ORGANIC LETTERS

2002
Vol. 4, No. 19
3297−3300

Bisbinaphthyl Macrocycle-Based Highly Enantioselective Fluorescent Sensors for α-Hydroxycarboxylic Acids

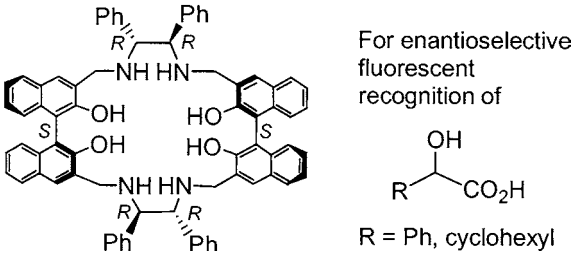
Jing Lin, Hui-Chang Zhang, and Lin Pu*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319

lp6n@virginia.edu

Received July 19, 2002

ABSTRACT



Bisbinaphthyl-based macrocycles are found to carry out highly enantioselective fluorescent recognition of α-hydroxycarboxylic acids. It is observed that within a certain concentration range, one enantiomer of the chiral acids can increase the fluorescence intensity of the macrocycles by 2–3-fold, while the other enantiomer scarcely enhances the fluorescence. Such unusually high enantioselective responses make these macrocycles very attractive as fluorescent sensors in determining the enantiomeric composition of α-hydroxycarboxylic acids.

Application of 1,1′-binaphthyl-based chiral macrocycles to molecular recognition has been extensively studied as represented by Cram's pioneering work.[1] Separation and NMR methods have revealed that macrocyclic bisbinaphthyl crown ethers are able to carry out highly enantioselective discrimination of amino ester salts. Changes in the UV−vis absorptions of binaphthyl-containing macrocycles have also been utilized for chiral recognition.[2] However, almost no enantioselective fluorescent study has been conducted using binaphthyl-based macrocycles for molecular recognition, despite that a number of acyclic binaphthyl compounds have been investigated for chiral discrimination in luminescence.[3,4] Using fluorescence in enantioselective recognition can provide a real-time method for determining the enantiomeric composition of chiral compounds. Such fluorescent sensors will be very useful in the high-throughput combinatorial screening of chiral compounds and catalysts.[5,6] In light of the high chiral recognition ability of bisbinaphthyl macrocycles, we have studied their application in enantioselective fluorescent sensing. We have discovered that one type of these chiral macrocycles is highly enantioselective in the fluorescent recognition of α-hydroxycarboxylic acids. Herein, our results are reported.

In 1994, Brunner and Schiessling reported the synthesis of the chiral bisbinaphthyl macrocycle (−)-**4** by condensation of (*S*)-**1** with (*R*,*R*)-**2** followed by reduction of the macrocyclic salen **3** (Scheme 1).[7] Using the same procedure, we

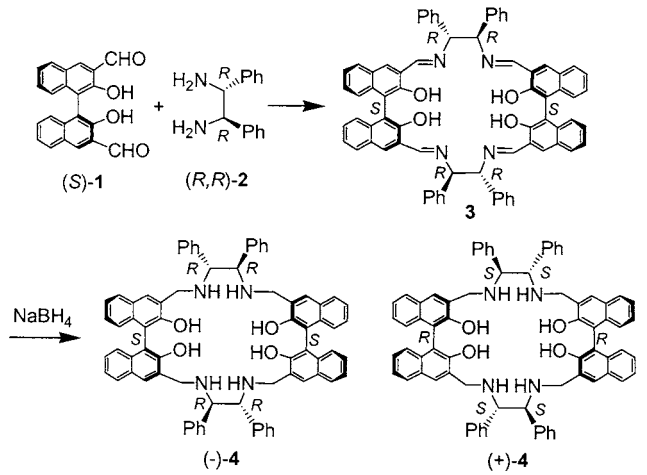
(1) (a) Cram, D. J. *Science* **1988**, *240*, 760−767. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494.

(2) Kubo, Y. *Synlett* **1999**, *2*, 161−174.

(3) Selected references on using chiral binaphthyl molecules in enantioselective fluorescent discrimination: (a) Irie, M.; Yorozu, T.; Hayashi, K. *J. Am. Chem. Soc.* **1978**, *100*, 2236−2237. (b) Yorozu, T.; Hayashi, K.; Irie, M. *J. Am. Chem. Soc.* **1981**, *103*, 5480−5484. (c) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Nature* **1995**, *374*, 345−347. (d) Iwanek, W.; Mattay, J. *J. Photochem. Photobiol. A: Chem.* **1992**, *67*, 209−226. (e) Avnir, D.; Wellner, E.; Ottolenghi, M. *J. Am. Chem. Soc.* **1989**, *111*, 2001−2003. (f) Parker, K. S.; Townshend, A.; Bale, S. J. *Anal. Proc.* **1995**, *32*, 329−332. (g) Beer, G.; Rurack, K.; Daub, J. *J. Chem. Soc., Chem. Commun.* **2001**, 1138−1139. (h) Pugh, V.; Hu, Q.-S.; Pu, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3638−3641. (i) Gong, L.-Z.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 2358−2367. (j) Pugh, V.; Hu, Q.-S.; Zuo, X.-B.; Lewis, F. D.; Pu, L. *J. Org. Chem.* **2001**, *66*, 6136−6140. (k) Lin, J.; Hu, Q.-S.; Xu, M. H.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 2088−2089. (l) One report recently appeared describing the use of binaphthyl-based organometallic macrocycles in fluorescent recognition: Lee, S. L.; Lin, W.-B. *J. Am. Chem. Soc.* **2002**, *124*, 4554−4555.

10.1021/ol026565c CCC: $22.00
Published on Web 08/29/2002

Scheme 1. Synthesis of the Bisbinaphthyl Macrocycles (−)-**4** and (+)-**4**



also prepared the enantiomeric macrocycle (+)-**4** by starting from (*R*)-**1** and (*S*,*S*)-**2**. We chose these macrocycles to undertake the desired fluorescent recognition of α-hydroxycarboxylic acids for the following reasons. (1) When (−)-**4** interacts with the chiral acids, protonation of its nitrogen atoms is expected to turn on the fluorescence of the macrocycle by inhibiting the photoinduced-electron-transfer (PIET)[8] of the nitrogen lone pair electrons. (2) The tetrahydroxyl and tetraamine groups of the macrocycle should bind α-hydroxycarboxylic acids well through multiple hydrogen bonds. (3) The four chiral centers of (−)-**4** together with the two axially chiral binaphthyl units may lead to good chiral recognition.

When a benzene solution (containing 2% DME = dimethoxyethylene) of (−)-**4** was excited at 340 nm, it exhibited two emission maxima at 365 (λ_{short}) and 424 nm (λ_{long}) (Figure 1). The addition of DME as a cosolvent in

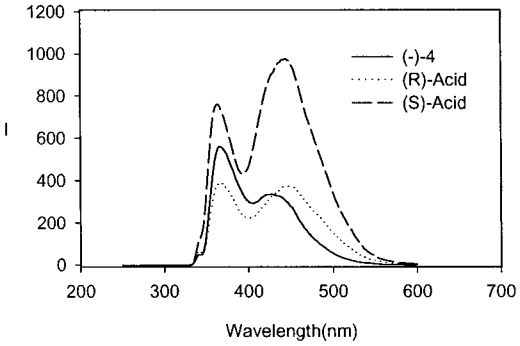


Figure 1. Fluorescence spectra of (−)-**4** (1.0×10^{-4} M in benzene containing 2% DME) both with and without (*R*)- and (*S*)-mandelic acid (2.0×10^{-2} M) (λ_{exc} = 340 nm).

the fluorescence measurement was to assist the dissolution of the highly polar α-hydroxycarboxylic acids because of their low solubility in benzene. When (−)-**4** was treated with (*S*)-mandelic acid, (−)-**4** showed greatly enhanced fluorescence especially at λ_{long}. However, there was very little fluorescence enhancement at λ_{long} when (−)-**4** was interacted with (*R*)-mandelic acid under the same conditions. This demonstrates that the fluorescent response of (−)-**4** toward the chiral acid is highly enantioselective.

In concentrations ranging from 5.0×10^{-3} to 2.0×10^{-2} M (*R*)- and (*S*)-mandelic acid in benzene containing 2% DME, the fluorescence enhancement of (−)-**4** (1.0×10^{-4} M) at λ_{long} was studied.[9] As shown by the results in Figure 2, there is a large increase in the fluorescence of (−)-**4** in

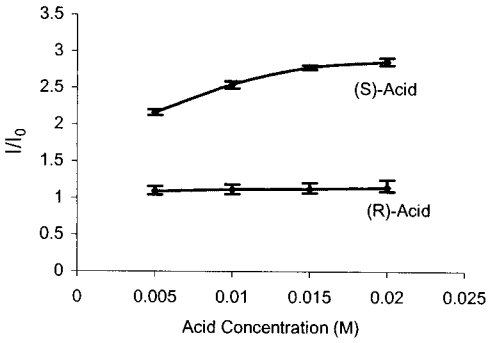


Figure 2. Fluorescence enhancement of (−)-**4** (1.0×10^{-4} M in benzene containing 2% DME) vs concentration of (*R*)- and (*S*)-mandelic acid.

the presence of (*S*)-mandelic acid but almost no change in the presence of (*R*)-mandelic acid. The enantiomeric fluorescence difference ratio, *ef* [$ef = (I_S - I_0)/(I_R - I_0)$, where I_0 is the fluorescence intensity in the absence of the chiral substrate], is greater than 12 when the acid concentration is 2.0×10^{-2} M.

We have also studied the interaction of (−)-**4** with mandelic acid at a much broader concentration range of the acid. Because of the low solubility of mandelic acid in

(4) Selected references on chiral recognition in luminescence: (a) Rau, H.; Ratz, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 550−551. (b) Metcalf, D. H.; Snyder, S. W.; Demas, J. N.; Richardson, F. S. *J. Am. Chem. Soc.* **1990**, *112*, 5681−5695. (c) Metcalf, D. H.; Stewart, J. M. M.; Snyder, S. W.; Grisham, C. M.; Richardson, F. S. *Inorg. Chem.* **1992**, *31*, 2445−2455. (d) Corradini, R.; Sartor, G.; Marchelli, R.; Dossena, A.; Spisni, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1979−1983. (e) Rexwinkel, R. B.; Meskers, S. C. J.; Dekkers, H. P. J. M.; Riehl, J. P. *J. Phys. Chem.* **1992**, *96*, 5725−5733. (f) Glover-Fischer, D. P.; Metcalf, D. H.; Bolender, J. P.; Richardson, F. S. *Chem. Phys.* **1995**, *198*, 207−234. (g) Meskers, S. C. J.; Dekkers, H. P. J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6413−6414. (h) Fox, M. A.; Singletary, N. J. *Tetrahedron Lett.* **1979**, *20*, 2189−2192. (i) Gafni, A. *J. Am. Chem. Soc.* **1980**, *102*, 7367−7368. (j) Tundo, P.; Fendler, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 1760. (k) López-Arbeloa, F.; Auweraer, M. V. D.; Ruttens, F.; De Schryver, F. C. *J. Photochem. Photobiol. A: Chem.* **1988**, *44*, 63−83. (l) Yang, H.; Bohne, C. *J. Photochem. Photobiol. A: Chem.* **1995**, *86*, 209−217. (m) Grady, T.; Harris, S. J.; Smyth, M. R.; Diamond, D. *Anal. Chem.* **1996**, *68*, 3775−3782. (n) Grady, T.; Joyce, T.; Smyth, M. R.; Harris, S. J.; Diamond, D. *Anal. Commun.* **1998**, *35*, 123−125. (o) Yan, Y.; Myrick, M. L. *Anal. Chem.* **1999**, *71*, 1958−1962. (p) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 2515−2520.

(5) Reviews on the combinatorial chiral catalyst screening: (a) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885−1889. (b) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284−310.

benzene especially at high concentration, more DME was used for this measurement. Figure 3 displays the fluorescence

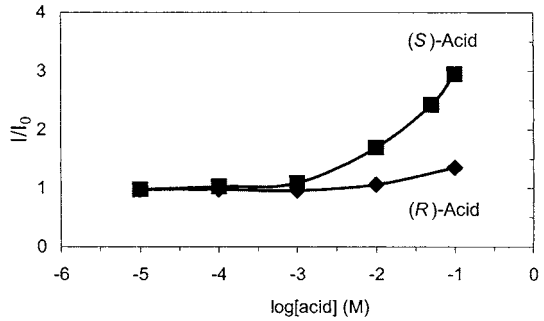


Figure 3. Fluorescence intensity change of (−)-**4** (1.0×10^{-4} M in benzene containing 10% DME) vs concentration of (*R*)- and (*S*)-mandelic acid.

intensity change of sensor (−)-**4** (1.0×10^{-4} M in benzene containing 10% DME) at λ_{long} in the presence of (*R*)- and (*S*)-mandelic acid in concentrations ranging from 1.0×10^{-5} to 1.0×10^{-1} M. At the high concentration of (*R*)- mandelic acid, it started to enhance the fluorescence of (−)-**4**, but the enhancement effect of (*S*)-mandelic acid is still much greater.

To ascertain whether the dramatically different fluorescent responses of (−)-**4** toward the two enantiomers of mandelic acid are due to chiral recognition, we have investigated the use of the enantiomeric macrocycle (+)-**4**. Compound (+)-**4** was treated with (*R*)- and (*S*)-mandelic acid. As Figure 4

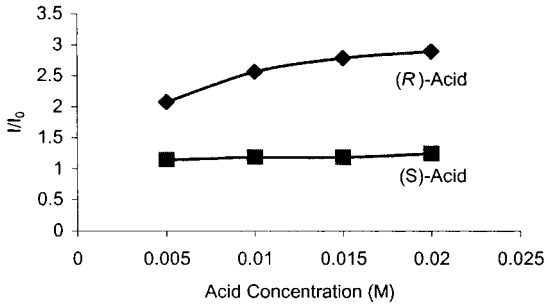


Figure 4. Fluorescence intensity change of (+)-**4** (1.0×10^{-4} M in benzene containing 2% DME) vs concentration of (*R*)- and (*S*)-mandelic acid.

shows, the fluorescence responses of (+)-**4** toward (*R*)- and (*S*)-mandelic acid are the mirror images of (−)-**4** toward the acid. (*R*)-Mandelic acid greatly enhanced the fluorescence intensity of (+)-**4** at λ_{long}, but (*S*)-mandelic acid did not. This study confirms that the observed large fluorescence difference of the chiral macrocyclic sensors with the two enantiomers of mandelic acid is indeed due to enantioselective recognition.

The ^{1}H NMR spectra of (+)-**4** and (*R*)-mandelic acid in a variety of ratios in benzene-d_6 containing 2% DME at a constant total concentration of 1.0×10^{-3} M were taken. It was found that the methine proton signal of (*R*)-mandelic acid at δ 5.153 underwent an upfield shift when treated with (+)-**4**. When (+)-**4** vs (*R*)-mandelic acid was 8:2, the methine proton signal appeared at δ 5.112. Figure 5 is a Job plot of

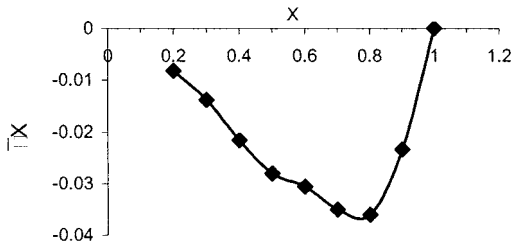


Figure 5. Job plot of (+)-**4** with (*R*)-mandelic acid [X = mole fraction of the acid, $\Delta\delta$ = chemical shift change of the acid].

$\Delta\delta X$ vs the mole fraction (X) of (*R*)-mandelic acid in the mixture.[10] A minimum at $X = 0.8$ was observed. This indicates that the sensor forms a 1:4 complex with the acid under the conditions. Probably all four nitrogen atoms of (+)-**4** are interacting with the acidic protons of four (*R*)-mandelic acids. The nitrogen atoms of the sensor are expected to quench the fluorescence of the binaphthyl chromophores by the PIET process.[8] Interaction of these nitrogen atoms with the acidic protons makes their lone pair electrons no longer available for PIET, leading to the observed large fluorescence enhancement. (*R*)-Mandelic acid should bind (+)-**4** much stronger than (*S*)-mandelic acid. In the same way, (*S*)-mandelic acid should bind (−)-**4** much stronger than (*R*)-mandelic acid, which explains the much greater fluorescence enhancement of (−)-**4** by (*S*)-mandelic acid. We found that only at a much higher concentration of

(6) Selected references on the combinatorial catalyst screening: (a) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361−362. (b) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306−4307. (c) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641−4642. (d) Klein, G.; Reymond, J.-L. *Helv. Chim. Act.* **1999**, *82*, 400−406.

(7) (a) Brunner, H.; Schiessling, H. *Angew Chem., Int. Ed. Engl.* **199**4, *3*3, 125; (b) *Bull. Soc. Chim. Belg.* **199**4, *10*3, 119.

(8) (a) Fox, M. A., M. Chanon, M., Eds. *Photoinduced Electron Transfer.* Elsevier: Amsterdam, 1988; Parts A−D. (b) Bissell, R. A.; de Silva, A. P.; Gunaratna, H. Q. N.; Lynch, P. L. M.; Maguire, G. E. M.; McCoy, C. P.; Sandanayake, K. R. A. S. *Top. Curr. Chem.* **1993**, *168*, 223−264. (c) Bissell, R. A.; de Silva, A. P.; Gunaratna, H. Q. N.; Lynch, P. L. M.; Maguire, G. E. M.; Sandanayake, K. R. A. S. *Chem. Soc. Rev.* **1992**, *21*, 187−195. (d) Czarnik, A. W. *Acc. Chem. Res.* **1994**, *27*, 302−308.

(9) General procedure for the fluorescent measurement. A benzene stock solution of the chiral macrocycle (2.0×10^{-4} M) was freshly prepared before each measurement. A 0.1 M stock solution of chiral mandelic acid in benzene containing 10% (V) DME was freshly prepared. Then, the sensor solution was mixed with the acid solution at room temperature in a 10 mL volumetric flask and diluted to the desired concentration. The resulting solution was allowed to stand at room temperature for 4 h before fluorescence measurement.

(10) (a) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626−4636. (b) Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stability;* Wiley-Interscience: New York, 1987; pp 24−28.

(*R*)-mandelic acid can it start to bind (−)-**4** significantly and enhance its fluorescence (see Figure 3).

The fluorescence intensity change of (−)-**4** with respect to the enantiomeric composition of mandelic acid was studied. As shown by Figure 6, the fluorescence intensity

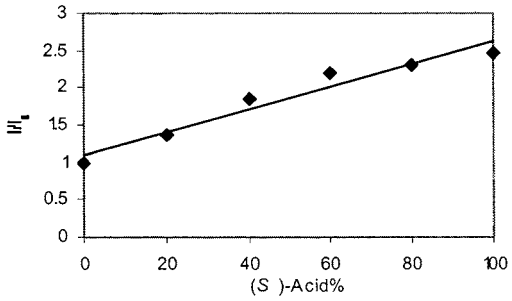


Figure 6. Fluorescence intensity change of (−)-**4** (1.0×10^{-4} M in benzene containing 1% DME) vs enantiomeric composition of mandelic acid (1.0×10^{-2} M).

of (−)-**4** increases monotonically as the (*S*)-component increases. Thus, the chiral bisbinaphthyl macrocycle can be used as a fluorescent sensor to readily determine the enantiomeric composition of mandelic acid.

We have also studied the interaction of (−)-**4** with hexahydromandelic acid. As shown in Figure 7, the fluo-

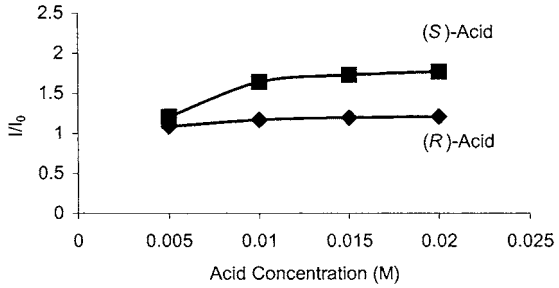


Figure 7. Fluorescence intensity change of (−)-**4** (1.0×10^{-4} M in benzene containing 2% DME) vs concentration of (*R*)- and (*S*)-hexahydromandelic acid.

rescent responses of (−)-**4** toward (*R*)- and (*S*)-hexahydromandelic acid are similar to those observed for (*R*)- and (*S*)-mandelic acid, except that both the magnitudes of the fluorescent enhancement and the enantioselectivity are smaller in the case of hexahydromandelic acid. In concentrations ranging from 5.0×10^{-3} M to 2.0×10^{-2} M, (*S*)-hexahydromandelic acid enhanced the fluorescence of (−)-**4** at λ_{long} significantly, but (*R*)-hexahydromandelic acid did not. The relationship between the fluorescence intensity of (−)-**4** and the enantiomeric composition of hexahydromandelic acid is shown in Figure 8.

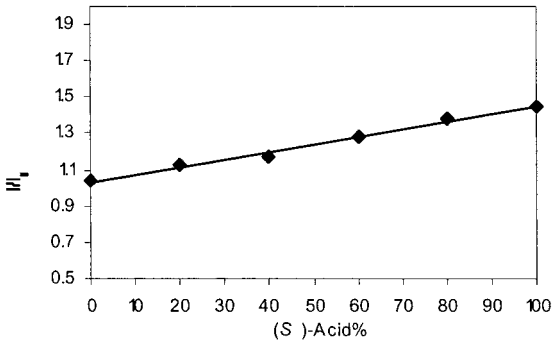


Figure 8. Fluorescence intensity change of (−)-**4** (1.0×10^{-4} M in benzene containing 1% DME) vs enantiomeric composition of hexahydromandelic acid (1.0×10^{-2} M).

In summary, we have discovered that bisbinaphthyl-based macrocycles can carry out highly enantioselective fluorescent recognition of α-hydroxycarboxylic acids. We have observed that within a certain concentration range, *one enantiomer of the chiral acids can increase the fluorescence intensity of the macrocycles by 2−3-fold, while the other enantiomer scarcely enhances the fluorescence*. Such unusually high enantioselective responses make these macrocycles very attractive as fluorescent sensors in determining the enantiomeric composition of α-hydroxycarboxylic acids. They are potentially useful for the combinatorial screening of the catalysts for the asymmetric synthesis of α-hydroxycarboxylic acids.[11,12]

Acknowledgment. Support of this work from the National Institutes of Health (R01GM58454) is gratefully acknowledged.

OL026565C

(11) Chiral α-hydroxycarboxylic acids are very useful in the asymmetric synthesis of organic compounds: Coppola, G. M.; Schuster, H. F. *α-Hydroxyl Acids in Enantioselective Synthesis*; VCH: Weinheim, Germany, 1997.

(12) A combinatorial method for the asymmetric synthesis of α-hydroxycarboxylic acids was recently reported: Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Gre'minon, C.; Grassi, J.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124−127.