ORGANIC LETTERS

2005
Vol. 7, No. 16
3525−3527

Enantioselective Recognition of 1,2-Amino Alcohols by Reversible Formation of Imines with Resonance-Assisted Hydrogen Bonds

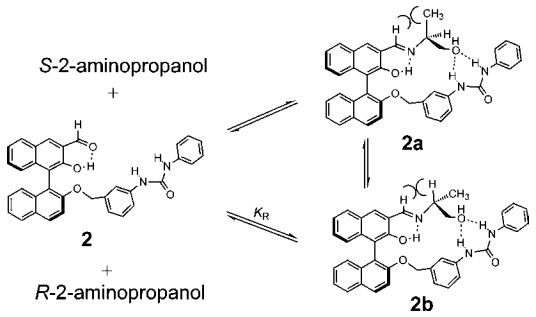
Kwan Mook Kim,*,† Hyunjung Park,† Hae-Jo Kim,‡ Jik Chin,*,‡ and Wonwoo Nam*,†

Department of Chemistry, Division of Nano Sciences, and Center for Biomimetic Systems, Ewha Womans University, Seoul 120-750, South Korea, and Department of Chemistry, 80 St. George Street, University of Toronto, Toronto, Ontario, Canada M5S 3H6

kkmook@ewha.ac.kr; jchin@chem.utoronto.ca; wwnam@ewha.ac.kr

Received May 30, 2005

ABSTRACT



A chiral aldehyde with three H-bond donating groups (2) has been synthesized. This aldehyde binds a variety of chiral 1,2-amino alcohols in benzene with the same sense of stereoselectivity. Computational and experimental data indicate that one imine bond, one resonance-assisted H-bond to the imine nitrogen, and two H-bonds to the alcoholic oxygen all play an important role in the stereoselective recognition.

Chiral amino alcohols are useful as intermediates for making a variety of biologically active molecules[1] and also as ligands for stereoselective catalysts.[2] Over the years there have been numerous publications on developing receptors for amines, amino acids, and amino alcohols.[3−5] In most of these studies, molecular recognition is based on noncovalent interactions such as hydrogen bonding, metal coordination, and hydrophobic hydrogen bonding, metal coordination, and hydrophobic interactions. Reversible imine formation has rarely been explored systematically for the recognition studies.[6] When compared to noncovalent interactions, imine bonds are slower to form but have the advantage of being much

† Ewha Womans University.
‡ University of Toronto.

(1) (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576;.

(2) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−876.

(3) (a) Bradshaw, J. S.; Izatt, R. M.; Bordunov, A. V.; Zhu, C. Y.; Hathaway, J. K. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon Press: New York, 1996; Vol. 1, pp 35−95. (b) Gokel, G. W.; Abel, E. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon Press: New York, 1996; Vol. 1, pp 511−535.

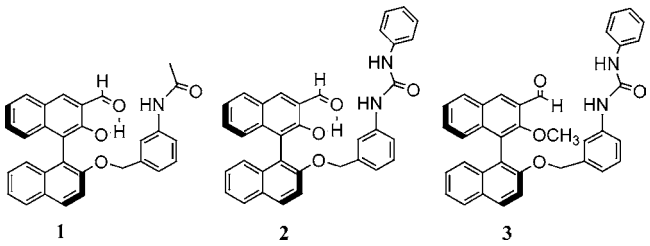
(4) (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (b) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313−3361. (c) Folmer-Andersen, J. F.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 5986−5987.

(5) (a) Kurtán, T.; Vesnas, N.; Li, Y.-Q.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2001**, *123*, 5962−5973. (b) Kim, S.-G.; Kim, K.-H.; Kim, Y. K.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2003**, *125*, 13819−138214.

(6) Feuister, E. K.; Glass, T. E. *J. Am. Chem. Soc.* **2003**, *125*, 16174−16175.

10.1021/ol051267b CCC: $30.25
Published on Web 07/07/2005

stronger and structurally well defined. These are features that are particularly desirable for developing stereoselective receptors. We recently showed that resonance assisted hydrogen bonds (RAHB)[7] can greatly increase the rate and equilibrium constants for imine formation.[8] Furthermor, RAHB can orient the imine and restrict its conformational mobility. Here, we compare three stereoselective receptors (**1**−**3**) for amino alcohols.



1 **2** **3**

Compounds **1**−**3** were synthesized from (*S*)-2,2′-binol-3-aldehyde[9] as described in the Supporting Information. All of the products were purified by column chromatography. Compound **2** is freely soluble in DMSO-d_6 and sparingly soluble in $CDCl_3$ and benzene-d_6, whereas compounds **1** and **3** are freely soluble in all three solvents.

Figure 1a shows the ^{1}H NMR spectrum for **2** in benzene-d_6 containing 5% DMSO-d_6. Addition of (*S*)-2-aminopropanol to **2** results in a rapid decrease in the aldehyde ^{1}H NMR signal at 9.74 ppm with concomitant increase in the imine (**2a**) C−H signal at 8.13 ppm (Figure 1b). Similarly, addition of (*R*)-2-aminopropanol to **2** results in an increase in the imine (**2b**) C−H signal at 8.21 ppm (Figure 1c). Aside from the imine C−H signals, the benzylic CH_2 signals are also useful for distinguishing **2a** and **2b**. The benzylic hydrogens are diastereotopic and appear as an AB quartet. Figure 1d shows the ^{1}H NMR spectrum for a mixture of **2a** and **2b** formed by the addition of two equivalents of racemic

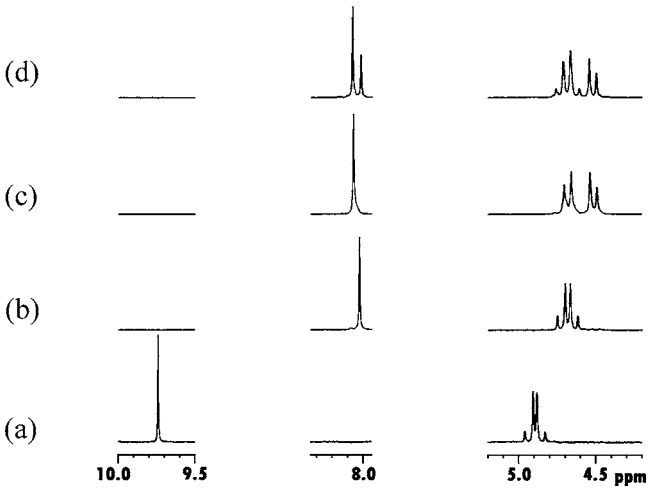


Figure 1. Partial ^{1}H NMR spectra (in benzene-d_6) of (a) **2**, (b) **2a**, (c) **2b**, and (d) mixture of **2a** and **2b** formed from addition of 2 equiv of racemic 2-aminopropanol to **2**.

Table 1. Enantioselective Imine Formation (K_R/K_S) between **2** and Chiral Amines As Determined by ^{1}H NMR

	δ, ppm				
	imine C−H		benzylic CH_2		
amines	*R*	*S*	*R*	*S*	K_R/K_S
phenethylamine	7.96	7.96	4.71	4.80	1.0
			4.65	4.72	
2-amino-1-propanol	8.21	8.13	4.85	4.88	3.7
			4.66	4.79	
2-amino-1-butanol	8.25	8.08	4.81	4.77	3.1
			4.61	4.69	
2-amino-3-phenyl-1-propanol	8.01	7.97	4.84	4.92	3.7
			4.64	4.83	
2-amino-2-phenylethanol	8.25	8.16	4.84	4.84	4.8
			4.61	4.77	

2-aminopropanol to **2**. The ratio of **2a** and **2b** can be measured from the imine C−H and benzylic hydrogen signals. Integration of the two peaks shows that the ratio of **2b**/**2a** is 1.9:1 at equilibrium. This indicates that the imine formation constant for **2b** (K_R) is larger than that for **2a** (K_S) by a factor of about 3.7 (1.9^2).[10] Even if **2a** is first formed by the addition of 1 equiv of (*S*)-2-aminopropanol, the above equilibrium ratio is obtained within 10 min upon addition of 1 equiv of (*R*)-2-aminopropanol to **2a**.

Table 1 shows that **2** compares favorably with previously reported receptors for stereoselective recognition of amino alcohols.[5] Furthermore, **2** binds all four amino alcohols with the same sense of stereoselectivity. Insight into the origin of stereoselectivity may be gained from molecular mechanics computation.[11] Aside from the RAHB between the phenolic proton and the imine, the alcohol group is within hydrogen-bonding distance of the urea group (Figure 2). In the imines formed with (*R*)-amino alcohols, the imine C−H comes in contact with the hydrogen attached to the chirality center. In the imines formed with (*S*)-amino alcohols, it is the alkyl or aryl group attached to the chirality center that comes in contact with the imine C−H. The greater steric effect in the (*S*)-imines appears to be the reason for the greater stability of the (*R*)-imines. Molecular mechanics computation was used to correctly predict the sense of stereoselectivity for all four amino alcohols in Table 1.

Several experimental results indicate that hydrogen bonds play an important role in stereoselective reognition of amino

(7) (a) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2000**, *122*, 10405−10417. (b) Gilli, G.; Bellucci, F.; Ferretti, V.; Bertolasi, V. *J. Am. Chem. Soc.* **1989**, *111*, 1023−1028. (c) Bertolasi, V.; Gilli, P.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **1991**, *113*, 4917−4925.

(8) (a) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A.; Chung, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 15276−15277. (b) Chin, J.; Kim, D. C.; Kim, H.-J.; Panosyan, F. B.; Kim, K. M. *Org. Lett.* **2004**, *6*, 2591−2593.

(9) (a) Kim, H. C.; Choi, S.; Kim, H.; Ahn, K.-H. *Tetrahedron Lett.* **1997**, *38*, 3959−3962. (b) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252−2260.

(10) K_R = [**2b**]/([**2**][R]) and K_S = [**2a**]/([**2**]/[S]) where [R] and [S] are concentrations of *R*- and *S*-2-aminopropanol, respectively. Thus, K_R/K_S = ([**2b**][S])/([**2a**][R]) = ([**2b**]/[**2a**])^2.

(11) Molecular mechanics computation was performed using Spartan '04 Windows from Wavefunction, Inc.

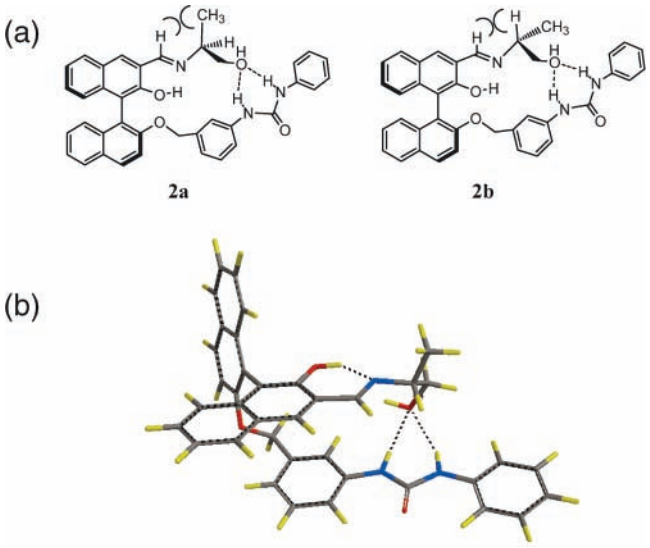


Figure 2. (a) Schematic representation showing steric repulsions in **2a** and **2b**. (b) Energy-minimized structure of **2b** formed from **2** and *R*-2-aminopropanol. Dotted lines indicate hydrogen bonds.

alcohols with **2**. Compound **2** does not bind phenethylamine with appreciable stereoselectivity (Table 1). Thus, hydrogen bonding with the alcohol group appears to be important. Compound **1** binds the four amino alcohols with the same sense of stereoselectivity as compound **2**. However, the stereoselectivity of compound **1** is only about half that of compound **2** presumably because the acetamide group in **1** has only one hydrogen bond donor whereas the urea group in **2** has two. Urea and thiourea groups have recently been shown to be excellent H-bond donors in chiral catalysts.[12] The stereoselectivity **2** is almost completely lost in DMSO where hydrogen bonds are much weaker than in benzene.

The stereoselectivity of compound **3** is about half that of compound **2** but with the opposite sense of stereoselectivity. Without the RAHB, the imine group is expected to rotate away about 180° from the phenoxy oxygen due to lone pair repulsion (Figure 3). Molecular mechanics calculations show that this has the effect of inverting the stereoselectivity. In the imines formed with (*S*)-amino alcohols, the imine C−H comes in contact with the hydrogen attached to the chirality center (Figure 3). In the imines formed with (*R*)-amino alcohols, the imine C−H comes in contact with the alkyl or aryl group attached to the chirality center. Therefore, it is the (*S*)-amino alcohols that form the more stable imines.

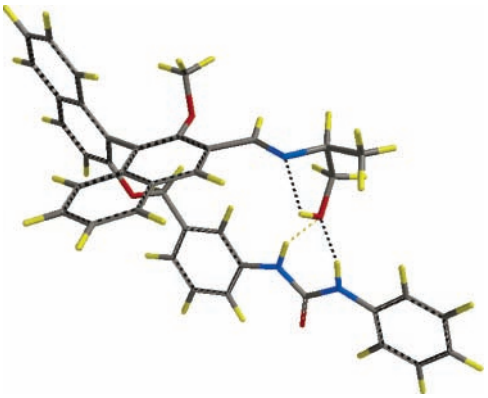


Figure 3. Energy-minimized structure of the imine formed from **3** and *S*-2-aminopropanol.

In summary, we have developed stereoselective receptors for amino alcohols based on reversible imine formation. Three-point interactions including an imine, an RAHB, and another hydrogen bond allow us to obtain high stereoselectivity as well as an understanding of the origin of the selectivity through molecular mechanics computation. Such understanding should be useful for developing evermore selective receptors.

Acknowledgment. This work was supported by a grant from MOST through the Creative Research Initiative Program, the Korea Research Foundation Grant (KRF-2004-005-C00093), and the Natural Sciences and Engineering Research Council of Canada.

Supporting Information Available: Synthesis of **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051267B

(12) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466−468. (c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.