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# A Cyclochiral Conformational Motif Constructed Using a Robust Hydrogen-Bonding Network

Kenji Mishiro,* Takumi Furuta,* Takahiro Sasamori, Kazuhiro Hayashi, Norihiro Tokitoh, Shiroh Futaki, and Takeo Kawabata

Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011, Japan

Supporting Information

**ABSTRACT:** A novel conformational motif constructed with a robust intramolecular hydrogen-bonding (H-bonding) network was discovered. A pyrrolidine derivative possessing four identical amide substituents at C(2) and C(5) formed a strong intramolecular H-bonding network consisting of all the amide groups. This conformation yielded a cyclochiral structure with a handedness that depended on the directionality of the H-bonding network. The most stable compound was isolated and applied to the acylative kinetic resolution of secondary alcohol. The handedness of the H-bonding network was biased by the presence of chiral substituents, and the preferred direction could be switched under an external stimulus. A structural analysis using NMR, X-ray crystallography, and theoretical calculation techniques indicated that the conformation of the substituents was highly ordered and depended on the directionality of the H-bonding network.

Higher-order structures of proteins, such as $\alpha$-helices and $\beta$-sheets, are supported by a continuous hydrogen-bonding (H-bonding) network constructed from alternating sequences of N−H and C═O moieties in a series of amide groups on the protein backbone.[1] Continuous H-bonding array is also widely employed to construct artificial helical[2] and sheet[3] structures. Rebek and other groups have reported cavity and capsule shaped functional molecules constructed using a continuous H-bonding network.[4]

Hydrogen bonding can give rise to conformational chirality in a molecule, the handedness of which will depend on the directionality of the intramolecular H-bonding as typically shown by enantiomeric structures of a malonamide derivative (Figure 1). Racemization barriers of these molecules tend to be low because the H-bonding stabilization energy is not sufficiently high to preserve the chiral conformation. The isolation of directional stereoisomers has been thought to be impossible without chiral auxiliary groups.[4j]

Significant efforts have been directed toward characterizing the strengths of H-bonding. The acidity of a H-bonding donor, the basicity of a H-bonding acceptor, the bond length, and the geometry (extent of orbital overlap) governing the donor and acceptor can critically affect the stability of a H-bonding.[5] Recently cumulative stabilizing effect of multiple H-bonding is attracting intense attention. Jorgensen suggested the importance of secondary electrostatic interactions in the stability of contiguous H-bonding array.[6] Kass explored the synergetic stabilizing effects of an appropriately arranged continuous H-bonding array. The synergetic stabilizing effects of the continuous H-bonding have been applied toward the development of strong Brønsted acids and bases.[7] These cumulative stabilizing effects might be also useful for the design of a robust higher-order structure.

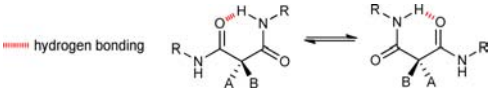


**Figure 1.** Interconversion of conformational central chirality of a malonamide derivative.

We developed several nucleophilic catalysts based on the 4-pyrrolidinopyridine (PPY) structure, which features amide substituents.[8] These catalysts were effective for the regioselective monoacylation of polyols[8a] and the acylative kinetic resolution and desymmetrization of diols.[8b−d] During the course of the catalyst development process based on PPY derivatives, we synthesized compound **1** having four identical amide substituents at the pyrrolidine moiety. The $^1$H NMR spectra of **1** displayed four identical amide protons as two sets of nonequivalent signals at a quite low field (12.17 and 11.95 ppm). The chemical shifts of these amide protons did not depend on the concentration of **1**, suggesting that all four amide groups were involved in a strong intramolecular H-bonding network. X-ray analysis of **1** revealed a $C_2$ symmetric cyclic intramolecular H-bonding network constructed entirely from the amide groups. The distances between the amide nitrogen and oxygen atoms were 2.695 Å and 2.819 Å, respectively (Figure 2).

In this conformation, **1** had a chirality depending on the directionality of the H-bonding network composed of two identical malonamide moieties having the same conformation. The interconversion of the enantiomers **1a** and **1b** (racemization) should occur by 180° rotation of all the amide groups (Figure 3a). Take the conformation in which all of the amide groups are arranged at appropriate positions into account, we envisioned that the H-bonding arrangement could be tuned to create a chiral structure that was sufficiently robust to permit isolation of each enantiomer. Herein, we report the first example of a stable and isolable cyclochiral structure derived from a directionality of a continuous H-bonding network.

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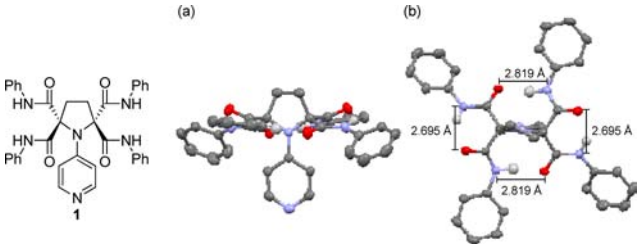



**Figure 2.** X-ray crystallographic analysis of **1**. (a) Side and (b) top views. Distances between the amide carbonyl oxygen and the nitrogen are given in Å.

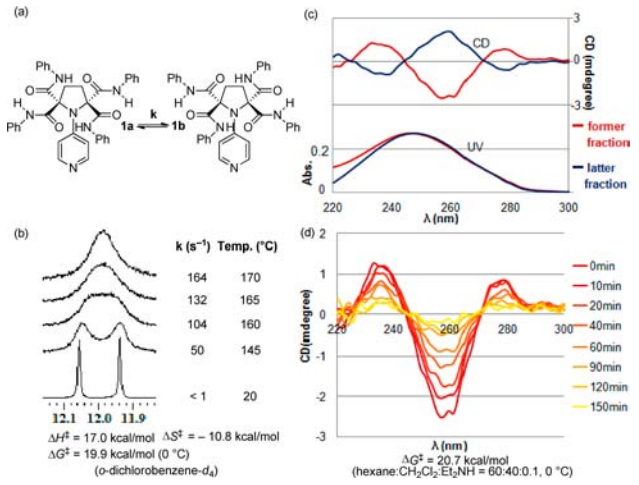


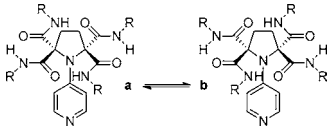

**Figure 3.** Analysis of the racemization barrier of **1**. (a) Interconversion of the enantiomers of **1** through rotation of the amide moieties. (b) Coalescence of the amide protons observed in a VT NMR study in *o*-dichlorobenzene-$d_4$. (c) CD spectra of both enantiomers in hexane:$CH_2Cl_2$:$Et_2NH$ (60:40:0.1). (d) A trace of racemization was observed based on the CD spectra.

The racemization barrier of **1** was evaluated based on full line shape analysis of variable temperature (VT) NMR spectra. The rotation of the amide groups, which was thought to be a key step in the racemization, was indicated by the coalescence of the two set of amide signals. The line shape analysis of these signals in *o*-dichlorobenzene-$d_4$ using WINDNMR-Pro,[9] and following Eyring plot gave $\Delta H^{\ddagger}$ = 17.0 kcal/mol, $\Delta S^{\ddagger}$ = −10.8 cal/mol·K and $\Delta G^{\ddagger}$ = 19.9 kcal/mol at 0 °C (Figure 3b).

Next, HPLC analysis of **1** using a chiral stationary phase was examined (see the Supporting Information, SI). Although the chromatogram indicated partial racemization of **1** during the analysis, the enantio-enriched isomers could be successfully separated and collected by preparative HPLC at 0 °C. The mirror image of the CD spectra obtained from the isomers indicated that the isomers were enantiomers (Figure 3c). The racemization barrier at 0 °C was found to be 20.7 kcal/mol, based on the decay of the CD intensity (Figure 3d). The racemization barrier was similar to the amide rotational barrier (19.9 kcal/mol) obtained through VT NMR analysis (Figure 3b). These results suggested that the amide rotation was the rate-limiting step to the racemization of **1**.

The effects of the amide substituents and solvent on the racemization barrier were investigated in a VT NMR study (Table 1, entries 1−10). $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of the racemization process varied depending on the amide substituents. These parameters were thought to be affected by both electronic and steric factors of the amide substituents. The strength of the H-bonding network is generally higher for combinations of more acidic H-bonding donors and more basic H-bonding acceptors; however, the strength of the cyclic H-bonding network seemed not controllable simply through the electronic tuning of the amide group because an increase in the acidity of one of the N−H group by electronic tuning weakens the basicity of the C═O group in the corresponding amide. In fact, *p*-Br and *p*-OMe substitution on the phenyl groups of **1** did not show the clear electronic effect (Table 1, entries 1−3). Although the steric effect of the amide substituents on the racemization process was not clearly observed, it might affect on various factors such as solvation to the amide groups, orbital overlap of the H-bonding, and steric repulsion of the neighboring amide groups. Solvent effect on the racemization was clearly explained by comparison of the activation parameters (Table 1, entries 7−10). Smaller values of $\Delta H^{\ddagger}$ and larger negative values of $\Delta S^{\ddagger}$ for **7** and **8** in DMSO-$d_6$ than those in *o*-dichlorobenzene-$d_4$ strongly suggested that the H-bonding network was disrupted by the solvation of DMSO-$d_6$.

**Table 1. Effects of Substituents and Solvent on the Racemization Barriers**




| Entry | R | Solvent | $\Delta G^{\ddagger a}$ | $\Delta H^{\ddagger b}$ | $\Delta S^{\ddagger b}$ |
|---|---|---|---|---|---|
| 1 | (1) | *o*-$C_6D_4Cl_2$ | 19.9 | 17.0 | − 10.8 |
| 2 | (2) | *o*-$C_6D_4Cl_2$ | 21.0 | 18.4 | − 9.4 |
| 3 | (3) | *o*-$C_6D_4Cl_2$ | 20.3 | 17.7 | − 9.8 |
| 4 | (4) | *o*-$C_6D_4Cl_2$ | 20.0 | 17.5 | − 9.2 |
| 5 | (5) | *o*-$C_6D_4Cl_2$ | 19.1 | 16.9 | − 8.3 |
| 6 | (6) | *o*-$C_6D_4Cl_2$ | 19.1 | 16.2 | − 10.8 |
| 7 | (7) | *o*-$C_6D_4Cl_2$ | 18.7 | 15.6 | − 11.5 |
| 8 | | DMSO-$d_6$ | 16.1 | 12.0 | − 15.0 |
| 9 | (8) | *o*-$C_6D_4Cl_2$ | 20.7 | 17.8 | − 10.6 |
| 10 | | DMSO-$d_6$ | 17.0 | 12.0 | − 18.0 |
| 11 | (9) | *o*-$C_6H_4Cl_2$ | 23.8 | 21.4 | − 8.8 |

[a]kcal/mol at 0 °C. [b]These activation parameters, $\Delta H^{\ddagger}$ (kcal/mol) and $\Delta S^{\ddagger}$ (cal/mol·K), were determined by VT NMR with line shape analysis and time-dependent racemization of an isolated enantiomer by HPLC analysis for entries 1−10 and entry 11, respectively, and following Eyring plots.

Introduction of dicyclohexylmethyl group dramatically increased the racemization barrier to 23.8 kcal/mol at 0 °C (Table 1, entry 11). The enantiomers of **9** could be completely separated and isolated by preparative HPLC using chiral stationary phase. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the racemization process of **9** were evaluated by Eyring plot based on temperature dependency of racemization rate constant obtained by chiral HPLC analysis (see the SI).

The half-life of racemization of **9** in hexane at 20 °C was found to be 173 h, corresponding to the racemization barrier of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25.5 kcal/mol. Furthermore, **9** was found to be quite stable in the solid form, and no racemization was observed, even after storing for one month at 20 °C. The energy-minimized structure of **9**, which was generated by a molecular modeling conformational search (see the SI), revealed that all of the amide groups played a role in the cyclic H-bonding network, as shown in Figure 4. All the dicyclohexylmethyl groups assumed

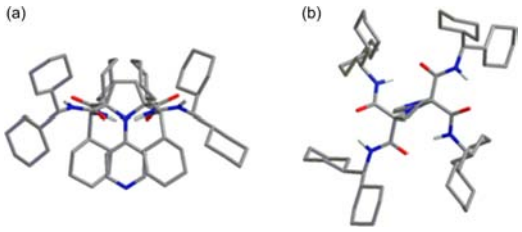


**Figure 4.** Energy-minimized conformation of **9**. (a) Side and (b) top views.

the same conformation, in which the hydrogen atoms were present in an eclipsed conformation with respect to the carbonyl groups, which minimized the 1,3-allylic strain.[10]

The stability of **9** might be explained by the following kinetic and thermodynamic reasons. The optimized structure generated by molecular modeling study indicated that the cyclohexyl groups are surrounding the cyclic H-bonding network. This might contribute to kinetic stabilization[11] of the H-bonding network by preventing from solvation. The cyclohexyl groups would also contribute to enhance the strength of the H-bonding network. The steric repulsion between neighboring these bulky groups might allow all amide groups in a homogeneous geometry, in which the orbital overlap of the H-bonding is facilitated. The large $\Delta H^{\ddagger}$ value (21.4 kcal/mol) for the racemization of **9** supports this thermodynamic factor.

The compounds we have described above were chiral, with a handedness that depends on the directionality of the H-bonding network; therefore, the introduction of chiral substituents should lead to the conversion of enantiomeric conformers to the diastereomeric isomers. Compound **10**, which included four identical (*R*)-1-(1-naphthyl)ethylamino moieties, was prepared to investigate the conformations of the diastereomeric conformers. As expected, two conformational isomers of **10** (**10a** and **10b**) were observed separately in the $^1$H NMR analysis in a ratio of 73:27 in $CDCl_3$. The HPLC chromatogram suggested that the molecules underwent interconversion among the diastereomeric conformers, even at 0 °C (see SI). The $^1$H NMR spectra of the conformers of **10** were quite characteristic. Figure 5 shows that the signals corresponding to the pyrrolidine hydrogen atoms in the major conformer were shifted upfield (2.2−1.8 ppm) relative to the corresponding hydrogen atoms of the minor isomer (2.8−2.6 ppm). On the other hand, the signals corresponding to the pyridine hydrogen atoms in the minor isomer were shifted upfield (7.2 and 5.4 ppm) relative to the corresponding hydrogen atoms of the major isomer (8.4 and 6.3 ppm). In general, the signals of the pyrrolidine and pyridine protons in **1**−**9** appeared around 2.5 and 8.0/6.0 ppm, respectively (see the SI). Therefore, the pyrrolidine proton signals of the major isomer and the pyridine proton signals of the minor isomer were substantially shifted upfield. These results indicated that the conformations of the amide substituents could be tuned

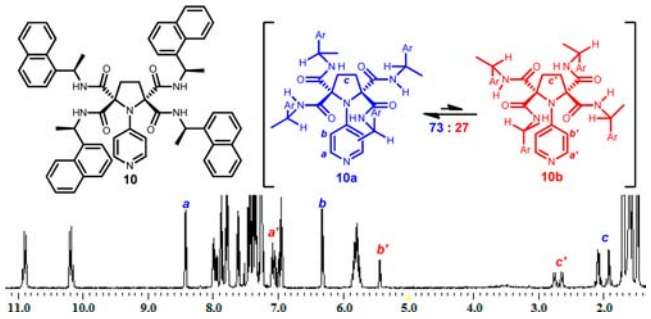


**Figure 5.** $^1$H NMR spectrum of **10** in $CDCl_3$ at 20 °C.

according to the directionality of the H-bonding network. Thus, all aromatic substituents were thought to be oriented in the same direction, thereby shielding one side of the molecule. As shown in Figure 4, all amide substituents were thought to prefer the same conformation to minimize the allylic strain on the carbonyl groups. Therefore, the conformations of the major and minor conformers were thought to resemble those of **10a** and **10b**, respectively. The X-ray crystallographic analysis of a single crystal of **10** supported the hypothesis that the conformations of the amide substituents depended on the directionality of the H-bonding network (Figure 6). Although

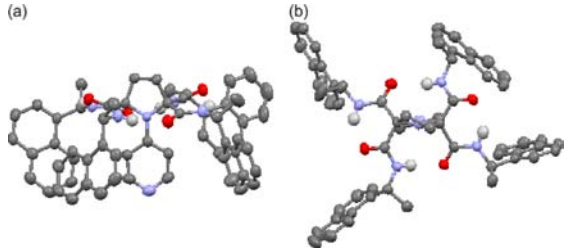


**Figure 6.** X-ray crystallographic analysis of **10**. (a) Side and (b) top views.

the reason why **10a** was a major conformer was not clear, van der Waals repulsion[4i] and associative $\pi-\pi$ or CH-$\pi$ interactions between side chains and pyrrolidine or pyridine moiety might play key roles to determine the population of **10a** and **10b**.[12]

Protonation of **10** by HCl yielded **10b-HCl** as the major isomer in $CDCl_3$ (**10a-HCl**:**10b-HCl** = 32:68, Figure 7). The pyridine signals in **10b-HCl** (6.0 and 4.9 ppm) were further shifted upfield from **10b** (7.2 and 5.4 ppm) despite its cationic form. The result suggests the cationic pyridinium moiety strongly associated with the naphthyl group by $\pi-\pi$ or CH$-\pi$

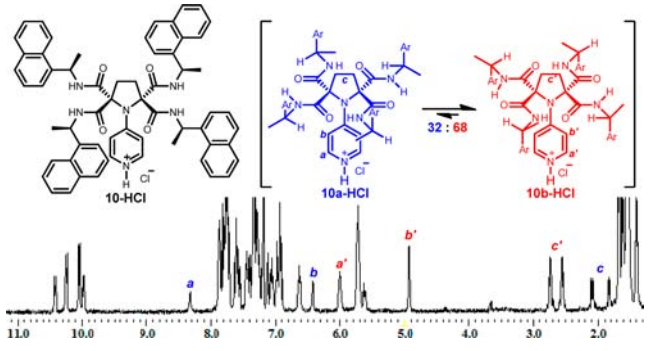


**Figure 7.** $^1$H NMR spectrum of **10-HCl** in $CDCl_3$ at 20 °C.


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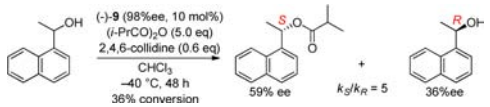
interactions.[13] These stabilization effects might contribute to the switching of the population of the directional isomers.

Finally the utility of the chiral structure of **9** for asymmetric reactions was investigated by the acylative kinetic resolution of *rac*-1-(1-naphthyl)ethylalcohol using isobutyric anhydride in the presence of (−)-isomer of **9** isolated by preparative HPLC with chiral stationary phase. The reaction proceeded to give the corresponding acylate and the recovered alcohol with a 59% ee and 36% ee in a 36% conversion ($k_S/k_R = s = 5$) without racemization of (−)-**9**. Thus, the chiral structure was proved to be applicable to asymmetric reaction (Scheme 1).

**Scheme 1. Kinetic Resolution of Racemic Secondary Alcohol in the Presence of (−)-9**




We succeeded in developing a cyclochiral structure constructed using a robust intramolecular H-bonding network, which enabled the first isolation and application of a stable cyclochiral molecule whose chirality derives from intramolecular H-bonding directionality. Conformational chemistry based on such robust H-bonding arrays will pioneer a new field of organic chemistry and provide useful functional molecules such as asymmetric catalysts, host molecules, and organic materials.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Authors

mishiro@fos.kuicr.kyoto-u.ac.jp
furuta@fos.kuicr.kyoto-u.ac.jp

### Notes

The authors declare no competing financial interest.

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