JOC Notes

Chromogenic Charge Transfer Cleft-Type Tetrahydrobenzoxanthene Enantioselective Receptors for Dinitrobenzoylamino Acids

Ana I. Oliva,† Luis Simón,† Francisco M. Muñiz,† Francisca Sanz,‡ Caridad Ruiz-Valero,§ and Joaquín R. Morán*,†

Departamento de Química Orgánica, Plaza de los Caídos 1-5, Universidad de Salamanca, Salamanca, E-37008, Spain

romoran@usal.es

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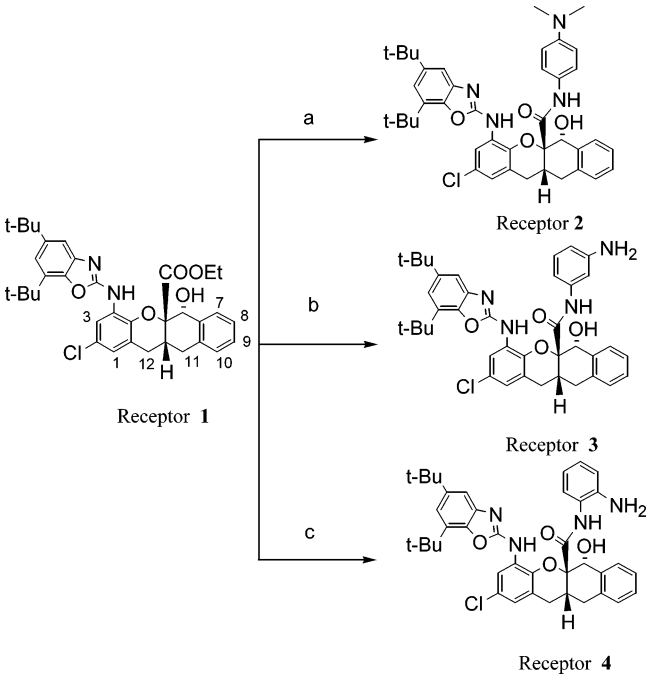
Abstract: A combination of a benzoxanthene cleft-type receptor with an electron-rich aromatic ring capable of establishing charge-tranfer interactions provides enantioselective receptors for dinitrobenzoylamino acids. Racemic mixtures of the receptor can be resolved with TLCs impregnated with the guest. The structure of the complexes has been established in an X-ray study. Enantiomeric amino acids provide complexes with different colors.

Interactions among aromatic rings are important in molecular recognition,[1] and charge-transfer receptors have already been shown to be useful in the resolution of racemic mixtures.[2] A combination of these forces with highly directional H bonds could provide good enantioselectivities. Receptor **1** (Scheme 1), based on a cis benzoxazole−tetrahydrobenzoxanthene skeleton, has shown good results in the association of carboxylic acids[3] and the structure of its complexes can be established through X-ray diffraction studies with *p*-toluic acid as guest (Figure 1). According, receptors **2** to **4** (Scheme 1) were prepared. In these molecules, the cleft-type receptor **1** is combined with an aromatic electron-rich ring acting in a charge-transfer interaction.

SCHEME 1 [a]



[a] Reagents and conditions: (a) BuLi, THF, −30 °C, *N*,*N*-dimethylbenzene-1,4-diamine, 74%; (b) BuLi, THF, −30 °C, benzene-1,3-diamine, 73%; (c) BuLi, THF, −30 °C, benzene-1,2-diamine, 80%.

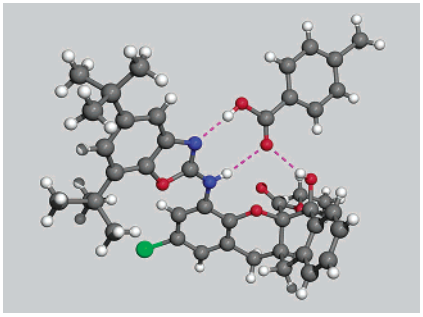


FIGURE 1. X-ray structure of the complex between receptor **1** and *p*-toluic acid.

Preparation of receptors **2**−**4** was carried out from receptor **1** and the lithium salt of the phenylendiamines (Scheme 1).

CPK models show that dinitrobenzoylamino acids fit into this cleft especially well as shown in Figure 2. *o*-, *m*-, and *p*-amino-substituted rings were tested to optimize the results.

The chiral recognition of receptors **2**−**4** was studied with the racemic receptors and enantiomerically pure dinitrobenzoylamino acids. ^{1}H NMR competitive titrations[4] were carried out in $CDCl_3$ at 20 °C, adding small amounts of the guest to the receptor solution. Plotting the receptor-split signals with respect to each other and treatment with a Monte Carlo based curve-fitting pro-

* To whom correspondence should be addressed. Fax: 0-03-49-23-294-574. Phone: 0-03-49-23-294-481.
† Departamento de Química Orgánica, Universidad de Salamanca.
‡ Present address: Servicio General de Difracción de Rayos X, Universidad de Salamanca, Plaza de los Caídos, 1-5, Salamanca, 37008, Spain.
§ Present address: Instituto de Ciencias de Materiales de Madrid, CSIC, Cantoblanco, Madrid, E-28049 Spain.

(1) (a) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210−1250. (b) Herm, M.; Molt, O.; Schrader, T. *Chem. Eur. J.* **2002**, *8*, 1485−1499. (c) Ashton, P. R.; Baldoni, V.; Balzani, V.; Credi, A.; Hoffmann, H. D. A.; Martínez-Díaz, M.-V.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *Chem. Eur. J.* **2001**, *7*, 3482−3493. (d) Goodnow, T. T.; Reddington, M. V.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1991**, *113*, 4335−4337.
(2) (a) Maier, N. M.; Schefzick, S.; Lombardo, G. M.; Feliz, M.; Rissanen, K.; Lindner, W.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 8611−8629. (b) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347−362. (c) Mikes, F.; Boshart, G.; Gil-Av, E. *J. Chem. Soc., Chem. Commun.* **1976**, 99−100.
(3) 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.

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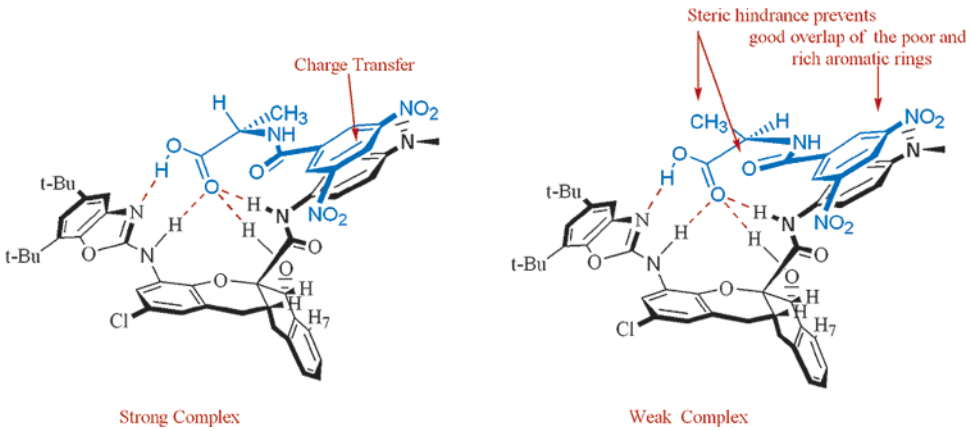

FIGURE 2. Strong and weak complexes between receptor **2** and dinitrobenzoylalanine.

TABLE 1. K_{ass} Ratio between Both Enantiomers of Receptors 2−4 and Several Dinitrobenzoylamino Acids in $CDCl_3$ at 20 °C

guest	2	3	4
dinitrobenzoyl-L-ethylhexylcysteine	54.0	54.0	7.4
dinitrobenzoyl-L-alanine	32.0	39.0	6.7
dinitrobenzoyl-L-leucine	23.0	25.0	4.9
dinitrobenzoyl-L-phenylglycine	12.0	12.0	2.8

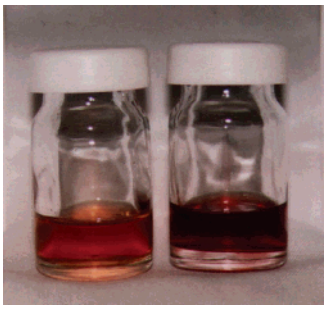

FIGURE 3. Photograph of the solutions of the two diastereomeric complexes of receptor **2** and dinitrobenzoylalanine (concentration 7.2 mM) in which the different color can be seen. The orange solution (left) corresponds to the weak complex while the strong one is red (right).

gram provided the K_{ass} ratio between both enantiomeric receptors.

The results are shown in Table 1, and from them the ortho-substituted receptor **4** was ruled out. Enantioselectivities were similar with receptors **2** and **3**. However, the para substitution was much more attractive. While both receptor **3** complexes are yellow, the strong complex in receptor **2** is red and the weak one is orange (Figure 3). Therefore, receptor **2** was chosen to resolve its racemic mixture.

Preparative TLCs (20 × 20 cm, SiO_2 16 g) impregnated in a chloroform/methanol (99/1) dinitrobenzoyl-L-alanine solution (*c* 3) were loaded with receptor **2** (100 mg) and eluted with toluene/dimethyl ether (8/2). A red band corresponding to the strong complex with R_f 0.44 was separated from the orange one with R_f 0.11. Extraction with ethyl acetate, washing this solution with 4% aqueous sodium carbonate, and crystallization in methanol afforded 45 mg of each optically pure receptor ($[\alpha]^{20}_D$ +177.6 (*c* 0.10, $CHCl_3$) for the enantiomer that forms the strong complex and $[\alpha]^{20}_D$ −181.8 (*c* 0.11, $CHCl_3$) for the one that forms the weak complex). The UV−visible spectra of the complexes (c = 3.6 mM) revealed the expected charge tranfer band, at 445 nm for the weak complex [ϵ = 130.6 L/(mol·cm) (A = 0.47)] and 477 nm for the strong one [ϵ = 197.22 L/(mol·cm) (A = 0.71)].

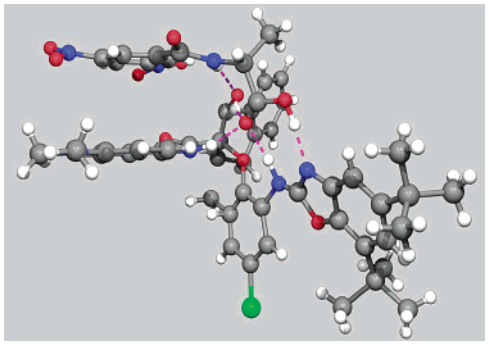

FIGURE 4. X-ray structure of the (5a*S*,6*R*,11a*R*·*S*) associate between receptor **2** and dinitrobenzoyl alanine.

The spectroscopic properties of the most stable associate between receptor **2** and dinitrobenzoyl-L-alanine are in good agreement with the proposed structure (Figure 2). The main clues pointing to this are NOE effects between the aromatic rings of the host and guest and the alanine methyl group (1.3%) and the H-7 proton in the receptor. After slow evaporation, crystallization of the racemic receptor and the racemic guest in chloroform/undecane yielded crystals suitable for X-ray analysis. Study of this strong complex also supported the previous geometry (Figure 4).

Semiempirical geometry optimizations 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.[5] These modeling studies also predicted this geometry and revealed the reasons for the enantioselectivity of these complexes. Exchange of the amino acid side chain with the α-proton should lead to the weak associate geometry. In this structure, the amino acid lateral chain collides with the dinitrobenzoyl carbonyl group, raising the energy of this structure by 4.28 kcal (Figure 2).

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

The circular dichroism spectrum of (+) receptor **2** showed a Cotton effect at 310 nm (extinction: 19.81). Comparison of this maximum with a similar tetrahydroxanthene molecule of known configuration[6] confirmed the (5a*S*,6*R*,11a*R*) receptor stereochemistry.

An estimate of the stability of these complexes was obtained for the dinitrobenzoyl derivative of *S*-ethylhexylcysteine. This unnatural amino acid was chosen owing to its solubility in chloroform. Direct measurement of the association constant in this solvent of the weak complex afforded a value of $K_{ass} = 1.1 \times 10^5\ M^{-1}$. From the competitive experiment, we evaluated the strong complex with $K_{ass} = 5.9 \times 10^6\ M^{-1}$.

The strong chiral discrimination of this receptor suggested its use in the resolution of the guest's racemic mixtures. Resolution of an amino acid racemic mixture was attempted in a biphasic chloroform/water system. The diastereomeric complexes of the (5a*S*,6*R*,11a*R*) receptor and the racemic dinitrobenzoylalanine were placed in an NMR tube. The spectrum displayed the alanine doublets of the methyl group at 1.74 and 1.66 ppm for each diastereomeric complex. Adding a water solution of 1 equiv of the racemic dinitrobenzoylalanine as its ammonium salt to the NMR tube led to an increase in the intensity of the signal at 1.74 ppm while the methyl group at 1.66 ppm showed only a small integral (ca. 10/1). A larger amount of the guest ammonium salt led to an undetectable signal at 1.66 ppm. The preference for the formation of the strong complex in the organic phase yielded the transfer of the *S*-guest molecules in the water phase to the organic solvent, while the guest with the *R* configuration led this phase to the water layer after proton exchange. The use of a "Cram machine"-like device[7] could provide the resolution of large amounts of racemic guests with a small quantity of this receptor. Moreover, the colorimetric chiral recognition achieved by using a molecular sensor capable of visual discrimination, such as receptor **2**, has attracted considerable attention because it is a convenient method for monitoring the chirality of the molecules.[8]

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Supporting Information Available: Experimental preparation of receptors **2**−**4**; UV−visible spectra of the complexes between receptor **2** and dinitrobenzoylalanine; binding data; ^{1}H and ^{13}C NMR spectra of receptor **2** and its complexes with dinitrobenzoylalanine; extraction experiment; atomic coordinates from X-ray analysis of complexes of receptor **1** and **2** (protein data bank file format), and X-ray analysis summary of both complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision 5.4; Gaussian, Inc.: Pittsburgh, PA, 1998.

(6) Oliva, A. I.; Simón, L.; Muñiz, F. M.; Sanz, F.; Morán, J. R. *Org. Lett.* **2004**, *6*, 1155−1157.

(7) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009−1020. (b) 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. (c) 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. (d) Pirkle, W. H.; Bowen, W. E. *Tetrahedron*: *Asymmetry* **1994**, *5*, 773−776.

(8) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522−524.