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A *trans*-tetrahydrobenzoxanthene receptor for the resolution of racemic mixtures of sulfonylamino acids

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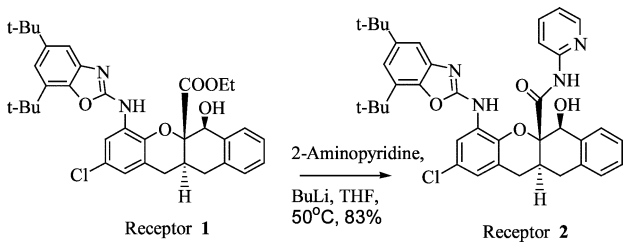
An enantioselective cleft-type receptor for sulfonylamino acids has been prepared and its use for the resolution of the amino acid racemic mixture is shown.

Enantioselective amino acid recognition is of current interest[1] and the resolution of large amounts of amino acid racemic mixtures, making use of supramolecular properties, is a very attractive possibility.[2] *trans*-Benzoxanthene receptors have been successful in the association of carboxylic acids.[3] Despite the fact that receptor **1** (Scheme 1) is a chiral compound, no enantioselective discrimination was found when acids with asymmetric α carbons were tested. Taking into account the previously reported geometry for the associates of receptor **1** and carboxylic acids, we expected that if a sulfonyl amino acid is used as the guest its conformation could be fixed due to the formation of a strong H-bond in receptor **2**, in which the carboxyl group is substituted by an aminopyridine group (Fig. 1).

The preparation of receptor **2** is straightforward from receptor **1** and the lithium salt of 2-aminopyridine (Scheme 1).†

The chiral recognition properties of receptor **2** were tested in $CDCl_3$ using competitive ^1H NMR titrations. Competitive experiments were carried out with the racemic receptors and enantiomerically pure amino acid derivatives, adding small portions of the guest to the receptor solution in $CDCl_3$.[4] The formation of the diastereomeric complexes led to a splitting of the ^1H NMR host **2** signals. A plot of the movement of the chemical shift of a single proton of one diastereomeric complex against the chemical shift of the other provides a curve characteristic for each chiral recognition. The use of a home-made curve-fitting program provided the enantioselectivities. The results are shown in Table 1 and from them the importance of the acidity of the guest NH can be seen.



Scheme 1 Synthesis of receptor **2**.

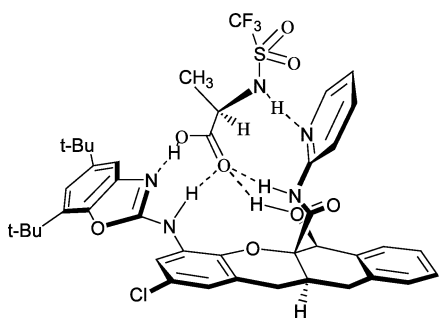


Fig. 1 Receptor **2** and the proposed complex with an amino acid triflate.

Sulfonyl amino acids provided the best recognitions, with chiral recognitions up to 20 in the case of the dansyl derivative.

Due to their high acidity, other amino acid triflates were also tested. Table 2 shows leucine to be the best substrate, while the large aromatic ring of phenylglycine probably undergoes steric hindrance, leading to low enantioselectivities.

While these results seem to be in agreement with the proposed structure for the complexes of receptor **2**, this could not be confirmed with the NMR experiments. Therefore, an X-ray diffraction study was undertaken. Slow evaporation of a solution of the racemic receptor **2** with racemic leucine triflate in chloroform–undecane yielded suitable cristals of the complex for X-ray analysis.‡ The structure of the complex is shown in Fig. 2 and it does not match our expectations or the structure of previous benzoxazole–tetrahydrobenzoxanthene associates.[3] The preference of the carboxylic acid for the pyridine nitrogen can be explained in terms of the higher basicity of this atom compared to the benzoxazole (pyridines are usually 10 000 times more basic than the oxazole with similar structure[5]). This is supported by the shorter H-bond distance of the carboxylic acid in this complex (COOH···N 2.53 Å) as compared to that previously observed, in which the oxazole acts as the H-bond acceptor (COOH···N 2.66 Å).[3] Another

Table 1 K_{ass} Ratios between the enantiomers of receptor **2** and some amino acid derivatives in $CDCl_3$ at 20 °C

Dansyl-L-leucine	20.0
Triflate-L-leucine	15.0
N-Phenyl-L-leucine	8.5
Mesylate-L-leucine	7.7
Carbamoyl-L-lactic acid	3.6
L-Mandelic acid	1.7
L-Lactic acid	1.2

Table 2 K_{ass} Ratios between the enantiomers of receptor **2** and some amino acid triflates in $CDCl_3$ at 20 °C

Triflate-L-leucine	15.0
Triflate-L-phenylalanine	13.0
Triflate-L-valine	11.0
Triflate-L-alanine	3.4
Triflate-L-phenylglycine	2.9

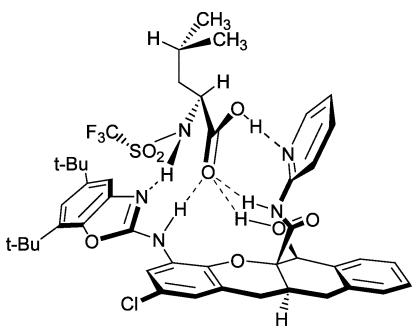


Fig. 2 Schematic representation of the complex between receptor **2** and the leucine triflate.

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interesting aspect of this associate is the formation of as many as six H-bonds, three of them with the carboxylic acid carbonyl group (Fig. 3). The new structure explains the source of the chiral discrimination very well since in the weak complex steric hindrance between the amino acid side chain and the sulfonyl group hinders the formation of the sulfonamide–benzoxazole H-bond.

The resolution of the receptor **2** racemic mixture was accomplished by complex formation with L-leucine triflate. A silica gel TLC impregnated with this guest provided very different R_f values for the receptor enantiomers. A preparative TLC plate impregnated with a solution or L-leucine triflate was charged with receptor **2** (100 mg) and eluted with methylene chloride. Two bands with R_f = 0.66 and 0.34 contained the diastereomeric complexes of receptor **2**. Washing the ethyl acetate solution of these complexes with 4% aqueous sodium carbonate afforded the pure enantiomers (*ca*. 40 mg each).

The good results with sulfonylamino acids suggested use of the enantiomerically pure receptors for the resolution of the amino acid racemic mixtures. Extraction of one of the guest enantiomers from an aqueous phase is an attractive procedure; However, the amino acid triflate is water-soluble in its carboxylate form, but this species does not fit in the cleft of receptor **2**. To overcome this, a mixture of both the amino acid and its carboxylate were used. A deuterochloroform solution of the enantiomerically pure receptor (3.10 mg, 4.76 mmol) and the racemic mixture of the guest (0.88 mg, 3.34 mmol) showed ^{1}H NMR split signals of the amino acid triflate (for leucine triflate the isobutyl methyl signals appeared at 1.09 and 0.96 ppm for the strong complex and 1.03 and 0.95 ppm for the weak complex). Adding the aqueous solution of the racemic guest ammonium salt (8.5 mg, 32.0 mmol) to this tube led to an equilibrium in which the formation of the strong complex was favoured due to the exchange of the guest enantiomers between the organic and aqueous phases. Since both guest enantiomers showed the same stability in the aqueous phase, there was a preference for the enantiomer that forms the strong complex in the organic layer. A new ^{1}H NMR spectrum revealed a high ratio (10:1) for one of the diastereomeric complexes under these conditions. Since the extraction is very enantioselective, this receptor should allow the resolution of large amounts of sulfonylamino acid racemic mixtures using a device similar to the "Cram Machine"[6] simply by transporting the amino acid to a secondary recipient in which basic pH prevents back-transport.

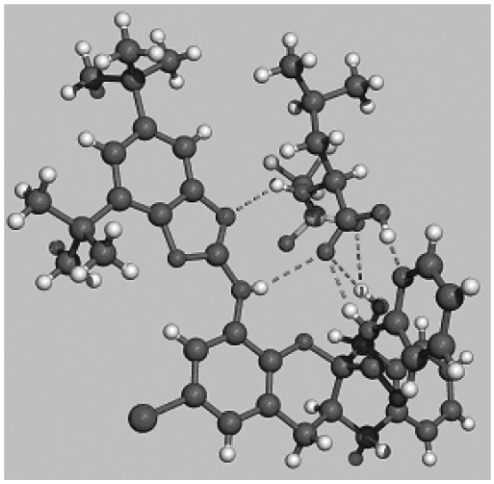

Fig. 3 X-Ray structure for the strong complex between receptor **2** and leucine triflate of configuration (5a*R*,6*R*,11a*R*·*R*).

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Notes and references

† *Selected experimental data* for receptor **2**: mp 315–317 °C for the racemic mixture and 275–277 °C for the enantiomerically pure receptors. ^{1}H NMR (400 MHz, DMSO): δ/ppm 10.12 (1H, s), 9.47 (1H, s), 8.34 (1H, d, *J* 2 Hz), 8.20 (1H, d, *J* 8 Hz), 7.87 (1H, d, *J* 8 Hz), 7.68 (1H, t, *J* 8 Hz), 7.59 (1H, d, *J* 8 Hz), 7.41 (1H, d, *J* 2 Hz), 7.25–7.15 (3H, m), 7.06 (1H, dd, *J* 5, 8 Hz) 7.10 (1H, d, *J* 2 Hz), 6.92 (1H, d, *J* 2 Hz), 6.59 (1H, d, *J* 2 Hz), 5.18 (1H, s), 3.30–3.16 (2H, m), 2.89 (1H, dd, *J* 4, 17 Hz) 2.78 (1H, dd, *J* 12, 17 Hz), 2.65–2.55 (1H, m), 1.50 (9H, s), 1.33 (9H, s). ^{13}C NMR (400 MHz, DMSO): δ/ppm 167.71 (1C), 157.42 (1C), 150.42 (1C), 147.92 (1C), 146.77 (1C), 143.13 (1C), 142.05 (1C), 139.75 (1C), 138.43 (1C), 135.74 (1C), 134.98 (1C), 131.87 (1C), 128.33 (1C), 127.44 (1C), 126.93 (1C), 125.89 (1C), 125.69 (1C), 124.70 (1C), 123.99 (1C), 122.11 (1C), 120.17 (1C), 116.23 (1C), 116.03 (1C), 113.49 (1C), 112.12 (1C), 83.97 (1C), 73.86 (1C), 34.69 (1C), 33.85 (1C), 33.85 (1C) 32.97 (1C), 31.65 (3C), 29.92 (3C), 28.11 (1C). IR ν/cm^{-1}: 3401, 3155, 2959, 1705, 1640, 1576, 1535, 1435, 1302, 1267, 1192, 1150, 1044, 1001, 860, 752. MS (FAB) *m*/*z* (rel. intensity): 57 (100), 121 (90), 651 (M^+ + 1) (72), 653 (32), 513 (28), 385 (15), 231 (12). Analysis: calc. for $C_{38}H_{39}ClN_4O_4$: C, 70.09; H, 6.04; N, 8.60; found: C, 69.97; H, 5.96; N, 8.50%. HRMS (FAB) *m*/*z*: calc. for $C_{38}H_{40}ClN_4O_4$: 651.2738, found: 651.2798 for (5a*S*,6*S*,11a*S*) receptor **2** and 651.2743 for (5a*R*,6*R*,11a*R*) receptor **2**. $[\alpha]^{20}_D$ −245.6 (*c* = 1.0%, DMSO) for (5a*S*,6*S*,11a*S*) receptor **2** and $[\alpha]^{20}_D$ +248.6 (*c* = 1.0% DMSO) for (5a*R*,6*R*,11a*R*) receptor **2**.

‡ *X-Ray structure analysis summary*: the intensity data were collected at 173(2) K on a Siemens Smart CCD diffractometer equipped with a normal focus 2.4 kW sealed tube X-ray source (Mo-Kα radiation, λ = 0.71073 Å). *Crystal data* for the complex between receptor **2** and the leucine triflate: $C_{90}H_{102}N_{10}O_{16}S_2Cl_2F_6$, *M* = 1828.84, monoclinic, space group *C*2/*c* (no. 15), *a* = 36.856(7), *b* = 21.666(4), *c* = 24.589(5) Å, β = 98.523(4)°, *V* = 19417.6(68) Å^3, *Z* = 8, D_c = 1.251 Mg m^{-3}, μ(Mo-Kα) = 0.187 mm^{-1}, *F*(000) = 7680. 51431 reflections were collected at $3.60 \leq 2\theta \leq 31.11°$ and merged to give 23863 unique reflections (R_{int} = 0.1083), of which 6587 with $I > 2\sigma(I)$ were considered to be observed. The structure was determined by direct methods using the SHELXTL™ suite of programs. Hydrogen atoms were placed in calculated positions. Full-matrix least squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors R_1 = 0.1045 and wR_2 = 0.2917. CCDC 216106. See http://www.rsc.org/suppdata/cc/b3/b312560b/ for crystallographic data in CIF or other electronic format.

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