Aminopyridine–Benzoxanthene Enantioselective Receptor for Sulfonylamino Acids

ARTICLE *in* ORGANIC LETTERS · JANUARY 2004

Impact Factor: 6.36

5 AUTHORS, INCLUDING:

Ana Isabel Oliva
ICIQ Institute of Chemical Research of Catalo…
32 PUBLICATIONS **459** CITATIONS
SEE PROFILE

Luis Simón
Universidad de Salamanca
66 PUBLICATIONS **920** CITATIONS
SEE PROFILE

Francisco Muñoz Muñiz
University of Concepción
26 PUBLICATIONS **119** CITATIONS
SEE PROFILE

Francisca Sanz
Universidad de Salamanca
81 PUBLICATIONS **766** CITATIONS
SEE PROFILE

ORGANIC LETTERS

2004
Vol. 6, No. 7
1155−1157

Aminopyridine–Benzoxanthene Enantioselective Receptor for Sulfonylamino Acids

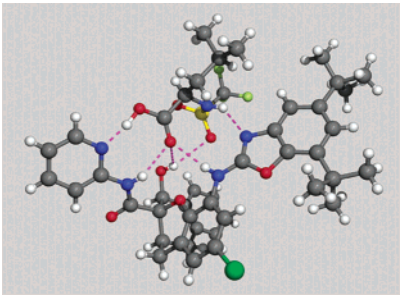
Ana I. Oliva,[†] Luis Simón,[†] Francisco M. Muñiz,[†] Francisca Sanz,[‡] and Joaquín R. Morán*,[†]

Department of Organic Chemistry, University of Salamanca, Plaza de los Caídos, 1-5, Salamanca 37008, Spain

romoran@usal.es

Received January 12, 2004

ABSTRACT



Combination of a *cis*-tetrahydrobenzoxanthene skeleton with a benzoxazole and an amidopyridine provides an enantioselective receptor for sulfonylamino acids with chiral recognitions of up to 18. The structure of the complex between receptor 1 and the leucine triflate is known by X-ray analysis. The receptor racemic mixture can be suitably resolved through crystalization in the presence of leucine triflate as guest. Receptor 1 can be used for the enantioselective extraction of sulfonylamino acids from aqueous solutions of their salts.

Enantioselective receptors for amino acids are of current interest.[1] *cis*-Tetrahydrobenzoxanthenes combined with benzoxazoles have been shown to be reasonable scaffolds for the association of carboxylic acids and their derivatives.[2] Amidopyridines have a well-known reputation in the association of carboxylic acids;[3] a combination of this fragment with the benzoxanthene cis skeleton afforded receptor **1** (Scheme 1).

From CPK models it can be observed that receptor **1** provides a cleft for amino acid derivatives (Figure 1).

Competitive experiments were carried out with the racemic receptors and enantiomerically pure amino acid derivatives,

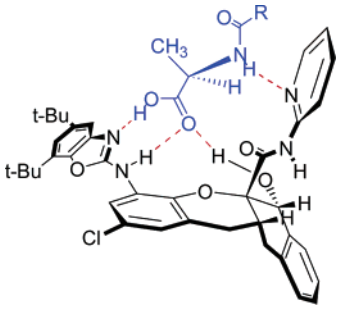


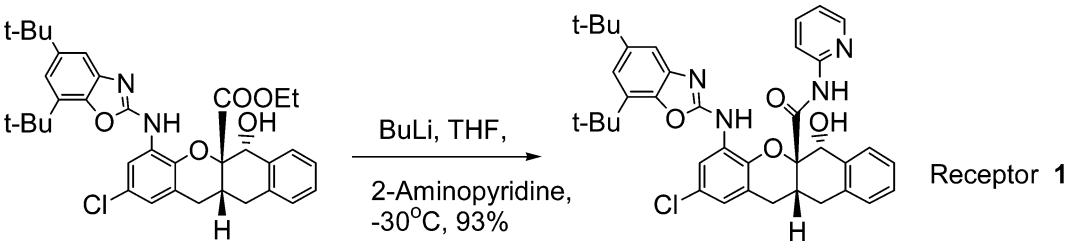
Figure 1. Proposed complex between receptor **1** and an amino acid derivative.

[†] Department of Organic Chemistry, University of Salamanca.
[‡] General X-ray Diffraction Service, University of Salamanca.

(1) (a) Kyne, G. M.; Light, M. E.; Hursthouse, M. B.; de Mendoza, J.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1258−1263. (b) Jullian, V.; Sheperd, E.; Gelbrich, T.; Hursthouse, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 3963−3966. (c) Tye, H.; Eldred, C.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 457−465. (d) Chin, J.; Lee, S. S.; Lee, K. J.; Park, S.; Kim, D. H. *Nature* **1999**, *401*, 254−257. (e) Lawless, L. J.; Blackburn, A. G.; Ayling, A. J.; Pérez-Payán, M. N.; Davis, A. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1329−1341. (f) Schmuck, C. *Chem. Eur. J.* **2000**, *6*, 709−718. (g) Hayashida, O.; Sebo, L.; Rebeck, J., Jr. *J. Org. Chem.* **2002**, *67*, 8291−8298. (h) Tsukube, H.; Fukui, H.; Shinoda, S. *Tetrahedron Lett.* **2001**, *42*, 7583−7585. (i) Kim, H. J.; Asif, R.; Chung, D. S.; Hong, J. I. *Tetrahedron Lett.* **2003**, *44*, 4335−4338.

10.1021/ol049933g CCC: $27.50
Published on Web 03/05/2004

Scheme 1. Synthesis of Receptor **1**



adding small portions of the guest to the receptor solution in $CDCl_3$.[4] Formation of the diastereomeric complexes afforded splitting of the ^1H NMR host **1** signals. Graphic representation of the chemical shifts of these protons with respect to each other, and the use of a curve-fitting program[5] provided the chiral discrimination. The results are shown in Table 1.

Table 1. Relative Constants between the Enantiomers of Receptor **1** and Several Guests in $CDCl_3$ at 20 °C

guest	K_{rel}
dansyl-L-leucine	16.0
triflate-L-leucine	13.0
carbamoyl-L-lactic acid	5.8
mesylate-L-leucine	3.4
N-phenylurea-L-leucine	2.9
L-mandelic acid	1.3
L-lactic acid	1.1

The best chiral discriminations were obtained for amino acid derivatives with acidic NH, which suggests that this group acts as an H-bond donor in the complex, as shown in Figure 1. Therefore, several amino acid triflates were tested as guests. Table 2 shows phenylalanine to be the best substrate, with a chiral recognition of up to 18. Large α groups, as in phenylglycine, provided poor results, however.

Table 2. K_{assoc} Ratios between the Enantiomers of Receptor **1** and Some Amino Acid Triflates in $CDCl_3$ at 20 °C

guest	K_{rel}
triflate-L-phenylalanine	18.0
triflate-L-leucine	13.0
triflate-L-valine	9.5
triflate-L-alanine	7.0
triflate-L-phenylglycine	2.7

Since NMR experiments were not conclusive in confirming the proposed structure of **1**, an X-ray diffraction experiment was undertaken. Crystallization of the racemic receptor **1** with racemic leucine triflate provided crystals suitable for X-ray analysis. The structure of the complex shows amidopyridine to be the H-bond acceptor of the carboxylic acid, while the benzoxazole acts as the sulfonamide mate (Figure 2). Six H-bonds stabilize this associate.

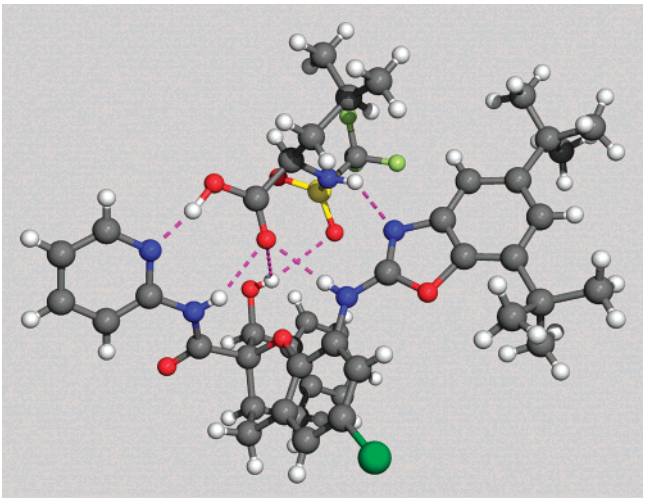


Figure 2. X-ray structure of the complex of receptor **1** and leucine triflate.

This structure is different from the one obtained with other benzoxazole−tetrahydrobenzoxanthene receptors and carboxylic acids[2] and also from the proposed complex in Figure 1 (Figure 3). Probably, the high basicity of pyridine is responsible for the geometry of the new complex, since pyridines are usually 10 000 times more basic than the oxazoles with similar structure.[6]

X-ray studies from previous complexes support this view since the oxygen carboxyl distance to the pyridine is only 2.57 Å while it increases to 2.66 Å for the benzoxazole.[7] The new structure for the complex shows the reason for the

(2) Oliva, A. I.; Simón, L.; Hernández, J. V.; Muñiz, F. M.; Lithgow, A.; Jiménez, A.; Morán, J. R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1050−1052.

(3) (a) Fitzmaurice, R. J.; Kyne, G. M.; Dourheret, D.; Kilburn, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841−864. (b) García-Tellado, F.; Goswani, S.; Chang, S. K.; Geib, S. J.; Hamilton A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394. (c) Alcázar, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1521−1523.

(4) (a) Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170. (b) Witlock, B J.; Witlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910−3915.

(5) A Monte Carlo based curve-fitting program of our own creation was used to evaluate the data.

(6) Brown, D. J.; Ghosh, P. B. *J. Chem. Soc.* **1969**, 270−276.

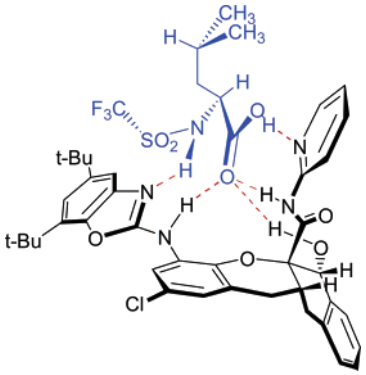


Figure 3. Representation of the strong complex of receptor **1** and leucine triflate.

chiral discrimination, since exchange of the amino acid substituent by the α-hydrogen would lead to a geometry in which the side chain would collide with the sulfonamide group.

Crystallization of 100 mg of the racemic receptor **1** with half the molar amount of carbamoyl-L-lactic acid in CH_2Cl_2/hexane afforded a precipitate (40 mg) of the optically pure (5a*S*,6*R*,11a*R*)-receptor **1**[8] while its enantiomer (5a*R*,6*S*,11a*S*) remained in the solution as the strong complex with the guest.

This result was expected since the complex is more soluble in nonpolar solvents than the free host, due to the absence of H-bond donors in this structure.

An attempt to assess the stability of the weak complex of receptor **1** and leucine triflate in $CDCl_3$ afforded $K_{assoc} = 2.5 \times 10^5\ M^{-1}$, a value outside the limits of an NMR titration;[4] therefore the stability of these complexes must be beyond $5 \times 10^4\ M^{-1}$. However, this experiment allows us to confirm the 1/1 stoichiometry using Job plots.

This racemic resolution is not general, and the tendency of many organic compounds to crystallize as the racemate prevents resolution of the racemic mixture.[9] Crystallization of racemic leucine triflate with the right amount of the optically pure receptor **1** afforded the racemic guest. The melting points explain why crystallization is a viable procedure for receptor **1** (pure 241−243 °C, racemic 218−220 °C) while it fails for this guest (pure 94−96 °C, racemic 129−131 °C). Therefore, an extraction procedure was used to show the potential use of this receptor for the resolution of amino acid racemic mixtures.

An ^1H NMR tube with 3.50 mg (5.4 mmol) of the pure (5a*S*,6*R*,11a*R*) receptor **1** and 1.02 mg (3.86 mmol) of leucine triflate in $CDCl_3$ showed two sets of equally intense signals for isobutyl groups in its spectrum, corresponding to the diastereomeric complexes of leucine. When this solution was treated with aqueous leucine triflate as its ammonium salt, and equilibrium was reached, the signals of the L-leucine showed a 10-fold lower intensity than its enantiomer. Since both leucine enantiomers show essentially the same stability in the aqueous solution, the system moves in a direction to maximize the amount of the D-enantiomer in the chloroform because the strong complex stabilizes this form. A device similar to the "Cram Machine"[10] should allow the resolution of large amounts of the sulfonylamino acid racemic mixtures.

Acknowledgment. We thank Anna Lithgow for the 400 MHz spectra and César Raposo for the mass spectra. We also thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant No. BQU-2002-00676) and JCL (SA 053/03) for their support of this work. The MEC is acknowledged for three fellowships (A.I.O., L.S., and F.M.M.).

Supporting Information Available: Experimental preparation of receptor **1** and its binding data, crystallographic data summary of the complex between receptor **1** and leucine triflate (CIF and atomic coordinates from X-ray analysis in protein data bank file format), and spectra of receptor **1** and complexes with leucine triflate and the ones recorded in the extraction experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049933G

(7) Pérez, E. M.; Oliva, A. I.; Hernández, J. V.; Simón, L.; Morán, J. R.; Sanz, F. *Tetrahedron Lett.* **2001**, *42*, 5853−5856.

(8) "Optical purity was established through TLC impregnated in optically pure carbamoyl-L-lactic acid, NMR experiment in the presence of optically pure carbamoyl-L-lactic acid that showed no signals splitting and consistent optical rotation".

(9) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 300−301.

(10) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009−1020. (b) Baragaña, B.; Blackburn, A. G.; Breccia, P.; Davis, A. D.; de Mendoza, J.; Padrón-Carrillo, J. M.; Prados, P.; Riedner, J.; de Vries, J. G. *Chem. Eur. J.* **2002**, *8*, 2931−2936. (c) Breccia, P.; Van Gool, M.; Pérez-Fernández, R.; Martín-Santamaría, S.; Gago, F.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **2003**, *125*, 8270−8284. (d) Pirkle, W. H.; Bowen, W. E. *Tetrahedron: Asymmetry* **1994**, *5*, 773−776.