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# Solid–liquid extraction of ω-amino acids using ditopic receptors

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**Abstract**

Five heteroditopic ligands have been prepared to be used in solid–liquid extraction of ω-amino acids into DMSO solutions. The prepared ligands contain crown ethers as cation binding sites and thiourea or amide groups for anion recognition. The aliphatic zone of the $^1$H NMR spectra suggests that two different species related to the amino acid are present in solution. One of these species is the complexed zwitterionic form and the other seems to be free non-zwitterionic amino acid. The presence of these two species allows extraction efficiencies higher than 100%.


## 1. Introduction

Heteroditopic receptors are a class of supramolecular compounds able to simultaneously bind cationic and anionic guests. These type of ligands have shown applications in several fields such as selective extraction of nuclear waste products,[1] or solubilisation of metal salts[2] and their transport through lipophilic membranes.[3] Among the different salts studied, α-amino acids in their zwitterionic form are the most preferred targets due to their relevance in the biological world.[4] However, less attention has been devoted to study linear aliphatic amino acids even though they also play important biological roles.[5] Thus, 4-aminobutyric acid (GABA) is an important neurotransmitter, 5-aminopentanoic acid is a metabolic product of cadaverine, and 6-aminohexanoic acid presents fibrinolytic properties.

Amino acids in their zwitterionic form are practically insoluble in common organic solvents and it is necessary to use derivatized compounds to carry out organic reactions in non-aqueous media. For this reason, in the course of our studies in carboxylate recognition and sensing we have focused in designing heteroditopic ligands for linear aliphatic amino acid (ω-amino acid) recognition. In addition, we have been also interested in studying the ability of the prepared ligands for dissolving linear aliphatic amino acids in organic solvents.

We report herein the synthesis of five new heteroditopic ligands and their use in solid–liquid extraction of ω-amino acids. All the prepared ligands contain in their structure crown ether moieties for cation recognition and different groups (amide or thiourea) susceptible to be used as anion binding sites. In some cases, both groups (the anion and cation binding sites) are bound to the 2 and 3 positions of a naphthalene. Due to its fluorescence properties, a naphthalene as central group could allow the use of these ligands in sensing processes. The prepared ligands are showed in Chart 1.

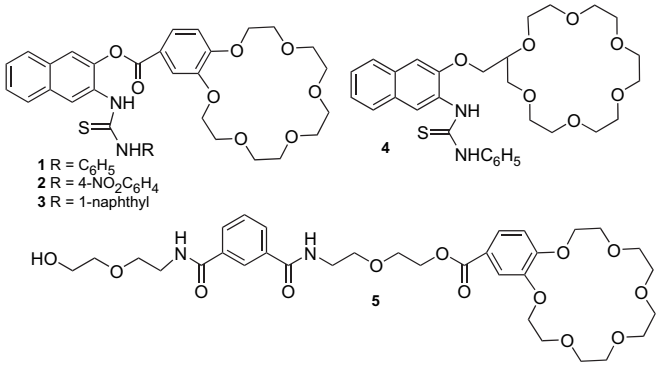


Chart 1.

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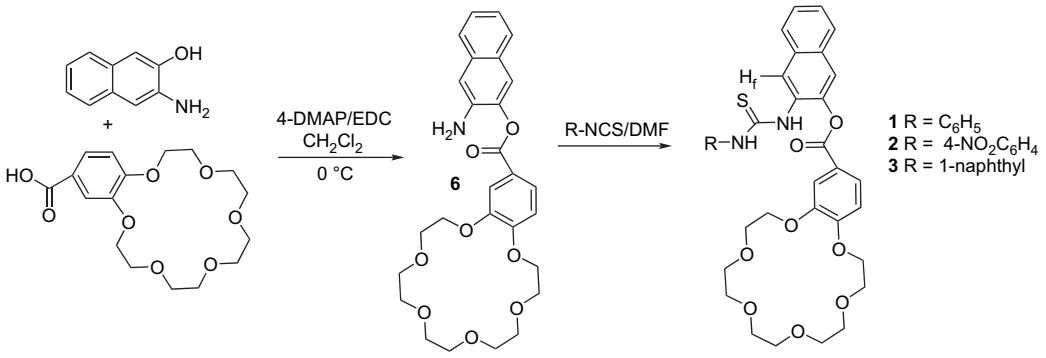
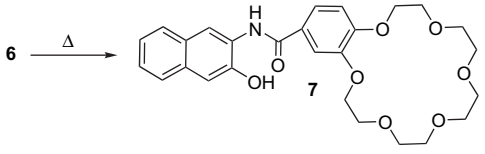



Scheme 1.

## 2. Results and discussion

The synthesis of ligands **1**–**3** was carried out as described in Scheme 1. The reaction between 3-amino-2-naphthol and 4-carboxybenzo-18-crown-6 under mildly basic conditions gives rise to compound **6** with high chemoselectivity and almost in quantitative yield.[6] This compound was converted into the ligands **1**–**3** by reaction with the corresponding isothiocyanates.[7]

Reaction of **6** with phenylisothiocyanate and 4-nitrophenylisothiocyanate could be carried out at temperatures below 60 °C giving rise to ligands **1** and **2** in 58 and 32% yields, respectively. By contrast the use of the more hindered 1-naphthylisothiocyanate required either higher temperatures or the presence in solution of tetrabutylammonium fluoride and under any of these conditions, in addition to the expected compound **3**, the amide derivative **7** was also isolated. Thus, the temperature in this reaction must be carefully controlled to avoid the transposition of compound **6** into the amide derivative **7** (Scheme 2). Compounds **1** and **2** were stable in DMSO solutions for long times. By contrast, ligand **3** in DMSO solutions is slowly converted into compound **7**. Probably the thiourea decomposition regenerates **6** and this compound is converted into the more stable amide **7**.

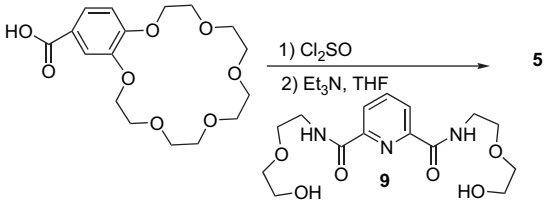



Scheme 2.

On the other hand, compound **4** was prepared as shown in Scheme 3. The mesylated derivative of hydroxymethyl-18-crown-6[8] was transformed into compound **8** by reaction with 3-amino-2-naphthol and $K_2CO_3$. Reaction of **8** with phenylisothiocyanate gave rise to ligand **4**.

Unfortunately compound **4** was not stable enough in solution and gave rise, after a short time, to a complex mixture of compounds. For this reason, compound **4** could not be used to carry out the corresponding extraction experiments.

Finally the synthesis of compound **5** (Scheme 4) was carried out by reacting the acyl chloride of 4-carboxybenzo-18-crown-6 with compound **9**, which was synthesized as reported in the literature.[9]

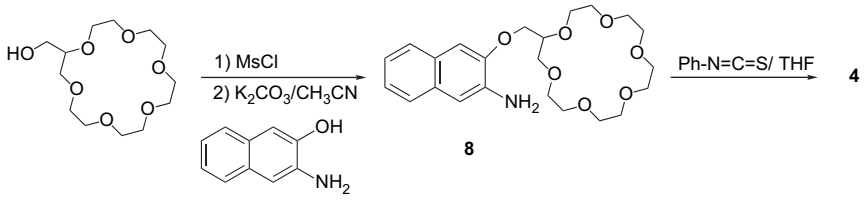



Scheme 4.

### 2.1. Solid–liquid extraction experiments

Solid–liquid extraction experiments were carried out in DMSO-$d_6$ with ligands **1**, **2** and **5** because the instability of **3** and **4** in DMSO solutions precluded their use. Obviously, control experiments were done both with pure solvent and with equimolar mixtures of the monotopic counterparts: the commercially available crown ether **10** plus the thiourea **11** that had been previously prepared in our research group[10] for ligands **1** and **2** (Chart 2) whereas for ligand **5**, the same crown ether **10** and compound **9** were used.

Continuous stirring was followed in all the experiments and the temperature was controlled at 25 °C. The extraction yield




Scheme 3.

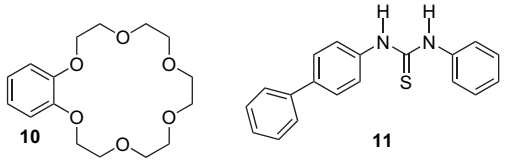



Chart 2.

was determined from the $^1$H NMR spectra of the DMSO-$d_6$ solutions registered at different times. Each experiment was repeated at least three times, and the results reported are the average of the determinations. The standard deviation from the main values among the data in each experiment was lower than 8%. This extraction yield was expressed as equivalents of amino acid/equivalents of ligand and it was obtained by means of the integration values of a signal corresponding to the ligand and the signal corresponding to the amino acid. The obtained results are reflected in Figure 1 for ligand **1** and 4-aminobutanoic acid.

Experiments carried out at different times demonstrated that no further extraction was produced after 9 h. In the control

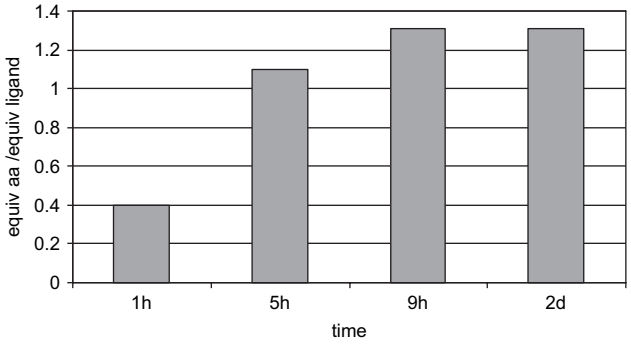



Figure 1. Extraction yield of 4-aminobutanoic acid with ligand **1** at different times (1, 5 and 9 h and 2 days).

experiments carried out with pure solvent no extraction of amino acid was observed even after times longer than a month.

The complexation process could be followed by NMR and Figure 2 shows the spectra corresponding to ligand **1** and 4-aminobutanoic acid. Thus, 1 h after the addition of the amino acid a new signal was observed at 8.41 ppm that can be

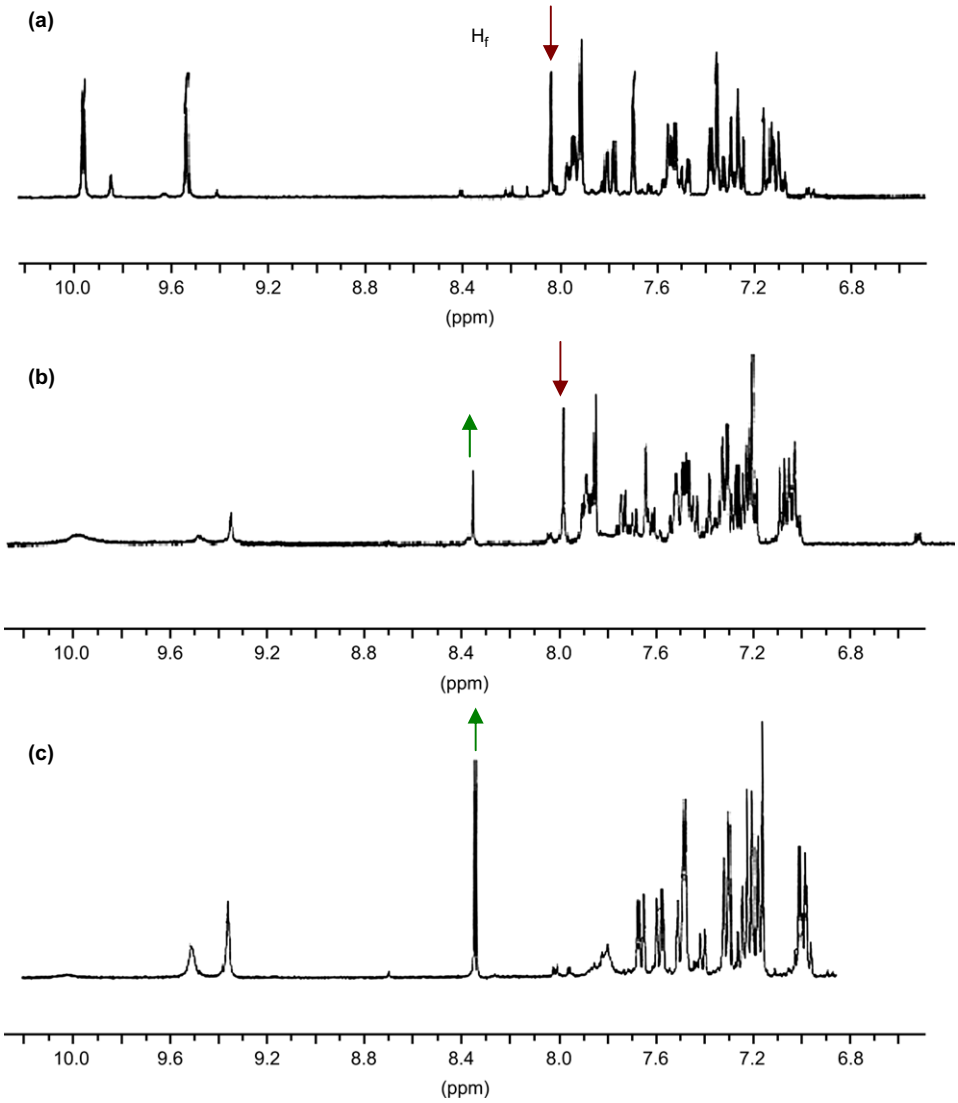



Figure 2. $^1$H NMR spectra (aromatic zones) of: (a) free ligand **1**, (b) **1**+5 equiv of 4-aminobutanoic acid after 1 h, (c) **1**+5 equiv of 4-aminobutanoic acid after 5 h.

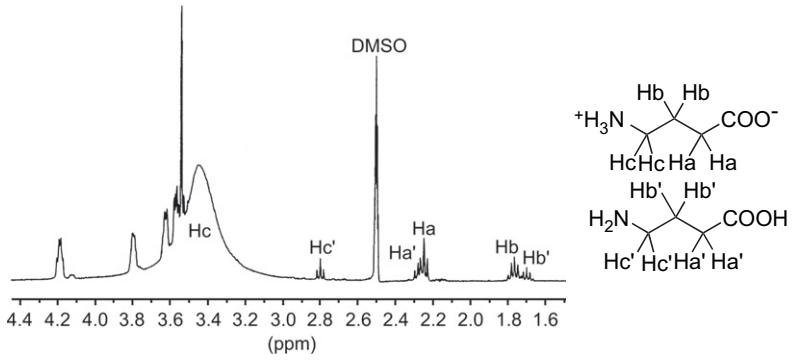



Figure 3. Aliphatic zone of the $^1$H NMR spectrum of **1** after 5 h of contact with 4-aminobutanoic acid.

assigned to the complex because the intensity of this signal increased with the contact time whereas the signals of the free ligand (for example, $H_f$ at $\delta$ 8.04 ppm) decreased in the same proportion.

The observation of differentiated signals for the ligand and the complex in the spectra indicates that the complex formation is slow in the NMR time scale. After 5 h of contact no free ligand was observed and only the signals corresponding to the complex appeared in the $^1$H NMR spectrum.

The extraction results demonstrated that the amount of amino acid in solution under saturation conditions was in all cases higher than 1 equiv of amino acid/equiv of ligand. These data suggest the presence of both complexed and free amino acid in solution what agree with the signals observed in the aliphatic zone of the $^1$H NMR spectra. As shown in Figure 3 two sets of signals can be observed for the hydrogen atoms of the amino acid.

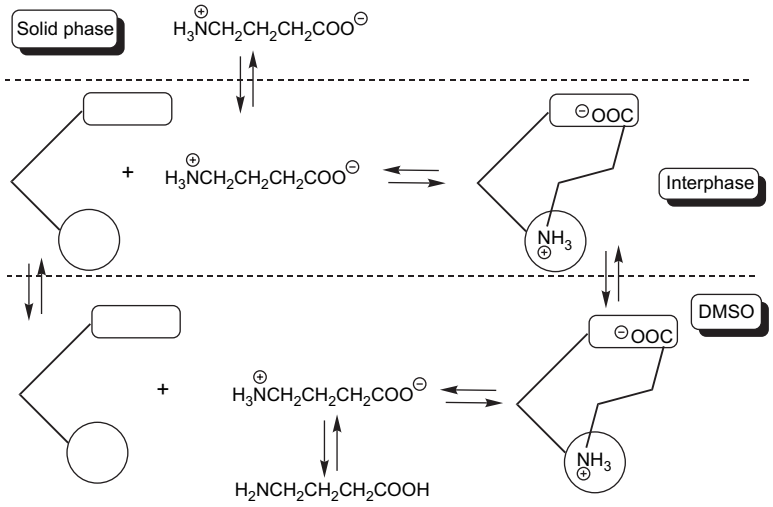
One set of signals corresponds to the complexed amino acid in its zwitterionic form whereas the other fits better with the free amino acid in its non-zwitterionic form, being the relationship between these two species around (1:0.5). These data suggest that as soon as the amino acid is released from the ligand, the higher basicity of the carboxylate in the organic solvent induces a proton transfer to give the corresponding amino acid in its non-zwiterionic form (Scheme 5).

Amino acids with different chain lengths (4-aminobutanoic acid, 5-aminopentanoic acid and 6-aminohexanoic acid) were studied under the same conditions and the extraction results are summarized in Figure 4. Even though extraction of the three amino acids occurred, the extraction yield of 4-aminobutanoic acid was 11% and 16% higher than those of 5-aminopentanoic acid and 6-aminohexanoic acid, respectively.

These results can be related to the solubility in DMSO of the non-zwiterionic amino acids provided that all the ligand (1 equiv) is present in its complexed form.

In order to know the influence of the ligand acidity in the extraction process, similar studies were carried out with ligand **2** that contains in its structure one nitro group. The amino acid extraction with ligand **2** was faster than that observed for ligand **1**. In fact the saturation was reached only 1.5 h after the sample preparation. However, only small variations in the extraction yields were observed (Fig. 5).

The differences between ligands **1** and **2** were not substantial because both possess thiourea groups for the anion recognition and in order to study the influence of stronger changes, ligand **5** was studied under similar conditions. This ligand presents in its structure the same cation receptor moiety but shows strong changes in the anion receptor unit (now it is an amide system) and it has also stronger flexibility to allow both recognition parts to become close to the ionic parts of




Scheme 5.

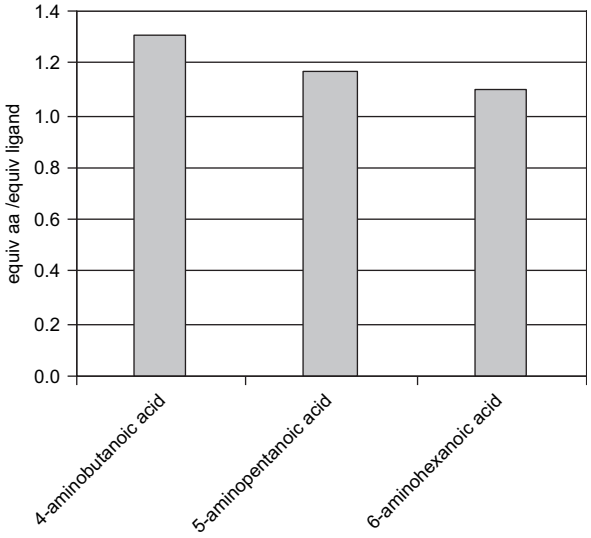



Figure 4. Extraction of 4-aminobutanoic acid, 5-aminopentanoic acid and 6-aminohexanoic acid into DMSO with ligand **1** at saturation time.

the zwitterion. The results obtained with these three ligands and the corresponding control mixtures (at the saturation time) in the extraction of 6-aminohexanoic acid and 4-aminobutanoic acid are summarized in Figure 5.

These results suggest that: (i) the three ligands **1**, **2** and **5** act as real heteroditopic ligands in the extraction process due to the large efficiency showed by them when they are compared with mixtures of the monotopic counterparts. (ii) The three ligands present similar efficiencies in the extraction of 6-aminohexanoic acid but they show different behaviour with 4-aminobutanoic acid. With this amino acid, ligands **1** and **2** are better extractants than **5**. These results can be related to the length of the aliphatic chain that allows 4-aminobutanoic acid to fit better in the complex (Chart 3). Thus ligands **1** and **2** are completely complexed in solution whereas **5** is only partially complexed what agrees with the $^{1}$H NMR data for this ligand.

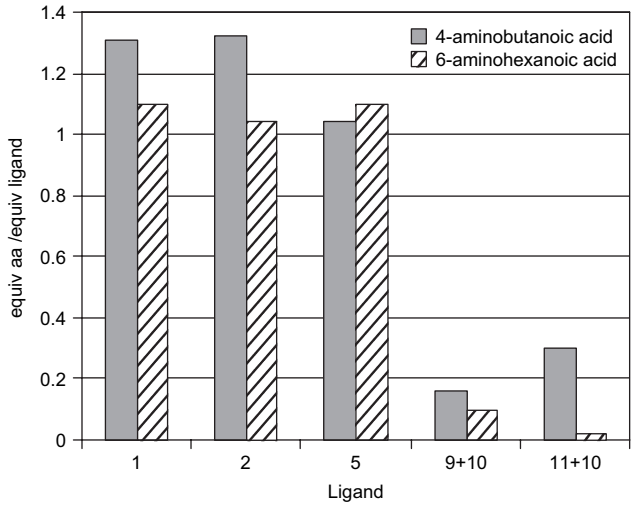



Figure 5. Solid–liquid extraction data at saturation time for ligands **1**, **2** and **5** and control experiments with **9**+**10** (1:1) and **10**+**11** (1:1) in DMSO.

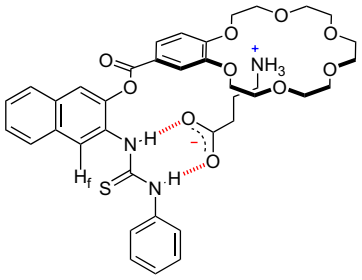


Chart 3.

Complementary studies were carried out with glycine and alanine but with the first one no extraction was observed with any ligand and alanine gave rise to very small extraction rates (0.50 and 0.35 equiv aa/equiv ligand for **1** and **5**, respectively). This behaviour can be related to the proximity of the cationic and anionic groups in the α-amino acids that precluded the efficient complexation by the heteroditopic ligands. By contrast the extraction results obtained with lysine (for example, 1.1 equiv aa/equiv ligand for **2**) were very similar to those observed for 6-aminohexanoic acid. These results were expected considering that for lysine, the most basic amino group is the one placed at the end of the aliphatic chain.

## 3. Conclusions

Ligands **1**, **2** and **5** are efficient solid–liquid extractant agents for lysine and 4-aminobutanoic, 5-aminopentanoic and 6-aminohexanoic acids. The three studied ligands act as real ditopic receptors where the simultaneous complexation of the anionic and cationic moieties by the ligand give rise to extraction values much higher than those obtained with the equimolar mixtures of the corresponding monotopic ligands. 4-Aminobutanoic acid is better extracted with the more rigid ligands **1** and **2** than with ligand **5**, probably due to a more appropriate chain length.

Changes in the anionic binding unit seem to have small influence on the total amount of amino acid extracted while the preorganization in the ligand has a strong effect. On the other hand, the introduction of a nitro group in the phenylthiourea makes the extraction process much faster. Finally, in solution not only the zwiterionic complexed amino acid is present but also free non-zwiterionic amino acid appears. As a consequence of the different acid–base character of the amino acids in DMSO solutions the relationship between amino acid extracted and ligands are higher than 1, reaching the highest value for 4-aminobutanoic acid.

## 4. Experimental section

### *4.1. General procedures and materials*

Compound **9** was prepared as previously reported.[9] All other reagents were commercially available, and were used without purification. Triethylamine was freshly distilled from $CaH_2$. THF was distilled from Na/benzophenone under argon

prior to use. Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Silica gel 60 F254 (Merck) plates were used for TLC. $^1$H and $^{13}$C NMR spectra were recorded on either Bruker Avance 300 MHz or 400 MHz spectrometers, with the deuterated solvent as the lock and residual solvent as the internal reference. High-resolution mass spectra (FAB) were recorded in the positive ion mode on a VG-AutoSpecE.

### 4.2. Syntheses

#### 4.2.1. 2-Oxycarbonyl-(4-benzo-18-crown-6)-3-aminonaphthalene (*6*)

3-Amino-2-naphthol (160 mg, 1.0 mmol) was dissolved in $CH_2Cl_2$ (50 mL) under argon and cooled to 0 °C and then a solution of 4-carboxybenzo-18-crown-6 (712 mg, 2.0 mmol), 4-DMAP (610 mg, 5 mmol) and EDC (720 μL, 4.1 mmol) in dry $CH_2Cl_2$ (40 mL) was added dropwise. The mixture was stirred at 0 °C overnight. $NH_4Cl$ (40 mL) was added under stirring. The organic phase was separated and washed with water, the solvent was removed and the resulting white solid was dried in vacuum to give **6** (485 mg, 99%). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ (ppm): 7.83 (d, $J$=6.4 Hz, 1H), 7.66–7.64 (m, 2H), 7.60–7.56 (m, 2H), 7.30 (t, $J$=8.3 Hz, 1H), 7.18–7.15 (m, 2H), 7.08 (s, 1H), 5.34 (br s, 2H, NH), 4.21–4.20 (m, 4H), 3.80–3.78 (m, 4H), 3.61–3.54 (m, 12H). HRMS (EI$^+$): found 497.2034; $C_{27}H_{31}NO_8$ ($M^+$) requires 497.2050.

#### 4.2.2. Synthesis of ligand *1*

A mixture of **6** (780 mg, 1.57 mmol) and 1.2 equiv of phenylisothiocyanate was dissolved in dry DMF (6 mL) and was heated at 60 °C for 11 h. Evaporation of the solvent under reduced pressure gave a pink oil, which was redissolved in chloroform and put into the fridge for 6 h. The resulting white precipitate was filtered off and dried in vacuum to yield **1** (887 mg, 58%). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ (ppm): 10.01 and 9.69 (s, 2H, 2NH), 8.10 (s, 1H), 8.03–7.97 (m, 2H), 7.98 (s, 1H), 7.85 (dd, $J$=8.5 and 1.9 Hz, 1H), 7.76 (d, $J$=1.9 Hz, 1H), 7.62–7.59 (m, 2H), 7.45–7.40 (m, 2H), 7.33 (t, $J$=7.4 Hz, 2H), 7.21 (d, $J$=8.5 Hz, 1H), 7.17 (t, $J$=7.4 Hz, 1H), 4.18 (s, 4H), 3.80 (s, 4H), 3.61–3.53 (m, 12H). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ (ppm): 181.6, 153.5, 148.2, 145.0, 139.7, 132.2, 131.5, 131.2, 128.9, 127.9, 127.7, 126.8, 126.8, 126.7, 126.5, 126.4, 125.0, 124.8, 124.0, 123.9, 121.4, 120.7, 113.9, 112.6, 70.5, 70.4, 70.3, 70.2, 70.1, 68.9, 68.8, 68.7. HRMS (FAB$^+$): found 633.2287; $C_{34}H_{37}N_2O_8S$ ($MH^+$) requires 633.2271.

#### 4.2.3. Synthesis of ligand *2*

*p*-Nitrophenylisothiocyanate (181 mg, 1.01 mmol) and $Et_3N$ (143 μL, 1.0 mmol) were slowly added to a solution of **6** (503 mg, 1.01 mmol) in THF (25 mL) at 60 °C. The mixture was refluxed overnight and then it was allowed to reach room temperature. The resulting yellow precipitate was filtered off and dried in vacuum, to give **2** as a yellow solid (215 mg, 32%). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ (ppm): 10.61 and 10.12 (br s, 2H, 2NH), 8.16 (d, $J$=9.3 Hz, 2H), 8.01–7.95 (m, 4H), 7.84 (d, $J$=9.3 Hz, 2H), 7.77 (d, $J$=2.1 Hz, 1H), 7.64 (s, 1H), 7.58–7.55 (m, 2H), 7.12 (d, $J$=8.7 Hz, 1H), 4.21–4.17 (m, 2H), 4.01–3.97 (m, 2H), 3.79–3.76 (m, 2H), 3.65–3.51 (m, 14H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ (ppm): 181.5, 164.4, 153.4, 148.2, 146.5, 144.8, 142.9, 132.4, 131.5, 130.7, 128.0, 127.7, 127.1, 126.9, 126.8, 126.6, 124.8, 121.8, 121.3, 121.0, 113.7, 112.8, 112.6, 70.3, 70.2, 70.1, 68.8, 68.7, 68.6. HRMS (FAB$^+$): found 679.2218; $C_{34}H_{37}N_3O_{10}S$ ($MH_2^+$) required 679.2200.

#### 4.2.4. Synthesis of ligand *3*

A solution of **6** (501 mg, 0.73 mmol) and 1-naphthylisothiocyanate (186 mg, 1.0 mmol) in DMF (5 mL) was stirred under argon at 60 °C for 22 h. DMF was concentrated almost to dryness. The crude was washed several times with $CHCl_3$. The product, which was soluble in $CHCl_3$ was identified as **7**. Cold hexane (50 mL) was added to the brown oil insoluble in $CHCl_3$ and the solution was stored in the fridge for 1 h. Ligand **3** was precipitated as a pale brown solid, which was separated by filtration and dried in vacuum (100 mg, 15%). $^1$H NMR (DMSO-$d_6$, 300 MHz) (mixture of conformers) $\delta$ (ppm): 10.50, 9.88, 9.43 and 8.47 (s, 2H, 2NH), 8.08–7.95 (m, 2H), 7.87–7.52 (m, 10H), 7.35–7.27 (m, 3H), 7.11 (d, $J$=8.3 Hz, 1H), 7.87–7.80 (m, 4H), 7.69 (d, $J$=8.7 Hz, 2H), 4.18 (s, 4H), 3.80 (s, 4H), 3.61–3.53 (m, 12H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ (ppm): 182.9, 164.7, 151.2, 148.0, 147.8, 135.3, 133.9, 131.2, 130.2, 128.8, 128.1, 128.0, 127.9, 127.8, 127.4, 127.2, 126.8, 126.7, 126.2, 125.9, 124.1, 123.3, 123.2, 121.8, 120.7, 112.1, 111.9, 109.1, 70.0, 69.9, 69.8, 69.7, 69.7, 68.6, 68.5, 68.2. HRMS (FAB$^+$): found 683.2416; $C_{38}H_{39}N_2O_8S$ ($MH^+$) requires 683.2427.

#### 4.2.5. Synthesis of compound *8*

3-Amino-2-naphthol (160 mg, 1.0 mmol) and anhydrous $K_2CO_3$ (691 mg, 5 mmol) were dissolved under argon in dry acetonitrile (35 mL) in a two-neck round bottom flask provided with magnetic stirring. The mixture was refluxed and a solution of the mesylated derivate of hydroxymethyl-18-crown-6[8] (372 mg, 1 mmol) in $CH_3CN$ (10 mL) was added dropwise for 30 min. The reaction was refluxed for 45 min. The reaction mixture was allowed to cool to room temperature and a white precipitate was removed by filtration. The solvent was evaporated and the residue was redissolved in 50 mL of dichloromethane. The organic layer was washed with water (3×20 mL) and dried over anhydrous $Na_2SO_4$. The solvent was evaporated to yield **8** as a brown oil (364 mg, 84%). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 7.60 (d, $J$=7.5 Hz, 1H), 7.57 (d, $J$=9.8 Hz, 1H), 7.26–7.18 (m, 2H), 7.09 (s, 1H), 7.01 (s, 1H), 4.25–4.23 (m, 2H), 4.11–4.07 (m, 1H), 3.88 (d, $J$=4.1 Hz, 1H), 3.81 (d, $J$=5.6 Hz, 1H), 3.73–3.67 (m, 20H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ (ppm): 147.7, 137.1, 130.1, 128.3, 126.5, 125.2, 124.1, 122.7, 108.8, 106.7, 71.6, 71.4, 71.2, 71.1, 71.0, 70.9, 70.8, 70.7, 70.6, 70.4, 70.2, 70.1, 68.4. HRMS (EI$^+$): found 435.225; $C_{23}H_{33}NO_7$ ($M^+$) requires 435.226.

*4.2.6. Synthesis of ligand **4***

A 1:1 mixture of **8** (397 mg, 0.9 mmol) and phenylisothiocyanate (110 μL, 0.9 mmol) was refluxed in THF (30 mL) for 3 days. The solvent was evaporated, and the black mixture was washed three times with 30 mL of hexane. The resulting insoluble oil was dried under vacuum to yield **4** as a black oil (482 mg, 94%). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ (ppm): 10.19 and 9.18 (s, 2H, 2NH), 8.39 (s, 1H), 7.79 (d, $J$=9.0 Hz, 2H), 7.53 (d, $J$=7.5 Hz, 2H), 7.44–7.35 (m, 5H), 7.17 (t, $J$=7.5 Hz, 1H), 4.25–4.17 (m, 2H), 3.91–3.88 (m, 1H), 3.73–3.64 (m, 2H), 3.73–3.51 (m, 20H). $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz) $\delta$ (ppm): 179.7, 150.5, 139.0, 131.8, 129.9, 127.9, 127.3, 126.4, 126.0, 125.6, 124.4, 123.6, 123.5, 107.1, 105.0, 76.9, 70.4, 70.2, 70.1, 69.9 (7C), 69.3, 68.5. HRMS (FAB$^+$): found 571.2483; $C_{30}H_{39}N_2O_7S$ ($MH^+$) requires 571.2478.

*4.2.7. Synthesis of ligand **5***

Benzo-18-crown-6 (98%) (0.965 g, 2.68 mmol) was added to an excess of thionyl chloride (30 mL). The suspension was refluxed under magnetic stirring until it became a clear solution (2 h). Then the excess of thionyl chloride was distilled, dry benzene was added and the solution was re-distilled. The solid obtained was dissolved in dry THF (30 mL) and added dropwise to a stirred mixture of **9** (0.45 g, 1.34 mmol) and dry triethylamine (0.27 g, 2.68 mmol) in dry THF (30 mL), at 0 °C, under argon atmosphere. When the addition was finished, the stirring was continued at room temperature. After completion of the reaction (TLC, 24 h) the solution was concentrated under reduced pressure. The crude reaction product was purified by chromatography through a neutral alumina column using $CH_2Cl_2$/MeOH (97:3) as eluent to give the desired compound as a pale yellow oil (0.357 g, 39% yield). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 8.73 (br s, 1H,), 8.49 (br s, 1H,), 8.28 (d, $J$=7.5 Hz, 1H), 8.24 (d, $J$=7.5 Hz, 1H), 8.00 (t, $J$=7.5 Hz, 1H), 7.52 (dd, $J_1$=2.3 Hz, $J_2$=8.3 Hz, 1H), 7.37 (d, $J$=2.3 Hz, 1H), 6.68 (d, $J$=8.3 Hz, 1H), 4.44 (m, 4H), 4.11 (m, 8H), 3.88 (m, 4H), 3.74–3.58 (m, 20H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 166.5, 163.9, 163.7, 152.9, 148.7, 148.6, 147.9, 138.9, 124.8, 124.7, 123.8, 122.1, 113.6, 111.5, 71.8, 70.7, 70.7, 70.6, 70.6, 70.5, 69.4, 69.3, 69.1, 63.5, 61.5, 39.4, 39.2. HRMS (FAB$^+$): found 680.3011; $C_{32}H_{46}N_3O_{13}$ ($MH^+$) requires 680.3030.

*4.3. Extraction experiments*

A known amount of the ligand was dissolved in DMSO-$d_6$ (1 mL), in such a way that the concentration of the ligand was 1 mM. The solution was kept under stirring and 5 equiv of the corresponding amino acid was added. The studies were carried out at different times, to study the extraction ability of the ligand as a function of time. In an NMR tube 0.75 mL of the solution was added and the $^1$H NMR spectra was recorded in a Varian Unity-400. After each measurement the solution was poured again into the vial and kept under stirring till the following measurement. The amino acids as zwitterions are not soluble in DMSO-$d_6$. However, $^1$H NMR spectra of DMSO-$d_6$ solutions containing only the amino acids in suspension were recorded at the same time than the ligand–mixture in order to compare them. At the same time $^1$H NMR studies in DMSO-$d_6$ were carried out to compare the behaviour of the corresponding monotopic ligands with our heteroditopic ligands. A 1:1 mixture of the corresponding control receptor for anions, and 4-carboxybenzo-18-crown-6, as receptor of cations, were prepared in DMSO-$d_6$. The ability of extraction of this mixture was studied parallel to the studies of the corresponding ligands.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.066.

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