

Computational Studies of Carbodiimide Rings

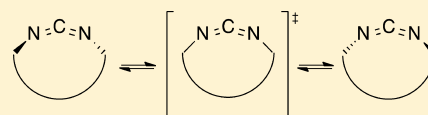
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S Supporting Information

ABSTRACT: Computational studies of alicyclic carbodiimides (RN=C=NR) (rings five through twelve) at the MP2/6-31G(d,p)//MP2/6-31G(d,p) level of theory were conducted to locate the transition states between carbodiimides isomers. Transition states for rings six through twelve were found. The RNCNR dihedral angle is $\sim 0^\circ$ for even-numbered rings, but deviates from 0° for rings seven, nine, eleven, and twelve. The even- and odd-numbered ring transition states have different symmetry point groups. C_s transition states (even rings) have an imaginary frequency mode that transforms as the asymmetric irreducible representation of the group. C_2 transition states (odd rings) have a corresponding mode that transforms as the totally symmetric representation. Intrinsic reaction coordinate analyses followed by energy minimization along the antisymmetric pathways led to enantiomeric pairs. The symmetric pathways give diastereomeric isomers. The five-membered ring carbodiimide is a stable structure, possibly isolable. A twelve-membered ring transition state was found only without applying symmetry constraints (C_1). Molecular mechanics and molecular dynamics studies of the seven-, eight-, and nine-membered rings gave additional structures, which were then minimized using ab initio methods. No structures beyond those found from the IRC analyses described were found. The potential for optical resolution of the seven-membered ring is discussed.



INTRODUCTION

On one extreme, carbodiimide (RN=C=NR) studies are exemplified by the importance of carbodiimides as synthetic reagents and on the other by questions concerning their structure and the nature of nitrogen configurational stability. Early reviews summarizing carbodiimide chemistry detailed their synthetic utility, notably as coupling reagents;^{1–3} more recent studies attest to the continuing importance of carbodiimide coupling.^{4,5} Questions concerning structure and nitrogen configurational stability in carbodiimides were considered early and have continued to be addressed,^{1–3,6–13} yet, in some ways, these issues are not well understood. These experimental and computational studies focused on carbodiimide structural features and the nature of the mechanism(s) transforming one enantiomer to another. The first mention of the possibility of optically active carbodiimides was made in 1932 by Roll and Adams,¹⁴ where attention was drawn to their obvious similarity to allenes and to the possibility of their resolution. Despite Roll and Adams' failure to report optically active carbodiimides, their paper offers a remarkable analysis of various aspects of nitrogen configurational stability in both amines and oximes, all the while analyzing the nature of nitrogen in carbodiimides. A simple valence bond picture of a carbodiimide suggests a linear N–C–N bond and a perpendicular R–N⋯N–R dihedral angle (the R–N⋯N–R angle is called the dihedral angle throughout this article).

The earliest systematic computational study of various diazacomulenes by Gordon and Fischer⁶ in 1968 using intermediate neglect of differential overlap (INDO) methodology investigated the R = H and R = F carbodiimides. Although no mention is given to the linearity of the N–C–N bond, the dihedral angles reported for the parent and the fluoro

derivatives are approximately 90° . For R = H, only a slight energy difference between stereoisomerization by inversion and rotation mechanisms (both ~ 8 kcal/mol) was determined, with rotation being slightly favored. The barrier for R = F was much higher (~ 22 kcal/mol), thus suggesting the possibility of isolating enantiomers. This compound has never been synthesized. It is generally recognized that isolation of interconvertible isomers requires a barrier near 20 kcal/mol at room temperature.^{15,16} The first ab initio computations of the R = H inversion barrier gave similar results.¹⁷ A somewhat later ab initio study by Nguyen and Ha in 1983 [Hartree–Fock 4-31G(d,p) and 6-31G(d,p)] reported the first indication of nonlinearity of the N–C–N bond angle,¹² as do all subsequent computational studies when larger basis sets and electron correlation effects are included. The rotation and inversion barriers were reported as being nearly equal and quite small (~ 4 kcal/mol).

Related INDO studies of dimethylcarbodiimide in 1969⁷ and 1971⁸ by Williams and Damrauer addressed these issues in a more chemically relevant way, given the importance of dialkylcarbodiimides in synthesis and the fact that the parent R = H is a very minor¹⁰ contributor to the cyanamide (N≡CNH₂) (>99%) \leftrightarrow carbodiimide (HN=C=NH) (<1%) tautomeric equilibrium. Surprisingly, at this level of theory, dimethylcarbodiimide has a C–N–C angle near 90° , very unlike the angles reported by Gordon and Fischer for R = H and F, although its computed dihedral angle is 90° . Inversion and rotation barrier estimates for the dimethyl compound are ~ 5 kcal/mol, similar to the computational values reported by Gordon and Fischer⁶ for R = H and in line with the

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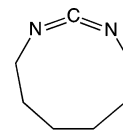
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low-temperature barrier of ~ 7 kcal/mol experimentally established for diisopropylcarbodiimide by Anet and co-workers¹⁸ in ^1H NMR studies in 1970. Thus, both experimental and early computation efforts indicate that the parent and alkyl-substituted carbodiimides barriers are too low for the isolation of enantiomers. Although it had been reported earlier¹⁹ that diferrocenylcarbodiimide had been partially resolved, this report has been questioned both on experimental and computational grounds.^{7,8,18,20} Other reports of the resolution of substituted carbodiimides have appeared; these will be discussed briefly in the Discussion section, although their results have not been verified or explained in light of other estimates of stereoisomerization barriers.^{21,22} During this period, various studies of substituted carbodiimides by other spectroscopic means (UV, photoelectron, ^{15}N NMR) also were reported.^{23–25} X-ray crystallographic structures established not only that $\text{R}-\text{N}\cdots\text{N}-\text{R}$ dihedral angles are $\sim 90^\circ$ also but that the $\text{N}-\text{C}-\text{N}$ bond angle deviates from linearity (with the exception of $\text{R} = \text{bis-}p\text{-nitrophenyl}$).^{26–28}

Since the time of the early work that was briefly reviewed, a great deal of experimental and computational effort in studying the parent carbodiimide ($\text{R} = \text{H}$) has led to a firmer understanding of this species. A series of related papers examining the parent have shed a more modern light on various structural and dynamic questions by studying the cyanamide \rightleftharpoons carbodiimide tautomerism spectroscopically. Both cyanamide and carbodiimide are known interstellar molecules, although because of their low particle densities they cannot interconvert in interstellar space.²⁹ Cyanamide overwhelmingly dominates the equilibrium mixture, but the parent carbodiimide can be detected (less than 1% at 383 K),¹⁰ and its torsional motions can be probed.^{9–11,13,30} Analysis of these spectral characteristics, combined with increasingly more sophisticated computational studies^{9,31} using a wide variety of basis sets and electron correlation strategies, has led to some fairly simple observations on the parent carbodiimide molecule: (1) the preferred mechanism of stereoisomerization is torsion over inversion at nitrogen,^{9,31} (2) the two torsional barriers (to cis and to trans transition states) are nearly identical,^{9,31} (3) both computation and experiment reveal large changes in $\text{H}-\text{C}-\text{N}$ angles as the torsional angle varies,^{10,11,31} (4) the $\text{N}-\text{C}-\text{N}$ angle in *cis*-HNCNH is bent ($\sim 170^\circ$), whereas in *trans*, it is linear,³¹ and (5) the vibrational motions of HNCNH are very complex.^{11,13} The previously referenced⁹ computational study using the CCSD(T) coupled-cluster method represents the most sophisticated computational work on the parent carbodiimide.

Although the parent carbodiimide occupies an essential position in understanding the structural and dynamic properties of carbodiimides, it lacks certain standing in practical terms given (1) its minor concentration in the cyanamide \rightleftharpoons carbodiimide tautomeric equilibrium and (2) the essential fact that the applied chemistry of carbodiimides involves substituted derivatives.^{1–3,7,8} As we began to address this,³² we initiated efforts to differentiate between torsional and inversion stereoisomerism mechanisms by situating the carbodiimide moiety in a “small” ring, reasoning that torsion through a 180° (*trans*) transition state (dihedral angle ($\text{C}-\text{N}\cdots\text{N}-\text{C}$) = 180°) would be impossible, whereas inversion at a nitrogen atom would not. This rationale underpinned our synthesis of the nine-membered ring, 1,3-diazacyclonona-1,2-diene (**1**).³² Dynamic NMR studies of **1** demonstrated that exchange of diastereotopic protons led to a free energy stereoisomerization barrier of ~ 7 kcal/mol. In discussing the low barrier for **1**,³² rotational (through a 180° transition state) and complex conformational effects were considered, but a

transition state with a dihedral angle of 0° (*cis*) was not explicitly discussed, although this possibility was subsequently suggested by Molina et al.³³

**1**

For the purposes of the alicyclic carbodiimide studies reported here, the most important aspect of the HNCNH reports identifies torsion from *cis* and *trans* isomers as being the dominant mechanism for stereoisomerism. In this article, we have concentrated on locating *cis* alicyclic carbodiimides transition states in ring sizes from five through twelve and examining whether the *cis* alicyclic structures found are transition states. Intrinsic reaction coordinate (IRC) pathways in both directions from the located transition states have been followed by full geometry optimizations to explore the isomerization products, thus allowing the determination of the barriers to these transition states. In so doing, questions concerning the nature and complexity of potential energy surfaces (PES) are considered. To do so, we have examined the PES of the seven-, eight-, and nine-membered rings in more detail using molecular mechanics (MM) and molecular dynamics (MD) techniques.

■ COMPUTATIONAL METHODS

Geometry optimizations based on previously described protocols^{34,35} were carried out for alicyclic carbodiimides of ring sizes five through twelve without symmetry constraints (C_1). An MP2/6-31G(d,p)//MP2/6-31G(d,p)^{36–39} protocol was employed throughout. When examination of the C_1 -optimized structures suggested higher symmetry, further computations were conducted with symmetry constraints. Harmonic frequency calculations were carried out using standard techniques on the optimized structures.⁴⁰ All reported species are local minima (no imaginary frequency) or transition states (one imaginary frequency), as indicated. The energies reported or referred to are ZPE-corrected. The transition states found were connected to their corresponding minima by following the reaction coordinate partway down in both directions using IRC methodology.^{41–44} Minima were computed by taking the resulting IRC structures and performing full geometry optimizations. These computations were carried out using the GAMESS suite of programs (1 May 2012 and 1 May 2013)⁴⁵ with MacMolPlot⁴⁶ visualization of the molecular structures. The convergence tolerance in GAMESS was increased 10-fold beyond the default (to $\text{OPTTOL} = 10^{-5}$) for all of the reported species.

MM studies of the seven-, eight-, and nine-membered rings were carried out to explore their potential energy surfaces more widely. Beginning from the seven-, eight-, and nine-membered carbodiimide ring transition states described, the Merck Molecular Force Field (MMFF94)⁴⁷ was employed to produce a number of structures that subsequently were submitted to geometry optimization (all carried out in C_1). Details are presented in the sections describing the seven-, eight-, and nine-membered rings in the Results section.

Born–Oppenheimer MD simulations were carried out on the eight- and nine-membered rings to explore the PES further. These were performed at the B3LYP/6-31G(d) level of theory^{48–50} (chosen as a compromise between computational accuracy and efficiency). The QMMM program (version 1.4.0.CO)⁵¹ was employed, which calls Gaussian09⁵² for single-point electronic structure calculations of gradients. The trajectories were propagated using the velocity Verlet algorithm⁵³ with a step size of 1 fs for 2 ps for the eight-membered ring and 3 ps for the nine-membered ring systems. The canonical (NVT) ensemble was chosen, where the temperature was maintained

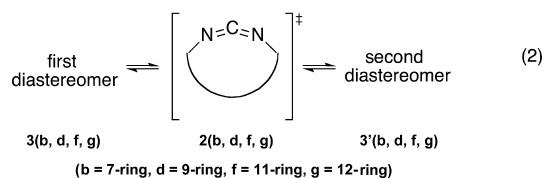
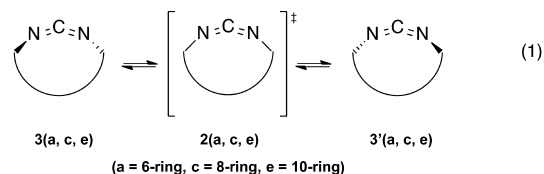
at 3000 K via coupling to a Berendsen thermostat⁵⁴ with a coupling parameter of 4.0 fs. The selection of 3000 K was determined from a number of tested temperatures between 200 and 20 000 K. It was considered to be the optimal temperature for efficient sampling of the conformational space without causing ring dissociation. By using the RATTLE algorithm,⁵⁵ all C–H bonds were held fixed to the values in the starting geometry (the optimized saddle point), which were close to 109 pm. Representative geometries were extracted every 0.2 ps from the trajectories and were used as the inputs for the subsequent geometry optimizations (in C_1) as described in the Results section.

RESULTS

This computational study focuses on locating a series of cis alicyclic carbodiimide transition states and studying their fate along the reaction coordinate to their isomeric products (also called minima). Although the planar five-membered ring is a stable molecule, seven cis transition states have been located for ring sizes six through twelve (2a–g). In this nomenclature, the number two refers to cis transition states, whereas the corresponding letter refers to the ring size throughout. Those structures designated with a single letter (2a, 3a, etc.) are ones whose energies are the lowest that have been found for such structures. Those structures designated with a two letters (2cc, 3cc, etc.) are ones found to have higher energies. This is described in the discussions of the individual ring species. Several higher-order saddle-point structures have been found as well. These have not been numbered but are described both in the text and in the Supporting Information.

The transition states separate into two groups: those that lead to enantiomeric products (ring sizes six, eight, and ten) (eq 1) and those that lead to diastereomeric products (ring sizes seven, nine, eleven, and twelve) (eq 2). The general protocol applied was (1) geometry optimization of each alicyclic species without symmetry constraints (C_1) while constraining the C–N–C–N–C part of each ring to be cis and planar, (2) removal of the constraint from the aforementioned optimized structures followed by geometry optimization and harmonic frequency analysis, and (3) determination of whether the resulting structures were transition states. After locating a transition state, IRC studies moving in both directions have been conducted followed by taking the last IRC coordinates as input for full geometry optimizations to reach the energy minima 3/3' (a–g). The structures corresponding to 3 and 3' are either enantiomers or diastereomers, depending on the symmetry characteristics of the transition states. From the energy of the minima (3a–g and 3'a–g), the barrier heights to the transition states were determined as were various structural characteristics of these minima. Inspection of the C_1 transition states of ring sizes six, eight, and ten were very close to C_s symmetry. These were reoptimized under C_s symmetry constraints, thus obtaining the same results as the C_1 computations. The seven-ring C_1 transition state was close to C_2 symmetry; its reoptimization with C_2 symmetry constraints produced the same results as the corresponding C_1 computation (see further results on the seven-membered ring below). The methodology described above for locating the nine-ring transition state in C_1 afforded a transition state with no obvious higher symmetry unlike the application of such methodology to smaller rings. As a result, two nine-membered ring structures, one with C_s and the other with C_2 symmetry, were constructed using the building features in MacMolPlot.⁴⁶ Only the C_2 structure was shown to be a transition state. Its energy is lower than the corresponding C_1 transition state structure by ~ 30 kcal/mol, and it is the species that was considered further. The C_1 transition states found for ring sizes eleven and twelve also displayed no obvious higher

underlying symmetry on inspection. A lower-energy C_2 transition state for the eleven-membered ring could be constructed and is considered further. No twelve-membered ring transition state beyond that found in C_1 was identified.



Although the methodology employed assures that the minima found derive from their corresponding transition states, fuller PE surfaces cannot be described using such an approach. MM of seven-, eight-, and nine-membered rings and MD studies of the eight- (C_s) and nine-membered (C_2) transition states were carried out as a basis for identifying additional structures to explore the corresponding PES further. These ring sizes were chosen because of their reduced flexibility compared to the larger rings and because of the greater likelihood that a more understandable view of their PES could result.

Only limited studies were carried out to find planar to near-planar trans transition states for rings ten, eleven, and twelve. These were unsuccessful for the ten- and eleven-rings. A trans twelve-membered ring studied in C_2 afforded a transition state with a dihedral angle far different ($\sim 136^\circ$) from any of the cis transition states described herein and was not considered further. Given the failure of these preliminary efforts to locate trans transition states, the results considered subsequently are limited to torsions from cis transition states having fairly small dihedral angles. (Properties of the carbodiimides studied in this work can be seen in Table 1 and in the Supporting Information.)

Five-Membered Ring. This planar ring system is a minimum on the PES, not a transition state, which suggests that, despite being a small ring that formally incorporates a $N=C=N$ moiety, it may be isolable. Its N–C–N angle is $\sim 162^\circ$, which deviates considerably from the “formal” valence bond angle of a 180° sp -hybridized linkage. Computational results for the HNCNH parent^{9,31} and the other ring sizes presented here suggest that the five-membered ring as a planar minimum is partly accommodated by distorting its N–C–N angle. The C–N bond length in this linkage at 126 pm. Although it is shorter than a typical C–N double bond of 129 pm,⁵⁶ it is slightly longer than the other ring system species to be discussed (see Supporting Information). The C–N bond length as well as both the C–C length (~ 161 pm) (compared to 154 pm for a normal C–C bond)⁵⁶ and the C–N–C angles ($\sim 84^\circ$) also contributes to accommodating this five-membered ring as a planar structure.

Six-Membered Ring. The optimized C_1 structure in which the C–N...N–C dihedral angle was constrained to 0° subsequently was shown to be a transition state when the dihedral angle constraints were removed. Visual examination of this structure indicated that it had close to C_s symmetry; computations in C_s verified this. Using the protocol described above to locate minima, enantiomers 3a and 3'a were found. The barrier to this TS is ~ 4 kcal/mol. The enantiomers have a dihedral angle of approximately $\pm 42^\circ$. A six-membered ring

Table 1. Various Properties of Carbodiimides Studied

N=C=N species, symmetry, and designation	barrier to transition state (kcal/mol)	R–N...N–R dihedral angle (degrees)
five-ring minimum	not applicable	0.0
six-ring transition state (C_2) (2a)	not applicable	0.0
six-ring minimum (C_1) (3a/3'a) enantiomers	3.9	± 41.6
seven-ring transition state (C_2) (2b)	not applicable	1.9
seven-ring IRC minimum (C_2) (3b) diastereomer	4.7	53.5
seven-ring minimum (C_2) (3'b) diastereomer	6.3	54.2
seven-ring transition state (C_s) (2bb)	not applicable	0.0
seven-ring IRC minimum (C_2) (3b) enantiomer	14.7 from TS 2bb	53.5
eight-ring transition state (C_s) (2c)	not applicable	0.0
eight-ring minimum (C_1) (3c/3'c) enantiomers	7.2	± 70.3
eight-ring transition state created in C_2 (2cc)	not applicable	5.6
eight-ring minimum (C_2) (3cc) diastereomer	10.0	69.1
eight-ring minimum (C_2) (3'cc) diastereomer	3.4	55.0
nine-ring transition state (C_2) (2d)	not applicable	9.0
nine-ring minimum (C_2) (3d) diastereomer	6.2	87.9
nine-ring minimum (C_2) (3'd) diastereomer	7.8	87.1
ten-ring transition state (C_s) (2e)	not applicable	0.0
ten-ring minimum (C_1) (3e/3'e) enantiomers	2.0	± 66.1
ten-ring transition state (C_2) (2ee)	not applicable	24.9
ten-ring minimum (C_2) (3ee) diastereomer	0.33	63.5
ten-ring minimum (C_2) (3'ee) diastereomer	7.5	81.5
eleven-ring transition state (C_2) (2f)	not applicable	3.5
eleven-ring minimum (C_2) (3f) diastereomer	4.8	94.0
eleven-ring minimum (C_2) (3'f) diastereomer	6.3	97.0
eleven-ring transition state (C_1) (2ff)	not applicable	1.3
eleven-ring minimum (C_1) (3ff) diastereomer	5.2	81.3
eleven-ring minimum (C_1) (3'ff) diastereomer	4.0	83.6
twelve-ring transition state (C_1) (2g)	not applicable	3.8
twelve-ring minimum (C_1) (3g) diastereomer	3.9	91.9
twelve-ring minimum (C_1) (3'g) diastereomer	5.6	93.3

carbodiimide constructed with C_2 symmetry proved to be a second-order saddle point (additional discussion of the seven-membered ring, third-order saddle point, follows below).

Seven-Membered Ring. Initially we identified one cis seven-membered ring transition state that was found to have C_2 symmetry (A). Its IRC pathways led to diastereomers **3b** and **3b'** whose energies were ~ 6 and ~ 5 kcal/mol below the C_2 transition state (see Supporting Information for additional structural data). Upon further exploration, a second cis transition state was found that has a boat shape and C_s symmetry (**2bb**). It was ~ 10 kcal/mol higher in energy than the C_2 transition state. Its IRC pathways led to the two enantiomers of **3b** with a barrier of ~ 15 kcal/mol. Thus, higher-energy diastereomer **3b** (C_2) is connected to its enantiomer through C_s transition state **2bb**. Attempts to locate another C_s transition state linking lower-energy diastereomer **3'b** to its enantiomer failed. Instead, a planar, third-order saddle point was located with two imaginary frequencies (~ 374 and 262 cm^{-1}) that indicated movement toward a C_2 structure and a third (~ 218 cm^{-1}) that suggested movement toward a C_s boat-like structure. This third-order saddle point is significantly higher in energy than than either **2b** or **2bb** (~ 22 and ~ 12 kcal/mol, respectively).

A substantial number of MM minimizations using the Merck Molecular Force Field 94⁴⁷ led to the identification of only two structures of different energy for the seven-membered ring. Geometry optimizations of these as starting points using the MP2 protocol described earlier led to diastereomers **3b** and **3'b**.

The seven-membered ring system, unlike the other alicyclic ring systems studied, begins to approach the point where the

resolution of enantiomers might be within experimental reach for **3b**. Appropriate substitution of a seven-ring could raise the barrier such that it is high enough for resolution.

Eight-Membered Ring. The eight-membered ring transition state has C_s symmetry (A'') and isomerizes along the reaction coordinate to enantiomers **3c** and **3'c** (barrier ~ 7 kcal/mol). The dihedral angles of the minima are approximately $\pm 70^\circ$. An eight-membered ring carbodiimide constructed with C_2 symmetry affords a transition state (A) ~ 4 kcal/mol higher in energy that yields two diastereomers along its reaction coordinate: one whose energy was lower than the C_2 transition state by ~ 10 kcal/mol and the other by ~ 3 kcal/mol (see Supporting Information for additional structural information).

MM minimizations led to the identification of five unique eight-membered ring structures. Geometry optimizations with these as starting points gave (1) enantiomers **3c** and **3'c** and (2) one of the diastereomers previously obtained from the C_2 transition state. A sampling of 13 of the MD simulation structures (\sim every 200 out of 2000 points) yielded four optimized structures: the three just described from MM studies and the other diastereomer previously found from the C_2 constructed transition state structure. Thus, all of the structures that previously had been found in the IRC studies were found using MD generated structures. Importantly, no lower-energy structures were found from the MM or MD structures identified.

Nine-Membered Ring. Two transition states have been located for the nine-membered ring system. The first obtained in C_1 has an energy ~ 30 kcal/mol higher than that constructed

using C_2 symmetry constraints (A). The C_2 structure isomerizes to diastereomers **3d** and **3'd** that have barriers of ~ 6 and ~ 8 kcal/mol (see Supporting Information for additional structural data). A constructed C_s structure was a second-order saddle point.

MM minimizations led to the identification of 13 nine-membered ring structures. These gave diastereomers **3d** and **3'd** as well as one of the two structures found in IRC studies of the C_1 transition state. In addition, a structure whose energy was ~ 0.05 kcal/mol lower than **3'd** was found. Sampling 16 MD simulation structures (\sim every 200 out of 3000 points) followed by geometry optimization yielded **3d** and **3'd** and five other structures in which only one was lower in energy than **3'd** (with the same energy as the " ~ 0.05 kcal/mol structure" just described). As a result, no significantly lower-energy structures were found using either MM or MD than were found in the IRC studies. Not surprisingly, visualization of the MD simulations demonstrates that the nine-membered ring is considerably more flexible than the eight-ring.

Ten-Membered Ring. Transition state **2e** (C_s) (A'') leads to enantiomers **3e** and **3'e**. The barrier to the transition state is ~ 2 kcal/mol, and the dihedral angles of these are approximately $\pm 66^\circ$. A constructed version of the ten-membered ring with C_2 symmetry (A) yields a transition state structure (**2ee**) with an energy ~ 2 kcal/mol higher than C_s transition state **2e**. The corresponding C_2 diastereomers (**3ee** and **3'ee**) are ~ 0.3 and ~ 8 kcal/mol lower in energy than the C_2 transition state (see Supporting Information for additional structural data).

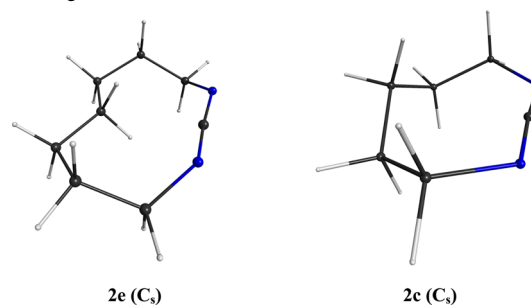
Eleven-Membered Ring. The constructed C_2 transition state (A) leads to diastereomers **3f** and **3f'** with ~ 5 and ~ 6 kcal/mol barriers and dihedral angles of ~ 94 and $\sim 97^\circ$. The energy of the C_2 transition state is ~ 2 kcal/mol lower than the corresponding C_1 transition state. The C_1 transition state (**2ff**) leads to two diastereomers (**3ff** and **3'ff**): one ~ 5 kcal/mol and the other ~ 4 kcal/mol lower in energy than the TS-**2ff** and with dihedral angles of ~ 81 and $\sim 84^\circ$. A C_s structure was found to be a third-order saddle point (see Supporting Information for additional structural data).

Twelve-Membered Ring. C_1 transition state **2g** led to diastereomers **3g** and **3'g** with ~ 6 and ~ 4 kcal/mol barriers and dihedral angles of ~ 93 and $\sim 92^\circ$, respectively. Constructed C_s and C_2 structures both afforded second-order saddle points (see Supporting Information for additional structural data).

Barrier Heights. Variations in the heights of the barriers determined for enantiomer interconversions are not readily interpreted, although they preclude enantiomer resolution at room temperature. Ring sizes six, eight, and ten (C_s) have barriers of ~ 4 , ~ 7 , and ~ 2 kcal/mol between enantiomers, respectively. Barriers between diastereomers in C_2 for ring sizes seven (~ 5 and ~ 6 kcal/mol, depending on direction), nine (~ 6 and ~ 8 kcal/mol), and eleven (~ 5 and ~ 6 kcal/mol) are low as well. The twelve-membered ring (C_1) barriers between diastereomers are ~ 6 and ~ 4 kcal/mol. Irrespective of symmetry or whether barriers are between enantiomers or diastereomers, medium size rings (seven, eight, and nine) have slightly higher barriers but not substantially so. The exception to this is the C_s seven-membered ring transition state **2bb** with a barrier between its enantiomers of ~ 15 kcal/mol.

Torsional Effects. One question of interest is how much torsion occurs from the transition states to the isomerized minima. Torsion of only approximately $\pm 41^\circ$ from the planar transition state of the six-ring to the enantiomeric minima suggests a trade-off between the 0° dihedral angle found in the

stable planar five-membered ring and a formal valence bond expectation of a 90° R–N \cdots N–R dihedral angle, which cannot be attained in a six-membered ring. Other dihedral angles increase (from TS to minima) as the ring size increases (seven-ring, $\sim 54^\circ$; eight-ring, $\sim 70^\circ$; nine-ring, $\sim 87^\circ$; eleven-ring, $\sim 95^\circ$; and twelve-ring, $\sim 93^\circ$). The exception is the ten-ring enantiomers, where a $\sim 66^\circ$ dihedral angle was found, indicating, as above with its low barrier, that the ten-ring has some unusual structural characteristics. Examination of ten-ring transition state **2e** reveals a feature that is not observed in the other transition states, namely, that the two hydrogen atoms attached to the CH_2 in the C_s plane face inward toward the central carbodiimide carbon (~ 2.1 Å distance between the closest hydrogen atom and the carbodiimide carbon). In the eight-ring transition state (**2c**), by contrast, the closest hydrogen to the central carbodiimide carbon atom in the C_s plane has a distance of ~ 2.7 Å. This suggests not only that relieving some hindrance is an important factor in the low barrier from the ten-ring transition state to its enantiomeric products but also that there is significant hindrance in the ten-ring enantiomer in approaching the ideal 90° dihedral angle.

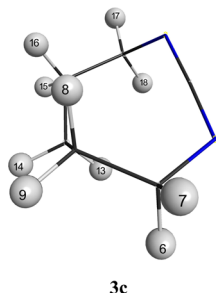


Carbodiimide Linkage Angles. The N–C–N angles of the transition states and their corresponding minima vary some with ring size. In the six- and seven-rings, the transition state N–C–N angle is larger than that of the minima (by ~ 7 – 8°), with the trend reversed for rings eight through twelve (by ~ 2 – 6°). The largest deviations from linearity for the transition state and enantiomers are found in the six-ring (~ 164 and $\sim 156^\circ$) (**2a** and **3a**), with the closest to linearity being the seven- and eight-ring transition states ($\sim 175^\circ$) (**2b** and **2c**). Surprisingly, the eleven- and twelve-rings have smaller transition state N–C–N angles ($\sim 165^\circ$) (**2f** and **2g**), although the N–C–N angles of their diastereomers are larger ($\sim 171^\circ$) (**3f**, **3'f**, **3g**, and **3'g**). The five-membered ring has one of the smaller N–C–N angles at $\sim 162^\circ$.

C–N Bond Lengths. As mentioned earlier, the C–N bond lengths in the five-membered ring are only slightly shorter (126 pm) than those of a typical carbon–nitrogen double bond (129 pm). The other rings studied, either their transition states or their minima reached along the reaction coordinate, have bond lengths within the very narrow range of 123–126 pm, indicating how insensitive bond length is as a feature in these alicyclic carbodiimides.

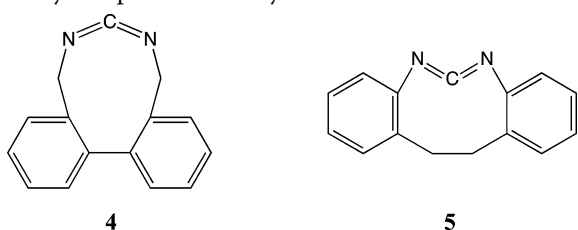
Vicinal Dihedral Angle Variations. The transition states for ring sizes six through eleven have H–C–C–H dihedral angles between ~ 133 and $\sim 179^\circ$, with the CH_2 – CH_2 groups closest to the carbodiimide linkage tending to have vicinal dihedral angles closer to 180° than those that are more distal. The ten-membered ring TS (**2e**), with its unusual structural characteristics compared with the other cyclic transition states notwithstanding, is not markedly different conformationally, having H–C–C–H dihedral angles between ~ 163 and $\sim 170^\circ$.

The various minima (both enantiomeric and diastereomeric) tend to have sections where the H–C–C–H dihedral angles are nearly staggered and sections that are nearly eclipsed. A typical example is eight-membered enantiomer **3c**, where three H–C–C–H dihedral angles are between ~ 167 and 175° but with a fourth dihedral angle, H₉–C₅–C₁₀–H₁₄, of $\sim 9^\circ$. Ten-membered ring enantiomer **3e**, which has two “inward-leaning” hydrogen atoms like its corresponding TS **2e**, has sufficient conformational mobility so that all of the H–C–C–H dihedral angles fall between 161 and 175° .



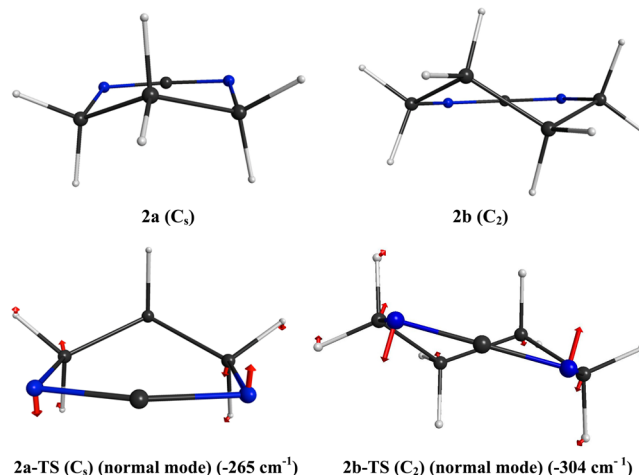
DISCUSSION

An important question concerning the structural/dynamic aspects of substituted carbodiimides is whether stereomutation in carbodiimides by torsion or inversion can be controlled, thus imparting configurational stability to such molecules and, as a result, allowing resolution of their enantiomers. Others have also considered whether placing a carbodiimide linkage in a ring would influence configurational stability,^{33,57} particularly in situations where biphenyl and phenyl groups are part of a nine-membered ring (**4** and **5**). Compound **4** has been prepared, but the authors did not comment on any studies to estimate its configurational stability.⁵⁷ Although dynamic NMR studies of **5** report a barrier of ~ 17 kcal/mol, that barrier is still low for room-temperature resolution.³³ A few resolution claims of carbodiimides have been made.^{19,21,22} One in particular has been criticized, as indicated earlier;^{7,8,16,18} others have lain fallow. Because none are particularly convincing or have received further attention, we have tried to address anew further prospects for chemical resolution in alicyclic carbodiimides by computational study.

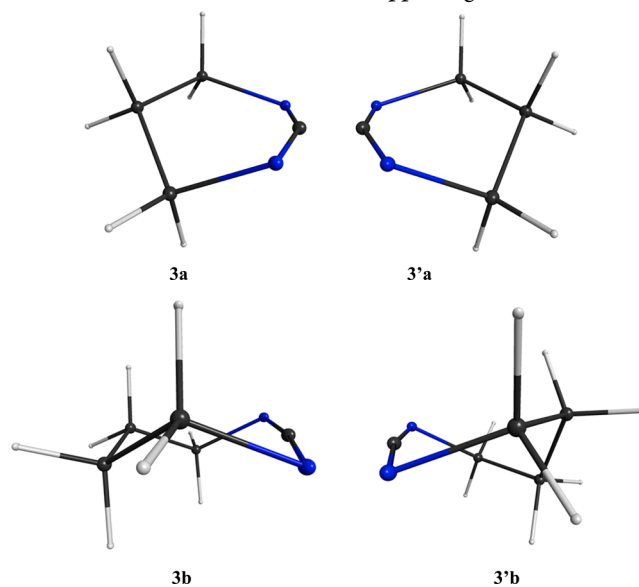


Our approach has concentrated on how the carbodiimide linkage and ring size affects structural characteristics and torsional barriers. A revealing structural feature of the transition states is exhibited by the R–N···N–R dihedral angle, where all of the C_s structures (six-, eight-, and ten-rings) have dihedral angles of $\sim 0^\circ$ and all of the C₂ transition structures (seven-, nine-, and eleven-rings) deviate from 0° (by as much as $\sim 9^\circ$). Structures **2a** and **2b** are typical C_s and C₂ transition states. The normal modes of motion for their single imaginary frequency (i.e., in the direction of the IRC) are represented as **2a-TS** and **2b-TS**. All transition state structures having a C_s transition state (six-, eight-, and ten-rings) exhibit an imaginary normal mode that transforms as the antisymmetric irreducible representation

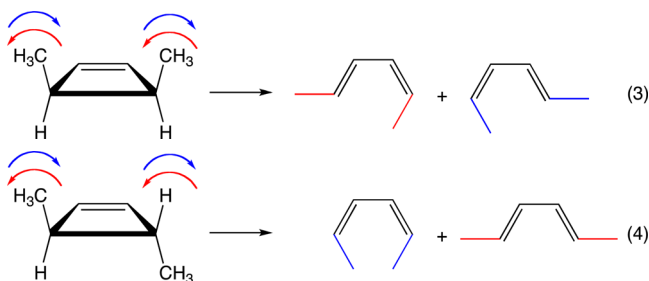
(A'') of the symmetry point group. This is illustrated in **2a-TS**, where the normal mode shown is antisymmetric to the reflection operation. However, in all cases where the transition state has C₂ point group symmetry (seven-, nine-, and eleven-rings), the imaginary normal mode of motion preserves the symmetry of the molecule, or, in other words, it transforms in the totally symmetric irreducible representation (A) of the group. This is illustrated in **2b-TS**, where the normal mode is symmetric to the 180° rotation operation. Note that those transition states exhibiting an antisymmetric normal mode (A'') provide an IRC that when followed in the two opposing directions leads to enantiomeric products, whereas transition states with a totally symmetric normal modes give rise to diastereomeric products. The C₁ twelve-membered ring transition state **2g** dihedral angle also deviates from 0° ($\sim 4^\circ$). Thus, transition state structures fall into two groups: (1) those that are C_s (A'') (dihedral angle $\sim 0^\circ$) that lead to enantiomeric products along the reaction coordinate and (2) the C₂ (A) and twelve-membered ring transition states (dihedral angle $\neq 0^\circ$) that lead to diastereomeric products.



For the six-ring, the enantiomers arising from **2a-TS** are illustrated below as **3a** and **3'a**. Their R–N···N–R dihedral angle is approximately $\pm 42^\circ$. For the seven-ring, diastereomers **3b** and **3'b**, arising from the C₂ transition state (**2b-TS**), have dihedral angles of ~ 54 and $\sim 53^\circ$, with **3'b** being lower in energy. The larger rings exhibit analogous features and are accounted for in Table 1 and the Supporting Information.



There are other examples where the motions of atoms are similar to those described for these alicyclic carbodiimides. A notable one is seen in the electrocyclic ring-opening in cyclobutenes.^{58,59} To illustrate this, consider the conrotations of C_s *cis*-3,4-dimethylcyclobut-1-ene. They follow an antisymmetric (A'') pathway to butadiene products of equal energy (eq 3). These electrocyclic ring-opening products are analogous in terms of motion to the enantiomers found for the C_s six-, eight-, and ten-membered alicyclic carbodiimides. The two carbodiimide enantiomers and the two equal-energy butadienes (for clarity, call them *2Z,4E*-hexa-2,4-diene and *2E,4Z*-hexa-2,4-diene, although they are identical) are transformed in C_s along the antisymmetric (A'') mode. Woodward and Hoffmann called the motions in the butadiene example enantiomeric.⁵⁸ In contrast, conrotations of C_2 *trans*-3,4-dimethylcyclobut-1-ene follow a symmetric (A) path, leading to two different butadienes (*2Z,4Z*-hexa-2,4-diene and *2E,4E*-hexa-2,4-diene) (eq 4). The *2Z,4Z* isomer is not detected experimentally for steric reasons.⁵⁸ This conrotatory example has analogous motions to those of the C_2 seven-, nine-, and eleven-membered alicyclic carbodiimide transition states, where two diastereomers are found. In essence, the C_s antisymmetric (A'') motion leads to two equal-energy products, and the C_2 symmetric (A) motion leads to two products of different energies in these cases.



Although the data on alicyclic carbodiimides possessing symmetry are limited to six cases (the six- through eleven-membered rings), the symmetry aspects of these alicyclic carbodiimides show consistent features, with the C_s structures leading to enantiomeric products and the C_2 ones leading to diastereomers. A great deal is known concerning conformational structural changes as a function of ring size in cycloalkanes; as expected, such molecules are quite conformationally flexible.^{16,60,61} The ease of such conformational changes in the carbodiimides studied here is analogous to such C–C bond rotations, thus leading to relatively low barriers for both the enantiomeric and diastereomeric products.

In concentrating on the simple reaction coordinates from the *cis* transition states, we have been cognizant that more complicated and difficult to examine PES are likely for these ring systems, particularly for the larger ones. In an effort to explore the conformational carbodiimide space in more detail, both MM and MD studies of the seven-, eight-, and nine-membered ring carbodiimides were carried out. Geometry optimizations of a large number of the structures obtained using MM and MD techniques (see Computational Methods section and earlier discussion) have not resulted in any structures having energies significantly lower than those found by examining the reaction coordinates along the IRC paths. Although MM and MD techniques provided an opportunity to sample a much larger conformational space, following the IRC paths from the *cis* transition states of the seven-, eight-, and nine-membered rings provided all of the key structures to determine barrier heights in these rings. If lower energy structures were found in the MM and

MD studies, then we would have expected higher barrier heights to result. That they have not suggests that these PES are simpler than we might have thought. Visualizations of the MD simulations clearly show that the nine-membered ring is far more flexible than the eight-membered carbodiimide.

In the *cis* transition state structures considered in this study, the lowest-energy one was considered in the greatest detail and supports the discussion above, particularly the correlations that are found with transition state symmetries. That said, we recognize that the PES of the ring systems studied here are undoubtedly more complex and likely would be a richly rewarding area for further study.

SUMMARY

Seven *cis* carbodiimide transition states from ring sizes six through twelve have been studied computationally. They generally fall into even-numbered transition states having C_s symmetry and odd-numbered rings having C_2 symmetry, with a twelve-membered ring having no symmetry (C_1). Rings with C_s symmetry have been followed along their antisymmetric reaction coordinate pathway to enantiomeric products. Along the symmetric reaction coordinate from the C_2 transition states, diastereomeric isomers were found. Various structural properties related to ring size were examined, as were questions concerning the complexity of the PES. None of the barriers determined suggest that such ring systems are candidates for optical resolution, although the seven-membered ring enantiomers (**3bb**/**3'bb**) have a fairly high barrier. It is conceivable that a related system with appropriate substitution could be optically resolved. One finding of possible synthetic significance is that these computations predict that a five-membered alicyclic carbodiimide could be an isolable compound.

ASSOCIATED CONTENT

Supporting Information

Zero point energy (ZPE) corrections have been applied to all of the stable products; in addition, explicit energies, optimized Cartesian coordinates of all the reported structures (as well as some that are only briefly considered), and additional structural characteristics are given. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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