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trans-Benzoxanthene receptors for enantioselective recognition of amino acid derivatives

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Abstract—Neutral cleft-type hydrogen-bonding receptors based on a *trans*-benzoxanthene skeleton have shown good stereoselective association towards carbamate derivatives of amino acids. Among these, the best results corresponded to the commercially available benzyloxycarbamate (Cbz) while the *t*-butyloxycarbamate (Boc) protecting group afforded disappointing results. Preparative TLC impregnated in ethoxycarbonyl proline provided a rapid way to resolve the receptor racemic mixture. X-Ray analysis and Overhauser effects allow us to suggest a structure for these complexes and the reasons for the observed chiral discrimination.

Stereoselective receptors[1] for α-amino acids or peptides could have many possible applications due to the technical and biological importance of these molecules.[2]

Chromenone-benzoxazole receptors are very suitable for carboxylic acid association.[3] However, the chromenone skeleton lacks chiral centers and hence has little attraction for the design of enantioselective receptors. This problem can be solved by the use of a new base molecule, *trans*-benzoxanthene, which already includes chirality. The *trans*-benzoxanthene skeleton is easily obtained and functionalized as shown in Scheme 1.

Oxidative cyclization[5] affords a mixture of the *trans*- and *cis*-benzoxanthenes; however, only the more rigid *trans* compound crystallizes. As one of our major purposes was to prove that the hydroxyl group in C-6 could settle a second H-bond with the carbonyl oxygen of the carboxylic acid, we decided to carry on with the *trans* isomer only.

Receptor **1** does not associate amino acids as zwitterions, probably due to their lack of solubility in apolar solvents, but it readily associates carboxylic acids and amino acid derivatives in chloroform solution. Association constants were obtained by standard NMR titrations[6] in $CDCl_3$ using the racemic mixture of receptor **1** and two different guests: naphthalene-1-carboxylic acid ($K_{ass}=6\times10^3$ M^{-1}) and ethoxycarbonylglycine ($K_{ass}=5.4\times10^4$ M^{-1}). The presence of the *t*-butyl groups in the receptor provide an easy way to follow these titrations even under high dilution conditions.

These high association constants permitted the crystallization of the complex between receptor **1** and several carboxylic acids. Slow evaporation of a solution of receptor **1** and propionic acid in THF yielded crystals suitable for X-ray analysis. The crystalline structure of the complex is shown in Fig. 1.

X-Ray analysis shows that receptor **1** is capable of establishing three hydrogen bonds with carboxylic acids. The secondary alcohol in C-6 and the NH group in C-4 bind the carbonyl oxygen of the carboxylic acid, while the basic nitrogen in the benzoxazole forms a strong hydrogen bond with the hydroxyl group of propionic acid. It should be noted that receptor **1** is already a chiral receptor, as the ethoxycarbonyl located on C-5a makes both faces of the *trans*-benzoxanthene different. Receptor **1** already shows a chiral cleft; however, it associates amino acid derivatives with low enantioselectivities or in most cases with no enantioselectivity at all. To increase discrimination, we attempted to establish a further interaction with the substituents on the amino acid α-carbon in order to prevent its free rotation. Molecular models show that

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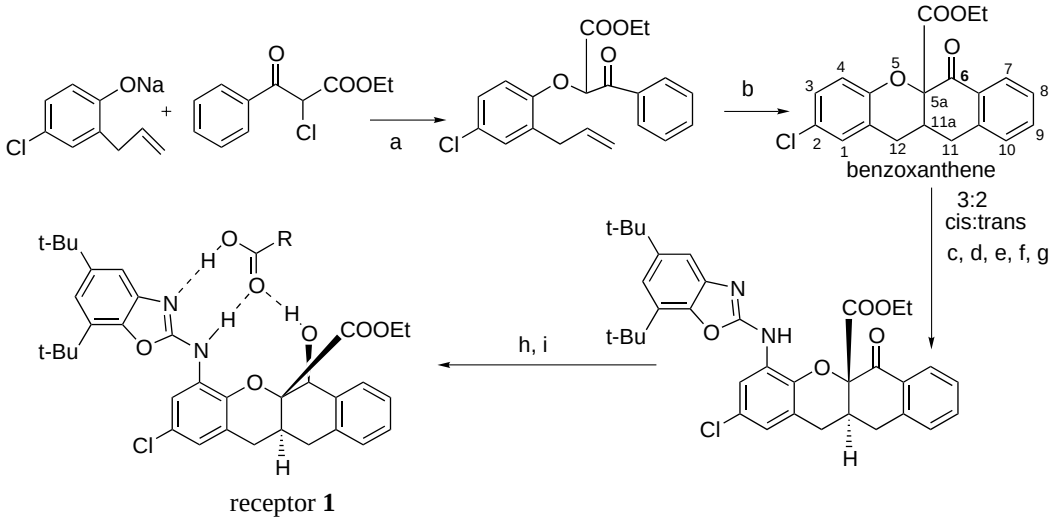


Scheme 1. Preparation of the benzoxanthene base molecule, receptor **1**[4], and its complex with a carboxylic acid. Numbering of the benzoxanthene has been included for clarity. (a) Diglyme, $T=80°C$, yield 70%; (b) $Mn(OAc)_3 \cdot 4H_2O$, $AcOH/Ac_2O$, $T=90°C$, yield 75%; (c) HNO_3/H_2SO_4, Ac_2O, $T=-10°C$, yield 83%; (d) $SnCl_2$, rt, yield 69%; (e) thiophosgene, Na_2CO_3, CH_2Cl_2/H_2O, rt, yield 90%; (f) 2-amino-4,6-di-*tert*-butylphenol, toluene, $T=50°C$, yield 80%; (g) MeI, 2,4,6-trimethylpyridine, EtOH/THF, rt, yield 85%; (h) $NaBH_4$, MeOH, rt, yield 96%; (i) carboxylic acid.

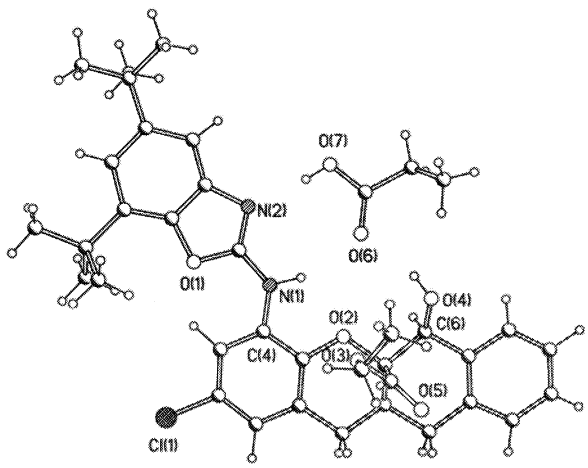


Figure 1. X-Ray structure[4] of receptor **1** complex with propionic acid.

this kind of interaction could occur in the complex between receptor **2** and amino acid ethoxycarbonyl derivatives. In these associates we expect a further H-bond to be set up from the receptor NH triflate to the carbonyl of the protecting group of the amino acid.

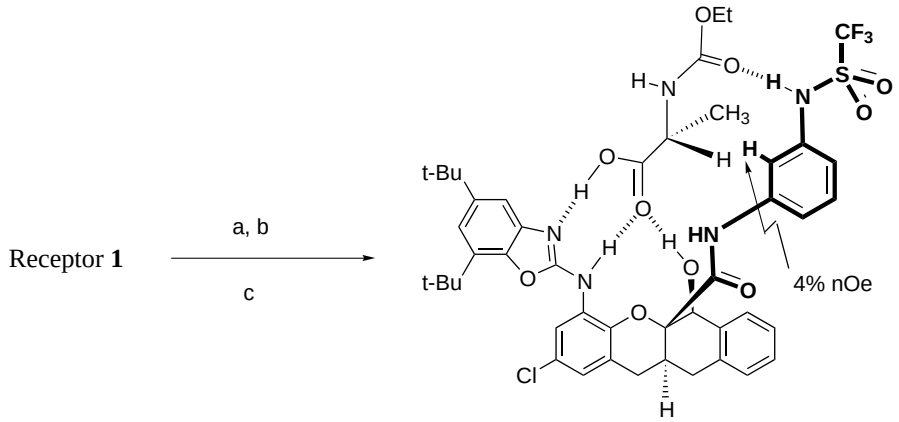
Preparation of receptor **2** from receptor **1** is straightforward (Scheme 2). Aminolysis of the ethoxycarbonyl group can be achieved with *m*-phenylenediamine lithium salt, and the new compound is triflated with trifluoromethanesulfonic anhydride in the absence of an added base since the benzoxazole group of the receptor is already suitable for this purpose.

By means of competitive experiments[7] in $CDCl_3$ it was clear that receptor **2** showed promising results, discriminating between amino acid enantiomers (Table 1).

The most interesting aspects in Table 1 are the important effects of the *N*-protecting group and the amino acid side chain. In both cases, steric hindrance can be invoked to explain why recognition is poor if these groups are bulky. *t*-Butyloxy carbonyl protecting groups probably collide with the triflate fluorine atoms, while the isopropyl group in valine cannot be placed close to the receptor in the conformation in which the fourth H-bond is set.

The best results are obtained with proline derivatives; apparently, the rigidity of the five member ring provides the best preorganization for a good fit in the strong complex.

The good results with the previous guest suggested that it might be possible to make use of its supramolecular properties to resolve the host **2** racemic mixture. Usually, these kind of strong complexes appear to be more apolar species than weak ones, as a result of their lack of suitable sites for interaction with SiO_2. In strong complexes, the hydrogen bonds are closed between the host and the guest and they cannot interact strongly with the SiO_2 of the stationary phase. Therefore these aggregates show low polarity and are easily eluted. If the complex is weak, SiO_2 competes by breaking the associate and fixing the receptor to its surface through many H-bonds. Therefore, large R_f differences are expected in chromatography for both enantiomeric receptors if an optically suitable host is present. Preparative SiO_2 TLCs impregnated in a 3% chloroform solution of L-ethoxycarbonyl-proline provided an easy way to achieve the separation of enantiomeric receptors, since upon elution with chloroform they show two spots corresponding to diastereomeric complexes of different stability. Each host is recovered from the SiO_2 as the corresponding proline complex. Washing an ethylacetate solution of the complex with aqueous sodium carbonate provides the pure receptors.[8]



receptor **2**

Scheme 2. Preparation of receptor **2** and its complex with ethoxycarbonyl alanine. (a) Benzene-1,3-diamine, BuLi, THF, $T=-30$°C, yield 74%; (b) trifluoromethanesulfonic anhydride, toluene, $T=-78$°C, yield 63%; (c) *N*-ethoxycarbonylalanine.

Table 1. Enantioselective discrimination of receptor **2**

Guest	K_{rel}[a]
Boc-L-leucine	2.7
Ethoxycarbonyl-L-leucine	7.4
Cbz-L-leucine	7.7
Ethoxycarbonyl-L-proline	14.0
Ethoxycarbonyl-L-alanine	8.5
Cbz-L-phenylalanine	4.5
Ethoxycarbonyl-L-valine	1.0

[a] K_{rel} refers to relative association constants between the guest and the two enantiomers of receptor **2**.

Once the optically pure receptors had been purified it was possible to measure the absolute association constants with conventional titration. Our first experiments suggested that the complexes were very stable in chloroform solution and that errors would be very large for the higher association constants. We therefore measured the smallest association constants and deduced the larger ones from competitive experiments. The results can be seen in Table 2.

The results in Table 2 again show the importance of steric hindrance in complex stability, both in the amino acid side chain and in the *N*-substituent. Alanine show the strongest associates.

Table 2. Association constants for receptor **2** and several amino acid derivatives measured in $CDCl_3$[a]

Guest	K_{ass} (+)receptor **2** (M^{-1})	K_{ass} (−)receptor **2** (M^{-1})
Ethoxycarbonyl-L-leucine	1.0×10^5	7.4×10^5
Ethoxycarbonyl-L-proline	1.1×10^5	1.5×10^6
Ethoxycarbonyl-L-alanine	2.3×10^5	1.9×10^6
Cbz-L-Leucine	2.4×10^5	1.8×10^6
Boc-L-Leucine	7.2×10^4	1.9×10^5

[a] These constants were calculated with an uncertainty of 20%.

ROESY experiments support the geometry shown in Scheme 2 for the strong complex between receptor **2** and ethoxycarbonylalanine. The Overhauser effect found between the amino acid α hydrogen and the *m*-phenylene diamine H-2 fixed the geometry of the complex. This proximity also explains the discrimination between the enantiomers, since exchanging the amino acid α hydrogen for the methyl group results in steric hindrance and therefore a weakening of the complex.

Acknowledgements

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4. Selected physical data for receptor **1**: FABMS: 57 (M+), 100%; 603, 50%; 605, 20%; 385, 15%; 483, 10%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, $J=2$ Hz, 1H), 7.65 (d, $J=8$ Hz, 1H), 7.41 (s, 1H), 7.29–7.21 (m, 2H), 7.14–7.11 (m, 2H), 6.70 (d, $J=2$ Hz, 1H), 5.09 (s, 1H), 4.07 (dd, $J=8$ Hz, 2H), 3.20–2.95 (m, 2H), 2.86 (d, $J=8$ Hz), 2.70–2.52 (m, 2H), 1.49 (s, 9H), 1.38 (s, 9H), 1.00 (t, $J=8$ Hz, 3H); mp 136–138°C.
   Crystal data for receptor **1**: $C_{38}H_{45}ClN_2O_7$, $M=677.21$, orthorhombic, space group *Pbca* (no. 61), $a=11.987(2)$,

$b=20.410(4)$, $c=29.438(6)$ Å, $V=7202.6(25)$ Å^3, $Z=8$, $D_c=1.249$ Mg/m^3, μ(Cu Kα)$=0.157$, $F(000)=2880$; data (3388 collected reflections and 3374 unique reflections [$I>2\sigma(I)$]) were measured on a Seifert 3003 SC rotating-anode diffractometer with Cu Kα radiation (graphite monochromator) using 2θ–ω scans at 268 K. Crystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Center as supplementary material no. CCDC 163614.

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6. ^{1}H NMR (200 MHz) titrations were carried out in $CDCl_3$ solutions at a constant 10^{-4} M host concentration to which a guest was added until saturation was reached. The changes in the chemical shifts of the host were analyzed using a Monte Carlo non-linear curve-fitting program.
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