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Causation in a Cascade: The Origins of Selectivities in Intramolecular Nitrone Cycloadditions

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Abstract

The factors controlling chemo-, regio-, and stereoselectivity in a cascade of reactions starting from a bis(cyanoalkenyl)oxime and proceeding via nitrone cycloadditions, have been unravelled through a series of density functional calculations with several different functionals. Both kinetic and thermodynamic control of the reaction cascade are important depending upon conditions. Kinetic control is analysed by the distortion/interaction model and is found to be dictated by differences in distortions of the cycloaddends in the transition states. A new mechanism competing with that originally proposed in the application of these reactions to the histrionicotoxin synthesis is discovered in these studies.

INTRODUCTION

Intramolecular 1,3-dipolar cycloadditions are an important tool for the assembly of complex molecular architectures.¹ Holmes² and Stockman³ used an intramolecular 1,3-dipolar cycloaddition between a nitrone and a cyano-substituted alkene as a key step in the synthesis of histrionicotoxin alkaloids (Scheme 1). The crucial 6,6,5-tricyclic intermediate **6** is derived from an intramolecular 1,3-dipolar cycloaddition of the *C*-(cyanoalkenyl)nitrone **3**. The nitrone is generated from the symmetrical ketone **1**, via the oxime **2** (NH₂OH·HCl/NaOAc, methanol, 50 °C), and undergoes intramolecular 1,3-dipolar cycloaddition spontaneously under these conditions. However, there are in total four regio- and stereochemically distinct modes of cycloaddition,⁴ and the major product at 50 °C is not **6** but the 6,5,5-tricyclic species **4**. Cycloadduct **4** is converted to **6** (the thermodynamically favored cycloadduct) by thermal equilibration (e.g. 180 °C, chlorobenzene).⁵

During experimental efforts to optimize the yield of the desired 6,6,5 cycloadduct **6**, we uncovered two intriguing phenomena:

1. A second 6,5,5-tricyclic species, **5** (Scheme 1), is formed transiently during the thermal isomerization of **4** to **6**.^{2d}

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Supporting Information. Calculated geometries and energies, and complete citations for refs. 7 and 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

2. An enantiomerically pure sample of (+)-**6**, when heated at 185 °C in chlorobenzene for 16 h, was found to undergo racemization.^{2d}

These observations were proposed to arise through the series of interconversions shown in Scheme 2.^{2d} In the scheme, we use a prime symbol to denote enantiomeric species whose optical rotations are not known. The racemization of (+)-**6** commences at the lower left with a retro-1,3-dipolar cycloaddition to form **3**. Cycloaddition in the opposite regio- and stereochemical sense then gives **5**. Opening of the piperidine ring of **5** leads to a bicyclic species, **8**, which re-cyclizes from the opposite face to give **4**. Retro-1,3-dipolar cycloaddition, followed by re-cycloaddition in the opposite regio- and stereochemical sense, gives (–)-**6**.

We report a computational investigation of the tandem oxime cyclization/1,3-dipolar cycloaddition route to the histrionicotoxin precursor **6**. The origins of thermodynamic and kinetic control in the intramolecular 1,3-dipolar cycloaddition of **3**, and the mechanism of the thermal racemization of (+)-**6**, have been explored with density functional theory computations. The calculations support the proposed racemization mechanism (Scheme 2), but also predict a second pathway that involves opening of the piperidine ring of (+)-**6** through an elimination reaction.

THEORETICAL CALCULATIONS

Geometries of reactants, transition states, and products were optimized at the B3LYP/6-31+G(d) level⁶ in Gaussian 03.⁷ Conformational searching was performed at the PM3 level in Spartan 08,⁸ and at the B3LYP/6-31+G(d) level. Frequency calculations at the B3LYP/6-31+G(d) level were used to determine the nature of minima and transition states, and IRC calculations⁹ were used to characterize transition states where appropriate. Zero-point energies and thermal corrections were obtained from the B3LYP frequency analyses, and are unscaled. Single-point energies were subsequently calculated at the M06-2X/6-311+G(d,p) level¹⁰ in Gaussian 09.¹¹ M06-2X free energies were computed from the M06-2X electronic energies by addition of the B3LYP zero-point and thermochemical corrections. Geometries of **4–6** and **TS-4–TS-6** were also optimized at the M06-2X/6-31+G(d) level. Optimization with M06-2X led to minor differences in the geometries, reaction energies, and activation energies; these are described in the Supporting Information. The effects of solvent were studied by means of single-point calculations with the CPCM method¹² (UAKS radii) at the M06-2X/6-31+G(d) level in methanol or chlorobenzene (Gaussian 09). Free energies are quoted at 298.15 K and 1 mol/L. Computed molecular structures were drawn with the CYLview program.¹³

RESULTS AND DISCUSSION

Thermodynamic control

We first performed calculations to examine the relative thermodynamic stabilities of the cycloadducts **4–6**. Geometries of the cycloadducts were optimized at the B3LYP/6-31+G(d) level, and single-point energies were then calculated at the M06-2X/6-311+G(d,p) level. The optimized geometries of **4–6** are shown in Figure 1, along with their free energies relative to the nitron **3** (M06-2X in bold, B3LYP in parentheses).

Consistent with experiment, both M06-2X and B3LYP predict the 6,6,5 tricyclic species **6** to be the thermodynamic product. This cycloadduct lies 7.9 kcal/mol below **5** and 11.1 kcal/mol below **4** at the M06-2X level. At the B3LYP level, **6** lies 6.1 kcal/mol below **5** and 10.0 kcal/mol below **4**. The tricyclic species **4–6** have previously been studied at the B3LYP/6-31G(d) level, which gave relative energies of 5.8, 4.5, and 0 kcal/mol, respectively

(ΔE).^{2d} The B3LYP data in Figure 1 underestimate the thermodynamic stabilities of the cycloadducts, predicting only **6** to be lower in energy than the starting nitron. In contrast, M06-2X predicts all three cycloadducts to be lower in energy than **3**. Recent benchmarking studies have shown that B3LYP in conjunction with the 6-31+G(d) basis set underestimates the exothermicity of the parent 1,3-dipolar cycloaddition between methylene nitron and ethylene by 5 kcal/mol.¹⁴ Substantial underestimation of reaction enthalpies by B3LYP have also been reported for Diels–Alder reactions of CN-substituted alkenes.¹⁵

Within the 6,5,5 series, **5** has the CH₂CN group in an equatorial position and is consequently favored by 3–4 kcal/mol over the axial isomer, **4**. The greater stability of the 6,6,5-tricyclic adduct **6** compared to either **4** or **5** is due both to a greater inherent stability of the 6,6,5-tricyclic core and to additional influences of the appended substituents. The 6,6,5 core is 4 kcal/mol more stable than the 6,5,5 core when the CN and CH₂CN groups are replaced by hydrogen atoms (Supporting Information).

Kinetic control

Under conditions of kinetic control (methanol, 50 °C), the intramolecular cycloaddition of **3** furnishes the least stable cycloadduct, **4**, in greatest amount. To explain this, transition states were calculated for the formation of **4–6** from the common nitron precursor **3**. Their structures are shown in Figure 2. Gas-phase activation energies (M06-2X and B3LYP) are shown below each structure, together with solution-phase values in methanol and chlorobenzene, obtained from CPCM calculations.

Both M06-2X and B3LYP correctly predict **4** to be the kinetic product. The M06-2X activation energies lie within the range 21.0–24.5 kcal/mol, and are more consistent with the experimental conditions than the B3LYP values, which are 5–8 kcal/mol higher. The activation energy for formation of **4** (TS-**4**, $\Delta G^\ddagger = 21.0$ kcal/mol) is 2.2 kcal/mol smaller than that for formation of **6**, and 3.5 kcal/mol smaller than for **5**. These values correspond to a 96:0:3 ratio of **4:5:6** under kinetic control at 50 °C.

Within the 6,5,5 series, the kinetic preference for **4** over **5** arises from steric effects. Axial–equatorial energy differences in the transition states are not large, because the nitron is still relatively flat. The pseudoequatorial TS-**5** is disfavored by 3–5 kcal/mol compared to the pseudoaxial TS-**4** because of steric crowding between the CH₂CN group and the approaching alkene. A close H–H distance of 2.28 Å is present in TS-**5** (see red line in Figure 2), which is absent in TS-**4**.

To explain why **4** is also kinetically favored over **6**, we evaluated the strain energies present in various fragments of the transition states TS-**4** and TS-**6**.¹⁶ Separate calculations were performed on the nitron ring, the tether connecting the nitron to the alkene, and the 5-membered bond-forming array. Most of the energetic difference was found to arise from poor alignment of the reacting groups in the 5-membered bond-forming array. In Figure 3 are shown the bond-forming arrays from TS-**4** and TS-**6**, after replacement of the alkyl groups by hydrogen atoms (TS-**4a** and TS-**6a**).¹⁷ Fully-optimized versions of these transition structures are also shown (TS-**4b** and TS-**6b**). While the fully-optimized transition states show a regioselectivity of 2.5 kcal/mol ($\Delta\Delta E^\ddagger$) in favor of **6**, the distorted arrays from the intramolecular TSs favor **4** by 3.8 kcal/mol. The intrinsic selectivity is reversed in the intramolecular structures, because the alkene fragment is more distorted and is oriented less ideally for bonding to the nitron. This is most clearly seen in the top views of the transition states included in Figure 3.

We also investigated the possible influence of the different solvents used for the intramolecular 1,3-dipolar cycloaddition under kinetic and thermodynamic conditions.

CPCM calculations on **TS-4**–**TS-6** in methanol and chlorobenzene gave the solution-phase activation energies shown in Figure 2. Solvation raises the barriers fairly uniformly by 1–2 kcal/mol, and mirrors the gas-phase prediction that **4** is the kinetic product. Likewise, **6** remains the predicted thermodynamic product in solution (Supporting Information).

These calculations offer insight into the mechanism responsible for the formation of transient **5** during the thermal isomerization of **4** to **6** (Scheme 1). At 180 °C in chlorobenzene, the activation energies for formation of **4**–**6** from the common nitrone **3** correspond to a 80:3:17 kinetic selectivity (**4**:**5**:**6**). The small proportion for **5** in this ratio is not sufficient to explain the quantities of **5** detected experimentally. The alternative route suggested previously,^{2d} involving the bicyclic species **8** (Scheme 2), is likely more significant.

Racemization

Calculations were also performed to explore mechanisms for the racemization of (+)-**6** at high temperatures. We searched for various types of transition states that could lead to the formation of the bicyclic intermediate **8** from **5** or **4** (Scheme 2). The proposed^{2d} interconversion **5**→**8**→**4** is related to the Cope elimination reactions of *N*-ethyl hydroxylamines,^{18–20} but with the added requirement of one or more protonation/deprotonation steps. Attempts to locate unimolecular (protonated) transition states related to those of known Cope elimination reactions²¹ gave only high-energy structures ($\Delta G^\ddagger$ 58 kcal/mol, see Supporting Information), while a transition state for the C–N bond formation step of an intramolecular conjugate addition of **8**^{20c} could not be located. The conversion **5**→**8**→**4** most likely involves ionic intermediates and proton-transfer steps mediated by adventitious hydroxylic molecules. Owing to the ionic character of the intermediates, and the likely stabilization of the intermediates and transition states by adventitious hydroxylic molecules, it is difficult to compare the rates of these elimination reactions with those of the neutral, unimolecular (retro-)1,3-dipolar cycloadditions. Upon optimization in a solvent continuum²² we were able to locate the zwitterionic intermediate **5-zw**, derived from **5**. Its free energy in chlorobenzene (24.4 kcal/mol) was 1.6 kcal/mol lower than that of **TS-5** (26.0 kcal/mol, Figure 2). We assume that the elimination reactions **5**→**8** and **4**→**8** are facile in solution.

We also explored an alternative racemization pathway where the piperidine ring opens directly from (+)-**6**. This new pathway is shown in Scheme 3, together with the original^{2d} proposal. Opening of the piperidine ring of (+)-**6** results in the bicyclic species **9**. Subsequent re-cyclization from the opposite face gives the intermediate **10'**, which is also the species that would result from a 6,6,5-cycloaddition onto the more crowded face of the nitrone. Retro-1,3-dipolar cycloaddition of **10'**, followed by re-cycloaddition from the less hindered face, furnishes (–)-**6**. A second alternative pathway involves these species in a different sequence: (+)-**6**→**3**→**10**→**9'**→(–)-**6**.

The energies of transition states and intermediates in the two racemization pathways are included in Scheme 3. Data for species **9**, **10**, and **TS-10** are included in the Supporting Information. The piperidine ring-opening steps are assumed not to be rate-limiting. The racemization pathway starting from (+)-**6** and involving **9/10'**/**3'** has a barrier of 23.4 kcal/mol (as does an alternative pathway involving **3/10/9'**), while the less direct route involving **3/5/8/4/3'** has a barrier of 24.5 kcal/mol. These barriers correspond to a ratio of 3:3:1 at 185 °C; hence, each of the three pathways is expected to be mechanistically significant. The tricyclic species **10** has not yet been detected, but trapping experiments are currently underway.

We also considered the possibility that nitrene **3** can revert to the oxime **2** at elevated temperatures (Figure 4). This would provide an alternative route for the interconversion of (+)-**6** and (–)-**6**, but would also be expected to lead to some *Z/E* alkene scrambling. Grigg⁴ has shown that additions of oximes to electron-deficient alkenes (1,3-azaprotio cyclotransfer reactions) are concerted processes. Figure 4 shows concerted transition states for ring opening of nitrene **3** to give an oxime with either a *Z* or an *E* pendant alkene. There is a small *Z/E* selectivity (1.3 kcal/mol). The computed barriers indicate that ring opening to give a *Z* alkene is of minor importance at 185 °C.

CONCLUSION

Density functional theory calculations have identified the factors responsible for kinetic and thermodynamic control in the intramolecular 1,3-dipolar cycloadditions of the *C*-(cyanoalkenyl)nitrene (**3**) employed in the Holmes/Stockman synthesis of histrionicotoxin. M06-2X and B3LYP calculations correctly predict that the 6,6,5-tricyclic species **6** is the thermodynamic product of the cycloaddition, and the 6,5,5-tricyclic species **4** is the kinetic product. The transition state leading to **6** is higher in energy due to the poor overlap between the nitrene and the alkene that is enforced by the tether. The observed racemization of (+)-**6** is suggested to occur by three pathways—two commencing with retro-1,3-dipolar cycloaddition and the other commencing with an elimination reaction that opens the piperidine ring. These pathways operate in parallel at elevated temperatures. A comprehensive understanding of the mechanistic pathway leading to the tricyclic bis-nitrile **6** provides an opportunity to address the synthesis of biologically important analogs that have hitherto not been accessible as well as to consider enantioselective syntheses from a simple achiral precursor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. The geometry of **5-zw** was optimized in methanol. Attempted optimization in chlorobenzene led to C–N bond cleavage.

Figure 1. Calculated structures of the tricyclic products **4**, **5**, and **6** (B3LYP/6-31+G(d)). M06-2X Gibbs free energies relative to the nitron **3** are shown in bold, with B3LYP values in parentheses (kcal/mol). Bond lengths are in Å.

Figure 2. Calculated transition structures for intramolecular 1,3-dipolar cycloadditions of the nitrone **3**, leading to the tricyclic species **4**, **5**, and **6**. Below each structure is listed the Gibbs free energy of activation in the gas phase by M06-2X (bold) and B3LYP (parentheses), along with solution values in methanol (brackets) and chlorobenzene (brackets, italics). Activation energies (in kcal/mol) are calculated with respect to the nitrone **3**. Bond lengths are in Å.

Figure 3.

(a) Truncated analogues of **TS-4** and **TS-6**, representing the 5-membered bond-forming array. **TS-4a** and **TS-6a** were obtained by replacing the alkyl groups of **TS-4** and **TS-6** by hydrogen atoms at a fixed distance of 1.09 Å. (b) The corresponding fully-optimized transition states for cycloadditions of methylene nitrene with acrylonitrile. Potential energies (all relative to **TS-6b**; ZPE exclusive) are given in kcal/mol [M06-2X/6-311+G(d,p)].

Figure 4. Transition states for ring opening of nitrone **3** to give an oxime with a *Z* or *E* pendant alkene (reverse 1,3-azaprotio cy-clotransfer reactions). The M06-2X activation energies are shown (gas phase, kcal/mol). Bond lengths in Å.

The Holmes/Stockman intramolecular nitrene 1,3-dipolar cycloaddition route to histrionicotoxin.^{2,3}

Scheme 2.

Mechanism previously proposed for the racemization of (+)-**6**.^{2d}

Scheme 3.

Revised mechanism for the interconversion of 6,6,5- and 6,5,5-tricyclic species. The M06-2X Gibbs free energies relative to the nitron **3** are shown (gas phase, kcal/mol).^a

^a The different arrangements drawn for the (CH₂)₃CN chain in **3/3'** are shown only to indicate the type of tricyclic framework that is to be formed upon cycloaddition; the energy listed underneath each of these structures is the energy of the most stable conformer.