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Chiral Receptor for N-Benzyloxycarbonyl Aminoacid Derivatives

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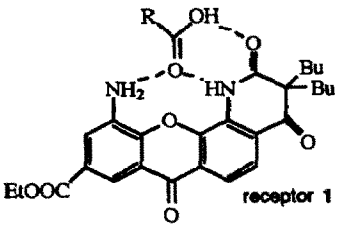
Abstract: *Chiral cleft-type receptors for N-benzyloxycarbonyl aminoacid derivatives have been prepared. Discrimination between aminoacids with non-polar side chains is modest. Better chiral recognition is obtained with serine. A receptor with an aminopyridine unit allows a high association constant with aspartic acid.*

Selective man-made receptors for aminoacids can be of great utility in the resolution of the complex mixtures obtained in protein hydrolysis, either by affinity chromatography or transport through membranes. A receptor capable of binding the aminoacid function[1], or a readily available derivative[2], is highly desirable, because it could constitute a frame for further synthetic work which may lead to high selectivity for different aminoacids. Compound **1** can be obtained in large quantities and is able to weakly associate acids in deuterochloroform by itself[3]. Dodecanoic acid presents an association constant (Ks) 264 M^{-1} and cinnamic acid a Ks= 376 M^{-1}.



receptor 1

R	Ks (M^{-1})
$C_{11}H_{23}$	264
PhCH=CH	376

Figure 1:Proposed structure for the complexes of cinnamic and dodecanoic acids with receptor **1** and their Ks ($CDCl_3$) values.

CPK models and modeling studies[4] show that if the free amine in receptor **1** is transformed into an urea function, four hydrogen bonds should be set with aminoacid benzyloxycarbonyl derivatives.

A receptor was prepared by reacting amine **1** with phenylisocyanate. This compound was very chloroform insoluble and was therefore ruled out. However, isocyanates derived from aminoesters such as phenylalanine or phenylglycine methyl esters yielded soluble ureas. These receptors **2** and **3** present asymmetrical carbon atoms and consequently can show potential chiral recognition with N-benzyloxycarbonyl(Cbz) aminoacids.

To check this possibility receptors **2** and **3** were prepared. The initial results indicate that both receptors show similar properties, so that further work was carried out only with compound **2**.

The enantiomeric receptors were prepared starting from (*D*) and (*L*)-phenylalanine, and their optical purity was checked by NMR: when racemic receptor **2** is treated with N-Cbz-(*L*)-phenylalanine, splitting of the receptor methoxyl signals takes place (0.03 ppm).

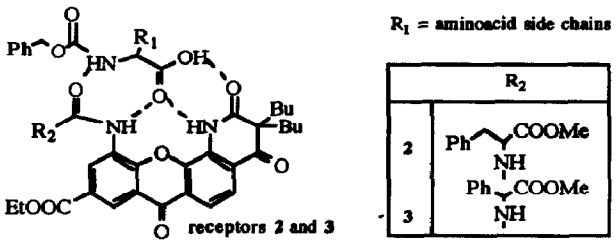


Figure 2: Proposed structure for the complexes of receptors 2 and 3 with N-benzyloxycarbonyl aminoacid derivatives.

No such splitting takes place with receptor 2 single enantiomers[5], and no contamination could be detected within the NMR sensitivity limits. Standard NMR titrations[6] were carried out in deuterochloroform with glycine, alanine and phenylalanine, all of them as their benzyloxycarbonyl derivatives. Results are shown in table 1. The highest association constant is obtained for glycine, probably due to some steric interference between the host 2 and guest (alanine and phenylalanine) side chains. Complexes of the (*L*)-2 receptor almost double the stability of the (*D*)-2 ones. This chiral recognition is high for the interaction of two asymmetrical centres which show free rotation. We do not consider these value as very reliable due to the following: the foregoing association constants were obtained making use of the methoxyl signal around 3.7 ppm. However, when an aromatic proton at 9.2 ppm is followed very different values were obtained (fig. 3). The curves, however, do not fit this second set of points very well.

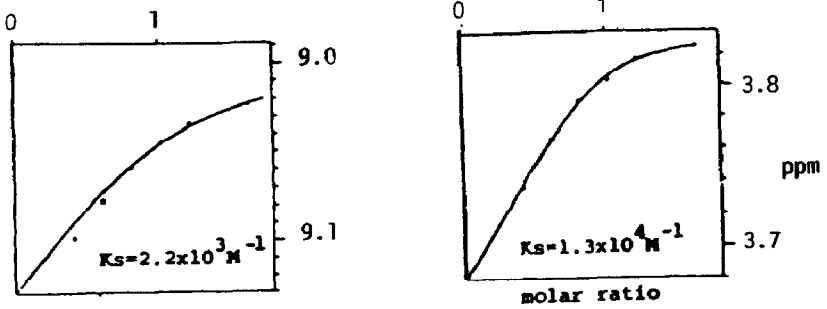


Figure 3: Plots of two different protons of receptor (*L*)-2 in the same titration with N-Cbz-(*L*)-phenylalanine

In our opinion, this problem is due to the fact that these receptors are partially dimerized in the chloroform solution in which the measurements are carried out. Further clues indicate the presence of a dimer: the chemical shift of the receptors signals depend on the concentration of the solution, the signals of the methyl groups of the butyl residues appear shielded and give rise to two different triplets at 0.42 and 0.63 ppm; this is not expected in the monomer in which these protons are distant from the asymmetrical centre. This anisotropic effect can be explained well if a dimer like 4 (fig. 4) is formed, because in it, the butyl groups are close to the asymmetrical centre of the second receptor molecule and in the shielding anisotropic cone of an aromatic ring. To measure the dimerization constant, samples of the receptor in deuterochloroform with concentrations ranging between 10^{-2} M and 10^{-4} M were prepared. The chemical shift of the methoxyl group was recorded and plotted against concentration. Computer generated curves[6] allowed us to deduce a dimerization constant of 7.5×10^3 M^{-1} as well as the chemical shifts of the methoxyl signals in the receptor 2 free form and in the dimer. Previous work, in which the influence of self association of host and guest was studied[7], showed that this effect does not strongly

change the value of the association constant. In these cases, however, the dimers are weaker than the host-guest complex.

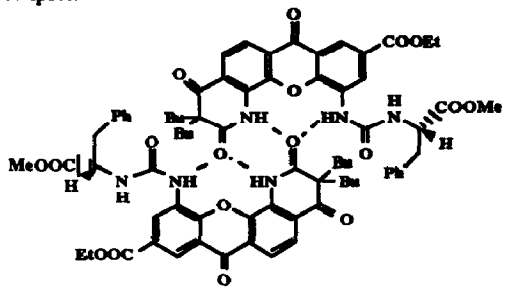


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Figure 4: Proposed structure for the dimer of (*L*)-2

The present dimerization constant is of the same order of magnitude and under these conditions a stronger interference should be expected. Once the dimerization constant is known, as well as the methoxyl chemical shift of the free receptor and its dimer, new curves including these data can be generated to fit the points obtained in the titrations and new values for the association constants are obtained (table 2). In general, both the association constants and the chiral recognition are smaller.

TABLE 1: Uncorrected Ks in $CDCl_3$

	(*L*)-2 (Ks M^{-1})	(*D*)-2 (Ks M^{-1})
N-Cbz-(*L*)-alanine	$9.1x10^3$	$5.5x10^3$
N-Cbz-(*L*)-phenylalanine	$1.3x10^4$	$6.4x10^3$
N-Cbz-glycine	$3.0x10^4$	
N-Cbz-(*L*)-serine	$2.5x10^4$	$2.0x10^3$

TABLE 2: Corrected Ks in $CDCl_3$

	(*L*)-2 (Ks M^{-1})	(*D*)-2 (Ks M^{-1})
N-Cbz-(*L*)-alanine	$8.7x10^3$	$5.8x10^3$
N-Cbz-(*L*)-phenylalanine	$5.9x10^3$	$4.4x10^3$
N-Cbz-glycine	$1.3x10^4$	
N-Cbz-(*L*)-serine	$1.5x10^4$	$5.0x10^3$

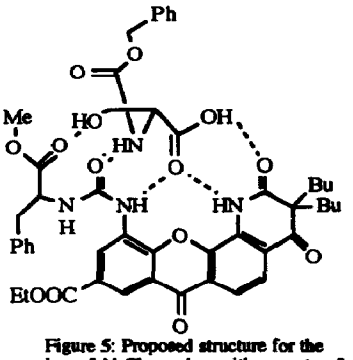
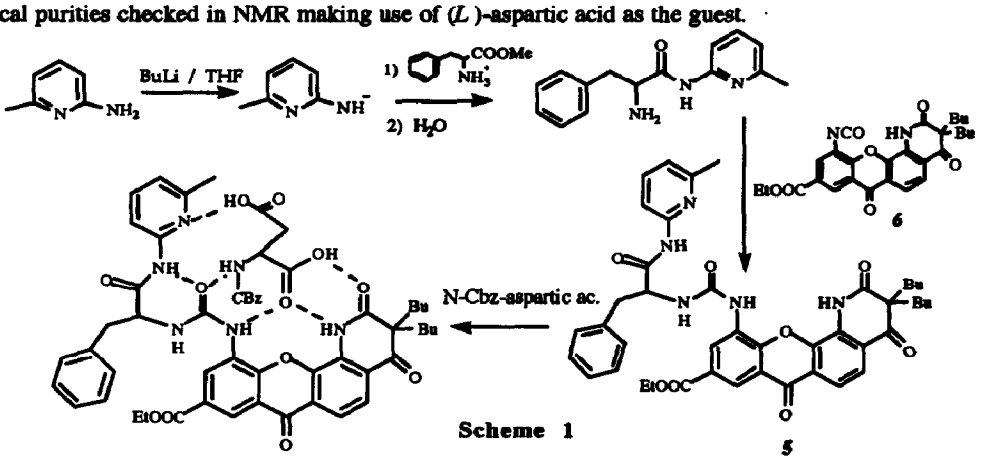


Figure 5: Proposed structure for the complex of N-Cbz-serine with receptor 2

Apparent and corrected association constants of receptors (*L*)-2, (*D*)-2 and different N-benzyloxycarbonyl aminoacids.

Molecular models show some interference between the aminoacid side chains in the complex. This accounts well for the higher association constant for N-Cbz-glycine as well as the chiral recognition. Probably, the free rotation of the asymmetrical centres prevents better discrimination. More rigid systems, however, could potentially show higher chiral recognition. Modeling studies indicate that the free hydroxyl group of a N-Cbz-serine guest could set an extra hydrogen bond with the methoxycarbonyl group of the host **2** (fig. 5). Uncorrected titrations with N-Cbz-(*L*)-serine show a high chiral recognition for the enantiomeric host (*L*)-2 and (*D*)-2 (table 2). Corrected data, due to the dimerization of the hosts, point to show a smaller association constant for the best complex, formed by receptor (*L*)-2, while the weaker (*D*)-2 complex shows an increased value, yielding only a modest chiral recognition. Chiral recognition is higher than for aminoacids with non-polar side chains, probably because only in the (*L*)-2 receptor can a weak hydrogen bond be set. Cbz aspartic and glutamic acids could also show potentially new hydrogen bonds with these receptors. The association constants, however, do not seem to be high and do not fit the titration curves well for a 1/1 model. If the second carboxylic group of these diacids do not close an extra hydrogen bond with the receptors, these free carboxylic groups will probably complex the excess of receptor during the titration, yielding larger chemical shifts than those expected. In order to improve the chances to close a hydrogen bond in the complex coming from the aspartic second carboxylic group, an aminopyridine unit was included in the receptor **5** structure. Hamilton has shown that this

fragment is a very good carboxylic group binder[6]. The preparation of receptor **5** is shown in scheme 1. A large excess of the lithiated amino picoline is needed. The free amine is then reacted with the isocyanate **6**, obtained from compound **1** and phosgene, to yield the desired receptor **5**. Both *D* and *L* compounds were prepared and their optical purities checked in NMR making use of (*L*)-aspartic acid as the guest.



Scheme 1

Titrations showed that the association constants of these receptors with N-Cbz-(*L*)-aspartic acid are higher than the preceeding ones. However, accurate values could not be obtained because during the titration a broadening of the receptors signals took place, increasing the uncertainty of the measurement. This fact prevented further work so far on these receptors. Nervertheless, a value between $6x10^4$ M^{-1} and $2x10^5$ M^{-1} does seem to be reasonable.

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4) Modeling studies were carried out with a COSMI force field of programme NEMESIS.

5) Receptor **2**: mp (methanol)175 °C ; $[\alpha]_D$ (c=1, $CHCl_3$): +5.4°(*L*) and -5.4°(*D*); ^1H NMR ($CDCl_3$) δ: 0.42 (3H, t, J=6 Hz), 0.63 (3H, t, J=6 Hz), 1.01 (8H, m), 1.43 (3H, t, J=7.2 Hz), 1.91 (4H, m), 3.05 (1H, dd, J=6.2, 13.8 Hz), 3.24 (1H, dd, J=6.2, 13.8 Hz), 3.67 (3H, s), 4.43 (2H, c, J=7.2 Hz), 4.92 (1H, m), 6.04 (1H, s broad), 7.22 (5H, m), 7.95 (1H, d, J=8.4 Hz), 8.11 (1H, d, J=8.4 Hz), 8.70 (1H, d, J=2.0 Hz), 8.98 (1H, s broad), 9.14 (1H, d, J=2.0 Hz), 10.18 (1H, s) ppm.-$C_{38}H_{43}N_3O_{10}.H_2O$ (701.75)(*L*)-**2** calc.C,64.98;H,6.12;N,5.98 found C,64.99;H,6.08;N,5.78, (*D*)-**2** found C,65.20;H,5.98;N,5.87 %.

6) Complexation was studied by 200-MHz and 500-MHz ^1H NMR in $CDCl_3$ at 293 K. The association and dimerization constants were obtained by nonlinear least-squared curve fitting of the titration data.

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