Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1997–2001
Tetrahedron Letters

# Discrimination between ω-amino acids with chromogenic acyclic tripodal receptors functionalized with stilbazolium dyes

Beatríz García-Acosta, Ramón Martínez-Máñez *, José V. Ros-Lis, Félix Sancenón *, Juan Soto

*Instituto de Química Molecular Aplicada, Departamento de Química, Universidad Politécnica de Valencia, Camino de Vera s/n, 46071, Valencia, Spain*

Received 30 November 2007; revised 15 January 2008; accepted 16 January 2008
Available online 20 January 2008

**Abstract**

A tripodal receptor functionalized with a stilbazolium dye derivative has been designed, synthesized and has been used for the colorimetric discrimination between certain ω-amino acids in mixed DMSO–water 90:10 v/v solutions.


*Keywords:* Chromogenic sensors; ω-Aminoacids; Tripodal receptor; Merocyanine

The field of chromogenic synthetic receptors for molecular sensing has been growing in interest during the past years through the design and synthesis of new colorimetric reporters for a number of anionic, cationic and neutral target guests.[1] Most of these abiotic receptors are based on one of the following protocols, namely (i) the binding site-signalling subunit approach, (ii) the use of displacement assays or (iii) the development of chemodosimeters.[2] Additionally, as an alternative, we and others have focused our attention into organic–inorganic hybrid materials[3] via grafting chromogenic receptors into certain nanoscopic inorganic solids[4,5] or the use of gate-like ensembles.[6] These achievements based on solid state supports together with the use of classical protocols stress the concept that supramoleclar chemistry is a very powerful tool for the design of new chromogenic receptors. Among different modes to coordinate anions the use of hydrogen bonds is of great importance. In this context, the search of new hydrogen bonding patterns is of interest. In general, most of the receptors designed for hydrogen bond interactions contain ureas, thioureas, imidazolium and guanidinium groups.[7] However, the use of simple phenol groups as anion binding centres has been less studied.[8]

In many cases, the complementarity between host and guest, the guest size and its shape are chief issues to prepare the host. These concepts have been developed in many cases via the design of receptors showing multiple coordination sites in a preorganized fashion. For instance, some remarkable examples involve the development of anion receptors based on 1,3,5-2,4,6-functionalized, benzene scaffoldings with 1,3,5-positions directed to one face of the ring to prepare trifurcate anion receptors containing three arms with coordinating groups in cooperative fashion.[9]

Additionally, in most cases, these receptors have been used for the chromo-fluorogenic recognition of inorganic anions but in contrast, studies directed towards the development of signalling reporters for the differential chromogenic recognition of certain components inside a family of organic molecules has been barely studied. Following our interest in the development of anion chemosensors, we report herein the synthesis of an acyclic tripodal receptor based on 1,3,5-trisubstituted-2,4,6-trimethylbenzene scaffoldings functionalized with the protonated form of stilbazolium betaine type dyes. This class of dyes have been employed as sentitizers in colour photography,[10] in non-linear optics[11] and in electrochromic applications.[12]

* Corresponding authors. Tel.: +34 963877343; fax: +34 963879349.
*E-mail addresses:* rmaez@qim.upv.es (R. Martínez-Máñez), fsanceno@upvnet.upv.es (F. Sancenón).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.076

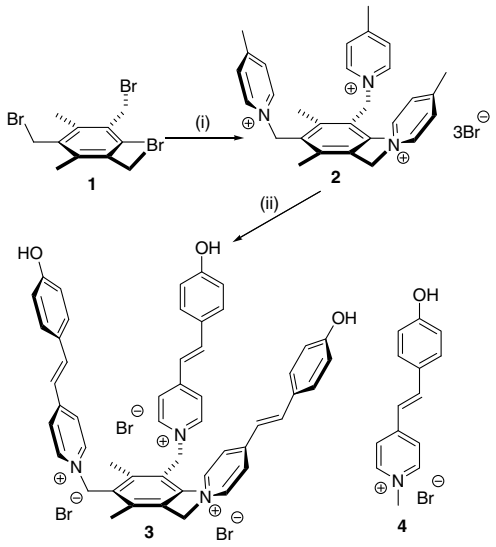
However, they have scarcely been used for the development of chromogenic chemosensors for target species.[13] As guest, we selected a family of ω-amino acids.

The synthesis of 1,3,5-tris-bromomethyl-2,4,6-trimethylbenzene (**1**) has been published elsewere.[14] Reaction of **1** with 4-methylpyridine in refluxing ethanol afforded product **2** in high yield. The $^1$H NMR of **2** showed three singlets centred at 2.18 (9H), 2.50 (9H) and 5.88 (6H) ppm that were assigned to methyl moieties attached to the benzene ring, the pyridine ring and to methylene moieties connecting the benzene ring and the quaternary nitrogens, respectively. The presence of these singlets clearly indicates a highly symmetric structure. Subsequent reaction of **2** with 4-hydroxybenzaldehyde and catalytic amounts of piperidine in refluxing ethanol afforded receptor **3** as an orange-red solid (Scheme 1). Again the presence of two singlets centred at 2.21 (9H) and 5.95 (6H) indicates that receptor **3** shows a high symmetric structure where the three merocyanine arms are equivalent within the NMR time scale. This fact was also reflected in the aromatic and olefinic protons. The latter appeared as two doublets centred at 7.25 and 7.92 ppm with a very large coupling constant ($J_{trans} = 15$ Hz) indicating that receptor **3** adopts an all-trans conformation in the ground state. The aromatic protons of the 1,4-disubstituted phenol and the 1,4-disubstituted pyridinium salt appeared as two pairs of doublets centred at 6.80 and 7.60 ($J = 7$ Hz) and at 8.10 and 8.67 ($J = 6.5$ Hz), respectively.[15] For comparative purposes, receptor **4** was synthesized as a model compound.[16]

DMSO–water 90:10 v/v mixtures buffered at pH 7.5 (HEPES $5 \times 10^{-2}$ mol dm$^{-3}$) of receptor **3** ($3.0 \times 10^{-5}$ mol dm$^{-3}$) show a very intense band at 400 nm and a very weak band at 560 nm. From previous studies on stilbazolium betaine derivatives,[17] we attributed the band at 400 nm to compound **3** (protonated form) whereas the band centred at 560 nm corresponds to deprotonated species of **3**. Under the working conditions, the latter is much less intense because the equilibrium is clearly displaced to the protonated form at pH 7.5 (p$K_a$ of **4** in water is 8.37).[18] DMSO–water 90:10 buffered solutions (pH 7.5 HEPES $5 \times 10^{-2}$ mol dm$^{-3}$) of monomer **4** showed similar UV–visible features.

The UV–visible response of receptor **3** was tested against several ω-amino acids (4-aminobutanoic, 5-aminopentanoic, 6-aminohexanoic, 7-aminoheptanoic and 8-aminooctanoic). Addition of increasing quantities of 4-aminobutanoic acid to DMSO–water 90:10 v/v solutions (buffered at pH 7.5) of receptor **3** ($1.0 \times 10^{-5}$ mol dm$^{-3}$) induced a clear change in colour from yellow to light orange. This colour modulation is due to the enhancement of the band centred at 560 nm and a partial decrease in intensity of the band at 400 nm. On changing from 4-aminobutanoic to 8-aminooctanoic acid the intensity of the band centred at 560 nm was enhanced greatly reaching the solution a strong orange colouration (see Fig. 1). The titration profiles obtained by the titration of **3** with increasing quantities of 5-aminopentanoic, 6-aminohexanoic and 7-aminoheptanoic acids lie between those presented by 4-aminobutanoic and 8-aminooctanoic acid (see Fig. 2). In all cases, the changes in the visible spectra showed clear isosbestic points at ca. 450 nm that allowed to determine the strength of the interaction through the calculation of the stability constants for the formation of 1:1 complexes between receptor **3** and the correspondent ω-amino acid (see Table 1).

Receptor **3** forms 1:1 anion-to-ligand complexes with all the ω-amino acids tested. The different stability of the complex formed appears to be related with the geometry of the receptor that is reflected in the different carboxylate p$K_a$ of the ω-amino acid (see below). At neutral pH, ω-amino acids show a zwitterionic structure[19] with a negatively charged carboxylate and positively charged quaternary ammonium group connected through several methylene




Scheme 1. Synthesis of receptor **3** and structure of model compound **4**. Reagents and conditions: (i) 4-methylpyridine–ethanol-reflux; (ii) 4-hydroxybenzaldehyde–piperidine–ethanol-reflux.

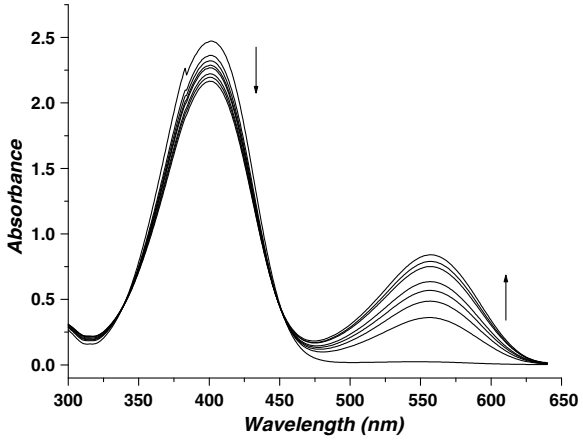



Fig. 1. Changes in the UV–visible spectra of receptor **3** ($1.0 \times 10^{-5}$ mol dm$^{-3}$) in DMSO–water 90:10 v/v solutions (buffered at pH 7.5) upon addition of increasing quantities of 8-aminooctanoic acid.

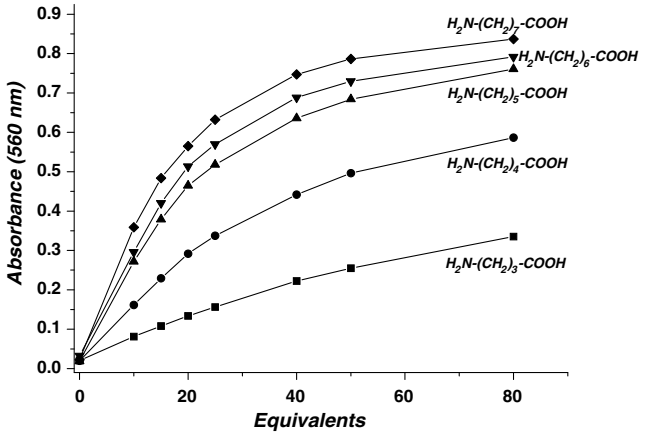



Fig. 2. Titration profiles of receptor **3** ($1.0 \times 10^{-5}$ mol dm$^{-3}$) with ω-amino acids in DMSO–water 90:10 v/v solutions (buffered at pH 7.5).

Table 1
Logarithms of the stability constants of the interaction of receptors **3** and **4** with ω-aminoacids

| ω-Amino acid | p$K_a$[a] | Length[b] (Å) | **3** | **4** |
|---|---|---|---|---|
| 4-Aminobutanoic acid | 4.44 | 6.94 | $3.40 \pm 0.08$ | $2.05 \pm 0.05$ |
| 5-Aminopentanoic acid | 4.61 | 8.19 | $3.81 \pm 0.08$ | $3.12 \pm 0.08$ |
| 6-Aminohexanoic acid | 4.68 | 9.45 | $4.00 \pm 0.07$ | $3.44 \pm 0.04$ |
| 7-Aminoheptanoic acid | 4.72 | 10.71 | $4.12 \pm 0.08$ | $3.58 \pm 0.05$ |
| 8-Aminooctanoic acid | 4.76 | 11.96 | $4.18 \pm 0.04$ | $3.60 \pm 0.05$ |

[a] p$K_a$ values from water.
[b] Calculated from Hyperchem 6.03.[21]

moieties. We believe that the change in colour is due to an interaction between the carboxylate groups and the phenolic moiety that results in a hydrogen transfer from the phenol proton to the carboxylate and in a modulation of the ratio between the protonated and unprotonated form of **3**. This complete proton transfer is confirmed because upon titration of DMSO–water 90:10 v/v solutions (buffered at pH 7.5) of receptor **3** with sodium hydroxide a new band corresponding to the deprotonated form of **3** appeared at 560 nm. The fact that this band is the same obtained in the titrations with ω-aminoacids discards partial hydrogen transfer and points towards a complete proton transfer. Thus, for receptor **3**, the selectivity observed is mainly related with the basicity of the anion (the carboxylate in the amino acids), that is, to the p$K_a$ of the conjugated acid.[20] This relation can be seen in Figure 3 that plots the intensity of the band at 560 nm of **3** upon the addition of 80 equivalents of the corresponding guest as a function of the p$K_a$ of the ω-amino acids. A good linear correlation is observed.

To understand this behaviour, it is necessary to be aware that the p$K_a$ values of the carboxylic group in these ω-amino acids can easily be rationalized bearing in mind simple electrostatic considerations based on the concept that it is more difficult to protonate a carboxylate placed close to an ammonium group and, therefore, the p$K_a$ values decrease as the distance between carboxylate and ammonium groups also decreases. This effect, that is, slight changes in the p$K_a$ in amino acids, is related with geometrical factors (i.e., length of the ω-amino acid) that results in a colorimetric discrimination as a function of the amino acid length (see Fig. 3).

Additional studies were also carried out with alkyl amines and alkyl carboxylates. The addition of the former amines (e.g., butylamine and heptylamine) to DMSO–water solutions of **3** resulted in no changes on the vis spectrum indicating that they were unable to deprotonate the phenol group on **3**. Moreover, addition of the carboxylates of different length (butanoate, pentanoate, hexanoate, heptanoate and octanoate) induced the rapid development of the band centred at 560 nm (data not shown). However, in all cases the response was exactly the same and, therefore, it was not possible to discriminate colorimetrically between these carboxylates. This contrasts with the results observed for the interactions of **3** with ω-amino acids that resulted in a clear colorimetric discrimination as a function of the amino acid length (see above).

In further studies, we were interested in comparing the colorimetric behaviour of cage **3** with the model compound **4**. Addition of increasing quantities of the corresponding ω-amino acid to DMSO–water 90:10 v/v solutions (buffered at pH 7.5) of receptor **4** ($3.0 \times 10^{-5}$ mol dm$^{-3}$) resulted in a more moderate colour change when compared with **3**. This poorer interaction ability is also observed in the stability constants determined for the interaction of **4** with the ω-amino acids (see Table 1). Receptor **4** also forms 1:1 complexes.

As can be seen by comparison between the stability constants for **3** and **4**, the former shows an enhanced response towards ω-amino acids when compared with the latter. In all cases, the stability constants for **3** are ca. 3–4 time larger than those shown by **4**. This cooperative effect in **3** most likely arises from the presence of three dye groups gathered together through the 2,4,6-trimethylbenzene scaffolding. This enhanced response of the acyclic tripodal receptor

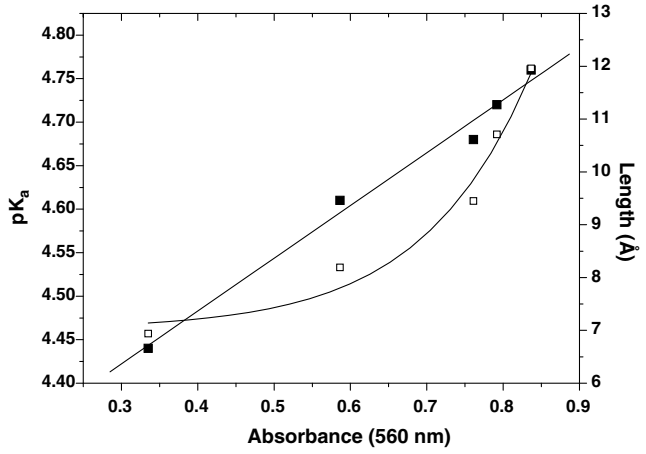



Fig. 3. Plot of p$K_a$ values (■) and lengths (□) of the ω-aminoacids versus the absorbance at 560 nm for DMSO–water 90:10 v/v solutions (buffered at pH 7.5) of receptor **3** ($1.0 \times 10^{-5}$ mol dm$^{-3}$) in the presence of 80 equivalents of the corresponding ω-amino acid.

would be tentatively ascribed to the fact that receptor **3** adopts a cone conformation with the three merocyanine subunits preorganized in the same face of the benzene scaffold. The formation of 1:1 stoichiometry complex between **3** and the corresponding ω-amino acid (as confirmed by titration experiences) points towards the formation of an inclusion complex. Similar host–guest conformations have also been reported for similar systems.[22]

In summary, we have used for the first time stilbazolium dye derivatives in a tripodal conformation as suitable chromogenic reporters for the colorimetric discrimination of ω-amino acids of different length in mixed DMSO–water. The colorimetric response is a function of the length of the ω-amino acid that is additionally related with the p$K_a$ of the corresponding carboxylate group in the guests. We are currently developing new anion receptors for the chromo-fluorogenic discrimination of closely related organic guests.

## Acknowledgements

We thank the Ministerio de Ciencia y Tecnología (project CTQ2006-15456-C04-01 FEDER), Generalitat Valenciana (project GV06/101) and Universidad Politécnica de Valencia (project 5711) for support. B.G.-A. thanks the Generalitat Valenciana for a Doctoral Fellowship. J.V.R.L. thanks Generalitat Valenciana for a postdoctoral fellowship.

## References and notes

1. (a) Löhr, G.-H.; Vögtle, F. *Acc. Chem. Res.* **1985**, *16*, 65; (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486; (c) Takagi, M.; Ueno, K. *Top. Curr. Chem.* **1984**, *121*, 39; (d) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192.
2. (a) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419; (b) Martínez-Máñez, R.; Sancenón, F. *Coord. Chem. Rev.* **2006**, *250*, 3081; (c) Wiskur, S. L.; Aït-Haddou, H.; Lavigne, J. J.; Anslyn, E. V. *Acc. Chem. Res.* **2001**, *34*, 963.
3. (a) Descalzo, A. B.; Martínez-Máñez, R.; Sancenón, F.; Hoffmann, K.; Rurack, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5924; (b) Coll, C.; Martínez-Máñez, R.; Marcos, M. D.; Sancenón, F.; Soto, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1675; (c) Lin, V. S.-Y.; Lai, C.-Y.; Huang, J.; Song, S.-A.; Xu, S. *J. Am. Chem. Soc.* **2001**, *123*, 11510; Radu, D. R.; Lai, C.-Y.; Wiench, J. W.; Pruski, M.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2004**, *126*, 1640.
4. (a) Coll, C.; Casasús, R.; Aznar, E.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Amorós, P. *Chem. Commun.* **2007**, 1957; (b) Descalzo, A. B.; Rurack, K.; Weisshoff, H.; Martínez-Máñez, R.; Marcos, M. D.; Amorós, P.; Hoffmann, K.; Soto, J. *J. Am. Chem. Soc.* **2005**, *127*, 184; (c) Comes, M.; Rodriguéz-López, G.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Villaescusa, L. A.; Amorós, P.; Beltrán, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2918.
5. (a) Comes, M.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Villaescusa, L. A.; Amorós, P.; Beltrán, D. *Adv. Mater.* **2004**, *16*, 1783; (b) García-Acosta, B.; Comes, M.; Bricks, J. L.; Kudinova, M. A.; Kurdyukov, V. V.; Tolmachev, A. I.; Descalzo, A. B.; Marcos, M. D.; Martínez-Máñez, R.; Moreno, A.; Sancenón, F.; Soto, J.; Villaescusa, L. A.; Rurack, K.; Barat, J. M.; Escriche, I.; Amorós, P. *Chem. Commun.* **2006**, 2239.
6. (a) Aznar, E.; Casasús, R.; García-Acosta, B.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Amorós, P. *Adv. Mater.* **2007**, *19*, 2228; (b) Casasús, R.; Aznar, E.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Amorós, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6661; (c) Casasús, R.; Marcos, M. D.; Martínez-Máñez, R.; Ros-Lis, J. V.; Soto, J.; Villaescusa, L. A.; Amorós, P.; Beltrán, D.; Guillem, C.; Latorre, J. *J. Am. Chem. Soc.* **2004**, *126*, 8612.
7. (a) Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Org. Biomol. Chem.* **2005**, *3*, 1495; (b) Choi, K.; Hamilton, A. D. *Coord. Chem. Rev.* **2003**, *240*, 101; (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486; (d) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3; (e) Nguyen, B. T.; Anslyn, E. V. *Coord. Chem. Rev.* **2006**, *250*, 3118; (f) Yoon, J.; Kim, S. K.; Singh, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355.
8. (a) Lee, D. H.; Lee, H. Y.; Lee, K. H.; Hong, J.-I. *Chem. Commun.* **2001**, 1188; (b) Lee, D. H.; Lee, K. H.; Hong, J.-I. *Org. Lett.* **2001**, *3*, 5; (c) Lee, K. H.; Lee, H. Y.; Lee, D. H.; Hong, J.-I. *Tetrahedron Lett.* **2001**, *42*, 5447; (d) Lee, D. H.; Im, J. H.; Son, S. U.; Chung, Y. K.; Hong, J.-I. *J. Am. Chem. Soc.* **2003**, *125*, 7752.
9. (a) Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649; (b) Wiskur, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2001**, *123*, 10109; (c) Aït-Haddou, H.; Wiskur, S. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2001**, *123*, 11296.
10. Brooker, L. S. G.; Keyes, G. H.; Sprague, R. H.; van Dyke, R. H.; van Lare, E.; van Zandt, G.; White, F. L. *J. Am. Chem. Soc.* **1951**, *73*, 5326.
11. (a) Williams, D. J. *Angew. Chem.* **1984**, *96*, 637; (b) Bosshard, C.; Pan, F.; Wong, M. S.; Manetta, S.; Spreiter, R.; Cai, C.; Guenter, P.; Gramlich, V. *Chem. Phys.* **1999**, *245*, 377; (c) Yang, G.; Li, Y.; Dreger, Z. A.; White, J. O.; Drickamer, H. G. *Chem. Phys. Lett.* **1997**, *280*, 375.
12. (a) Grinwald, A.; Frostig, R. D.; Lieke, E.; Hildesheim, R. *Phys. Rev.* **1985**, *8*, 263; (b) Pan, F.; Wong, M. S.; Bosshard, C.; Guenter, P.; Gramlich, V. *Adv. Mater. Opt. Electron.* **1996**, *6*, 261.
13. (a) Koopmans, C.; Ritter, H. *J. Am. Chem. Soc.* **2007**, *129*, 3502; (b) Nicolini, J.; Testoni, F. M.; Schuhmacher, S. M.; Machado, V. G. *Tetrahedron Lett.* **2007**, *48*, 3467; (c) Linn, M. M.; Poncio, D. C.; Machado, V. G. *Tetrahedron Lett.* **2007**, *48*, 4547.
14. Van der Made, A. W.; Van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262.
15. *Synthesis of compound* **2**: A mixture of **1** (800 mg, 2 mmol) and γ-picoline (600 mg, 6.4 mmol) in ethanol (30 ml) was refluxed for 16 h. After cooling to 25 °C, the solvent was removed in vacuo giving a residue, which was washed with diethyl ether to yield compound **2** as a white solid (1240 mg, 1.82 mmol, 91%). $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 8.40 (d, 6H, $J = 6.5$ Hz), 7.78 (d, 6H, $J = 6.5$ Hz), 5.85 (s, 6H), 2.50 (s, 9H), 2.15 (s, 9H); $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 160.6, 143.7, 141.9, 128.9, 128.4, 57.9, 21.1, 16.2.
*Synthesis of receptor* **3**: A mixture of **2** (678 mg, 1 mmol) and *p*-hydroxybenzaldehyde (122 mg, 1 mmol) was dissolved in 50 ml of ethanol. Then, few drops of piperazine were added and the mixture refluxed for 16 h. On cooling to 25 °C, receptor **3** precipitated as a brownish solid that was isolated by filtration and washed with cold ethanol (790 mg, 0.8 mmol, 80%). $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 8.70 (d, 6H, $J = 6.5$ Hz), 8.10 (d, 6H, $J = 6.5$ Hz), 7.93 (d, 3H, $J_{trans} = 15$ Hz), 7.60 (d, 6H, $J = 7$ Hz), 7.30 (d, 3H, $J_{trans} = 15$ Hz), 6.80 (d, 6H, $J = 7$ Hz), 5.92 (s, 6H), 2.25 (s, 9H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 160.2, 154.2, 143.6, 143.4, 132.5, 130.9, 129.7, 125.5, 123.8, 120.5, 116.6, 58.5, 17.3.
16. Brooker, L. S. G.; Keyes, G. H.; Heseltine, D. W. *J. Am. Chem. Soc.* **1951**, *73*, 5350.
17. (a) Catalán, J.; Mena, E.; Meutermans, W.; Elguero, J. *J. Phys. Chem.* **1992**, *96*, 3615; (b) Burda, C.; Abdel-Kader, M. H.; Link, S.; El-Sayed, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 6720.
18. Davidson, S. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 225.
19. The first p$K_a$ of these ω-aminoacids is about 4.50 and the second p$K_a$ around 10.5.
20. (a) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909; (b) Boiocchi, M.; Del Boca, L.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani,

E., *J. Am. Chem. Soc.* **2004**, *126*, 16507; (c) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem. Eur. J.* **2005**, *11*, 120; (d) Boiocchi, M.; Del Boca, L.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Chem. Eur. J.* **2005**, *11*, 3097; (e) Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M. *J. Org. Chem.* **2005**, *70*, 5717.

21. Hyperchem 6.0. Molecular Modeling System, Hypercube, Inc.

22. (a) Tobey, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2003**, *125*, 14807; (b) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem. Eur. J.* **2005**, *11*, 5648; (c) Ajami, D.; Schramm, M. P.; Volonterio, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2007**, *46*, 242; (d) Biros, S. M.; Rebek, J., Jr. *Chem. Soc. Rev.* **2007**, *36*, 93; (e) Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068; (f) Amaya, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 14149.