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Ternary enantioselective complexes from α-amino acids, 18-crown-6 ether and a macrocyclic xanthone-based receptor ☆

José V. Hernández, Ana I. Oliva, Luis Simón, Francisco M. Muñiz, Manuel Grande and Joaquín R. Morán*

Departamento de Química Orgánica, Plaza de los Caídos 1-5, Universidad de Salamanca, Salamanca E-37008, Spain

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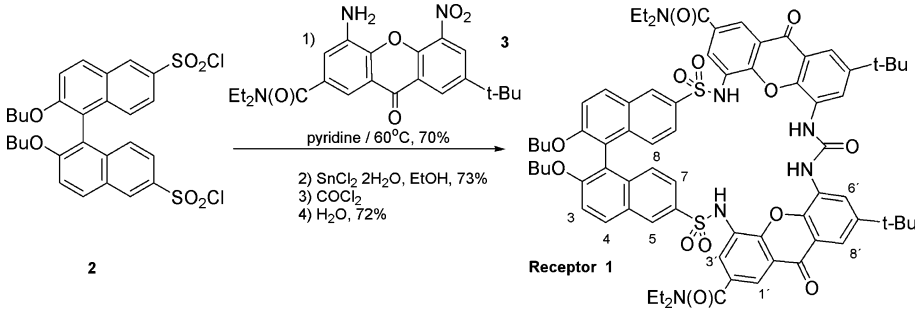
Abstract—A macrocyclic receptor shaped by two xanthone units bonded to binaphthyl is able to extract zwitterionic amino acids enantioselectively from water to chloroform in the presence of 18-crown-6 ether. Based on ^{1}H NMR and circular dichroism spectra, the most stable associate of receptor **1** with alanine is assigned to the (*M*,*S*) configuration while the opposite configuration in phenylglycine yields the strong associate (*M*,*R*).

Amino acid chiral recognition[1] is of current interest due to the huge biological and technical importance of these compounds. Receptors able to resolve their racemic mixtures have been widely sought.[2] Here we report receptor **1**, which was prepared as shown in Scheme 1 with the binaphthol derivative **2** and compound **3**[3] as starting materials. This receptor was initially designed to associate organic carboxylates. However, the acidity of its sulfonamide protons prevents the association of acetate-like anions, since proton transfer takes place. The field effect in amino acids provides fewer basic carboxylates and, in this case, association with receptor **1** seems to be possible.

While racemic receptor **1** alone was unable to extract enantiomerically pure zwitterionic amino acids from water to chloroform, adding 18-crown-6 ether to the biphasic system resulted in a splitting and shift of the receptor **1** ^{1}H NMR signals. The combined effect of the receptor as a hydrogen bonding donor and the crown ether as the acceptor for the ammonium group makes the extraction of amino acids into the organic phase



Scheme 1. Preparation of receptor **1**.

Keywords: Macrocyclic receptor; Xanthone; Anions; Zwitterionic amino acids; Chiral recognition; Enantioselectivity.
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* Corresponding author. Tel.: +34-923294481; fax: +34-923294574; e-mail: romoran@usal.es

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possible. The signals of amino acids, like phenylglycine, show strong anisotropic shifts in the complex (Fig. 1) but, in general, protons of the amino acid in ^{1}H NMR spectra are difficult to assign in the chloroform solution. Therefore the classic ninhydrin test[4] was used to assess the amount of amino acid extracted. Table 1 shows the results.

Hydrophilic amino acids such as histidine, tyrosine, aspartic and glutamic acids or their primary amides were not extracted at all. However, lipophilic compounds such as alanine (Ala), phenylalanine (Phe) or phenylglycine (Phy) were completely extracted. In order to assess the enantioselectivity for receptor **1**, competitive experiments were carried out by adding small portions of 18-crown-6 ether to the biphasic system of water/deuterochloroform with the racemic receptor **1** and ^{1}H NMR spectra were recorded. Graphic plotting of the movement of the receptor protons usually allows calculation of the chiral recognition,[5] but not in this case. The self-association of receptor **1** probably provides a complex system with more than one equilibrium, from which different chiral recognitions can be obtained depending on the proton that is monitored.[6] Therefore, a different procedure was used to assess the enantioselectivity of the receptor.

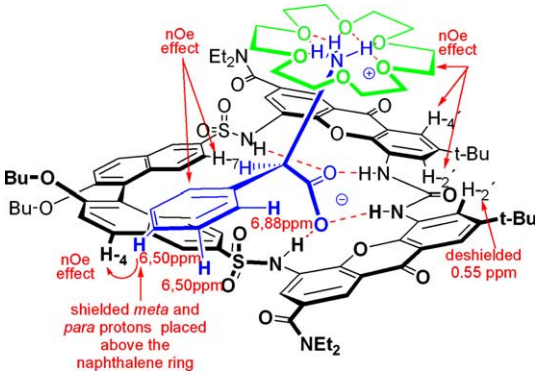

Figure 1. Strong complex of receptor **1** with phenylglycine with configuration (*M*,*R*).

Table 1. Extraction of several amino acids from water to chloroform in the presence of receptor **1** (4.0×10^{-4} M) and 18-crown-6 ether (8.0×10^{-4} M) established by the ninhydrin test (the aqueous phase was saturated with the amino acid)

Amino acid	Extraction[a] (%)
Phe	100
Phy	100
Ala	100
Gly	83
Trp	45
Thr	27

[a] Extraction percentage is given respect to receptor **1**.

Extraction of a racemic amino acid with the racemic receptor **1** afforded an ^{1}H NMR spectrum in which no splitting of the receptor signals took place. Once the chemical shift of a certain proton is known for the strong and weak complexes, the new chemical shift (δ_x) obtained in the previous experiment can be easily related to the relative amount of both complexes making use of Eq. 1. Since all the receptor is forming the complexes, receptor self-association does not take place in solution and therefore it cannot interfere in the K_{rel} measurement. The results are shown in Table 2, in which it may be seen that alanine and phenylglycine are the best enantioselectively complexed substrates. An explanation of the observed selectivity will be delayed until the geometry of the complexes is discussed.

$$K_{rel} = \frac{[\text{strong complex}]}{[\text{weak complex}]} = \frac{\delta_x - \delta_{\text{weak complex}}}{\delta_{\text{strong complex}} - \delta_x} \quad (1)$$

The resolution of the racemic receptor **1** was done by chromatography using its supramolecular properties.[7] Thus, preparative silicagel TLC plates were prepared with an 1% aqueous solution of (L)-alanine and the stoichiometric amount of the crown ether. After elution with $CHCl_3$/diethyl ether 9/1, receptor **1** was split into two spots with $R_f = 0.6$ and 0.4. No elution was observed in a blank experiment on a TLC plate without the amino acid, so complex formation is probably responsible for the elution and therefore the strong complex has the larger R_f. The complexes were scraped from the TLC plate, placed in a short-path silicagel column, and eluted with CH_2Cl_2/MeOH 1/1, affording the enantiomerically pure receptors {$[\alpha]_D^{20}$ +146 (*c* 0.9, $CHCl_3$) for the enantiomer that forms the strong complex with (L)-alanine and $[\alpha]_D^{20}$ −145 (*c* 1.1, $CHCl_3$) for the enantiomer that forms the weak complex with (L)-alanine}.

Since phenylglycine showed the best recognition, this amino acid was used to establish the geometry of the complexes. Figure 1 shows the configuration assigned to the strong complex, including the anisotropic shifts and NOE effects obtained from the ^{1}H NMR spectra. The most stable associate (*M*,*R*), corresponding to the *M* binaphthyl configuration, showed the smallest steric hindrance between the phenylglycine aromatic ring and the binaphthyl aromatic sheet.

The circular dichroism spectrum of receptor (+) **1** was also in agreement with the proposed configuration. Apart from the presence of some maxima above 255 nm related to the absorption bands of the xanthone ligands, the CD spectrum of receptor **1** showed a strong bisig-

Table 2. Chiral recognition of several amino acids and receptor **1** (4.0×10^{-4} M) in the biphasic system chloroform/water in the presence of 18-crown-6 ether (8.0×10^{-4} M) (the aqueous phase was saturated with the amino acid)

Guest	Ala	Ser	Phe	Trp	Leu	Val	Phy
K_{rel}[a]	7	6	3	2	1	2	9

[a] Ratio between the two association constants of both diastereomeric complexes.

nate Cotton effect (Davidov splitting),[8] with maxima at 241 nm ($\Delta\varepsilon$, +1390) and 227 nm ($\Delta\varepsilon$, −1200). The receptor had two aromatic systems that could originate the couplet: the naphthalene rings of the binaphthyl and the xanthone groups. The (+) chirality of the xanthone ligands and the (−) chirality for the binaphthyl moiety (see Supplementary information) allow us to conclude that the (+) **1** receptor should have *M* helicity ($=R_a$ absolute configuration) for the binaphthyl, as shown in Figure 1.

To our surprise, other amino acids such as alanine showed the opposite configuration in the strong complex. The unexpected selectivities shown in Table 2 can be explained taking into account that amino acids with small substituents, such as alanine, preferred the (*M*,*S*) configuration; while larger groups, such as phenylalanine, showed only small selectivities; greater hindrance close to the amino acid α carbon, as in valine, changed the preferred configuration, and the even larger aromatic ring of phenylglycine showed the best recognition.

In an experiment in which aqueous racemic phenylglycine was extracted with a chloroform solution of the enantiomerically pure receptor **1** and 18-crown-6 ether, the organic phase essentially showed only the signals corresponding to the strong complex. The protons of the phenylglycine in the weak complex were broad and very small and hence integration of these signals was difficult. An estimation of the chiral discrimination was achieved from the chemical shift of H-6, a proton that showed up at 8.850 ppm, between the respective absorption signals in the pure strong complex ($\delta = 8.843$ ppm) and the weak complex ($\delta = 8.911$ ppm) (see Supplementary information), suggesting a ninefold higher concentration of the strong complex as compared to the weak one. In our opinion, this is a very good result for a single extraction experiment. A 'Cram Machine'[9] could be suitable for large-scale resolution of zwitterionic amino acids since chiral receptors are not consumed during the process.

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