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A xanthone-based neutral receptor for zwitterionic amino acids

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Abstract—Combination of a xanthone and crown ether provides a receptor that extracts phenylalanine from water. Strong anisotropic shifts were observed for the guest aromatic ring in the complex. The ninhydrin test was used to assess the amount of other amino acids extracted by this receptor.

Molecular recognition of carboxylic acids,[1] and especially α amino acids,[2] is of current interest due to the great biological and technical importance of these molecules. Successful extraction of amino acids from water to apolar solvents has been achieved with charged receptors.[3] However, neutral systems[4] may have advantages, since the geometry and properties of neutral complexes are easier to predict because they do not need a counterion. Xanthones[5] and chromenones[6] have been shown to be useful for the development of carboxylate hosts. Modelling studies suggest that receptor **1** may be suitable for amino acid association, since it combines a crown ether for the ammonium group with strong xanthone based hydrogen bonds for the carboxylate (Fig. 1).

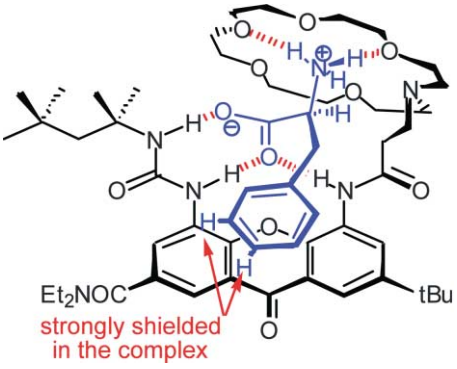

Figure 1. Proposed structure for the associate of receptor **1** and L-phenylalanine.

Scheme 1 shows the synthesis of this compound.

Addition of the amino acids to the receptor in a biphasic system of $CDCl_3$/ D_2O led to significant shifts in the ^1H NMR of the receptor signals, which suggests associate formation. However, owing to the complex spectra, identification of the amino acid signals in the spectrum was, in general, not easy. An exception was phenylalanine; the aromatic ring of this guest was strongly shielded in the complex, and therefore easy to identify. *ortho* Protons appeared at 6.86 ppm, *meta* at 6.33 ppm, and *para* at 6.26 ppm, probably because they lay in the xanthone shielding cone (Fig. 1). Semiempirical geometry optimisations were carried out at the restricted Hartree–Fock (RHF) level using the PM3 semiempirical SCF-MO method, including molecular mechanics correction for HCON linkages (keyword PM3MM), as implemented in the Gaussian 98W program.[7] These modelling studies reveal that the phenyl ring of the guest lays over the xanthone and that stacking effects are probable (Fig. 2).

Integration of the ^1H NMR signals showed 70% extraction of this amino acid. Since NMR was not a suitable tool for assessing the extent to which other amino acid association was taking place, the classic ninhydrin[8] test was used. The results, summarised in Table 1, showed that aromatic amino acid such as phenylalanine and tryptophan are the best substrates. The stacking effect is a good explanation for this preference, since other lipophilic amino acids such as leucine or valine were poorly extracted. The exception was glycine, which owing to its small size seems to fit the cleft especially well. Other more hydrophilic amino acids (serine, asparagine, tyrosine) could not be extracted with this system.

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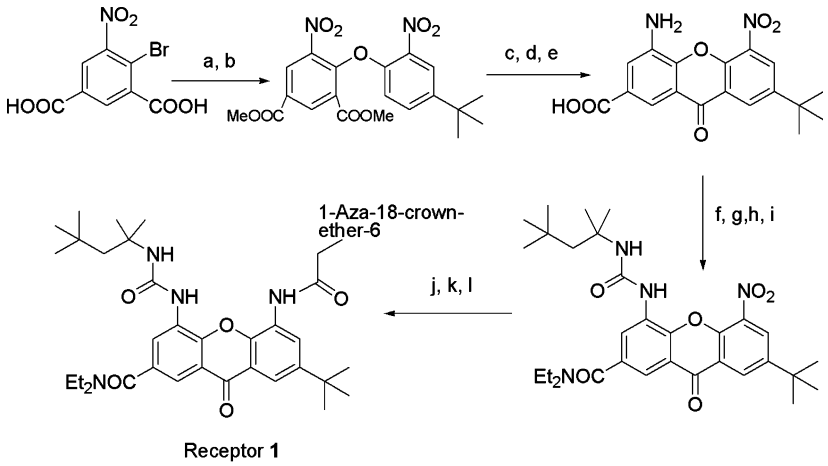

Scheme 1. Preparation of receptor **1**. *Reagents and conditions*: (a) MeOH, $SOCl_2$, 92%; (b) 4-*t*-butylnitrophenolate potassium salt, DMF, 96%; (c) Fe, MeOH/AcOH, 96%; (d) HBr, reflux, 95%; (e) $P_2O_5/MeSO_3H$, 86%; (f) $SOCl_2$; (g) NEt_2, 75%; (h) $COCl_2$; (i) *t*-octylamine, 96%; (j) $SnCl_2$, MeOH, 98%; (k) acryloyl chloride, THF, 72%; (l) 1-aza-18-crown-ether-6, THF, 80%.

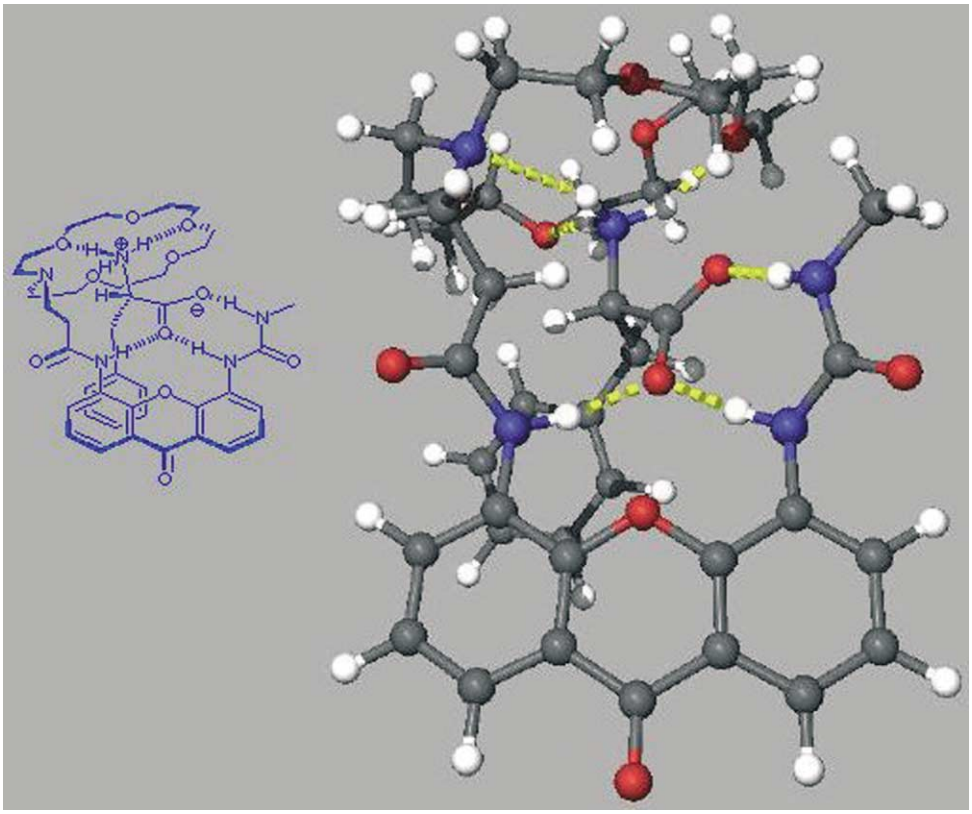

Figure 2. Modelling study of receptor **1** and L-phenylalanine. The diethyl carboxamide and the *t*-octyl group are omitted for simplicity.

Table 1. Results of the extraction of saturated water solutions of several amino acids (0.2 ml) at 20°C with receptor **1** (4 mg) in chloroform solution (2 ml)

Receptor **2**	Glycine	Alanine	Phenylalanine	Tryptophan	Phenylglycine	Valine	Leucine
Extraction	98%	25%	74%	49%	8%	4%	7%

We hope that further developments on this structure may provide highly selective amino acid extraction systems.

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