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A Highly Enantioselective Receptor for Carbamoyl Lactic Acid

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Dedicated to Professor Pilar Prados on the occasion of her retirement

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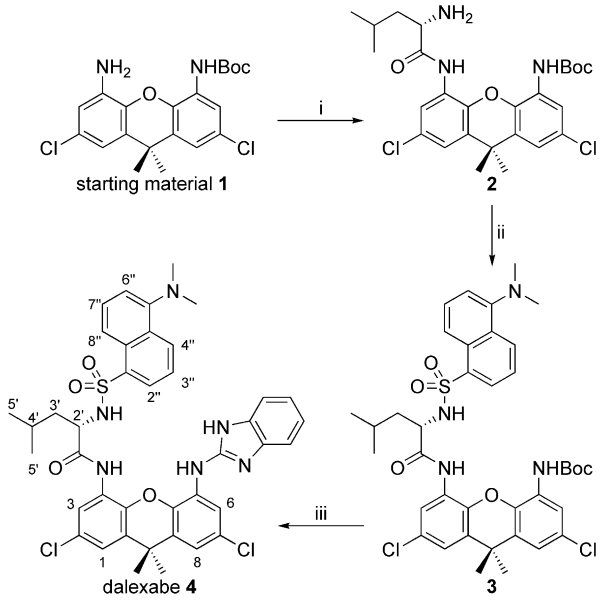
A new receptor based on a 9,9-dimethylxanthene framework was synthesized. Owing to its suitable oxyanion hole structure, this receptor is able to associate carboxylic acids and anions. The introduction of a chiral center provides enantioselective properties to this receptor as a result of its different interactions with both enantiomers of the substrate. The combination of this skeleton with a fluorescent unit such as dansyl allows the detection of small amounts of carboxylic acids by making use of fluorescent techniques.

Introduction

The enzyme oxyanion hole[1–10] is a suitable geometry for the association of carbonyl and carboxyl groups, as the enzyme establishes in this region two or three linear H-bonds with the carbonyl oxygen atom in the substrate.[11–13] 4,5-Diamine-9,9-dimethylxanthenes have shown to be suitable mimics for this geometry,[14,15] and therefore, their combination with benzo[*d*]imidazoles may provide useful receptors for carboxylic acids.[16] These two fragments (oxyanion hole mimic and benzo[*d*]imidazole) are combined in receptor **4** jointly with a dansylamino acid. The chirality of this third component in the receptor framework may induce chiral recognition, as different association with opposite enantiomers could be expected from the asymmetry included in the receptor.

Results and Discussion

The synthesis of receptor **4** is depicted in Scheme 1, starting from a previously described material, **1**.[14] Receptor **4** was named dalexabe because this compound is made up of a *da*nsyl group, a *le*ucine unit, a *xa*nthene skeleton, and a *be*nzo[*d*]imidazole moiety.



Scheme 1. Synthesis of receptor dalexabe (**4**).

The ^{1}H NMR spectrum in $CDCl_3$ of receptor **4** shows an unusual chemical shift values for the leucine methyl signals (–0.02 and 0.55 ppm), which are very different from the expected values around 1.0 ppm (for NMR spectra, see Supporting Information). To understand this surprising re-

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sult several experiments were carried out. First, dilution experiments in $CDCl_3$ showed a small dependence of the chemical shifts of the signals on the concentration. Graphical representation of the chemical shifts from the dilution experiments afforded a small dimerization constant (K_d = 2.7 M^{-1}). Secondly, NMR diffusion experiments (DOSY)[17,18] in the presence of a molecule with similar size, daxacyan (which is well-known to not form a dimer),[15] confirmed that in diluted solutions receptor **4** stands as a monomer, as the diffusion coefficients differed by less than 10%.

The chemical shift of a NH singlet signal at 9.60 ppm is almost not modified by the dilution. This might imply that this NH is involved in the formation of a strong intramolecular H-bond. This proton can be unambiguously assigned by H–C long-range correlation experiments, in which it shows correlations with C-3, C-4, and C-1 (see spectra in the Supporting Information). Regrettably, the signals of the other NHs cannot be detected in the NMR spectrum; probably, the combination of the high acidity of the sulfonamide moiety with the basicity of the aminobenzimidazole unit leads to fast hydrogen exchange, broadening the NMR signals.

Modeling, combining conformational searches and semiempirical methods (see details in the Supporting Information), show a preferred conformation that is in full agreement with the observed physical properties. In this conformation, H-bonds are established between sulfonamide oxygen atoms and receptor NH groups. These interactions might explain the absence of dimers and strong intermolecular aggregates, as formation of these aggregates would require breaking the intramolecular H-bonds. The most stable conformation that shows the three H-bonds with the sulfonamide oxygen atom is shown in Figure 1.

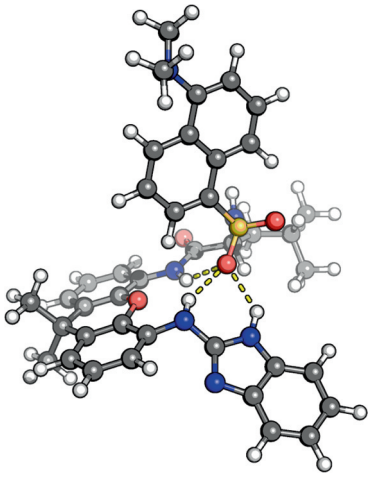

Figure 1. Structure of the most stable conformation of dalexabe (**4**) obtained by modeling.

The shielded position of the methyl groups in the ^{1}H NMR spectrum can be now explained as a result of the anisotropic effect of the benzimidazole ring. Whereas the pro *R* methyl group (–0.02 ppm) stands in the shielding cone of the benzimidazole group directly above the aromatic surface, this effect is less pronounced for the pro *S* methyl group (0.55 ppm), as the protons move away from the ring.

To explore the ability of dalexabe to bind anions we chose tetraethylammonium chloride as a guest. NMR titration showed the formation of a complex (K_a = 5.2×10^3 M^{-1}) with a 1:1 stoichiometry determined by Job plot analysis. Although the chemical shifts of the leucine methyl signals (0.62 and 0.35 ppm) are different from those in the unbound receptor, they are still far apart from the expected shifts at 1 ppm for the free leucine. Nevertheless, the NH singlet signal at 9.60 ppm in the free dalexabe (**4**) is shifted downfield to 9.99 ppm upon complexation with chloride, which points out that this NH must be involved in the formation of a different hydrogen bond than in the free receptor.

When ^{1}H NMR titrations were performed with carboxylic acids as guests, the unusual chemical shifts for the leucine methyl protons were kept for most of them (Table 1). The association constants of these complexes are displayed in Table 2.

Table 1. Chemical shifts [ppm] of the leucine methyl signals in free receptor **4** and in its complexes, in deuteriochloroform at 298 K.

	Pro *S*	Pro *R*
dalexabe (**4**)	0.55	–0.02
dalexabe (**4**)–tetraethylammonium chloride	0.62	0.35
dalexabe (**4**)–acetic acid	0.47	0.01
dalexabe (**4**)–decanoic acid	0.50	0.14
dalexabe (**4**)–toluic acid	0.17	–0.13
dalexabe (**4**)–3,5-dinitrobenzoic acid	0.08	–0.12
dalexabe (**4**)–chloroacetic acid	0.80	0.62
dalexabe (**4**)–dichloroacetic acid	0.96	0.88

Table 2. K_a values of dalexabe (**4**) with carboxylic acids in deuteriochloroform at 298 K.

Entry	Guest	K_a [M^{-1}]
1	tetraethylammonium chloride	5.2×10^{3}[a]
2	acetic acid	1.5×10^{2}[a]
3	decanoic acid	2.1×10^{2}[a]
4	toluic acid	9.4×10^{2}[a]
5	3,5-dinitrobenzoic acid	2.4×10^{4}[b]
6	chloroacetic acid	2.1×10^{4}[c]
7	dichloroacetic acid	1.4×10^{5}[c]

[a] K_a measured by direct ^{1}H NMR titrations. [b] K_a calculated by fluorescence absolute titration. [c] K_a measured by competitive NMR titrations.[19,16]

Carboxylic acids such as acetic acid, decanoic acid, and toluic acid showed low values of association constants (in the range of 10^2 to 10^3 M^{-1}). Additionally, during the NMR titrations, the NH signal at 9.60 ppm does not shift at all; it seems that these carboxylic acids are not able to break the intramolecular H-bonds in the free receptor.

The behavior of more acidic guests such as 3,5-dinitrobenzoic acid, chloroacetic acid, or dichloroacetic acid proved to be more satisfactory, with association constants varying from 2.1×10^4 to 1.4×10^5 M^{-1} (Table 2, Entries 5–7), as expected for binding in a cleft where up to three H-

bonds could be set. Moreover, when the guest had very acidic protons, as was the case of dichloroacetic acid (pK_a = 1.29), the ^1H NMR chemical shifts of the leucine methyl groups were close to 1.0 ppm, which is their expected value.

To study the possible proton transfer between these acidic guests and the basic centers of the receptor, UV experiments were carried out. The UV spectrum of the free dalexabe receptor (10^{-5} M in $CHCl_3$) did not change upon addition of acetic, monochloroacetic, dichloroacetic, or trifluoroacetic acids (concentrations varying from 6×10^{-4} to 7×10^{-3} M). Nevertheless, when the concentration of TFA reached 0.2 M (2×10^4 times the concentration of the receptor) a clear proton transfer was observed.

The presence of nitro groups in the guests induces strong quenching of the receptor fluorescence; for example 3,5-dinitrobenzoic acid strongly reduces the light emission of the dansyl group (at 516 nm). Probably, this is a consequence of a photoinduced electron transfer (PET) effect in which the guest is able to oxidize the excited receptor, but in any case, it allows the easy determination of the association constant by using a fluorimeter (Figure 2).

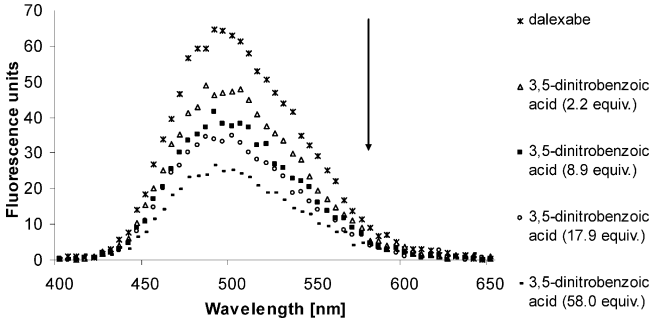

Figure 2. Fluorescence titration of dalexabe (**4**) (500 nm, 7×10^{-5} M) upon the addition of 3,5-dinitrobenzoic acid (2.2–58 equiv.) in chloroform at 293 K.

As a result of the presence of L-leucine, dalexabe (**4**) is a chiral receptor, thereby the following experiments were aimed to explore the ability of **4** to participate in chiral recognition. Because dalexabe had proved to be suitable for the association of carboxylic acids and it is well-known that at least three-point simultaneous interactions are mandatory for enantiomeric discrimination,[20] this receptor could be appropriate for recognition of α-hydroxy acids, such as mandelic or lactic acid,[21] and their O-derivatives.[22] In principle, more than three H-bonds could be set between receptor **4** and the guests.

As anticipated, those guests that could only establish H-bonds between the carboxylic acid moiety and the dalexabe receptor (**4**) showed no chiral recognition. However, when the guest presented a carbamoyl group in the α position to the carboxylic acid (like carbamoyl derivatives of hydroxy acids), good chiral recognition was observed. In these cases, the complex of one of the enantiomers is favored due to the formation of additional H-bonds leading to chiral discrimination. For example, competitive titrations of *S*-dalexabe (**4**) with the two enantiomers of carbamoyl lactic acid revealed that the (*S*,*S*) complex had an association constant of 1.3×10^5 M^{-1}, which is 20 times higher than the (*S*,*R*) complex, $K_a = 6.5 \times 10^3$ M^{-1} (see the Supporting Information).

These results were in agreement with the complex proposed with the CPK models, where the most stable conformation of carbamoyl hydroxy acid allowed new H-bonds to be set and with modeling studies performed by using the ONIOM[23] method (B3LYP[24]/6-31G*[25] level of theory in the high-level layer and Molecular Mechanics UFF[26] in the low level layer; Figure 3).

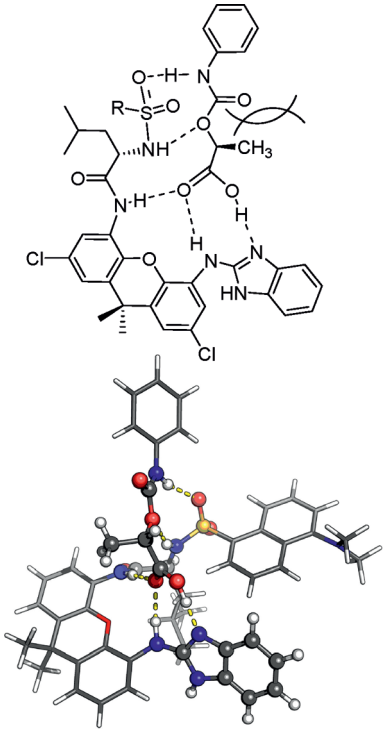

Figure 3. Geometry of the (*S*,*S*) complex between receptor and carbamoyl lactic acid. Atoms of the high-level layer in the ONIOM calculation are represented by a "ball-and-stick" model, and those included in the low-level layer by a wireframe model.

In this conformation, the (*S*,*S*) complex is stabilized by several H-bonds; three of them are established between the carboxylic group and the receptor. Only in the case of *S*-carbamoyl lactic acid can two extra hydrogen bonds be formed, leading to chiral discrimination according to the rule of the three-point interaction. One of these additional hydrogen bonds is set between the carbamoyl NH and one of the sulfonamide oxygen atoms, and the other can be established by interaction of the sulfonamide NH with the carbamoyl oxygen atom. The formation of these new binding sites demands the *S* configuration of the guest, as steric hindrance between the lactic acid methyl group and its carbamate carbonyl group in the *R* enantiomer affords a geometry that prevents the formation of the two extra H-bonds. Although the association constant for this complex is high (1.3×10^5 M^{-1}), the methyl leucine protons (0.38 and 0.05 ppm) are still shielded.

Conclusions

In summary, dalexabe has proved to be a fine receptor for carboxylic acids of high acidity. Additionally, it is able to discriminate between enantiomers of derivatized lactic acid and with certain guests, as its fluorescence is quenched. These two features could be used to develop fluorescent sensors or be used for racemic resolutions.

Experimental Section

General Methods: IR spectra were recorded with a Nicolet IR100 or a Bomem MB-100FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at room temperature with Bruker model WP-200-SY, Varian model Mercury VS 2000, or Bruker Advance DRX spectrometers in deuterated chloroform (unless otherwise stated). The solvent signal was used as an internal standard. Mass spectra were recorded with an Applied Biosystems QSTAR XL. Fluorescence spectra were collected at 20 °C by using a Shimadzu RF-5301PC series spectrophotometer. Job plots were used to determine the stoichiometry of the complexes; in this method, the total molar concentration of receptor and guest was held constant, but their mol fractions were varied.[27]

(*S*)-*tert*-Butyl 5-(2-Amino-4-methylpentanamido)-2,7-dichloro-9,9-dimethyl-9*H*-xanthen-4-ylcarbamate (2): Compound **1**[14] (3.1 g, 7.5 mmol) was dissolved in THF (30.0 mL) under an argon atmosphere and (*S*)-leucine chloride hydrochloride[28] (3.0 g, 16.2 mmol) was added with stirring. The progress of the reaction was monitored by TLC (CH_2Cl_2). Upon completion (about 20 min), water (20.0 mL) was added to hydrolyze the excess amount of acid chloride, and the mixture was stirred for an additional 10 min. The organic solvent was then removed under reduced pressure, and the residue was extracted with ethyl acetate and sodium carbonate solution (4 wt.-%, 100 mL). The combined organic layers were dried with sodium sulfate, and the solvent was evaporated to dryness. The crude product was purified by crystallization from hexane/diethyl ether to give **2** (2.4 g, 61%). $[\alpha]_D^{20}$ = –3.0 (*c* = 3.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 2 Hz, 1 H, 3-H), 8.15 (br. s, 1 H, 6-H), 7.38 (s, 1 H, NH), 7.09 (d, *J* = 2 Hz, 1 H, 1-H), 7.04 (d, *J* = 2 Hz, 1 H, 8-H), 3.60 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H, 2′-2 H), 1.95–1.75 (m, 2 H, 3′-H), 1.61 (s, 3 H, CH_3-C-CH_3), 1.58 (s, 3 H, CH_3-C-CH_3), 1.56 [s, 9 H, C(CH_3)$_3$], 1.54–1.50 (m, 1 H, CH_3-C*H*-CH_3), 1.05 (d, *J* = 4 Hz, 3 H, CH_3-CH-CH_3), 1.01 (d, *J* = 4 Hz, 3 H, CH_3-CH-CH_3) ppm. IR: $\tilde{\nu}$ = 3390, 3208, 1710, 1690, 1600, 1540, 1411, 1216, 1170 cm^{-1}. MS: *m*/*z* = 522.190 $[M + H]^+$.

Sulfonamide 3: Compound **2** (1.7 g, 3.3 mmol) and dansyl chloride (1.4 g, 5.2 mmol) were dissolved in pyridine (1.0 mL) and stirred at room temperature for 3 h. The reaction mixture was then added over 2 N HCl (50.0 mL) and extracted with ethyl acetate (50.0 mL). The combined organic layers were washed with sodium carbonate solution (4 wt.-%, 50.0 mL) and dried with sodium sulfate, and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel (dichloromethane), yielding compound **3** (1.9 g, 77%). M.p. 120–124 °C. $[\alpha]_D^{20}$ = –52.6 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 6 Hz, 2 H, 4′′-H, 2′′-H), 8.31 (d, *J* = 6 Hz, 1 H, 8′′-H), 8.05 (d, *J* = 2 Hz, 1 H, 3-H), 7.58 (br. s, 1 H, 6-H), 7.54 (t, *J* = 6 Hz, 1 H, 7′′-H), 7.50 (t, *J* = 6 Hz, 1 H, 3′′-H), 7.18 (d, *J* = 2 Hz, 1 H, 8-H), 7.16 (d, *J* = 6 Hz, 1 H, 6′′-H), 7.08 (d, *J* = 2 Hz, 1 H, 1-H), 3.60 (br. s, 1 H, 2′-H), 2.82 (s, 6 H, CH_3-N-CH_3), 1.60 (s, 3 H, CH_3-C-CH_3), 1.56 (s, 3 H, CH_3-C-CH_3), 1.53 [s, 9 H, C(CH_3)$_3$], 1.42–1.25 (m, 3 H, 3′-H, CH_3-C*H*-CH_3), 0.63 (d, *J* = 6 Hz, 3 H, CH_3-CH-CH_3), 0.21 (d, *J* = 6 Hz, 3 H, CH_3-CH-CH_3) ppm. IR: $\tilde{\nu}$ = 3344, 1710, 1696, 1631, 1530, 1200, 1150, 1050, 872, 800 cm^{-1}. MS: *m*/*z* = 777.223 $[M + Na]^+$.

Dalexabe (4): 2-Chloro-1*H*-benzo[*d*]imidazole (650 mg, 4.3 mmol) and compound **3** (1.7 g, 2.2 mmol) were suspended in sulfolane (2.5 g). Oxygen was evacuated, and the reaction mixture was heated at 130 °C for 2 h. The progress of the reaction was monitored by TLC (CH_2Cl_2/ethyl acetate, 6:1). Then the solution was cooled down to room temperature and methanol (10.0 mL) was added. This mixture was slowly poured into a solution of NaOH (1.0 g, 25 mmol) in water (75.0 mL) with vigorous stirring. The resulting precipitate was filtered off and purified by silica gel chromatography (dichloromethane/ethyl acetate, 6:1) to afford compound **4** (1.2 g, 73%). M.p. 220–224 °C. $[\alpha]_D^{20}$ = –165.0 (*c* = 2.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.60 (s, 1 H, NH), 8.88 (d, *J* = 6 Hz, 1 H, 8′′-H), 8.60 (d, *J* = 6 Hz, 1 H, 4′′-H), 8.35 (d, *J* = 6 Hz, 1 H, 2′′-H), 8.23 (d, *J* = 2 Hz, 1 H, 3-H), 7.72 (d, *J* = 2 Hz, 1 H, 6-H), 7.57 (t, *J* = 6 Hz, 1 H, 7′′-H), 7.54 (t, *J* = 6 Hz, 1 H, 3′′-H), 7.34 (d, *J* = 2 Hz, 1 H, 8-H), 7.25 (d, *J* = 6 Hz, 1 H, 6′′-H), 7.23 (br. s, 2 H, 4′′′-H, 7′′′-H), 7.07 (d, *J* = 2 Hz, 1 H, 1-H), 7.06 (br. s, 2 H, 5′′-H, 6′′-H), 3.78 (dd, J_1 = 10 Hz, J_2 = 4 Hz, 1 H, 2′-H), 2.92 (s, 6 H, CH_3-N-CH_3), 1.63 (s, 6 H, CH_3-C-CH_3), 1.46 (m, 1 H, 3′-H), 1.28 (m, 1 H, 3′-H), 1.06 (m, 1 H, CH_3-C*H*-CH_3), 0.55 (d, *J* = 6 Hz, 3 H, CH_3-CH-CH_3), –0.02 (d, *J* = 6 Hz, 3 H, CH_3-CH-CH_3) ppm. IR: $\tilde{\nu}$ = 3377, 3305, 1657, 1625, 1566, 1145, 729, 619 cm^{-1}. MS: *m*/*z* = 771.230 $[M + H]^+$, 793.213 $[M + Na]^+$.

Supporting Information (see footnote on the first page of this article): Dalexabe (**4**) spectra (^{1}H NMR, ^{13}C NMR, HMQC, HMBC, COSY, ROESY, IR and MS); absolute association titrations of **4** with tetraethylammonium chloride, acetic acid, decanoic acid; Job plot for the complex between **4** and tetraethylammonium chloride; fluorescence absolute titration of **4** and 3,5-dinitrobenzoic acid; competitive titration of both enantiomers of carbamoyl lactic acid and *S*-**4**; ^{1}H NMR spectrum of the complex of *S*-**4** and *S*-carbamoyl lactic acid; Job plot for the same complex; UV spectra of free **4** and **4** in the presence of several carboxylic acids; modeling of **4**.

Acknowledgments

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