Helical Stereocontrol of 2,6-Bis{(2-arylcarbamoylphenyl)carbamoyl}pyridine Derivatives by Use of Chiral Auxiliaries

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The helical stereochemistry of 2,6-bis{(2-arylcarbamoylphenyl)carbamoyl}pyridine derivatives **1** can be controlled by the chiral auxiliaries bonded to the terminal carbonyl groups. Their preferred helical stereochemistry was determined from the signs and shapes of their CD spectra by the exiton chirality method.

The helical molecules have received considerable attention because of promising candidates for chiral ligands and auxiliaries in asymmetric synthesis.[1] Recently, an efficient method for the synthesis of optically active helicene derivatives has been developed by the use of chiral auxiliaries.[2,3] We have interested in the control of helical stereochemistry of 2,6-bis{(2-arylcarbamoylphenyl)carbamoyl}pyridine derivative **1**, which was reported by Hamilton (R = OMe).[4,5] Pyridine derivatives **1** have a single turn helical structure stabilized by intramolecular hydrogen bonding and π–π stacking interactions to form a tight coil with close contact between the two terminal aromatic rings. The introduction of chiral auxiliaries to the terminal aromatic rings of **1** would be expected to gain a predominance of left- or right-handed helical stereochemistry imposed by the steric effects of their stereogenic centers.[6] In this paper, we wish to report the stereoselective synthesis of **1** by the use of chiral auxiliaries and properties of circular dichroism (CD).

The introduction of chiral auxiliaries to the terminal carbonyl groups of **1** was carried out by the condensation of isatoic anhydride with chiral amines or chiral alcohols to afford 2-carbamoyl- and 2-oxycarbonylaniline derivatives,[7] which gave **1a**–**1k**[8] in Chart 1 by Hamilton's procedure.[4] The ^{1}H NMR signals of **1a**–**1k** were assigned by NOESY experiments. The helical structures of these derivatives were confirmed by the ^{1}H NMR spectra, which indicate large down-field shift of amide N*H* resonance and up-field shift of protons attached to the 4-position of the terminal aromatic rings.[4] Although ^{1}H NMR measurement revealed the helical structures of **1a**–**1k**, information about the helical chirality and the diastereomer ratio were not obtained.

In order to determine the helical stereochemistry (*M* and *P*) of **1**, the exiton chirality method[9] was applied. The two 2-arylcarbamoylphenyl groups in C_2-symmetrical structure of **1** are suitable chromophores for this method. The observed UV spectra of **1a** and its half part **2a** showed absorption due to the 2-arylcarbamoylphenyl chromophores (Figure 1b). The CD spectrum of **1a** at 290–360 nm typically showed bisignate shapes and large magnitude (Figure 1a). Expectedly, the CD spectrum of **1b** which have chiral auxiliaries of opposite configuration derived from (*S*)-phenethylamine showed mirror imaged CD spectrum compared to that of **1a**. On the other hand, the CD spectrum of **2a** only showed positive Cotton effect. The presence of such a bisignate CD curves clearly demonstrates that the exiton coupling mechanism is operative. According to the exiton-coupled CD curve of **1a**, the exiton chirality is defined as negative (i.e., the sign of the first Cotton effect of the couplet at longer wavelength is negative and the sign of the second Cotton effect of the couplet at shorter wavelength is positive). The exiton chirality method strongly suggests that this result showed the left-handed screwness between the two 2-arylcarbamoylphenyl groups. Thus, compound **1a** has the *M*-helical conformation predominantly.[10] Independently, the absolute helical stereochemistry of **1a** was determined to be (*R*,*M*,*R*)-form by X-ray crystallography (Figure 2).[11] The left-handed helical structure of **1a** determined by the X-ray structural analysis agrees with the result of CD measurement. In contrast the exiton chirality of **1b** is defined as positive. This suggests compound **1b** has the *P*-helical conformation predominantly. Therefore, the exiton coupled chirality method could be applied to the determination of the preferred helical stereochemistry of **1**.[12]

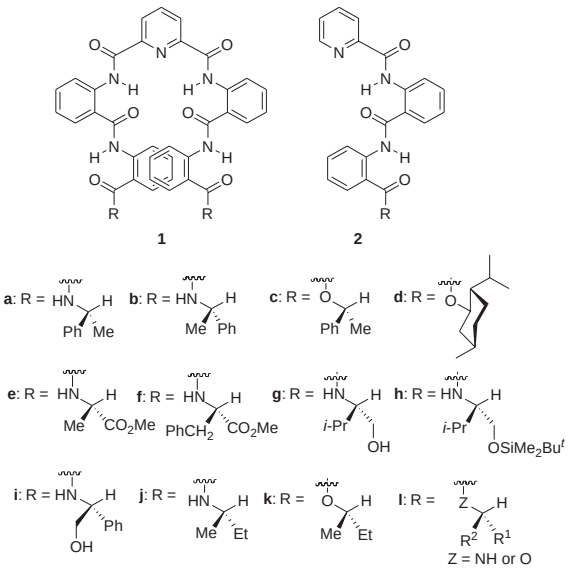

Chart 1.

Similar assignment is applicable to the derivatives **1c**–**1k**. The results of CD measurement are shown in Table 1. Pyridine derivatives **1c**–**1i** indicate the effective stereocontrol because these CD spectrums showed bisignate coupled patterns. Since the exiton chirality of **1c**, **1d**, **1f**, and **1g** are defined as negative, the predominance of their helical stereochemistry are *M*-form. In the case of **1e**, **1h**, and **1i**, the exiton chirality are defined as positive and the predominant helical stereochemistry are *P*-form. Therefore, the helical chirality of **1** can be controlled by the chiral auxiliaries. On the other hand, **1j** and **1k** did not exhibit significant bisignate CD curves.

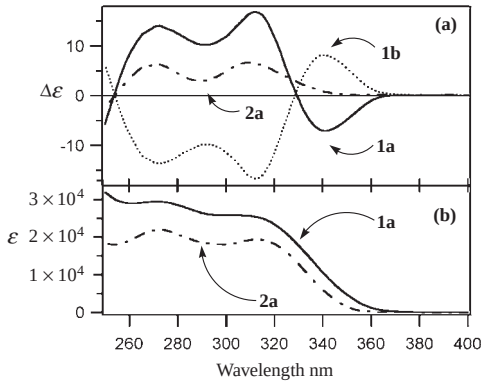

Figure 1. CD and UV spectra of **1a**, **1b**, and **2a**.

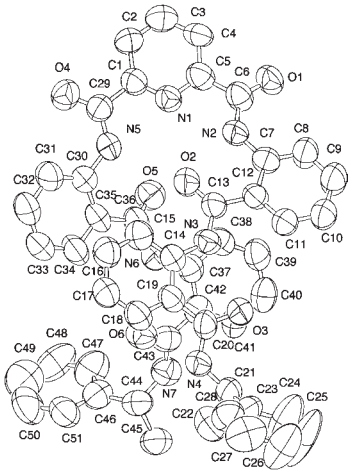

Figure 2. ORTEP drawing of **1a**.

Table 1. Signs of split Cotton effects and molar ellipticities for **1**[a]

Compounds	First Cotton $\Delta\varepsilon/\lambda$	Second Cotton $\Delta\varepsilon/\lambda$	Helical stereo-chemistry
1a	−7.07 (341)	+16.8 (312)	**M**
1b	+7.18 (340)	−16.7 (313)	**P**
1c	−2.70 (352)	+13.7 (320)	**M**
1d	−8.42 (347)	+8.02 (320)	**M**
1e	+3.45 (342)	−8.18 (315)	**P**
1f	−14.1 (339)	+5.70 (298)	**M**
1g	−31.5 (339)	+8.39 (314)	**M**
1h	+13.7 (333)	−8.48 (292)	**P**
1i	+29.7 (341)	−17.7 (315)	**P**
1j[b]	none	none	—
1k[c]	2.33 (343)	none	—

[a]All spectra was measured in CH_3CN (ca. 5×10^{-5} M).
[b]No significant Cotton effect was detected.
[c]Only small positive Cotton effect was observed.

The probable mechanism for the helical stereocontrol of **1** by the chiral auxiliaries can be explained by the conformation of **1l**.[13] The predominance of left- and right-handed stereochemistry of **1** is governed by the steric bulkiness of substituent R^1 and R^2. If R^2 was sterically more bulky than R^1 (**1a**, **1c**, **1d**, **1f**, and **1g**), *M*-form was predominant owing to minimizing the steric repulsion between the two R^2 groups. Compounds **1j** and **1k** gave no predominant isomer of *P*- or *M*-form, because the steric bulkiness of the two substituents on (*S*)-2-butyl group is nearly equal.

In conclusion, we have developed a simple method to control the left- and right-handed helical stereochemistry of **1** by the use of chiral auxiliaries bonded to the terminal carbonyl groups and have reported a reliable nonempirical assignment of the absolute helical stereochemistry of **1**. Work is now in progress to extend to this approach to design of a novel CD probe of chiral compounds.

References and Notes

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10 Although the exiton moment of chromophore in **1** is unclear, the C_2 symmetrical structure of **1** gave the same relative crossover arrangement between the dipole moments of chromophores.

11 See supporting information.

12 Unfortunately, the ratio of diastereomers was unclear in solution, but only one diastereomer was detected by the X-ray study of **1a**.

13 In the conformation of **1l**, hydrogen atom attached the stereogenic center is located far a way from the terminal aromatic ring. R^2 is placed above or below the plane, which was formed by the one arm of the hydrogen-bonded helical structure. This model was supported by the X-ray crystallography of **1a** and the MM2 calculation. A similar structural analysis was reported. A. Bilz, T. Stork, and G. Helmchen, *Tetrahedron: Asymmetry*, **8**, 3999 (1997).

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