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Preparation of Carbodiimides with One-Handed Axial Chirality

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Supporting Information Placeholder

ABSTRACT: The axial chirality of carbodiimide was proposed in 1932, but the synthesis of carbodiimide with one-handed axial chirality has not been achieved because of the low barrier of racemization. This work presents a strategy to use a conformationally-restrained cyclic structure for creating carbodiimides whose biases of the axial chirality (labeled as $S_{\text{NCN}/R_{\text{NCN}}}$) are higher than 100:1, as determined by vibrational circular dichroism spectroscopy and density functional theory calculations.

Carbodiimide (R–N=C=N–R) is an important class of molecules in life science for its reactivity to form amide and ester linkages and in polymer science for its utility as monomers for polycarbodiimide synthesis.¹ Despite the daily use of carbodiimides worldwide, little is known about the nature of their axial chirality analogous to the chirality of allenes (C=C=C). Axially chiral allenes were predicted to exist by van't Hoff in 1875² and were first obtained in 1935,³ which led to the development of broad research areas such as asymmetric synthesis and drug development.⁴ In contrast, since the first proposal of the possibility of optically active carbodiimides by Roll and Adams in 1932,⁵ no studies have been considered successful in obtaining carbodiimides with one-handed axial chirality.⁶

Access to axially chiral carbodiimides has been hampered by the low barrier of racemization. In 1970, Anet et al. performed a low-temperature NMR measurement of diisopropylcarbodiimide down to -150 °C and estimated the barrier height to be *ca*. 7 kcal/mol (Figure 1A).⁷ Similar values were proposed using intermediate neglect of differential overlap method for H–N=C=N–H by Gordon and Fischer in 1968 and for dimethylcarbodiimide by Williams and Damrauer in 1969 and 1971.⁸ These values are much lower than a threshold for isolability of stereoisomers at room temperature (*ca*. 20 kcal/mol).⁹ Damrauer and co-workers later experimentally studied a 9-membered cyclic carbodiimide **1** (Figure 1B),¹⁰ and recently performed an extensive computational study on carbodiimides with various ring sizes.⁶ Both studies suggested little influence of the ring structures on the isomerization barriers. Although a few reports claimed isolations of chiral carbodiimides,¹¹ their validity has been questioned by other studies.⁶⁻⁸ Thus, creation of a carbodiimide with one-handed axial chirality, which should open up a new research field involving chiral carbodiimides, remains to be accomplished.



Figure 1. Studies on the axial chirality of carbodiimides. Both (A) acyclic carbodiimides and (B) cyclic carbodiimides exist as inseparable racemic mixture. (C) Acyclic carbodiimides with chiral substituents were studied in our preliminary study. See the Supporting Information for details. (D) Carbodiimides with conformational restraint.

In an initial attempt at enriching the axial chirality of carbodiimide (labeled as $S_{\rm NCN}/R_{\rm NCN}$), we have synthesized several acyclic carbodiimides with chiral substituents (Figure 1C). The $S_{\rm NCN}$: $R_{\rm NCN}$ ratios of prepared carbodiimides were studied by vibrational circular dichroism (VCD) spectroscopy in combination with density functional theory (DFT) calculations. As VCD spectroscopy detects all the structural isomers that interconvert slower than a picosecond,¹² it enabled us to analyze the diastereomeric ratio of chiral acyclic carbodiimides. However, none of the prepared acyclic carbodiimides showed a high $S_{\rm NCN}$: $R_{\rm NCN}$ ratio, with the highest value being 4:1, and

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thus we have abandoned our initial approach using acyclic carbodiimides (Figure S1). Having seen slightly greater biases in the S_{NCN} : R_{NCN} ratio for bulkier chiral substituents, we envisioned the possibility to bias the axial chirality by using steric interactions between two substituents. To enhance such interactions, we sought to connect two substituents and form carbodiimides with conformationally-restrained cyclic structures (Figure 1D). Here, we report the synthesis and structural analysis of several cyclic carbodiimides, some of whose S_{NCN} : R_{NCN} ratio is higher than 100:1.

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A chiral 1,1'-binaphthyl structure with varied ring sizes was chosen as a cyclic framework.¹³ The chirality of binaphthyl and biphenyl units is labeled as S_{nap}/R_{nap} and $S_{\rm ph}/R_{\rm ph}$, respectively. The synthesis of 9-membered ($S_{\rm nap}$)-2 started with the conversion of commercially available (S_{nap}) -6 to (S_{nap}) -7 (Scheme 1). Transformation of (S_{nap}) -7 into urea (S_{nap}) -9 resulted in low yield (up to 13%), and subsequent dehydration of (S_{nap}) -9 by TsCl and base was also inefficient (0-13%). Optimization of the reaction conditions from (S_{nap}) -7 to (S_{nap}) -2 led to a synthetic pathway through thiourea (S_{nap}) -8. Treatment of (S_{nap}) -7 with CS₂, pyridine, and I₂ and the following removal of hydrogen sulfide using MsCl afforded (S_{nap}) -2 in a moderate yield. As (S_{nap}) -2 readily decomposed during reaction and work-up, it was crucial to quench the reaction immediately after checking the disappearance of (S_{nap}) -8 on TLC and purify the product using neutral silica-gel column chromatography. Starting from (Snap)-1,1'-bi-2-naphthol, 13-membered (S_{nap}) -3 and 19-membered (S_{nap}) -4 were also synthesized.¹⁴ Enantiomeric (R_{nap}) -2 and (R_{nap}) -3 were prepared to validate the VCD results.¹⁴

Next, DFT calculations and VCD measurement of the carbodiimides **2-4** were carried out to study the biases in their axial chirality. DFT optimizations of (S_{nap}) -**2** with varying C11-N1••N1'-C11' dihedral angle at the B3LYP/6-311++G(d,p) level found two energy minima corresponding to (S_{nap}) - (S_{NCN}) -**2** (+69.2°) and (S_{nap}) - (R_{NCN}) -**2** (-54.5°) geometries (Figure 2a). Both dihedral

angles are deviated from the values predicted for the most stable conformers of dimethylcarbodiimide (±96.0°) (Figure S2). Importantly, (Snap)-(SNCN)-2 was 4.3 kcal/mol more stable than (S_{nap}) - (R_{NCN}) -2,¹⁵ which corresponds to a S_{NCN} : R_{NCN} ratio of approximately 1000:1. The validity of the computational results was evaluated by comparison of the measured VCD/IR spectra of (S_{nap}) -2 and the calculated ones for (S_{nap}) - (S_{NCN}) -2 and (S_{nap}) - (R_{NCN}) -2. Both (S_{nap}) - (S_{NCN}) -2 and (S_{nap}) - (R_{NCN}) -2 were predicted to show a strong IR absorption originating from the N=C=N stretching vibration at around 2100 cm⁻¹, with their locations separated by more than 25 cm⁻¹ (Figure 2b). Significantly, the signs of the corresponding theoretical VCD signals were negative for (S_{nap}) - (S_{NCN}) -2 and positive for (S_{nap}) - (R_{NCN}) -2. The experimental spectra of (S_{nap}) -2 in CDCl₃ exhibited a sharp IR absorption band associated with a negative VCD signal at 2099 cm⁻¹ (Figure 2c). The entire VCD pattern observed in the N=C=N stretching region as well as below 1600 cm⁻¹ closely resembled that predicted for (S_{nap}) - (S_{NCN}) -2, with no discernible features of (S_{nap}) - (R_{NCN}) -2. These results bolstered the predicted strong bias in the carbodiimide axial chirality. Thus, we consider 2 as the first carbodiimide whose axial chirality is virtually one-handed (>100:1). Similar conclusions were reached when using different levels of theory such as B3LYP/TZVP. wB97DX/6-311++G(d,p),and B3LYP/6-311++G(d,p)/PCM (chloroform) (Figure S3).

Meanwhile, little preference for carbodiimide chirality was computationally predicted for (S_{nap}) -**3** and (S_{nap}) -**4** $(S_{NCN} : R_{NCN} = 3:2$ for (S_{nap}) -**3**,¹⁶ and 1:1 for (S_{nap}) -**4**). In line with these predictions, a weaker VCD signal was observed for (S_{nap}) -**3** and no VCD signal was recognized for (S_{nap}) -**4** at around 2100 cm⁻¹ in CDCl₃ despite the strong IR absorption (Figure 2d and 2e). We concluded that the flexible linkers in (S_{nap}) -**3** and (S_{nap}) -**4** reduced stereochemical influences by the chiral binaphthyl on the carbodiimide moiety and that the carbodiimide chirality of (S_{nap}) -**2** is effectively regulated by conformational restraints.

Scheme 1. Synthesis of (Snap)-2, (Snap)-3, and (Snap)-4



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Figure 2. (a) Calculated energies and geometries for (S_{nap}) - $(S_{\rm NCN})$ -2, $(S_{\rm nap})$ - $(R_{\rm NCN})$ -2, and the transition state (TS). The dihedral angle θ is defined as C11-N1••N1'-C11'. The Boltzmann populations (P) were calculated at 298 K. The VCD (top) and IR (bottom) spectra of (b) calculated (S_{nap}) - (S_{NCN}) -2 (red) and (S_{nap}) - (R_{NCN}) -2 (black), (c) observed (S_{nap}) -2, (d) observed (S_{nap}) -3, and (e) observed (S_{nap}) -4. The spectra of (S_{nap}) -4 in DMSO- h_6 (2200-1900 cm⁻¹), DMSO- d_6 (below 1900 cm⁻¹), and in DMF- h_7 (2200-1900 cm⁻¹) are also shown. The calculated VCD spectra below 1600 cm⁻¹ are for clarity. Calculation magnified conditions: DFT/B3LYP/6-311++G(d,p). Measurement conditions: c = $0.1 \text{ M}; l = 50 \text{ }\mu\text{m}.$

The isomerization barrier of (S_{nap}) -2 was studied through transition state calculations and intrinsic reaction coordinate analysis. Three isomerization mechanisms have been proposed for carbodiimides: *cis*-rotation, inversion, and *trans*-rotation.^{8,10} Exploration of each transition state found *cis*-rotation to be the only possible isomerization pathway for (S_{nap}) -2.¹⁷ The identified *cis*-rotation transition state possessed the C11-N1••N1'-C11' dihedral angle close to zero (-5.9° by B3LYP/6-311++G(d,p); see Figures S3 for other calculation conditions), and was 7.4 kcal/mol less stable than the most stable S_{NCN} state (Figure 2a). This barrier height is comparable with that calculated for dimethylcarbodiimide (Figure S2) and those previously estimated for acyclic and cyclic carbodiimides.^{6a,7,8,10} Thus, we concluded that the conformational restraints of (S_{nap})-2 excluded inversion and *trans*-rotation mechanisms but did not elevate the barrier. These results also suggested that the experimentally detected single-handedness of the carbodiimide unit of (S_{nap})-2 is thermodynamically but not kinetically regulated.

Interestingly, (S_{nap}) -4 in DMSO and DMF exhibited a moderately strong VCD signal with little changes in the corresponding IR absorption at 2132 cm⁻¹ (Figure 2e). Meanwhile, rigid (S_{nap}) -2 in DMSO showed only minor changes in the VCD band at 2099 cm⁻¹ (Figure S4). These results pointed out that the solvent-induced VCD signal of (S_{nap}) -4 was due to the changes in the equilibrium between S_{NCN} and R_{NCN} states.¹⁸ To our knowledge, this is the first example where the axial chirality of a carbodiimide is altered by external stimuli. With more elaborate molecular design, N=C=N group should find various usages such as a mobile unit for molecular machines¹⁹ and a chiroptical ON/OFF switch.^{13e,20}

Intrigued to construct a carbodiimide with one-handed axial chirality from achiral building blocks instead of chiral ones, we then studied structurally-related 5. Simpler structure of 5 should also be useful for future studies correlating the reactivity and structure of carbodiimides. Synthesis of 5 has been described in only one report, which performed neither stereostructural analysis nor enantioseparation.²¹ We synthesized **5** from achiral **10** using a similar procedure to that for (S_{nap}) -2 (Figure 3a). Gratifyingly, chiral HPLC (Chiralpak IC column, Daicel) using hexane/EtOAc/Et₃N eluent resulted in baseline separation of the first-eluted (R_{ph}) -5 and second-eluted (S_{ph}) -5 (Figure S7). No racemization of the biphenyl unit was observed after heating at 70 °C for 1 hour (see Figure S8) and after storing at rt in EtOAc for 3 months. DFT calculations and VCD spectroscopy of (S_{ph}) -5 found its stereochemical properties to be comparable to those of (S_{nap}) -2. Namely, (S_{ph}) - (S_{NCN}) -5 was predicted to be more stable than $(S_{\rm ph})$ - $(R_{\rm NCN})$ -5 (ΔG 4.3 kcal/mol and ΔG^{\ddagger} 7.6 kcal/mol; Figure 3b).¹⁵ The calculated preference for the $S_{\rm NCN}$ chirality of $(S_{\rm ph})$ -5 was corroborated by agreement between the VCD spectrum observed for (S_{ph}) -5 and the one simulated for (S_{ph}) - (S_{NCN}) -5 (Figure 3c and 3d). The (S_{ph}) - (R_{NCN}) -5 species, on the other hand, was not detected experimentally. Therefore, this study showcased the utility of a conformationally-restrained structure to create carbodiimides with highly biased, virtually onehanded axial chirality from chiral as well as achiral components.

Our attempts to crystallize (S_{nap}) -2, (S_{nap}) -3, (S_{nap}) -4, and (S_{ph}) -5 were not successful. Fortunately, racemic (\pm) -

5 formed needle-like crystals from a hexane/EtOAc solution. X-ray diffraction analysis revealed its solid-state structure as a mixture of (S_{ph}) - (S_{NCN}) -**5** and (R_{ph}) - (R_{NCN}) -**5**, in line with the stability of S_{NCN} chirality of (S_{ph}) -**5** in the solution state (Figure 3e). The C7-N1••N1′-C7′ dihedral angle for (S_{ph}) -**5** in the crystal (+77.5°) was slightly different from the DFT-optimized structure (Table S1). Of note, although the N=C=N angles of various carbodiimides are known as nonlinear (~170°),^{6.22} that for the crystalline **5** is almost linear (179.6°). This finding proposed the usefulness of conformational restraints for regulating not only the carbodiimide chirality but also the N=C=N angle.

The existence of a carbodiimide with one-handed axial chirality has been elusive for more than 85 years. Here, we present a strategy to obtain such carbodiimides using conformationally-restrained systems, and have demonstrated the preparation of (S_{nap}) -2 and (S_{ph}) -5, whose biases in the carbodiimide chirality are higher than 100:1. Furthermore, this study observed that the chiral properties of carbodiimides were modified by external stimuli. The insight obtained in this work should lead to the preparation of various carbodiimides such as ones useful for asymmetric reactions and molecular machines. Just as the emergence of chiral allenes developed various scientific fields, we hope this work to ultimately open new research areas of chiral carbodiimides.



Figure 3. (a) Synthesis and enantioseparation of **5**. (b) Calculated energies and geometries for (S_{ph}) - (S_{NCN}) -**5**, (S_{ph}) - (R_{NCN}) -**5**, and the transition state (TS). The dihedral angle θ is defined as C7-N1••N1'-C7'. The Boltzmann populations (*P*) were calculated at 298 K. The VCD spectra of (c) calculated (S_{ph}) - (S_{NCN}) -**5** (red) and (S_{ph}) - (R_{NCN}) -**5** (black) and (d) observed for (S_{ph}) -**5** in CDCl₃. The entire strong peak at *ca*. 2100 cm⁻¹ calculated for (S_{ph}) - (R_{NCN}) -**5** is shown in the inset. Calculation conditions: DFT/B3LYP/6-311++G(d,p). Measurement conditions: *c* = 0.1 M; *l* = 50 µm. (e) Molecular structure of (S_{ph}) -**5** in the solid state determined by X-ray crystallography of (±)-**5**. Thermal ellipsoids are drawn at the 50% probability level.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Procedures for experiment and calculation, synthesis, and characterization; supporting figures and table; coordinates of selected calculated geometries (PDF) Crystallographic data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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- (14) See Supporting Information.
- (15) The energy differences between S_{NCN} and R_{NCN} diastereomers are virtually unchanged when ΔE , not ΔG , is used (4.1 kcal/mol for (S_{nap})-2 and 4.6 kcal/mol for (S_{ph})-5).
- (16) Unexpectedly, both (S_{nap}) - (S_{NCN}) -**3** and (S_{nap}) - (R_{NCN}) -**3** were predicted to show a negative induced VCD signal at around 2100 cm⁻¹, which hampered the analysis of its S_{NCN} : R_{NCN} ratio through VCD spectroscopy (Figure S5).
- (17) Due to the conformational restraints by the binaphthyl unit and the small ring size, no geometries amenable to DFT structural optimization were obtained for *trans*-rotation (θ close to 180°) and for inversion transition states.
- (18) In accordance with the low racemization barrier of carbodiimide, no meaningful signal broadening informative for S_{NCN} : R_{NCN} ratio was observed by the low-temperature ¹H NMR measurement of (S_{nap})-4 in CDCl₃ above its freezing point (Figure S6).
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Figure 1. Studies on the axial chirality of carbodiimides. Both (A) acyclic carbodiimides and (B) cyclic carbodiimides exist as inseparable racemic mixture. (C) Acyclic carbodiimides with chiral substituents were studied in our preliminary study. See the Supporting Information for details. (D) Carbodiimides with conformational restraint.

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Figure 2. (a) Calculated energies and geometries for (S_{nap}) - (S_{NCN}) -**2**, (S_{nap}) - (R_{NCN}) -**2**, and the transition state (TS). The dihedral angle θ is defined as C11-N1••N1'-C11'. The Boltzmann populations (*P*) were calculated at 298 K. The VCD (top) and IR (bottom) spectra of (b) calculated (S_{nap}) - (S_{NCN}) -**2** (red) and (S_{nap}) - (R_{NCN}) -**2** (black), (c) observed (S_{nap}) -**2**, (d) observed (S_{nap}) -**3**, and (e) observed (S_{nap}) -**4**. The spectra of (S_{nap}) -**4** in DMSO- h_6 (2200-1900 cm⁻¹), DMSO- d_6 (below 1900 cm⁻¹), and in DMF- h_7 (2200-1900 cm⁻¹) are also shown. The calculated VCD spectra below 1600 cm⁻¹ are magnified for clarity. Calculation conditions: DFT/B3LYP/6-311++G(d,p). Measurement conditions: c = 0.1 M; l = 50 µm.

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Figure 3. (a) Synthesis and enantioseparation of **5**. (b) Calculated energies and geometries for (S_{ph}) -(S_{NCN})-**5**, (S_{ph}) -(R_{NCN})-**5**, and the transition state (TS). The dihedral angle θ is defined as C7-N1••N1'-C7'. The Boltzmann populations (*P*) were calculated at 298 K. The VCD spectra of (c) calculated (S_{ph})-(S_{NCN})-**5** (red) and (S_{ph})-(R_{NCN})-**5** (black) and (d) observed for (S_{ph})-**5** in CDCl₃. The entire strong peak at *ca*. 2100 cm⁻¹ calculated for (S_{ph})-(R_{NCN})-**5** is shown in the inset. Calculation conditions: DFT/B3LYP/6-311++G(d,p). Measurement conditions: c = 0.1 M; l = 50 µm. (e) Molecular structure of (S_{ph})-**5** in the solid state determined by X-ray crystallography of (±)-**5**. Thermal ellipsoids are drawn at the 50% probability level.

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