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Blueprints for the Geometric Control of *N*-Heterocyclic Carbene–Carbodiimide Isomers

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Rational control of the 3D presentation of atoms—stereochemistry—lies at the heart of synthetic organic and materials chemistries. Here, researchers report detailed computational studies on conformational isomerism in *N*-heterocyclic carbene–carbodiimide (NHC–CDI) zwitterionic adducts. By varying the steric and electronic parameters of the NHC and CDI components, criteria for controlling isomerization thermodynamics and predicting energetically favorable conformations are identified. These criteria is validated experimentally using a novel synthetic approach to NHC–CDIs, which exploits the thermodynamic equilibrium between sterically unencumbered NHC dimers to access NHC–CDI adducts with low barriers to conformational isomerization, including the first example of an (*E*/*E*)-NHC–CDI.

1. Introduction

Molecules that can adopt distinct diastereomeric forms (e.g., cis or trans) are ubiquitous and can be found in pharmaceuticals, materials, and commodity chemicals.[1] The differing physical properties of diastereomers and the ability to control their interconversion have enabled applications ranging from the control of cell wall function to the operation of molecular motors.[2] To date, switchable diastereomers based on planar motifs such as olefins, azobenzenes, or imines have been used as building blocks for constructing complex molecular scaffolds (**Figure 1**a).[3] By contrast, 3D motifs that isomerize substituents in perpendicular planes are comparably rare and remain underdeveloped. Synthetic routes to motifs with controlled 3D isomerization processes may enable novel applications that build on existing precedents with their 2D congeners or in unexplored reticular frameworks.

N-heterocyclic carbene–carbodiimide (NHC–CDI) adducts may be good candidates for control of 3D conformational isomerism (Figure 1b).[4] These adducts result from the nucleophilic addition of an NHC to a CDI, forming a zwitterionic species with an inherent 3D twisted shape due to steric repulsion of the NHC and CDI substituents. Thus, controlling NHC–CDI conformation could enhance the utility of these species as building blocks for novel materials.[5] Additionally, NHC–CDI adducts have been applied as metal ligands, catalysts, and promoters for CO_2 reduction.[6]

In these contexts, NHC–CDI isomerization could serve as a powerful tool for tuning structure and reactivity. For example, access to the nucleophilic amidate nitrogens of NHC–CDIs may be optimized in the *E/E* isomer relative to the sterically encumbered *E/Z* and *Z/Z* isomers. The (*E*/*E*) NHC–CDIs would then have enhanced chelating abilities toward metals and may unlock novel applications as ligands in transition-metal catalysis or coordination chemistry. To date, however, there are no reports of NHC–CDI adducts that adopt a preferred *E/E* conformation in the absence of metal coordination.[4e,6,7] Therefore, we set out to understand what molecular features of NHC–CDIs may enable the predictive design of *Z/Z*, *E/Z*, and *E/E* isomers, which would provide full access to the conformational space available to this unique class of molecules.

2. Results and Discussion

We performed computational studies of previously reported NHC–CDI adducts to understand the key criteria responsible for conformer stability. A survey of the Cambridge Structural

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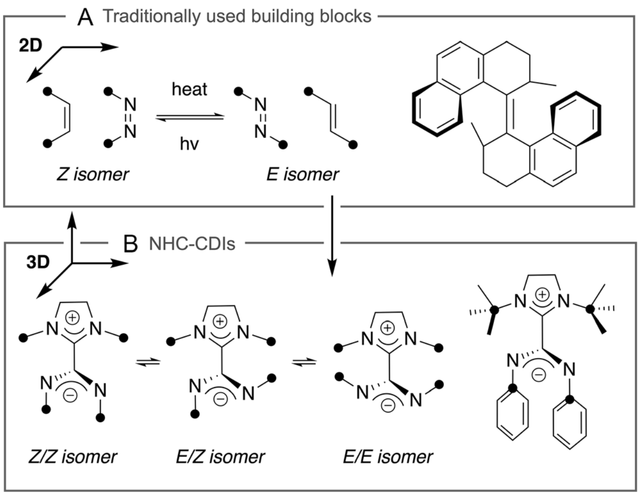

Figure 1. Functional groups that undergo isomerization (A) Traditional functional groups (B) NHC-CDIs as potential motifs.

Database yielded 22 distinct NHC–CDI adducts, 13 of which did not contain metals (see Supporting Information Computational Details). None of the 13 structures without metals were isolated in the *E*/*E* conformation (*Z*/*Z* = 7, *E*/*Z* = 6, Figure S14, Supporting Information).[4b,4c,6f,7a] Geometric optimizations of the 13 X-Ray structures were performed, followed by constrained potential energy scans and relaxations to determine the relative energies of conformers and barriers to their interconversion. The library of experimental NHC–CDI crystal structures was supplemented with 15 theoretical NHC–CDIs to afford a systematic investigation into the steric and electronic factors of NHC–CDI conformer stability (Figure S14–S17, Supporting Information). These computational investigations showed that steric repulsion between the NHC and CDI *N*-substituents significantly destabilized the *E*/*E* isomer compared to the *Z*/*Z* or *E*/*Z* isomers (**Figure 2**, example *E*/*E* = 10.3 kcal mol^{-1}, *E*/*Z* = 0 kcal mol^{-1}, *Z*/*Z* = 1.7 kcal mol^{-1}), a likely explanation for the dearth of *E*/*E* isomers reported to date.

Next, we set out to identify interactions that could stabilize the *E*/*E* conformation (**Figure 3**). Due to the proximity of the *N*-aryl substituents of the NHC and CDI in the *E*/*E* isomer, we hypothesized that *N*-aryl motifs that could engage in π-stacking or hydrogen bonding may stabilize this conformation (see Figure S15, Supporting Information). From a series of computed structures (Figure 3 and Figure S15–S17, Supporting Information), we identified an electron-rich NHC (bis-3,4,5-trimethoxylbenzene, **A**) and an electron-deficient CDI (bis-pentafluorobenzene, **B**) that formed a candidate (*E*/*E*)NHC–CDI adduct **1**. This adduct exhibited π-stacking interactions that favored the *E*/*E* conformer, with the *E*/*Z* and *Z*/*Z* conformers being 4.4 and 2.9 kcal mol^{-1} higher in energy, respectively. Transition state calculations revealed low barriers (≈14 kcal mol^{-1}) for interconversion between these conformers, which would allow for all isomers to be accessed at room temperature (Figure S18, Supporting Information).

Encouraged by these results, we set out to synthesize **1**, which possesses NHC and CDI components not previously reported in the literature (**Figure 4**). First, we sought to optimize the synthesis of NHC–CDIs based on sterically unencumbered NHCs using the

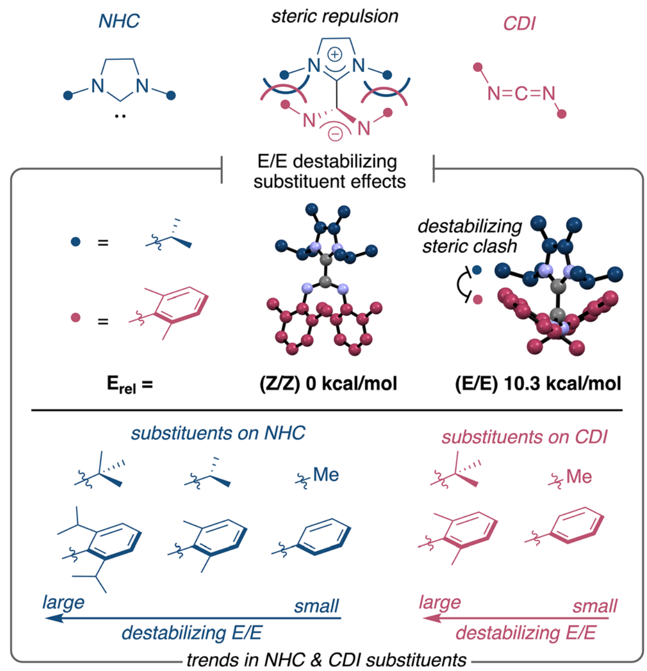

Figure 2. Computational studies reveal that steric interactions preclude the formation of (*E*/*E*)NHC–CDIs.

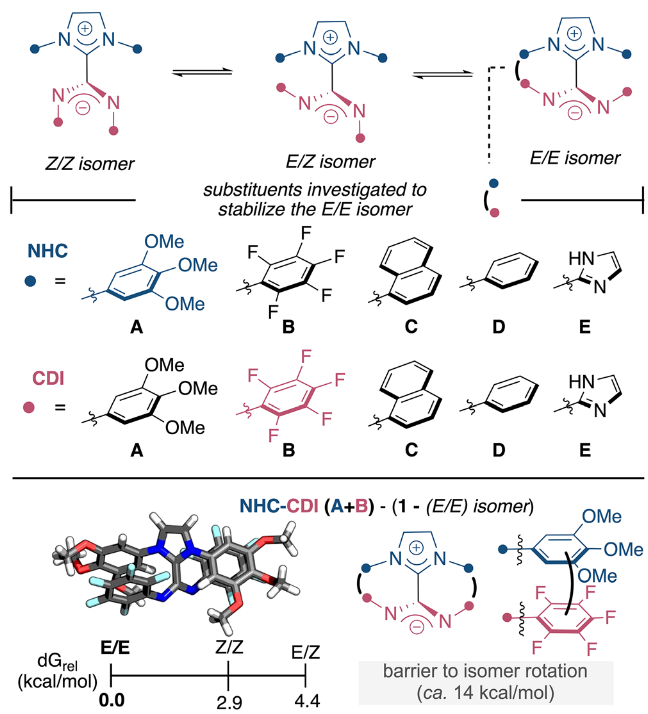

Figure 3. Computational investigations into intramolecular interactions that favor the E/E isomer of NHC–CDIs.

previously reported naphthyl imidazolium salt **2** as a model;[8] however, attempts to kinetically trap the NHC by deprotonation of **2** in the presence of excess[6e] **3** were unsuccessful, yielding only NHC dimer **4**.[9] While this kinetic approach failed, we hypothesized that the thermal reversibility of **4** at elevated temperatures and the anticipated stability of the NHC–CDI adduct

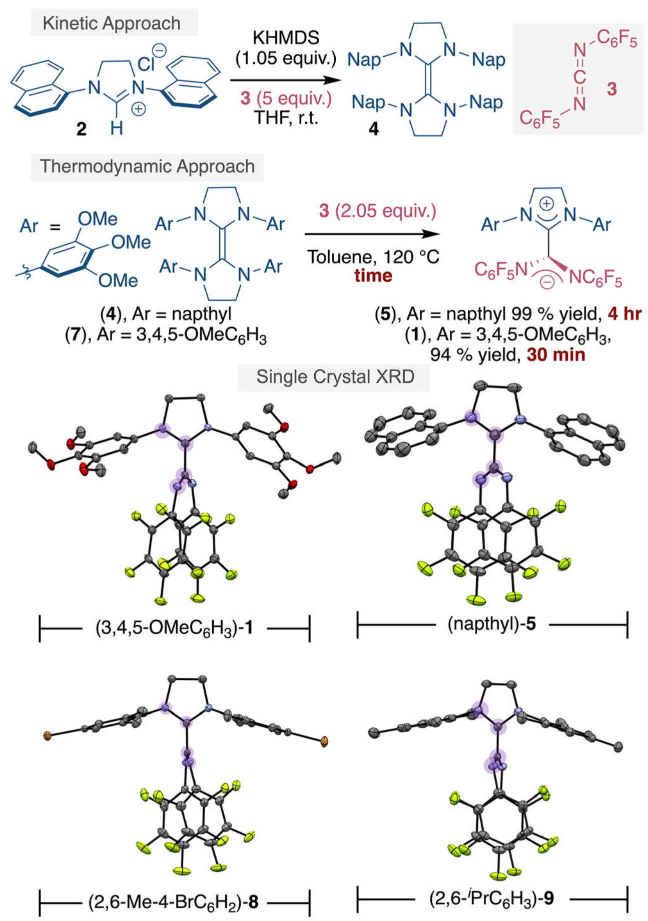

Figure 4. Synthesis of NHC–CDIs and their characterization by X-Ray crystallography.

could enable an alternative thermodynamic approach. Indeed, after optimization, exposing NHC dimer **4** to CDI **3** at 120 °C for 4 h cleanly afforded the target NHC–CDI **5** in quantitative yield. Single-crystal X-Ray diffraction (XRD) confirmed the structure of **5** as the *Z/Z* isomer in the solid state.[10]

With this new synthetic route to NHC–CDI adducts in hand, we turned our attention to the synthesis of the 3,4,5-trimethoxy imidazolium salt (**6**). Due to the ubiquitous use of NHCs as organocatalysts or ancillary ligands in transition-metal catalysis, it was surprising that **6** has not previously been reported. Attempts to follow standard synthetic approaches toward **6** initially proved unsuccessful. After various attempts, we found that the synthesis could be accomplished by adapting an earlier reported procedure by Grubbs and coworkers.[11]

The key modification was the addition of dimethylformamide (DMF) as a nonnucleophilic, polar cosolvent in the ring-closing reaction between the formimide intermediate and 1,2-dichloroethane (DCE), as the 3,4,5-trimethoxy formimide proved insoluble in DCE even at 160 °C. With **6** in hand, the corresponding NHC dimer **7** was readily prepared via deprotonation with KHMDS.

Gratifyingly, compound **1** was obtained in 94% yield following an analogous procedure to that used to synthesize **5**. Single-crystal XRD analysis of **1** validated our structural assignment, but to our surprise, **1** adopted the *Z/Z* conformation in the solid state. Further calculations identified significant packing effects originating primarily from CH–π to π–π interactions between neighboring compounds in the solid state for the Z/Z conformation (≈20 kcal mol^{-1}), which is of a greater magnitude than the stabilization of the E/E conformation in solution (≈10 kcal mol^{-1}). Ultimately, this favors the *Z/Z* conformation in the solid state (Table S9, Supporting Information). To compare these sterically unencumbered NHC–CDIs to their sterically encumbered analogs, two NHC–CDI adducts with NHC containing the *N*-aryl groups 2,6-Me-6-BrC_6H_2 (**8**) and 2,6-^{i}PrC_6H_3 (**9**) were synthesized. Single-crystal XRD of **8** and **9** identified that they also form the *Z/Z* isomers in the solid state.

Given these findings, we turned to NMR spectroscopy studies to probe the conformations of these NHC–CDIs in solution (**Figure 5**). ^{19}F NMR measurements of **1** and **9** revealed that **1** displayed a broad line shape ($\Delta V = 362$ Hz, compared to **9**, $\Delta V = 92$ Hz), which is consistent with the high fluxionality of the *N*-C_6F_5 aryl rings in **1**. Variable temperature ^{19}F NMR of **1**

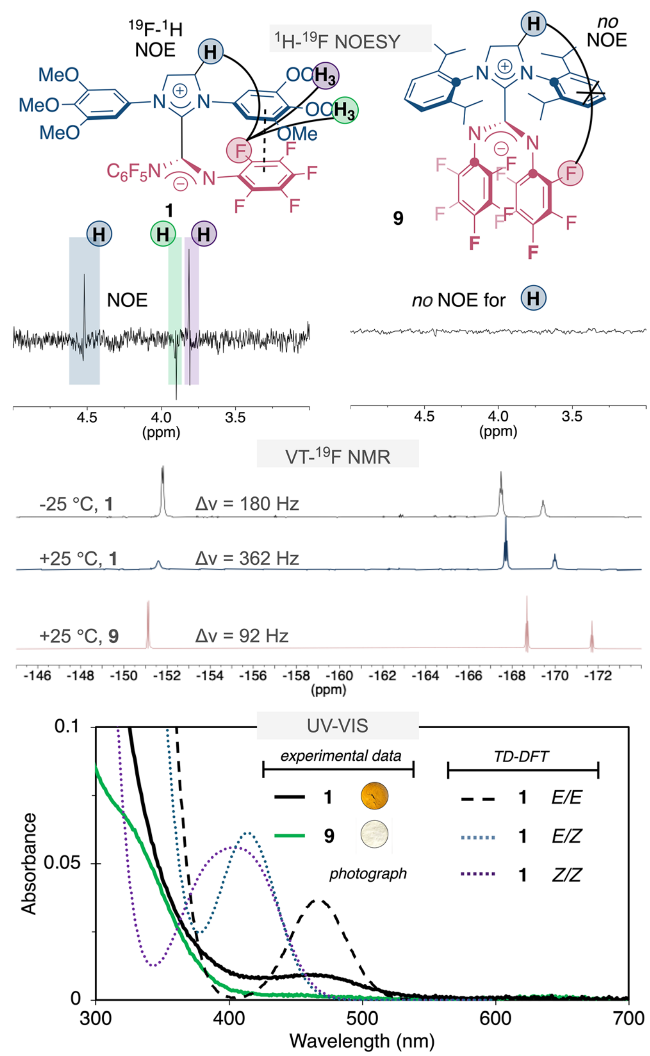

Figure 5. Spectroscopic studies of sterically encumbered and unencumbered NHC–CDIs.

suggested that this fluxionality decreased upon cooling to −25 °C, where the broad singlet resolved into a doublet ($\Delta V = 180$ Hz).

These findings were consistent with the earlier computations of the isomerization of **1** and the corresponding low barrier of interconversion (≈14 kcal mol^{-1}). ^{1}H-^{19}F NOESY NMR experiments of **1** identified that the *N*-C_6F_5 aryl groups and aliphatic NHC backbone are in close proximity to each other, which is consistent with **1** forming *E/E* and *E/Z* isomers in solution (no NOE was observed with the sterically encumbered **9**).

UV vis spectra also displayed significant differences between **1** and **9**, wherein an absorbance band ($\lambda_{max} = 471$ nm) of **1** was observed in MeCN that was not present in **9** (Figure 5 and Figure S19, Supporting Information). Time-dependent-DFT calculations suggested that this additional band in the spectrum of **1** corresponds to a charge transfer state resulting from electron transfer from the CDI π system to the NHC π system, which is most consistent with the (*E/E*) isomer (Figure 5 and Figure S20, Supporting Information). These transitions for the *E/Z* and *Z/Z* isomers are computed to be blue-shifted.

3. Conclusion

In summary, we have identified blueprints for the design of NHC–CDI adducts that can sample 3D space through isomerization between *Z/Z*, *E/Z*, and *E/E* conformations. The keys to stabilizing *E/E* conformers are (1) reducing steric crowding between the NHC and CDI *N*-substituents and (2) installing favorable interactions (e.g., π-stacking) between those same substituents. A new synthetic strategy that leverages the thermodynamic stability of NHC–CDI adducts over NHC dimers was invented to prepare a novel NHC–CDI that adopts an *E/E* conformation in solution. These advances in the synthesis and understanding of NHC–CDIs are expected to advance their applications as building blocks for materials and as ligands for catalysis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 3D structures · carbodiimide · geometric control · isomerization · N-heterocyclic carbine · NHC–CDI

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[10] Deposition numbers 2346688 (**1**), 2336943 (**5**), 2352917 (**8**), 2365683 (**9**), and 2333364 (**10**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service https://www.ccdc.cam.ac.uk/structures.
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