	8.8	0.12	0.10	1.2
17	**4**	Toluene	8.8	0.25	0.25	1.0
18	**5**	Octanol	8.8	0.84	0.81	1.0
19	**5**	DCE	8.8	0.54	0.53	1.0
20	**5**	3-pentanone	8.8	0.46	0.50	1.1[a]
21	**5**	Toluene	8.8	0.24	0.24	1.0
22	**6**	Toluene	3.0	0.28	0.26	1.1
23	**6**	toluene	7.0	0.24	0.22	1.1
24	**7**	Toluene	8.8	0.04	0.03	1.3
25	**8**	Toluene	8.8	0.03	0.02	1.5
26	**9**	Octanol	8.8	0.74	0.77	1.0
27	**9**	3-pentanone	8.8	0.38	0.41	1.1
28	**9**	DCE	8.8	0.46	0.50	1.1
29[b]	**10**	DCM	6.9	95.8	12.9	7.4
30[b]	**11**	DCM	6.9	72.2	11.7	6.2
31[c]	**12**	DCM	7.0	0.84	0.88	1.0[a]
32[d]	**12**	Octanol	4.9	4.27	4.05	1.1
33[d]	**12**	Octanol	7.0	0.96	0.88	1.1
34[c]	**13**	DCM	7.0	0.54	0.51	1.1
35[c]	**14**	DCM	7.0	0.82	0.89	1.1[a]

Conditions: 5 mM host in solvent, 2 mM aqueous DL-α-MPGA, $V_{aq}/V_{org} = 1$, T = 25 °C.
[a]Selectivity towards D-enantiomer.
[b]Conditions: $V_{aq}/V_{org} = 2.75$, [host] = 2.93 mM, $[DL\text{-}\alpha\text{-MPGA}]_{in} = 1.84$ mM.
[c]The concentration host was here 1 mM.
[d]Conditions: $V_{aq}/V_{org} = 2.5$, [host] = 2 mM, $[DL\text{-}\alpha\text{-MPGA}]_{in} = 0.72$ mM.

versatility of these hosts, as recently metal-BINAP-based hosts were found applicable in ELLE for a wide range of substrates.[27,29,51–55] Similar to the BINAP-based hosts, binol-based phosphoric acids have recently been demonstrated to be selective for a range of benzylic amines. Therefore, these were also applied in this study. In contrast to our expectations on the basis of the work by Feringa and coworkers,[34,47] none of the hosts **12–14** displayed a selectivity above 1.1 under the applied conditions.

Based on the results from the screening study, it was decided to study the extraction of DL-α-MPGA with $PdCl_2$-(*S*)-BINAP and $PdCl_2$-xylyl-(*S*)-BINAP in more detail.

ELLE Studies With $PdCl_2$-(S)-BINAP and $PdCl_2$-xylyl-(S)-BINAP Hosts

Because the distributions in experiments 29 and 30 in Table 1 were very high, the hosts **10** and **11** were studied with a lower host concentration of 2 mM in the organic phase, and with V_{aq} = 5.5 mL, and V_{org} = 2 mL. In Figure 3 the extraction yields and selectivities are presented using DCM as solvent.

In Figure 3 it can be seen that the yield increases with increasing pH, which is in line with the results presented in Figure 2 for pure physical extraction without the host present. Furthermore, it can be seen that going from pH 5.5 to pH 7.0, the operational selectivity is increasing, while further increasing the pH to 7.7 results in such an increase in the extracted amount of both enantiomers that the operational selectivity is dropping again. When comparing the yields and selectivities in Figure 3a,b with those in Figure 3c,d, it can be observed that both the yields and the selectivities are higher at a lower initial racemate concentration. The higher operational selectivity at lower racemate concentration (and thus a larger excess of host) is an indication that the complexation constants are relatively small. When the complexation is very strong instead, increasing the host excess leads typically to lower operational selectivity due to excessive coextraction of the undesired enantiomer.[48] In the case of less strong complexation, increasing the host concentration will result in an increasing operational selectivity with increasing host excess.[33] It can be concluded from Figure 3. that both $PdCl_2$-(*S*)-BINAP and $PdCl_2$-(*S*)-xylyl-BINAP dissolved in DCM are highly selective towards L-α-MPGA. By manipulating the conditions, the extraction yields can easily be tuned to be applied in a multistage extraction process with a limited number of equilibrium stages where a full enantioseparation will be possible.

The results displayed in Figure 3 were obtained using the solvent DCM, which is from a processing point of view not an ideal solvent because of its high volatility. When enantioseparation processes are envisioned making use of immobilized liquids, the solubility of DCM in water (13 g/L) requires the eluting aqueous phase to be presaturated with DCM, which is not ideal either. Hence, if DCM can be replaced by another solvent that is less volatile and less soluble in water, that would be a big improvement. Therefore, for both host **10** and **11**, a series of solvents were studied, including 1-octanol, 1,2-dichloropropane, chlorobenzene, 2-chlorotoluene, 1-chloropentane, and 1-chlorooctane.

Solutions of **10** in 1-octanol were found to be unstable, and the $PdCl_2$-(*S*)-BINAP precipitated from the solution (X-ray analysis of the crystals confirmed that the precipitated matter was indeed $PdCl_2$-(*S*)-BINAP). For that reason the solvent 1-octanol was considered not suitable for further studies. Nonchlorinated and otherwise nonfunctionalized aliphatic and aromatic hydrocarbons do not normally work well for ELLE, because of precipitation and interference in the π–π interactions, respectively.[21] Therefore, chlorinated versions were investigated. The experimental results using $PdCl_2$-(*S*)-BINAP in 1,2-dichloropropane, chlorobenzene and 4-chlorotoluene are displayed in Figure 4. Results obtained with $PdCl_2$-(*S*)-xylyl-BINAP in 1,2-dichloropropane, chlorobenzene, 4-chlorotoluene, 1-chloropentane, and 1-chlorooctane are displayed in Figure 5.

From Figures 4 and 5 it follows that for the aliphatic solvents the extraction yields follow the same trend that was observed in DCM (Fig. 3) for both **10** and **11**, but in none of the solvents

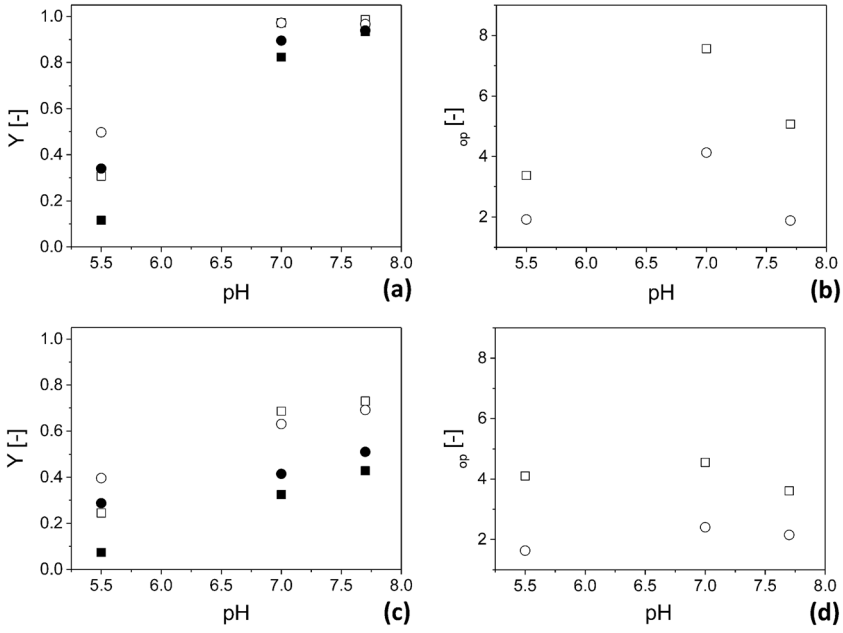

Fig. 3. Extraction yields Y_L (open symbols) and Y_D (closed symbols) for experiments with **(a)** 0.724 mM DL-α-MPGA, and **(c)** 1.50 mM DL-α-MPGA. V_{aq} = 5.5 mL and V_{org} = 2 mL, organic phase: 2 mM **10** and **11** in DCM. Panels **(b)** and **(d)** display the operational selectivities corresponding to the yields in panels **(a)** and **(c)**. Squares represent results for **10**, circles for **11**.

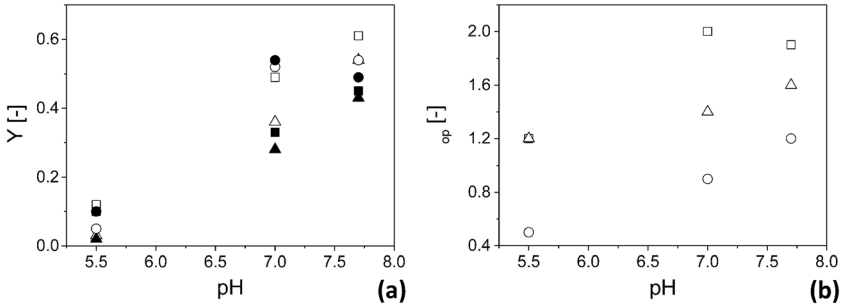

Fig. 4. **(a)** Extraction yields Y_L (open symbols) and Y_D (closed symbols) for experiments with 1.62 mM DL-α-MPGA, V_{aq} = 5.5 mL and V_{org} = 2 mL, organic phase: 2 mM **10** in solvents 1,2-dichloropropane (squares), chlorobenzene (triangles) and 4-chlorotoluene (circles). **(b)** operational selectivities corresponding to results displayed in **(a)**.

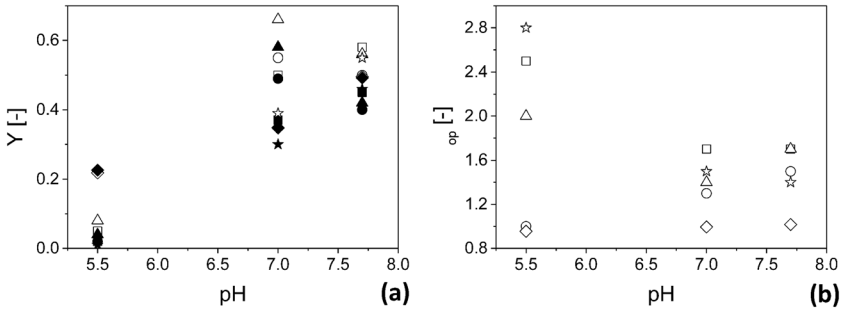

Fig. 5. **(a)** Extraction yields Y_L (open symbols) and Y_D (closed symbols) for experiments with 1.62 mM DL-α-MPGA, V_{aq} = 5.5 mL and V_{org} = 2 mL, organic phase: 2 mM **11** in solvents 1,2-dichloropropane (squares), chlorobenzene (triangles), 4-chlorotoluene (circles), 1-chloropentane (stars), and 1-chlorooctane[a] (diamonds). **(b)** operational selectivities corresponding to results displayed in **(a)**. [a]Racemate concentration 1.50 mM.

did the selectivity approach that of DCM. The highest selectivity was observed using the dichlorinated 1,2-dichloropropane, while the observed operational selectivity (1.5) with a reasonable yield of 0.39 for L-α-MPGA using **11** in 1-chloropentane is still high enough to achieve a full enantioseparation within a reasonable number of stages. With **11** in 1-chlorooctane, however, no significant selectivity was observed. With regard to volatility and therewith related solvent losses, the solvent 1-chloropentane appears to be the best aliphatic solvent for **11**.

Because chlorobenzene and 4-chlorotoluene show relatively environmentally benign and low toxic characteristics compared to other chlorinated solvents, the aromatic solvents chlorobenzene and 4-chlorotoluene were also investigated. From both Figures 4 and 5 it follows that at the lower pH investigated (pH 5.5) the selectivity seems to be towards D-α-MPGA, rather than towards L-α-MPGA. The results at pH 5.5 need to be viewed with care, however, because of the low yields. At higher pH, it appears that both the yield and the selectivity are good for chlorobenzene, which in combination with the relatively mild character with respect to the environment and toxicity makes this an interesting solvent. The two most promising solvents to replace DCM are 1-chloropentane and chlorobenzene.

CONCLUSIONS

From the primary screening study, it was found that many hosts that have been successful in enantioselective extractions of structurally related racemates were not able to combine reasonable distributions with a significant selectivity for the enantioselective liquid–liquid extraction of DL-α-MPGA. Apparently, the amide functionality brought in a significant disturbance of the enantiorecognition mechanism for these chiral selectors. Among the screened selector classes, $PdCl_2$-(*S*)-BINAP and $PdCl_2$-xylyl-(*S*)-BINAP were found to be highly selective. Operational selectivities towards L-α-MPGA higher than 7 were observed.. This shows that a dedicated selector search for a given racemate can yield selectivities high enough to develop an enantioselective liquid–liquid extraction process. The system was further examined in various solvents, and a less volatile alternative for DCM was found in 1-chloropentane, still exhibiting selectivities up to 1.5. The BINAP and xylyl-BINAP complexes have been reported several times recently in enantioselective liquid–liquid extraction studies,[27,29,51–55] and also here they were the selectors with the highest selectivity (by far). Therefore, the development of metal-BINAP-complexes appears promising to further broaden the library of hosts for enantioselective liquid–liquid extraction.

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NOMENCLATURE

Symbols

D	distribution [(mol/L) / (mol/L)]
V	volume [mL]
K_b	basicity constant [-]
Y	extraction yield [-]

Superscripts and Subscripts

aq	aqueous phase
D	D-α-MPGA
DL	DL-α-MPGA
in	initial
L	L-α-MPGA
max	maximum
org	organic phase
tot	total

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