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Combination of a New Chiroptical Probe and Theoretical Calculations for Chirality Detection of Primary Amines

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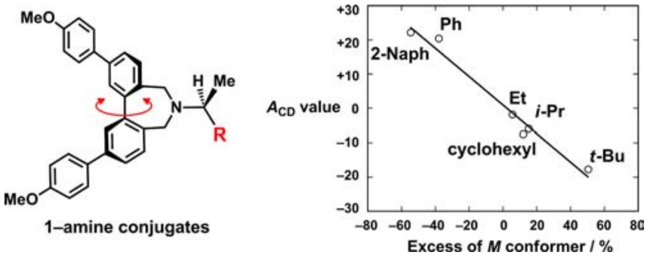
ABSTRACT



A method to determine absolute configurations of primary amines by combined use of a chiroptical probe 1 and theoretical calculations is reported. Probe 1 is linked to chiral primary amines yielding 1−amine conjugates, which exhibited exciton coupled circular dichroism in the *m*-quaterphenyl chromophores. The ratios between the *P* and *M* conformers of the 1−amine conjugates, which are calculated with DFT, were correlated highly with the sign and amplitude of the observed CD spectra.

The development of a practical approach to determine the absolute configuration and enantiomeric excess (ee) of natural and artificial molecules is a challenge in the life and material sciences fields. One of the practical methods to determine absolute configurations of chiral molecules is ^{1}H NMR anisotropy.[1] Especially, the modified Mosher method using the ring current effect of the aryl moiety has been widely used to determine the absolute configurations of chiral alcohols.[1−6] Owing to the complexity of the conformational distribution, application of the method to chiral amines has been limited.[7−10] Circular dichroism (CD) is a powerful tool for determination of the stereochemistry of chiral molecules on the microgram scale.[11−14] To amplify and detect the chirality of monofunctional molecules by CD, an effective probe which has the following features is required: (i) the probe can be readily coupled to analytes, (ii) the probe can detect a slight difference in steric bulkiness, and (iii) the probe can indicate absolute configurations in a nonempirical way.

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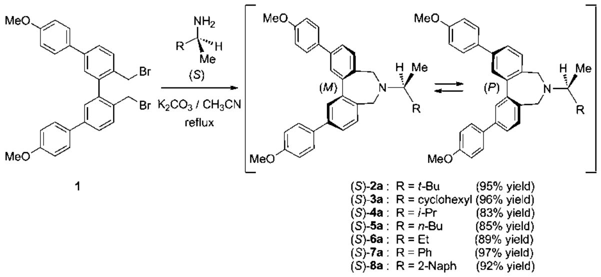
Recently, researchers have reported effective probes to determine the absolute configurations and ee of chiral monoamines by CD.[15−27] Such methods previously reported, however, do not fully meet the above criteria. Elaborate derivatizations of analytes and complicated conformational analysis are required.

Exciton-coupled CD (ECCD) is a potentially sensitive method for chiral detection. The relationship between the sign of the CD Cotton effect and the twist of the two electric transition moments of molecules has been established in a nonempirical manner.[11−14,28−30] In connection with a previous paper,[30] we designed a new chiroptical probe **1** with a *m*-quaterphenyl group to determine the absolute configurations of primary amines. We expected that (i) probe **1** would couple readily with chiral primary amines yielding **1**−chiral amine conjugates with a seven-membered ring, (ii) information on the absolute configurations of the amines would be transcribed into a spacial arrangement of two biphenyl units in the *m*-quarter phenyl group which is detected directly by the ECCD method,[30] and (iii) the conformers of the **1**−chiral amine conjugates would be predicted by the analysis of conformational distributions using theoretical calculations. As a result, the combination of the new chiroptical probe **1** and theoretical calculations would permit determination of the absolute configurations in a nonempirical manner. We here report an effective method to determine the absolute configurations of chiral primary amines.[31]

The chiroptical probe **1** was synthesized from 4-bromobenzoic acid via six steps with an overall yield of 20% (see the Supporting Information (SI)). **1**−amine conjugates, (*S*)-**2a**−(*S*)-**8a**, were prepared by the reaction of **1** with chiral primary amines in the presence of K_2CO_3 in CH_3CN (Scheme 1).

Scheme 1. Coupling Reaction of **1** and Chiral Primary Amines



(*S*)-**2a** :	R = *t*-Bu	(95% yield)
(*S*)-**3a** :	R = cyclohexyl	(96% yield)
(*S*)-**4a** :	R = *i*-Pr	(83% yield)
(*S*)-**5a** :	R = *n*-Bu	(85% yield)
(*S*)-**6a** :	R = Et	(89% yield)
(*S*)-**7a** :	R = Ph	(97% yield)
(*S*)-**8a** :	R = 2-Naph	(92% yield)

Figure 1 shows the UV and CD spectra of the **1**−primary amine conjugates, (*S*)-**2a**, (*S*)-**3a**, (*S*)-**6a**, and (*S*)-**7a**, in hexane. The UV spectrum of (*S*)-**2a** exhibits an intense absorption at 257 nm due to the $\pi-\pi^*$ transition arising from polarization along the long axes in the *m*-quaterphenyl group. The CD spectrum of (*S*)-**2a** exhibits significant CD Cotton effects due to the exciton coupling between the two methoxy-biphenyl chromophores; λ_{ext} = 278.8 nm ($\Delta\varepsilon_1$ = −9.2) and λ_{ext} = 256.2 nm ($\Delta\varepsilon_2$ = +8.5). The amplitude of ECCD (A_{CD} value),[11,16−19] which is defined as A_{CD} = $\Delta\varepsilon_1$(first Cotton effect) − $\Delta\varepsilon_2$(second Cotton effect), is −17.7. The negative exciton chirality indicates that the two long axes in the *m*-quaterphenyl group constitute an *M* twist.

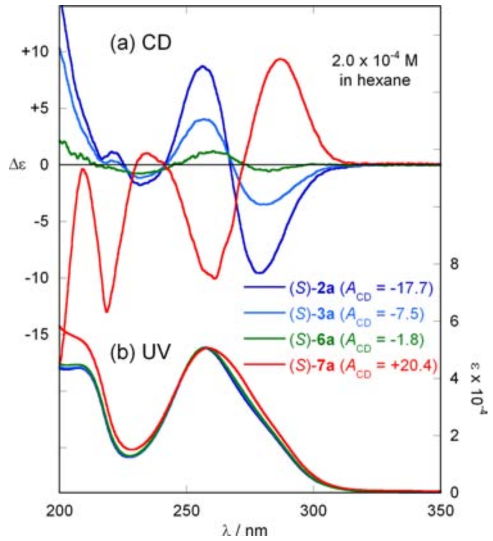


Figure 1. CD (a) and UV (b) spectra of (*S*)-**2a**, (*S*)-**3a**, (*S*)-**6a**, and (*S*)-**7a** (2.0×10^{-4} M in hexane, 293 K).

On the other hand, (*R*)-**2a** exhibited the mirror image of the CD spectrum of (*S*)-**2a** (Figure S29 in the SI). Also varying the solvents for (*S*)-**2a** from EtOH to CH_3CN to 1,2-dichloroethane resulted in almost no change in the CD amplitude and shape (Figure S30 in the SI).

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The CD spectra of the **1**−aliphatic amine conjugates, (*S*)-**3a**−(*S*)-**6a**, had the same sign for the Cotton effects as (*S*)-**2a**. It is important to note that even the differences in steric bulkiness for methyl and ethyl groups in (*S*)-**6a** can be discriminated. The CD spectra of **1**−aromatic amine conjugates, (*S*)-**7a** and (*S*)-**8a**, exhibited the opposite sign for the Cotton effects compared with (*S*)-**2a**−(*S*)-**6a**. This inversion of Cotton effects cannot be explained by the steric features of the substituents using the Charton steric parameters.[32]

To clarify the mechanism of the inversion of the CD, theoretical calculations were carried out using a methoxy-omitted model (*S*)-**2b**−(*S*)-**4b** and (*S*)-**6b**−(*S*)-**8b** (Figure S31 in the SI). To obtain the relative amounts of *M* and *P* conformers of (*S*)-**2b**, preliminary conformational searches were carried out using an MMFF model and then all local minimum conformers were optimized with DFT using the B3LYP/6-31G* model.[33] Three conformers with the lowest energies in (*S*)-**2b** were found within 3.0 kcal/mol (Figure 2). Using Bolzmann's equation (T = 298 K), the relative amounts of each conformer in (*S*)-**2b** were determined as 75:25 (*M*/*P*).

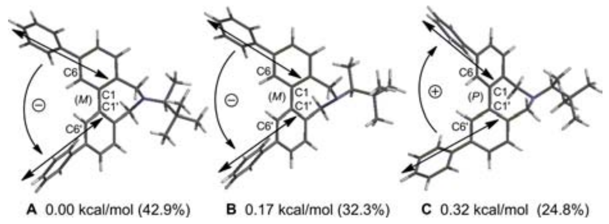

Figure 2. Three major conformers of (*S*)-**2b** based on B3LYP/6-31G*. Dihedral angles (C6−C1−C1′−C6′) are −42.8° (A), −42.2° (B), and 43.5° (C).

In the **1**−aliphatic amine conjugates, (*S*)-**2b**−(*S*)-**4b**, and (*S*)-**6b**, the amounts of the *M* conformers were greater than those of the *P* conformers (Tables S2−S5 in the SI). On the other hand, for the **1**−aromatic amine conjugates, (*S*)-**7b** and (*S*)-**8b**, the amounts of the *P* conformers were greater than those of the *M* conformers (Tables S6 and S7 in the SI).[34] These results were consistent in terms of the sign of the observed CD Cotton effect. In addition, the A_{CD} values were directly estimated by the relative amounts of the *M* and *P* conformers because the C6−C1−C1′−C6′ dihedral angle in all quaterphenyl units in the theoretical models were approximately constant (plus or minus ca. 42°, Tables S2−S7 in the SI). A linear relationship between the A_{CD} values and the calculated excess of *M* conformers was obtained with R^2 = 0.975 (Figure 3). By comparing the observed and calculated sign and the amplitude of the A_{CD} values, the absolute configurations of chiral primary amines were determined.

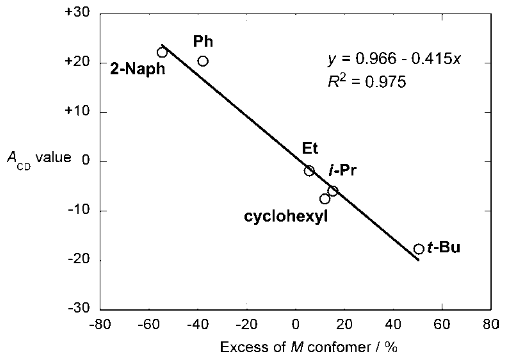

Figure 3. Relationship between the A_{CD} values and excess of *M* conformer. Excess of *M* conformer (%) = ([*M*] − [*P*])/([*M*] + [*P*]) × 100, where [*M*] and [*P*] are the amounts of *M* and *P* conformers calculated by B3LYP/6-31G*, respectively.

To evaluate the practical utility of the method for the determination of the ee of chiral primary amines, a calibration graph was prepared using (*S*)- and (*R*)-**2a** for varying ee (−100, −80, −60, −40, −20, 0, +20, +40, +60, +80, +100%ee of (*S*)-**2a**). The values for %ee were plotted versus the A_{CD} values (Figure S45 in the SI). The calibration graph was linear, with R^2 = 0.999 (Figure 4). This result indicated that the method is applicable to the quantitative determination of the ee of primary amines.

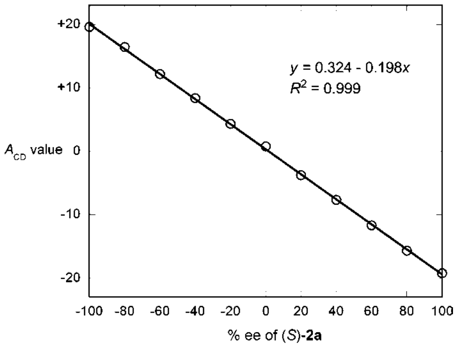

Figure 4. Calibration graph for A_{CD} values based on (*S*)-**2a** and (*R*)-**2a** with varying %ee values.

We also obtained crystal structures for (*S*)-**2a**, (*S*)-**3a**, and (*S*)-**6a**. For (*S*)-**2a** and (*S*)-**3a**, which showed a high amplitude in the CD spectra, only *M* conformers were observed (Figure 5a and 5b). On the other hand, both *M* and *P* conformers were observed in (*S*)-**6a** which showed a low amplitude in the CD spectrum (Figure 5c). The twist angles (C6−C1−C1′−C6′) of the quaterphenyl units in (*S*)-**2a**, (*S*)-**3a**, and (*S*)-**6a** were in the range 41°−44°. The results of the X-ray structures roughly reflected the A_{CD} values.

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[34] From the calculated conformers of (*S*)-**7b** and (*S*)-**8b**, significant interactions between the aryl group and quaterphenyl probe were not observed. Therefore, the ratios between the *P* and *M* conformers are only dependent on the steric bulkiness of substituents attached to the chiral center of amines. We consider that the methyl group is more sterically hindered than the planar aryl groups in the conjugates.

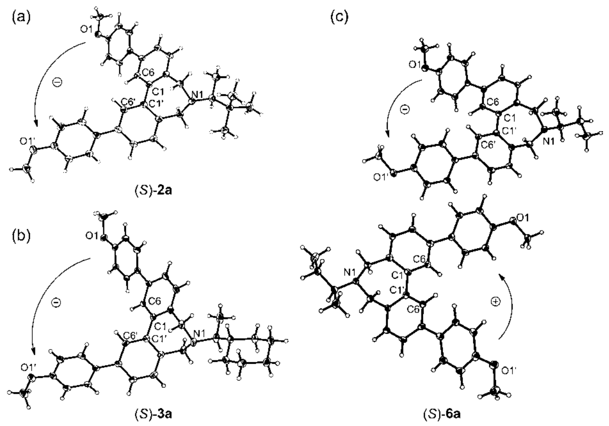

Figure 5. ORTEP drawing of (*S*)-**2a** (a), (*S*)-**3a** (b), and (*S*)-**6a** (c). Dihedral angles (C6−C1−C1′−C6′) are −41.1° (a), −41.8° (b), −42.6° (c, upper), and 44.0° (c, lower).

In conclusion, we have developed a novel chiroptical probe **1** which is linked to chiral primary amines yielding **1**−amine conjugates in high yield. The ECCD in the quaterphenyl unit of the conjugates was dependent on the chirality of the primary amines. The combination of the new probe and theoretical calculations represents an effective method to determine both the absolute configuration and the ee of chiral primary amines in a nonempirical manner. Further studies are in progress.

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Supporting Information Available. Experimental procedures, physicochemical properties, X-ray structures, molecular calculations (PDF), and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.