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# Chiral Lipophilic Ligands. 5. Enantioselective Ester Cleavage of α-Amino Esters by Cu(II) Complexes of Chiral Diamino Alcohols in Aqueous Surfactants Solutions†

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**Abstract:** A series of lipophilic ligands, **1-3**, featuring an 1,2-ethylendiamino moiety as chelating subunit, one (**1**, **3**) or two (**2**) chiral carbons, and an hydroxy function (except for **3**) in the proximity of the coordination center, have been synthesized. Their Cu(II) complexes have been investigated as catalysts for the cleavage of *p*-nitrophenyl esters of phenylalanine (PhePNP) and phenylglycine (PhgPNP) in the presence of cationic aggregates formed by cetyltrimethylammonium bromide (CTABr) or ditetradecyldibutylammnonium bromide (DMDBAB). Large rate accelerations (up to two order of magnitude) and quite remarkable enantioselectivities (from 11 to 35, as the ratios of the rate constants measured for the faster and slower reacting enantiomers) have been observed. In the case of ligands **1** the *S*-ligand complex reacts faster with the *S*-substrate and the enantioselectivity increases with the lipophilicity of the substituent of the chiral carbons. Using ligands **2**, having two chiral centers, the most favoured situation is reached when all the chiral carbons of ligands and substrate have the same absolute configuration; in such a case, and using DMDBAB as cosurfactant, enantioselectivities as high as 35 have been observed. The results are explained on the basis of a different reaction mechanism due to the compartmentalization of the reacting species (a ternary complex ligand/Cu(II)/substrate) in different loci of the aggregate. It is suggested that, depending on the hydrophobicity of the ternary complex, the effective nucleophile may switch from the Cu(II)-bound ligand's hydroxyl to a Cu(II) bound water molecule. The first mechanism is faster and prevails for the more lipophilic ternary complex.


## INTRODUCTION

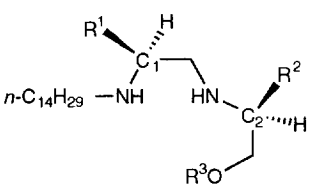
It has long been recognized that aqueous surfactant aggregates can influence chemical rates and equilibria.[1] Large rate enhancements, particularly in the case of functionalized aggregates in hydrolytic processes, have been reported and their source largely discussed and reasonably well defined.[2] The selectivity of a chemical reaction can also be affected by the microenvironment provided by the aggregates: remarkable enantioselectivities have been reported by several groups[3] in the hydrolytic cleavage of chiral esters by histidine containing chiral oligopeptides in the presence of micelles.

In recent years much attention has been focused on metalloaggregates made up of ligand surfactants (or containing lipophilic ligands) and bound metal ions.[4,5] Of particular interest are the aggregates of functionalized ligands with transition metal ions which are able to catalyze some chemical reactions by acting as Lewis acids and activating functions including coordinated water molecules. In most cases the ligands employed contain a hydroxyl group favourably positioned in the proximity of the ligand subunit so that it may be activated by

† For previous parts see ref. 7.

transition metal ions such as Cu(II) or Zn(II) and act as an effective nucleophile in a transacylation process.[5c-e] The effectiveness and the mode of action of the systems investigated in this laboratory, somehow mimicking those of hydrolytic metalloenzymes, have been reported and discussed.[5e,6] More recently, we have turned our attention to the enantioselectivity observed employing chiral lipophilic ligands containing a 2-aminomethylpyridine or a β-amino amide block in the chelating subunits. The Cu(II) complexes of these ligands catalyze the cleavage of *p*-nitrophenyl esters of chiral α-amino acids and remarkable effects were observed, as reported in previous Parts.[7]

In the search for more effective systems both enantioselectively and hydrolytically and for further evidence to implement the rationale offered concerning the effects of the aggregates, this paper presents the results of an investigation of the reactivity of the chiral diamino alcohols **1a-d** and **2a-b** shown in Chart 1. These structures are related to one of the early simple models of metalloenzymes reported by Sigman and Jorgensen[8]: the Zn(II) complex of N-(β–hydroxyethyl)ethylenediamine is catalytically active in the cleavage of *p*-nitrophenyl picolinate. Ligands **1** contain one chiral center of *S* absolute configuration in the hydroxyethyl residue and ligands **2** two chiral centers: one near the hydroxyl group of *S* or *R* configuration and one in the ethylenediamino part of *S* configuration. The lipophilic ligand **3,** the O-methylated analog of **1d** was also synthesized with the aim of defining the role of the hydroxy function in the complexes with ligands **1** and **2**. The present study is a kinetic analysis of the hydrolytic cleavage of the chiral *p*-nitrophenyl esters of phenylalanine, PhePNP, and phenylglycine, PhgPNP, in the presence of the Cu(II) complexes of ligands **1-3** comicellized with cetyltrimethylammonium bromide (CTABr) and, in the case of the **2a** complex, in aggregates formed by the surfactant ditetradecyldibutylammonium bromide (DMDBAB).



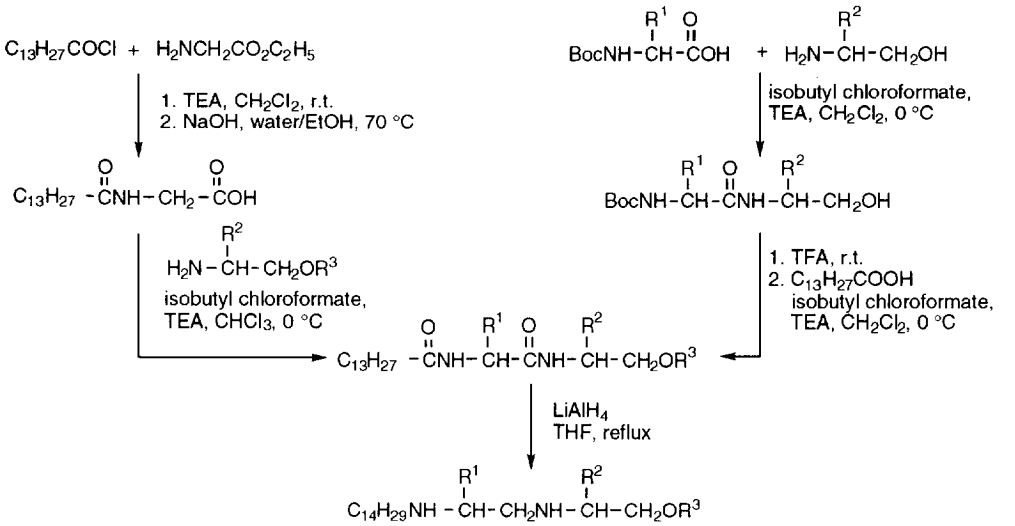

| Ligand | $R^1$ | $R^2$ | $R^3$ | Absolute configuration | |
|---|---|---|---|---|---|
| | | | | $C_1$ | $C_2$ |
| **1a** | H | $CH_3$ | H | - | *S* |
| **1b** | H | $CH(CH_3)_2$ | H | - | *S* |
| **1c** | H | $CH_2CH(CH_3)_2$ | H | - | *S* |
| **1d** | H | $CH_2C_6H_5$ | H | - | *S* |
| **2a** | $CH_3$ | $CH_2C_6H_5$ | H | *S* | *S* |
| **2b** | $CH_3$ | $CH_2C_6H_5$ | H | *S* | *R* |
| **3** | H | $CH_2C_6H_5$ | $CH_3$ | - | *S* |

Chart 1

## RESULTS

Ligands **1, 2,** and **3** were obtained, as outlined in Scheme 1, from the corresponding diamides by reduction with $LiAlH_4$. They are barely soluble in neutral water and their solubility increases upon binding Cu(II) ions, although not to such an extent as to form homomicelles. They can be dispersed in micellar solutions of CTABr and the kinetic experiments were normally carried out using a 10:1 CTABr: ligand ratio, above the

c.m.c. (in the range 4-6 x $10^{-4}$ M) of the resulting comicelles. The binding constants of the different ligands with Cu(II) have not been determined; however, they may be assumed to be very close to the value reported for N-(β–hydroxyethyl)ethylenediamine[9] (log $K_{Cu}$ = 10.3 for the 1:1 complex) although in cationic micelles such a value may decrease by up two orders of magnitude.[10]




Scheme 1

A preliminary set of kinetic experiments indicated that ligands **1** and **2**, in the presence of Cu(II) ions, are enantioselective catalysts for the hydrolytic cleavage of the esters of choice and that the reactivity depends on pH, ligand's structure, type of cosurfactant and substrate. The rate dependence on pH (as the plot of $\log k_{\psi}$, the pseudo-first-order rate constants, *vs.* pH) for the cleavage of *S*-PhePNP by the Cu(II) complex of **1d** (**1d·Cu**) and **3** (**3·Cu**) is shown in Fig.1. The inflections in the rate-pH profiles are diagnostic of an operative $pK_a$ value of *ca.* 6.2 and 6.4 respectively, for the effective nucleophilic species. Similar rate-pH profiles are also observed employing the Cu(II) complexes formed by ligands **1b-d** and **2a**. This indicates that the two possible competing nucleophiles, the ligand hydroxyl and a water molecule both coordinated to the metal ion (*see infra*), have a very similar $pK_a$ value (6.2-6.4) and it may be reasonably assumed that, in each case at pH = 7.5 or above, the nucleophilic function is in its dissociated form and the rate differences observed between the Cu(II) complexes of the different ligands are not due to differences in the $pK_a$ of the nucleophile. On the other hand, the similarity of the $pK_a$ values of alcoholic functions and water molecules when coordinated to a Cu(II) ion, as inferred by the close resemblance of the rate-pH profiles in the case of the complexes with **1d** and **3** and in line with previous observations,[11] does not allow use of such experiments to discriminate between the two possible nucleophiles.

The measurements were thus carried out under the following standard conditions: [ligand] = $[Cu(NO_3)_2]$ = 0.1 mM, [CTABr] = 1 mM, [ester] = 0.01mM in a pH = 7.5, 10 mM HEPES buffer. The $k_{\psi}$, values for the cleavage of *R*- and *S*-PhePNP are reported in the Table together with the enantioselectivity ratio, ER = $k_S/k_R$.

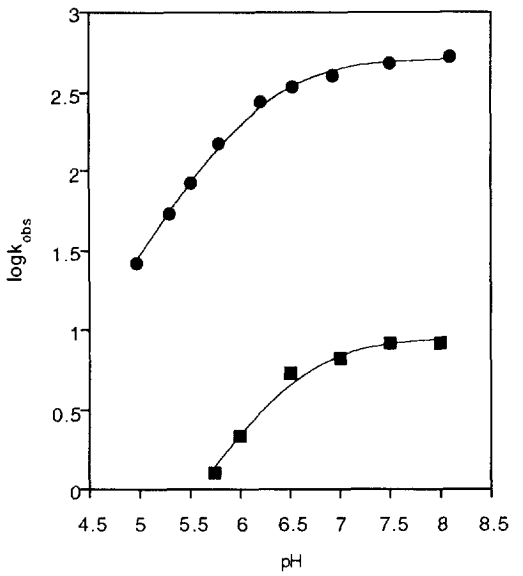



**Figure 1.** Logk$_\psi$ *vs* pH profiles for the cleavage of *S*-PhePNP by the Cu(II) complex of **1d** (●) and **3** (■) in the presence of 1 mM CTABr at 25 °C. See Table 1 for other conditions.

**Table.** Pseudo-first-order Rate Constants, $k_\psi$ ($s^{-1}$), and Enantioselectivity Ratios (ER = $k_S/k_R$.) for the Cleavage of *S*- and *R*-PhePNP (or PhgPNP where indicated) in Aggregate Solutions.[1]

| Entry | Additive[2] | $k_S$ | $k_R$ | ER |
|---|---|---|---|---|
| 1 | none | 0.05 | 0.05 | 1 |
| 2 | Cu | 4.4 | 4.4 | 1 |
| 3 | **1a·Cu** | 220 | 115 | 1.9 |
| 4 | **1b·Cu** | 317 | 97 | 3.3 |
| 5 | **1c·Cu** | 330 | 59 | 5.6 |
| 6 | **1d·Cu** | 480 | 42 | 11.3 |
| 7 | **3·Cu** | 9.1 | 8.2 | 1.1 |
| 8 | **2a·Cu** | 582 | 41 | 14.2 |
| 9 | **2a·Cu**[3] | 338 | 14 | 24.1 |
| 10 | **2a·Cu**[4] | 953 | 34 | 28.0 |
| 11 | **2a·Cu**[5] | 567 | 16 | 35 |
| 12 | **2b·Cu** | 224 | 78 | 2.9 |

[1]For general conditions: see text. [2]Cu = Cu(II) added as $Cu(NO_3)_2$. [3]Using PhgPNP as substrate. [4]Using PhgPNP and 1.0 mM DMDBAB, instead of CTABr, as cosurfactant. [5]At 5 °C, otherwise as under note 4.

From the data of the Table, the main indications are the following: (i) the rate of cleavage of PhePNP is enhanced by almost two order of magnitude by addition of free Cu(II) ions and is further increased by factors ranging from 50 to 140 by addition of Cu(II) complexes with **1**; (ii) taking the analogs **1d** and **3** as an exemplary case (entries 6 and 7), methylation of the hydroxy function virtually offsets all the rate and enantioselectivity benefits of the **1·Cu** (and **2·Cu**) complexes relative to the free Cu(II) ion; (iii) increasing the size and lipophilicity of the side chain in the hydroxyethyl portion of the ligand, *i.e.* on going from ligands **1a** to **1d** (entries 3-6), causes a rate increase for the *S* enantiomer of the ester and a rate decrease for the corresponding *R* enantiomer, thus enhancing the enantioselectivity ER value from 1.9 to 11.6; (iv) in the case of diastereomeric ligands **2**, the presence of the methyl group in the ethylenediamino segment causes quite remarkable effects in the rate and enantioselectivity *vis-à-vis* the structurally closest ligand **1d** (entries 6, 8, and 12). When the chiral centers of the ligand, as in **2a** are of the same absolute configuration (*S*) the ER value increases as a consequence of the higher reactivity toward the *S*-ester. When the two chiral centers are of opposite configuration (the one in the hydroxyethyl segment being of *R* configuration) a dramatic decrease in enantioselectivity is observed due to a decrease in the rate of cleavage of the *S*-ester and an increase in that of its *R* enantiomer. (v) At least by employing **2a·Cu**, the enantioselectivity is much higher in the case of PhgPNP than in that of PhePNP (entries 9 and 10) and, on changing the cosurfactant from CTABr to DMDBAB (entries 9-11), the rate of cleavage of PhgPNP is approximately twice as high as in the presence of CTABr and the ER value remarkably increases to 28 at 25 °C and to 35 at 5 °C.

To sum up, the enantioselectivity effects observed point to a generalized preference for ligands and substrates with chiral carbon atoms with the same absolute configuration. The magnitude of the effects, however, appear to be the result of a delicate balance between relative size and lipophilicity of substituents at the chiral centers which is highlighted by the case of the diastereomeric ligands **2**. We note also that the ER value of 35 observed in the case of ligand **2a** with PhgPNP is one of the highest ever reported for such relatively simple micellar catalysts.[3,7]

## DISCUSSION

We assume that the rate accelerations observed can be ascribed to the mode of action already defined for structurally analogous complexes.[7] The key step is the formation of a ternary Cu(II) complex comprising the ligand and the amino ester. Typically, Cu(II) coordinates up to six donors in an octahedral geometry; the strongest coordination positions being the four coplanar (or distorted coplanar) and the weak ones are the two apical ones.[12] Thus the above mentioned ternary complex may be represented as in Fig. 2A where the two amino nitrogens and the hydroxyl of the ligands **1** and **2** and the amino nitrogen of the esters occupy the strongest position in a planar configuration. However, the hydroxyl not being a strong donor[9] may be displaced by a water molecule as indicated in Figure 2B. In the first closer configuration the activated hydroxyl acts as the nucleophile (mode A) whereas, in the second case, the bound water molecule is taken to be responsible for the cleavage (mode B). Mode A, which is effective in aggregate systems (micelles or vesicles) and leads to a transacylation intermediate (which is then rapidly hydrolyzed to water), is the faster way of cleavage and gives rise to large kinetic benefits. Mode B is the path most favoured in water, in the absence of aggregates, (*e.g.* using non lipophilic models) or in the case of the O-methylated ligand such as **3**, and brings about a slow cleavage which, in some cases, is even slower than that observed in the presence of uncomplexed Cu(II) ions.

More to the point and relevant to the present study, in the case of chiral ligands with one asymmetric carbon in the hydroxyethyl arm and using the enantiomers of α-amino esters as substrates, mode A brings about a substantial enantioselection that fades out when mode B becomes operative. In the latter case, although a diastereomeric ternary complex is still formed, the ligand's chiral center is somehow removed from the reactive site.

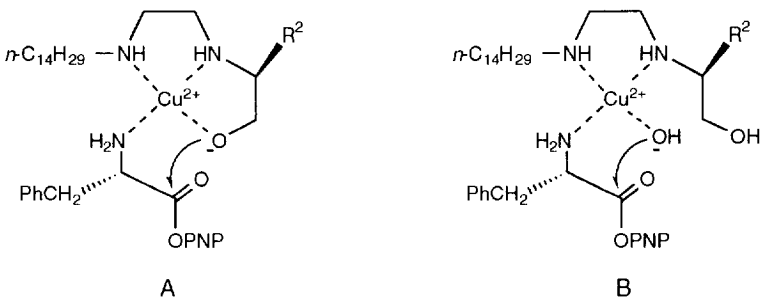



Figure 2

Clearly, there cannot be any clear-cut confinement of the complexes depicted in A or B depending on the microenvironment: so, while mode B is largely prevailing (if not the exclusive) in bulk water, in the aggregate pseudophase where regions of different hydrations are present, modes A and B may compete for the ester cleavage and this is the main source of the large enantioselections observed in micelles or vesicles. This is the rationale offered and not contradicted by the present results (see *infra*). However, the crucial and still open question is the following: why one of the two diastereomeric type A ternary complexes (taken as the precursors of the corresponding transition states) with one enantiomer of the ester is favoured over the other one in the aggregate microenvironment?

The results here presented may offer helpful hints. On the one hand, they indicate that mode A of reaction is at the origin of the kinetic benefits observed with complexes **1·Cu** and **2·Cu** as inferred by their absence when the hydroxyl is methylated as in **3·Cu**. On the other hand, with the exception of **2b·Cu**, there is a definite trend: in the case of the *faster* enantiomeric substrate the rate benefits increase (see the $k_S$ values of the Table) as the apparent lipophilicity (as on going from **1a** to **1d** and **2a** and from PhePNP to PhgPNP, excluding the case of **2b**) of the ternary complex increases while in the case of the slower enantiomer the opposite (see $k_R$) is observed. As a result, the ER values increase with increasing apparent lipophilicity of the ternary complexes.

Inspection of tree-dimensional models, assuming a square planar geometry around the Cu(II) ion in the ternary complexes with ligands **1**, indicates that in the case of the faster reacting diastereomeric complex, the *S-S* couple, the two bulky groups at the chiral centers are on the opposite side of the plane (*anti*, as shown in Figure 2A) while in the slower *S-R* complex they lie on the same side (*syn*). In the case of the complexes with **2a** in the faster couple (the *SS-S*) the substrate bulky group is *anti* relative to the two of the ligand and in the slower *SS-R* (the slowest among the complexes investigated) they are all *syn*. Finally, in the case of the

complexes with **2b**, in both the couples *SR-S* and *SR-R* one group is *anti* to the other two and the rates of cleavage, $k_S$, and $k_R$ approach each other to give a very modest ER value (2.9).

The above analysis suggests that the *anti* arrangements are either more stable or more lipophilic than *syn* ones. Steric interactions may play a role making the *syn* complexes less stable, although from inspection of model and on the basis of results previously reported with analogous systems this appears as a minor factor. We suggest that the *syn* are relatively more hydrophilic or more hydrated, and as a result they may be inserted in more hydrated regions of the micelles where the competition with mode B is stronger and the overall effect is a slower reactivity. Such hypothesis finds experimental support and explanations in the literature for other type of Cu(II) complexes;[13] for the present systems, work is in progress to obtain independent evidence to confirm the above hypothesis.

## CONCLUSION

In the present paper we have presented a new series of chiral lipophilic ligands characterized by a 1,2-diaminoethane subunit. Their copper complexes dissolved in cationic aggregates proved to be efficient and enantioselective catalysts of the cleavage of α-aminoacid esters. On the basis of precedent finding the present results have been interpreted with the formation of a ternary complex, ligand/Cu(II)/substrate, in which the metal-bound ligand hydroxyl cleaves the ester in a fast pseudo-intramolecular process. This reaction pathway is in competition with a slower process in which the ligand hydroxyl is displaced by a water molecule and this competition is driven by the interaction of the ternary complex with the aggregate. When the reaction occurs in a less hydrated region of the aggregate the first mechanism prevails and the system is able to display in full its efficiency. The enantioselection seems to have the same origin. The two diastereomeric ternary complexes, probably because of different hydrophobicity, partition in different regions of the aggregate thus reacting at different rates.

From a practical point of view we note that, using very simple ligands, readily accessible type of aggregates and reaction conditions, we obtained ER values as high as to allow a kinetic resolution of a racemic mixture of α-aminoesters. Work is in progress to optimize experimental conditions to realize such a goal.

## EXPERIMENTAL

*General.* Melting points are uncorrected. $^1$H-NMR spectra were recorded on a Bruker WP 200 SY spectrometer operating at 200 MHz, and chemical shifts are reported relative to internal $Me_4Si$. Elemental analyses were performed by the Laboratorio di Microanalisi of our Department. $Cu(NO_3)_2$ was an analytical grade Carlo Erba product. Metal ion stock solutions were titrated against EDTA following a standard procedure.[14] Buffers were made up from Milli-Q water. The buffer components[15] were used as supplied by the manufacturers: MES (Fluka), HEPES (Sigma) and EPPS (Aldrich). Abbreviations for the buffers are: MES, 4-morpholinoethanesulfonic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; EPPS, 1-(2-hydroxyethyl)-piperazine-4-(3-propanesulfonic acid). Cetyltrimethylammonium bromide (CTABr) was purchased from Aldrich and purified by standard methods.[16] The substrates[17] ((*S*)- and (*R*)-phenylalanine 4-

nitrophenyl ester hydrobromide; (*S* )- and (*R* )-phenylglycine 4-nitrophenyl ester hydrobromide) and (*S*)-(-)-2-amino-1-methoxy-3-phenylpropane[18] were prepared according to literature.

*Kinetic measurements.* The correct amount of ligand to obtain a concentration of 2.0 x $10^{-4}$ M was dissolved into a buffered solution (0.1 M) containing CTABr (2.0 x $10^{-3}$ M). In the case of DMDBAB, the suspension was heated at 60 °C until an optically clear solution was obtained. This was stable for a time long enough to perform the kinetic experiments. To the solution of ligand an aliquot of a 5.0 x $10^{-2}$ M $Cu(NO_3)_2$ was added to give a 2.0 x $10^{-4}$ M concentration of $Cu^{2+}$ (solution 1). The buffers used at pH = 6.3 - 6.8, pH = 7.3 - 7.8 and pH = 8.3 - 8.8 were MES/NaOH, HEPES/NaOH and EPPS/NaOH respectively. The substrate solution (2.0 x $10^{-5}$ M) was prepared in water at pH = 3.5 (solution 2). The kinetic measurements were performed with a Applied Photophysics SF.17MV stopped-flow spectrophotometer. In the stopped-flow apparatus equal amounts (0.1 ml) of solutions 1 and 2 were mixed. The release of 4-nitrophenolate was followed by the increase of absorption at 400 nm. The absorbance *vs* time data obeyed a pseudo-first order rate profile, and the rate constants were calculated as the average value of 6 repeated runs using the software package provided with the stopped-flow work station.

*General procedure for the synthesis of ligands 1 and 3.* To 5.0 g (39.7 mmol) of glycine ethyl ester hydrochloride and 0.1 mol triethylamine (TEA) dissolved in 150 mL of $CH_2Cl_2$ was slowly added a solution of 39 mmol of tetradecanoylchloride in 50 mL of $CH_2Cl_2$. The reaction mixture was stirred for 2 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in 150 mL of $CHCl_3$ and washed with a 0.5 M HCl solution. The organic phase was separated, dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was dissolved in 150 mL of ethanol and 3 g of NaOH in 25 mL of water was added. After heating for 3 h at 70 °C the reaction mixture was concentrated *in vacuo* and the residue dissolved in 200 mL of water. The pH of the solution was adjusted to 1 using concentrated HCl and the suspension thus obtained was extracted with hot $CHCl_3$. The hot organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was stirred overnight with 150 mL of $CH_2Cl_2$ and the solid material left was collected by filtration, washed with $CH_2Cl_2$ and dried *in vacuo* giving 9.8 g (88 %) of pure tetradecanoylglycine. $^1$H-NMR ($CD_3OD$): 0.9 (t, 3 H, $CH_3$); 1.3 (m, 20 H, $(CH_2)_{10}CH_3$); 1.65 (m, 2 H, $CH_2CH_2CO$); 2.25 (t, 2 H, $CH_2CONH$); 3.9 (s, 2 H, $NHCH_2CO$).

To a solution of 0.7 g (2.46 mmol) of tetradecanoylglycine dissolved in 12 mL of $CHCl_3$ and 3 mL of DMF was added 0.33 ml of isobutyl chloroformate at 0 °C. After 1 min 3.0 mmol of TEA was added and the solution stirred for 2 min. Subsequently, 2.5 mmol of the appropriate aminoalcohol ((*S*)-2-amino-1-propanol, (*S*)-2-amino-3-methyl-1-butanol, (*S*)-2-amino-4-methyl-1-pentanol, (*S*)-2-amino-3-phenyl-1-propanol or (*S*)-2-amino-1-methoxy-3-phenylpropane) was added. The cooling bath was removed and the solution was stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 30 mL of $CHCl_3$ and washed with a dilute HCl solution. The organic phase was dried ($Na_2SO_4$) and concentrated *in vacuo* to give a solid which was purified by column chromatography (silica, $CHCl_3$/MeOH, 96:4). The following diamides were obtained from the different aminoalcohols:

*(S)-Tetradecanoyl-glycine-[N-2-(1-hydroxy)propyl]amide.* Yield: 75%. $^1$H-NMR ($CD_3OD$): 0.92 (t, 3 H, $CH_3$); 1.15 (d, 3 H, $CHCH_3$); 1.3 (m, 20 H, $(CH_2)_{10}CH_3$); 1.65 (m, $CH_2CH_2CO$); 2.28 (t, 2 H, $CH_2CH_2CO$); 3.52 (d, 2 H, $CH_2OH$); 3.83 (s, 2 H, $NHCH_2CO$); 3.98 (m, 1 H, CH).

*(S)-Tetradecanoyl-glycine-[N-2-(1-hydroxy-3-methyl)butyl]amide.* Yield: 72%. $^1$H-NMR ($CD_3OD$): 0.93 (m , 9 H, 3 $CH_3$); 1.33 (m, 20 H, $(CH_2)_{10}CH_3$); 1.65 (m, 2 H, $CH_2CH_2CO$); 1.9 (m, 1 H, $CH(CH_3)_2$); 2.28 (t, 2 H, $CH_2CH_2CO$); 3.61 (m, 2 H, $CH_2OH$); 3.72 (m, 1 H, NHCH); 3.9 (s, 2 H, $NHCH_2CO$).

*(S)-Tetradecanoyl-glycine-[N-2-(1-hydroxy-4-methyl)pentyl]amide.* Yield: 68%. $^1$H-NMR ($CDCl_3$): 0.82 (t, 3 H, $CH_3$); 0.85 (2d, 6 H, $CH(CH_3)_2$); 1.2 (m, 22 H, $(CH_2)_{10}CH_3$ and $CHCH_2CH$); 1.55 (m, 3 H, $CH_2CH_2CO$ and $CH(CH_3)_2$); 1.95 (br s, 1 H, OH); 2.2 (t, 2 H, $CH_2CH_2CO$); 3.4 - 3.7 (m, 2 H, $CH_2OH$); 3.75 - 4.05 (AB system, 2 H, $NHCH_2CO$); 4.0 (m, 1 H, NHCH); 6.45 (br m, 2 H, 2 NH).

*(S)-Tetradecanoyl-glycine-[N-2-(1-hydroxy-3-phenyl)propyl]amide.* Yield: 71%. $^1$H-NMR ($CD_3OD$): 0.93 (t, 3 H, $CH_3$); 1.35 (m, 20 H, $(CH_2)_{10}CH_3$); 1.65 (m, 2 H, $CH_2CH_2CO$); 2.3 (t, 2 H, $CH_2CH_2CO$); 2.85 (m, 2 H, $CH_2C_6H_5$); 3.55 (m, 2 H, $CH_2OH$); 3.82 (AB system, 2 H, $NHCH_2CO$); 4.15 (m, 1 H, CH); 7.3 (m, 5 H, $C_6H_5$).

*(S)-Tetradecanoyl-glycine-[N-2-(1-methoxy-3-phenyl)propyl]amide.* Yield: 76%. $^1$H-NMR ($CDCl_3$): 0.88 (t, 3 H, $CH_3$); 1.25 (m, 20 H, $(CH_2)_{10}CH_3$); 1.63 (m, 2 H, $CH_2CH_2CO$); 2.21 (t, 2 H, $CH_2CH_2CO$); 2.86 (m, 2 H, $CH_2C_6H_5$); 3.29 (m, 2 H, $CH_2OH$); 3.34 (s, 3 H, $OCH_3$); 3.87 (m, 2 H, $NHCH_2CO$); 4.26 (m, 1 H, CH); 6.12 (br s, 2 H, NH); 7.24 (m, 5 H, $C_6H_5$).

To the previous diamides (1.4 mmol) 10 mL of a 1.0 M $LiAlH_4$ solution in THF was added and the reaction mixture was refluxed for 14 h under $N_2$. The excess $LiAlH_4$ was *carefully* destroyed with water under $N_2$. The resulting slurry was concentrated *in vacuo* and the residue was extracted with ethanol. The ethanol fractions were concentrated *in vacuo* leaving a solid which was taken up with 50 mL of ether. An insoluble material was filtered off and the organic solvent was evaporated *in vacuo*. The residue was dissolved in 25 mL ethanol and 4 mL of 1.0 M HCl in methanol were added. The solution was concentrated *in vacuo* and 30 mL of ether were added. The solid material was collected by filtration, washed with ether, dried and recrystallized from acetone/methanol. The following compounds were obtained:

*(S)-1,2-diamino-[N-tetradecyl-N'-(1-methyl-2-hydroxyethyl)]ethane·2HCl (**1a**·2HCl).* Yield = 75 %, m.p. 172-173 °C, $[\alpha]_D^{20}$ = + 3.9 (c = 1.0; MeOH). $^1$H-NMR ($CD_3OD$): 0.92 (t, 3 H, $CH_3$); 1.3 (m, 22 H, $(CH_2)_{11}CH_3$); 1.38, (d, 3 H, $CHCH_3$); 1.8 (m, 2 H, $CH_2CH_2N$); 3.1 (t, 2 H, $CH_2CH_2N$); 3.48 (m, 5 H, $NCH_2CH_2NCH$); 3.77 (AB system, 2 H, $CH_2O$). Anal. Calcd. for $C_{19}H_{44}N_2OCl_2$: C, 58.90; H, 11.45; N, 7.23. Found: C, 57.89; H, 11.34; N, 7.09.

*(S)-1,2-diamino-[N-tetradecyl-N'-(1-isopropyl-2-hydroxyethyl)]ethane·2HCl (**1b**·2HCl).* Yield = 71 %, m.p. 175-176 °C, $[\alpha]_D^{20}$ = + 4.2 (c = 1.0; MeOH).$^1$H-NMR ($CD_3OD$): 0.92 (t, 3 H, $CH_3$); 1.15 (2d, 6 H, $CH(CH_3)_2$); 1.38 (m, 22 H, $(CH_2)_{11}CH_3$); 1.78 (m, 2 H, $CH_2CH_2N$); 2.23 (m, 1 H, $CH(CH_3)_2$); 3.1 (t, 2 H, $CH_2CH_2N$); 3.22 and 3.55 (2m, 2 H, $CH_2NCH_2$); 3.48 (m, 2 H, $NCH_2CH_2N$); 3.65 (m, 1 H, NCH); 3.9 (AB system, 2 H, $CH_2O$). Anal. Calcd. for $C_{21}H_{58}N_2OCl_2$: C, 56.86; H, 13.18; N, 6.32. Found: C, 56.21; H, 12.99; N, 6.19.

*(S)-1,2-diamino-[N-tetradecyl-N'-(1-isobutyl-2-hydroxyethyl)]ethane·2HCl (**1c**·2HCl).* Yield = 68 %, m.p. 167-168 °C, $[\alpha]_D^{20}$ = + 4.6 (c = 1.0; MeOH). $^1$H-NMR ($CD_3OD$): 0.9 (t, 3 H, $CH_3$); 1.05 (2d, 6 H, $CH(CH_3)_2$); 1.3 (m, 23 H, $(CH_2)_{11}CH_3$ and $CH(CH_3)_2$); 1.8 (m, 4 H, $CH_2CH_2N$ and $CHCH_2CH$); 3.1 (t, 2 H, $CH_2N$); 3.45 (m, 5 H, $NCH_2CH_2NCH$); 3.22 and 3.94 (AB system, 2 H, $CH_2O$). Anal. Calcd. for $C_{22}H_{50}N_2OCl_2$: C, 61.51; H, 11.73; N, 6.52. Found: C, 61.40; H, 11.88; N, 6.38.

*(S)-1,2-diamino-[N-tetradecyl-N'-(1-benzyl-2-hydroxyethyl)]ethane·2HCl (**1d**·2HCl).* Yield = 73 %, m.p. 192-193 °C, $[\alpha]_D^{20}$ = - 6.0 (c = 1.0; MeOH).$^1$H-NMR ($CD_3OD$): 0.92 (t, 3 H, $CH_3$); 1.35 (m, 22 H,

$(CH_2)_{11}CH_3$); 1.8 (m, 2 H, $CH_2CH_2NCH$); 3.1 (m, 4 H, $CH_2N$ and $CH_2C_6H_5$); 3.45 (m, 2 H, $NCH_2CH_2N$); 3.55 (m, 3 H, $NCH_2CH_2NCH$); 3.62 and 3.8 (m, 2 H, $CH_2O$); 7.35 (m, 5 H, $C_6H_5$). Anal. Calcd. for $C_{25}H_{48}N_2OCl_2$: C, 64.77; H, 10.44; N, 6.04. Found: C, 63.78; H, 10.33; N, 5.97.

*(S)-1,2-diamino-[N-tetradecyl-N'-(1-benzyl-2-methoxyethyl)]ethane (3).* The dihydrochloride salts of this compounds was an oil. The free diamine was purified by column cromatography (silica, $CHCl_3$/MeOH 10:1) giving a clear oil. Yield = 61 %, $[\alpha]_D^{20}$ = + 3.2 (c = 0.5; $CHCl_3$).$^1$H-NMR ($CDCl_3$): 0.88 (t, 3 H, $CH_3$); 1.26 (m, 22 H, $(CH_2)_{11}CH_3$); 1.43 (m, 2 H, $CH_2CH_2NCH$); 2.53 (m, 2 H, $CH_2N$) 2.73 (m, 6 H, $NCH_2CH_2N$ and $CH_2C_6H_5$); 2.92 (m, 1 H, $NCH_2CH_2NCH$); 3.28 (m, 2 H, $CH_2OCH_3$); 3.37 (s, 3 H, $OCH_3$); 7.28 (m, 5 H, $C_6H_5$). Anal. Calcd. for $C_{26}H_{48}N_2O$: C, 77.17; H, 11.96; N, 6.92. Found: C, 76.46; H, 12.13; N, 6.55.

*General procedure for the synthesis of ligands 2.* To 5.0 mmol of N-(*tert*-butoxycarbonyl)-*L*-alanine dissolved in 20 mL of $CH_2Cl_2$ and cooled at 0 °C were added 5.0 mmol of isobutyl chloroformate. After 1 min of stirring 6 mmol of TEA were added. The mixture was stirred for an additional 2 min and then 5.2 mmol of (*R*)- or (*S*)-2-amino-3-phenyl-1-propanol were added. The cooling bath was removed and the solution stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in 20 mL of $CH_2Cl_2$ and washed first with 0.5 M HCl and then with a $Na_2CO_3$ solution. The organic phase was dried over $Na_2SO_4$ and concentrated *in vacuo* leaving the protected dipeptides. These were deprotected by treatment for 1 h at r.t. with 5 mL of trifluoroacetic acid. The reaction mixture was concentrated *in vacuo* and the obtained products were reacted with tetradecanoic acid, isobutyl chloroformate and TEA as described above. The final diamides were purified by column chromatography (silica, $CHCl_3$/MeOH 96: 4).

*(S)-Tetradecanoyl-alanine-[N-(S)-2-(1-hydroxy-3-phenyl)propyl]amide.* Yield 70%. $^1$H-NMR ($CDCl_3$): 0.8 (t, 3 H, $CH_3$); 1.2 (m, 20 H, $(CH_2)_{10}CH_3$); 1.28 (d, 3 H, $CHCH_3$); 1.55 (m, 2 H, $CH_2CH_2CO$); 2.1 (t, 2 H, $CH_2CO$); 2.8 (d, 2 H, $CH_2C_6H_5$); 3.55 (AB system, 2 H, $CH_2O$); 4.1 (m, 1 H, $CHCH_2$); 4.45 (m, 1 H, $CHCH_3$); 6.4 (d, 1 H, NH); 7.15 (m, 6 H, $C_6H_5$ and NH).

*(S)-Tetradecanoyl-alanine-[N-(R)-2-(1-hydroxy-3-phenyl)propyl]amide.* Yield 68%. $^1$H-NMR ($CDCl_3$): 0.82 (t, 3 H, $CH_3$); 1.15 (d, 3 H, $CHCH_3$); 1.2 (m, 20 H, $(CH_2)_{10}CH_3$); 1.55 (m, 2 H, $CH_2CH_2CO$); 2.12 (t, 2 H, $CH_2CO$); 2.8 (m, 2 H, $CH_2C_6H_5$); 3.1 (br s, 1 H, OH); 3.54 (AB system, 2 H, $CH_2O$); 4.15 (m, 1 H, $CHCH_2$); 4.45 (m, 1 H, $CHCH_3$); 6.55 (d, 1 H, NH); 7.05 (d, 1 H, NH); 7.2 (m, 5 H, $C_6H_5$ ).

The previous diamides were reduced with $LiAlH_4$ as described for the other ligands. The final dihydrochloride salts were recrystallized from acetone.

*(S)-1,2-diamino-[N-tetradecyl-N'-((S)-1-benzyl-2-hydroxyethyl)]-1-methylethane·2HCl* (**2a**·2HCl). Yield 65%, m. p. 209-210 °C, $[\alpha]_D^{20}$ = - 8.8 (c = 1.0; MeOH).$^1$H-NMR ($CD_3OD$): 0.9 (t, 3 H, $CH_3$); 1.4 (m, 22 H, $(CH_2)_{11}CH_3$); 1.55 (d, 3 H, $CHCH_3$); 1.8 (m, 2 H, $CH_2CH_2N$); 2.9-3.3 (m, 4 H, $CH_2CH_2N$ and $CH_2C_6H_5$); 3.61 (AB system, 2 H, $CH_2O$); 3.65 (m, 3 H, $CHCH_2O$ and $CHCH_2N$); 3.8 (m, 1 H, $CHCH_3$); 7.35 (m, 5 H, $C_6H_5$). Anal. Calcd. for $C_{26}H_{50}N_2OCl_2$: C, 65.39; H, 10.55; N, 5.87. Found: C, 64.59; H, 10.68; N, 5.80.

*(S)-1,2-diamino-[N-tetradecyl-N'-((R)-1-benzyl-2-hydroxyethyl)]-1-methylethane·2HCl* (**2b**·2HCl). Yield 69%, m. p. 204-205 °C. $[\alpha]_D^{20}$ = - 5.4 (c = 1.0; MeOH).$^1$H NMR ($CD_3OD$): 0.9 (t, 3 H, $CH_3$); 1.35 (m, 22 H, $(CH_2)_{11}CH_3$); 1.55 (d, 3 H, $CHCH_3$); 1.8 (m, 2 H, $CH_2CH_2N$); 2.95-3.3 (m, 4 H, $CH_2C_6H_5$ and $CH_2CH_2N$); 3.45 (m, 1 H, $CH_2O$); 3.65 (m, 3 H, $NCHCH_2N$ and $CH_2O$); 3.7-3.9 (m, 2 H, 2 x CH), 7.35

(m, 5 H, $C_6H_5$). Anal. Calcd. for $C_{26}H_{50}N_2OCl_2$: C, 65.39; H, 10.55; N, 5.87. Found: C, 64.49; H, 10.58; N, 5.77.

*Ditetradecyldibutylammonium bromide* (DMDBAB). 50 mmol of dibutylamine, 0.15 mol of 1-bromotetradecane, and 15 g of $Na_2CO_3$ were refluxed in 50 mL ethanol for 48 h. A solid material was then removed by filtration and the ethanol solution was concentrated *in vacuo*. The residue was treated with 100 mL of $CHCl_3$ and a solid material left was removed by filtration. The $CHCl_3$ was washed 2 times with a 1.0 M HBr solution and 3 times with a 2 M NaBr solution, dried over NaBr and concentrated *in vacuo*. The residue was triturated with 300 mL ether. After standing for 2 h, the precipitate was collected by filtration and thoroughly washed with ether. The crude product was then recrystallized from acetone/ether 1:1. The yield amounted to 47 %, m. p. 70 °C. $^1$H-NMR ($CDCl_3$): 0.82 (t, 6 H, $(CH_2)_{13}CH_3$); 0.93 (t, 6 H, $CH_3$); 1.25 (m, 48 H, $(CH_2)_{11}CH_3$ and $CH_2CH_3$); 1.6 (m, 8 H, $NCH_2CH_2$); 3.32 (m, 8 H, $NCH_2$ ).

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