Pergamon

Tetrahedron Letters, Vol. 35, No. 50, pp. 9413-9416, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01983-5

Enantioselective Dual N···HO Bonding between (*R,R*)-4,4'-bi [5-((*Z*)-*N*-isopropylimino)-1,3-dioxolane] and (*S*)-1,1'-bi-2-naphthol.

Yasuo Dobashi* and Akira Dobashi*

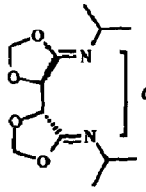
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Yoichi Iitaka

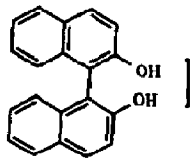
Department of Biological Sciences, Faculty of Science and Engineering, The Nishi-Tokyo University, Uenohara, Kitatsuru, Yamanashi 409-01, Japan

Abstract: The title compounds underwent enantioselective complexation via hydrogen bond formation in $CDCl_3$, and X-ray analysis of the co-crystal comprised of these compounds indicated dual N···HO bonding as the mode of complexation. Binding geometry was examined by PM3 calculation

Determination of the binding geometry of a molecular complex consisting of a selector and selectand is a matter of fundamental importance in the chemistry of molecular recognition.[1] We recently introduced a new concept of "complementary twist" into the mode of dual hydrogen bonding to generate enantioselectivity.[2] In an artificial system based on this concept, the relative orientation of each binding site of selector and selectand for dual hydrogen bonding showed a twist whose rotation sense reflected the absolute configuration. A chiral selector in such a system interacts preferentially with a selectand enantiomer which exhibits complementary twist by maximizing hydrogen bonding and minimizing untoward steric interaction. This relation can be likened to that between an interior and external screw both having the same sense of spiral groove. Our initial work in this series demonstrated the molecular design of (*R,R*)-4,4'-bi[5-((*Z*)-*N*-isopropylimino)-1,3-dioxolane] (**1**) as a twisted acceptor with high enantioselectivity toward a 1, 2-diol.[3] In the present study, the binding geometry of (*R,R*)-**1** with a twisted donor is disclosed by the X-ray crystal structure of a 1:1 complex of (*R,R*)-**1** and (*S*)-1,1'-bi-2-naphthol (**2**). The relevance of the static crystal structure to enantioselective complexation of these species in solution is discussed in reference to the results of NMR study and PM3 calculations.



(*R,R*)-**1**



2

After a warm solution of a 1.2:1 mixture of (*R,R*)-**1** and (*S*)-**2** in toluene (0.43 M in (*R,R*)-**1**) had stood at room temperature, single crystals of a 1:1 complex of these species were observed to have grown spontaneously. By X-ray analysis[4] of the co-crystal, the molecular structure of the complex was determined and dual N···HO bonding was unambiguously shown to be the mode of complexation, as indicated in Figure 1. A van der Waals surface of the complex in Figure 1 (center) clearly demonstrates close contact between

isopropyl methyls of (*R*,*R*)-**1** and aromatic rings of (*S*)-**2**. This close contact indicates that maximum approach between (*R*,*R*)-**1** and (*S*)-**2** is achieved through dual hydrogen bonding. This complex possesses a pseudo-C_2 axis passing through both centers of the bond between two naphthyl rings of (*S*)-**2** and that between two iminodioxolane rings of (*R*,*R*)-**1**. Each component of this complex adopts an energetically favored conformation. The torsion angle between the two naphthyl rings of (*S*)-**2** is sufficiently large to minimize steric interaction between these rings.[5] The *S*-configuration is represented by a clockwise twist between two aromatic rings each containing a hydroxyl as a hydrogen bond donor. (*R*,*R*)-**1** provides an anti relationship between two C-C bonds each consisting of an imino and asymmetric carbon so that maximum separation between the two bulky isopropyl substituents is attained.[6] In the conformer of (*R*,*R*)-**1**, the relative orientation of the two iminodioxolane rings containing binding sites displays a propeller-like twist with counterclockwise rotation, as expected in the stage of our molecular design. Complexation through dual interactions between the twisted acceptor sites of (*R*,*R*)-**1** and donor sites of (*S*)-**2** results in twisting between these molecules about the pseudo-C_2 axis as shown in Figure 1 (right). Such twisting serves to maximize hydrogen bonding by eluding steric interaction in the process of complexation, and characterizes the mode of complexation based on the concept of "complementary twist".

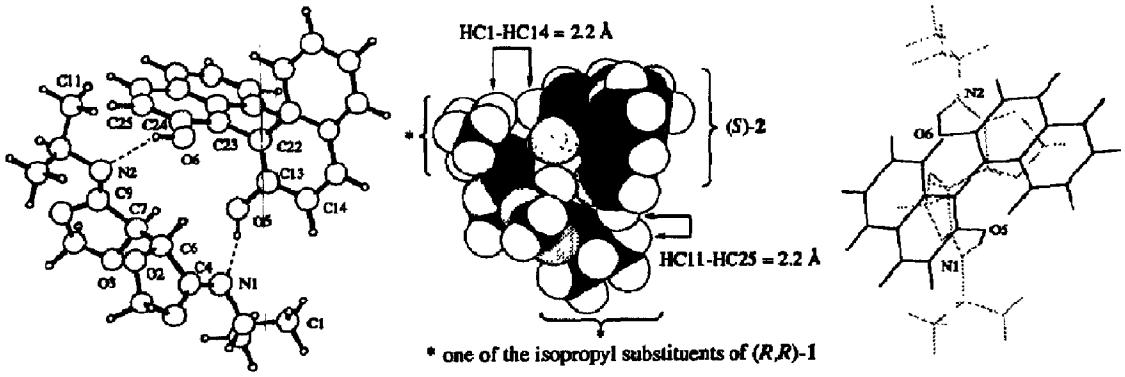


Figure 1. X-ray crystal structure of the complex of (*R*,*R*)-**1** with (*S*)-**2**. Selected structural parameters: N2-O6 = 2.846 (4) Å, N1-O5 = 2.786 (4) Å, N2-HO6 = 2.06 (4) Å, N1-H05 = 1.91 (4) Å, O3-C7-C6-O2 = -65.9 (3)°, C9-C7-C6-C4 = 162.3 (2)°, C24-C23-C22-C13 = 82.5 (3)°. Center: Space-filling representation of the complex of (*R*,*R*)-**1** with (*S*)-**2** generated by Chem 3D Plus, based on the X-ray coordinates. Right: Projection of the X-ray crystal structure of the complex (*R*,*R*)-**1** with (*S*)-**2** as viewed along the pseudo C_2 axis from the (*S*)-**2** side.

Interactions of (*R*,*R*)-**1** toward (*R*)- and (*S*)-**2** in solution could be easily monitored by ^{1}H NMR spectroscopy. Downfield shift noted for hydroxyl protons of **2** in a $CDCl_3$ solution containing (*R*,*R*)-**1** indicated the formation of intermolecular hydrogen bonding and consequently, a titration experiment could be carried out to determine thermodynamic parameters of the complexation.[7] Analysis of a set of data using a least-squares method indicated the association constant $K_{RR\text{-}S} = 9.9 \pm 0.3$ M^{-1} for the (*R*,*R*)-**1**-(*S*)-**2** system and $K_{RR\text{-}R} = 9.4 \pm 0.2$ M^{-1} for the (*R*,*R*)-**1**-(*R*)-**2** system at 298 K.[7] The magnitude of enantioselection at this temperature was only slight but became greater with decrease in temperature. Thus, definitive *S*-selectivity of (*R*,*R*)-**1** toward **2** was confirmed with $K_{RR\text{-}S} = 91.2 \pm 1.3$ M^{-1} and $K_{RR\text{-}R} = 59.2 \pm 0.3$ M^{-1} at 263 K. Temperature dependence of the association constants was assessed from a van't Hoff plot which indicated in ΔH = -9.9 Kcal/mol and ΔS = -28.6 e.u. for the (*R*,*R*)-**1**-(*S*)-**2** system and ΔH = -8.2 Kcal/mol and ΔS = -23.3 e.u. for the (*R*,*R*)-**1**-(*R*)-**2** system.[7,8] The level of ΔH in both systems was quite consistent with

the formation of dual hydrogen bonds, but it should be noted that the binding enthalpy of (*R*,*R*)-**1** with (*S*)-**2** was greater by 1.7 Kcal/mol than that of (*R*,*R*)-**1** with (*R*)-**2**.

Resonance of the isopropyl methyl protons of free (*R*,*R*)-**1** appeared at 1.128 and 1.131 ppm as a pair of doublets at 263 K. The shift difference between these signals was enlarged on complexation with **2**. The observed peak splitting was ascribable to restriction of rotation about a single bond between the imino nitrogen and isopropyl methine carbon due to access of the **2** molecule through dual N···HO bonds. Limiting chemical shifts[9] of these protons in the complex at 263 K were 1.17 and 1.43 ppm for the (*R*,*R*)-**1**-(*S*)-**2** system, and 0 .84 and 1.14 ppm for the (*R*,*R*)-**1**-(*R*)-**2** system. Resonance of the isopropyl methines shifted downfield by 0.15 ppm when the complex had formed throughout with (*S*)-**2**. In contrast, an upfield shift of 0.14 ppm occurred for the (*R*,*R*)-**1**-(*R*)-**2** system. These shifts may possibly have been due to anisotropic effect based on the ring current of **2**. It should be noted that the arrangement of *N*-isopropyl substituents of (*R*,*R*)-**1** and naphthyl rings of (*S*)-**2** in the X-ray crystal structure of the complex made it possible for the naphthyl rings to deshield some of the isopropyl protons. The downfield shift observed for the (*R*,*R*)-**1**-(*S*)-**2** system is thus consistent with the binding geometry of the crystal structure.

All geometrical parameters of the complex in the solid state were optimized by semiempirical PM3 calculation[10,11] to eliminate the packing effects in the crystal lattice. The calculation was converged through slight modification of structure. For example, hydrogen bond distances (N···H) were shortened to 1.83 Å and 1.86 Å and the close contact observed in the crystal structure was preserved. The calculated heat of formation of the optimized (*R*,*R*)-**1**-(*S*)-**2** complex was -149.04 Kcal/mol. Interaction energy of -10.08 Kcal/mol was obtained by subtracting the energy of unrelaxed structures[12] of isolated components from the energy of the complex.

The results of above computation indicated the geometrical arrangement of the X-ray crystal structure of the complex to be reproducible without the packing effects. The NMR study showed the relevance of the complex motif in the crystal structure to the enantioselective complexation in $CDCl_3$. We thus conclude that the X-ray structure of the co-crystal comprised of (*R*,*R*)-**1** and (*S*)-**2** is equivalent to the core structure in dynamic complexation involving molecular motion such as twisting and rocking between these components in solution.

The present data confirm dual hydrogen bonding proposed as our working hypothesis for enantioselective complexation. The binding geometry demonstrated here should serve as a basis for simulating molecular recognition effected by a selector-selectand system that applies complementarity of twists[13] in dual interactions.

Acknowledgments. We thank Mrs. T. Sakuma (Tokyo College of Pharmacy) for NMR measurements. This research was partly supported by grants from the Ministry of Education of Japan (Grant-in Aid No. 03771698 and No. 06772081)

REFERENCES and NOTES

1. In this respect, an X-ray crystal structure of such a complex is of significance because of its geometrical parameter integrity. For examples of the crystal structure relevant to chiral molecular recognition in solution, see: (a) Wang, X.; Erickson, S. D.; Imori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128-4137. (b) Izatt, R. M.; Zhu, C. Y.; Dalley, N. K.; Curtis, J. C.; Kou, X; Bradshaw, J. S. *J. Phys. Org. Chem.* **1992**, *5*, 656-662. (c) Daeppen, R.; Rihs, G.; Mayer, C.W. *Chirality* **1990**, *2*, 185-189. (d) Harata, K *J. Chem. Soc., Perkin Trans. 2* **1990**, 799-804. (e) Pirkle, W. H.; Burke, J. A., III; Wilson, S. R. *J. Am. Chem. Soc.* **1989**, *111*, 9222-9223. (f) Francotte, E.; Rihs, G. *Chirality* **1989**, *1*, 80-85. (g) Dobashi, Y.; Hara, S.; Iitaka, Y. *J. Org. Chem.* **1988**, *53*, 3894-3896. (h) Knobler, C. B.; Gaeta, F. C. A.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 330-333. (i) Hamilton, J. A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 5833-5841. (j) Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1984**, *49*, 353-357.
2. Dobashi, Y.; Dobashi, A.; Ochiai, H.; Hara, S. *J. Am. Chem. Soc.* **1990**, *112*, 6121-6123.
3. In ref. 2, (*R,R*)-**1** was found to be highly enantioselective in complexation with *trans*-9,10-dimethyl-9,10-dihydrophenanthrene-9,10-diol in $CDCl_3$. The expected *S,S*-selectivity of (*R,R*)-**1** toward this diol was confirmed and enantioselection of ca. 0.9 Kcal/mol ($\Delta(\Delta G)$ was achieved at 296 K.
4. (a) Crystal data for (*R,R*)-**1**: (*S*)-**2** complex ($C_{12}H_{20}O_4N_2 \cdot C_{20}H_{14}O_2$, *Mr* 542.6): crystal system monoclinic; space group $P2_1$; lattice constants, a = 14.670 (7), b = 8.833 (4), c = 11.250 (5) Å, β = 92.98 (5)°, V = 1456 Å^3, Z = 2, D_{calc} = 1.238 g cm^{-3}. A total of 3029 reflections above the 2σ(I) level, with the 2θ range of 6° through 156°, was collected on a Philips PW 1100 diffractometer using Cu Ka radiation (μ 6.6 cm^{-1}). The 126 reflections were symmetry equivalent and gave an RF value of 0.029. The structure was determined by the direct method using the MULTAN program,[4b] and the refinement was carried out by the block-diagonal least-squares method. The 2903 reflections were used for the refinement and the final R value was 0.049. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located on the difference electron-density map and refined including their isotropic temperature factors. (b) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A.* **1971**, *27*, 368-376.
5. (a) A torsion angle of 87.8° corresponding to that of C24-C23-C22-C13 in this study was calculated from X-ray coordinates of a single crystal of 1,1'-bi-2-naphthol.[5b] (b) Gridunova, G. V.; Furmanova, N. G.; Shklover, V. E.; Struchkov, Yu. T.; Ezhkova, Z. I.; Chayanov, B. A. *Sov. Phys. Crystallogr.* **1982**, *27*, 290-294.
6. The conformer equivalent to that presented in this study was observed for an X-ray crystal structure of (*R,R*)-**1**. Computational simulation indicated this type of conformer to be most stable. Details will be published elsewhere.
7. A 7.1x10^{-3} M solution of each enantiomer of **2** was used for the titration experiment since the self-association of a single enantiomer of **2** was negligible at this concentration. The concentration of (*R,R*)-**1** was varied from 8.7x10^{-3} to 0.150 M for (*S*)-**2**, and 0.027 to 0.139 M for (*R*)-**2**. Data were collected at five and six different concentrations of (*R,R*)-**1** for (*R*)- and (*S*)-**2**, respectively. All solutions were prepared at 298 K, and thermal expansion was corrected. Analysis for obtaining the association constants was conducted assuming 1:1 stoichiometry for complexation. A correlation coefficient exceeding 0.999 was obtained in all cases.
8. Temperatures used were 263 K, 273 K, 283 K, and 298 K. A plot of ln$K$ versus 1/T gave a straight line with a correlation coefficient over 0.999 for each diastereomeric system.
9. Limiting chemical shifts were determined by extrapolation of the linear plot of observed chemical shifts versus % complexation, calculated using the association constant.
10. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209-220.
11. Calculations were carried out using version 5.0 of the MOPAC program, as it was implemented in SYBYL 6.0 (TRIPOS Associates, Inc., St. Louis, MO). PRECISE option was used throughout.
12. Topiol, S.; Talbot, G. *J. Am. Chem. Soc.* **1990**, *112*, 8734-8736.
13. A twisted receptor for molecular recognition of cyclohexane triol derivatives via formation of geometrically complemental triple hydrogen bonding was recently developed. (a) Huang, C. Y.; Cabell, L. A.; Lynch, V.; Anshlyn, E. V. *J. Am. Chem. Soc.* **1992**, *114*, 1900-1901. (b) Huang, C. Y.; Cabell, L. A.; Anshlyn, E. V. *J. Am. Chem. Soc.* **1994**, *116*, 2778-2792.

(*Received in Japan* 29 *July* 1994)