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Origins of 1,6-Stereoselection in Torquoselective 6π Electrocyclizations

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Abstract

A novel stereoselective electrocyclicization developed for the total synthesis of reserpine has been explored by both experiment and theory. A stereocenter 6 atoms away from the newly forming chiral center is responsible for the diastereoselectivity of the ring closure. This stereogenic center – lying at the junction of two 6-membered rings – defines the conformation of the substrates' fused ring skeleton that ultimately distinguishes between the two allowed, disrotatory triene geometries at the transition state. The presence of allylic strain in the disfavored transition state results in a torquoselective ring closure (dr up to 15.7:1).

Introduction

The 6π electrocyclicizations of hexatrienes were an impetus for the formulation of the ground-breaking orbital symmetry rules formulated by Woodward and Hoffmann.¹ The orbital symmetry rules predict that the thermal 6π electrocyclicization is disrotatory, while the photochemical process is conrotatory. (Scheme 1).²

Two modes of disrotation exist for all thermal 6π electrocyclicizations. For a chiral substrate, these two disrotatory modes of electrocyclicization yield diastereomeric products. If one diastereomer is formed preferentially, such a ring closure is said to be torquoselective (Scheme 2).^{3,4}

While the orbital symmetry rules clearly explain that thermal 6π electrocyclicizations must occur through disrotation, it is less clear what specific factors control the preference for one disrotatory mode of 6π electrocyclic ring closure over the other. Examples of the torquoselective thermal 6π electrocyclicization of hexatrienes date back to 1963,⁵ and many examples have been reported since then.^{6–15} However, the origins of stereoselectivities in these examples remain unclear.

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Author Contributions

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Supporting Information. All relevant NMR data, synthetic details, and coordinates for computed structures in xyz format can be found in the Supporting Information. Details regarding the conformational analysis of the setransition states are also provided in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We recently reported an approach to the reserpine alkaloids based upon a highly torquoselective thermal 6π electrocyclization.¹⁶ Pentacyclic structures were prepared with extremely high levels of selectivity by employing a tandem cross-coupling/electrocyclization protocol that relied on a remote stereocenter to induce a diastereoselective ring closure (Scheme 3). Intrigued by the high levels of selectivity observed in these reactions, we explored the scope of this chemistry computationally. Initial results suggested that the methyl ester at the 3-position of the triene could be engaged in allylic strain with the adjacent D-ring methylene. We proposed that varying the steric bulk of groups at the 3-position would have a significant impact on the diastereoselectivity of the electrocyclization. Herein, we report our experimental and computational results investigating the origins of this remote 1,6-stereoiduction.

Synthesis and Electrocyclization of Trienes

In order to assess the effect of substituent size on the electrocyclization reaction, we envisioned an expedient route to several trienes with variations in the size of the functional groups at the 3-position. Our synthetic plan began with the addition of propenylmagnesium bromide to the BF_3 -complexed dihydroisoquinoline **1** (Scheme 4). Allylation of amine **2** provided enyne **3a** that was functionalized at the alkyne terminus with groups of varying steric requirement. We then prepared and studied the electrocyclization of six distinct trienes derived from the tandem carbopalladation/cross-coupling of enynes **3a–f** (Table 1).

The tandem carbopalladation/Suzuki coupling sequence generated the corresponding trienes, which upon heating provided the 6π electrocyclization products. Table 1 provides experimental diastereoselectivities and the A-values of the C3 substituent, as a measure of size, for each triene examined. All of the electrocyclizations took place at 120 °C in xylenes, except for R = CO_2Me and R = TMS which underwent cyclization in the cross-coupling reaction at 80 °C. Starting with the smallest substituent, R = H (Table 1), we observed an increase in the diastereomeric ratio from 3.5:1 to 6.7:1 for R = SPh and then to 15.7:1 and 13.3:1 for R = CO_2Me and R = Me respectively. The diastereomeric ratio is greater for the reaction of triene **4c** (R = CO_2Me) compared to the ring closure of **4d** (R = Me) due to differences in reaction temperature; however, the experimentally determined $\Delta\Delta G^\ddagger$ is larger for the triene **4d** than **4c**. (*vide infra*). The observation that trienes bearing larger substituents provide greater levels of diastereoselectivity than trienes with smaller substituent is intuitive. Surprisingly, with the larger R = TMS and R = *t*Bu substituents, we observe that the diastereomeric ratio decreases to 4.3:1 and 3.2:1, respectively.

Computational Methods

All structures examined computationally were initially prepared using Avogadro, a freely-available molecular editor/builder program that includes a constrained force field optimization feature useful in generating reasonable starting geometries for QM optimization.¹⁷ Quantum mechanical calculations were performed using Gaussian 09.¹⁸ Geometries were initially optimized *in vacuo* using the meta-hybrid density functional M06-2X¹⁹ with the 6-31+G(d,p) basis set. Normal-mode analysis confirmed that all optimized reactants and products were, indeed, minima, and that all transition states located were first order saddle points. Activation barriers ($\Delta H^\ddagger$ and $\Delta G^\ddagger$) were also determined using M06-2X/def2-TZVPP²⁰//M06-2X/6-31+G(d,p) single points with thermal corrections determined at the M06-2X/6-31+G(d,p) level of theory; whereas reaction energies (ΔH_{rxn} and ΔG_{rxn}) were only calculated at the M06-2X/6-31+G(d,p) level of theory. All QM calculations were performed using an “ultrafine” numerical integration grid, consisting of 99 radial shells and 590 angular points per shell. Errors in computed entropies introduced by the treatment of low frequency modes as the harmonic motions were corrected by raising all

harmonic frequencies below 100 cm^{-1} to exactly 100 cm^{-1} as described by Truhlar.²¹ The discussion of stereoselectivity is restricted to only the lowest energy transition state conformers. A more extensive survey of the structures of transition state conformers can be found in the Supporting Information.

Computational Results

The electrocyclizations of trienes **4a–f** are all highly exergonic with ΔG_{rxn} ranging from -18 kcal/mol for the reaction of triene **4a** to -27 kcal/mol for the reaction of triene **4f**. Consequently, the stereoselectivity observed experimentally is due to differences in the energies of the two electrocyclicization transition states. The activation energies for this series of electrocyclicization reactions are approximately 30 kcal/mol and is consistent with the elevated temperatures required experimentally for the electrocyclicization. However, the barriers of the electrocyclic ring closures of trienes **4e** and **4f** are lower ($\Delta G^\ddagger = 26\text{ kcal/mol}$) than those for the electrocyclizations of **4a–d**. The computed and experimentally-determined energy differences between the lowest energy conformers of the α and β transition states for electrocyclicization of **4a–f** are listed in Table 2.

In general, computed selectivities for this series of electrocyclic reactions are in reasonable agreement with experiment, although we are not able to reproduce the experimental selectivity of the reaction of triene **4f** ($R = t\text{Bu}$). As shown in Table 2, computations overestimate the diastereoselectivity of the electrocyclizations of trienes **4c**, **4d**, and **4e** and underestimate the selectivities of the electrocyclic reactions of **4b** and **4f**. The mean absolute deviation (MAD) between the computed $\Delta\Delta G^\ddagger$ and corresponding experimental values is 0.6 kcal/mol for this series of electrocyclizations.

For the reactions of **4a**, **4c**, and **4d** a simple relationship between the steric bulkiness of the C3 substituent, as measured by A-values, and selectivity exists. Triene **4a**, bearing only a hydrogen atom at C3, undergoes ring closure with little diastereoselectivity ($\Delta\Delta G^\ddagger = 1.0\text{ kcal/mol}$). Trienes **4c** and **4d** with ester and methyl substituents, respectively, yield more highly selective electrocyclizations ($\Delta\Delta G^\ddagger = 1.5\text{--}1.9\text{ kcal/mol}$). Despite the relative bulkiness of TMS and $t\text{Bu}$, the electrocyclization of trienes **4e** and **4f** are not very selective, according to experiment and suggests that the neither the α nor the β transition state can effectively accommodate the extremely bulky C3 substituents like TMS or $t\text{Bu}$.

Transition states **TS4d α** and **TS4d β** of the electrocyclization of triene **4d** are shown in Figure 2. The triene adopts a boat-like geometry in the disrotatory transition structures, and the two modes of ring closure can be viewed on the right side of Figure 1. In the favored **TS4d α** , the C-terminal methyl group rotates downward through a “concave down” boat geometry. The key difference between the two transition states can be found in the dihedral highlighted in green in Figure 2. This dihedral angle is nearly planar (7°) in the disfavored transition structure (**TS4d β**), and more staggered (73°) in the lower-energy **TS4d α** . The Newman projections of **TS4d α** and **TS4d β** in Figure 2 show more clearly this difference between the two transition structures. The planar arrangement in **TS4d β** introduces allylic strain in this transition state between the C3 substituent and the methylene hydrogens of the piperidine (highlighted). This effect includes contributions from steric clashes between the piperidine hydrogen (highlighted) and the methyl group as well as torsional strain between the two coplanar bonds.

The electrocyclic reactions of tricyclic trienes **4b** and **4f** merit further discussion, as factors beside allylic strain are also important in explaining the torquoselectivity of these ring closings. Triene **4b** possesses a flexible thiophenyl substituent at the C3 position of the triene, introducing the possibility that several rotameric α and β transition states exist. The

lowest energy transition state rotamers leading to the α and β diastereomers, **TS4b $_{\alpha}$** and **TS4b $_{\beta}$** , respectively, are shown in Figure 3. **TS4b $_{\alpha}$** is 0.8 kcal/mol lower in free energy than **TS4b $_{\beta}$** according to the large basis set calculations. This $\Delta\Delta G^{\ddagger}$ is smaller than 1.5 kcal/mol value observed experimentally. The difference in the corresponding H–C–C–C dihedral between **TS4b $_{\alpha}$** and **TS4b $_{\beta}$** is even larger than that of **TS4d $_{\alpha}$** and **TS4d $_{\beta}$** , as the dihedral angle in **TS4b $_{\beta}$** is 0.7° presumably because thiophenyl substituent is conjugated with the triene in this structure. Allylic strain in **TS4b $_{\beta}$** may, however, be attenuated by electrostatic attraction between the electronegative sulfur atom and the positively charged hydrogen atom; however, torsional strain will still destabilize **TS4b $_{\beta}$** relative to **TS4b $_{\alpha}$** .

TS4b $_{\alpha}$ and **TS4b $_{\beta}$** are both stabilized by intramolecular C–H π interactions that could provide stabilization by dispersion. In **TS4b $_{\alpha}$** the C–H interaction occurs between the *S*-phenyl group and the C2 hydrogen of the triene (2.85 Å). A similar interaction occurs in **TS4b $_{\beta}$** between *S*-phenyl group and an aromatic hydrogen of the aromatic A ring (2.84 Å). Because the reactions are performed in xylenes, the solvent may be competing with the *S*-phenyl group for these weak interactions in such way that the two transition states may not be differentially stabilized. In order to estimate the selectivity that would exist in the absence of these intramolecular dispersion interactions, we replaced the phenyl group with a hydrogen atom or methyl group and performed single point energy calculations on these structures. $\Delta\Delta E$ between these model trienes are 5.9 and 4.9 kcal/mol, respectively, favoring the formation of the α -diastereomer.

According to computations, the reaction of **4f** proceeds with a $\Delta G^{\ddagger}$ of 25 kcal/mol and a ΔG_{rxn} of –27 kcal/mol. These values are similar to corresponding values determined for the reaction of **4e**. In comparison to the electrocyclizations of trienes **4a–d**, **4e** and **4f** undergo ring closures with a 3–5 kcal/mol lower barrier and are also 3–7 kcal/mol more exergonic. The diminished barrier and the increased exergonicity of the electrocyclizations of both **4e** and **4f** is due to a decrease in steric demand for the bulky C3 substituent as the reactant progresses along the reaction coordinate toward the product. Computations also indicate that the electrocyclic reaction of triene **4f** (R = *t*Bu) is essentially nonselective, with a slight preference for β stereoisomer (minor product). Illustrated in Figure 4 are the α and β transition states for this electrocyclization. Both **TS4f $_{\alpha}$** and **TS4f $_{\beta}$** suffer from a number of steric clashes, some of which are quite severe and range in terms of interatomic (H–H) distances from 1.94 Å to 2.07 Å. The introduction of additional steric clashes in the α transition state of **4f** leads to the erosion of selectivity.

Origins of Differential Allylic Strain in the Electrocyclization Transition States of Trienes 4a–f

The piperidine ring (C-ring, Scheme 5) directly fused to the triene discriminates between the two modes of disrotation. This ring prefers to adopt a half-chair conformation, which places the hydrogen at the stereocenter in an axial position. Overlaying the piperidine rings (heavy atoms only) of the α and β transition structures (**TS4 $_{\alpha}$** and **TS4 $_{\beta}$**) reveals the conformations of this heterocycle in either transition state are nearly identical (RMSD 0.17 Å).

How does this piperidine ring cause the two disrotatory modes to have different energies? In the α transition states, the triene adopts a “concave-down” boat geometry. This arrangement places the C3 substituent (see Figure 1 and 2) between the pseudoaxial and pseudoequatorial hydrogens of the piperidine ring. Eclipsing strain is avoided as the C3–C4 bond of the triene also lies between these hydrogens. In the β transition states, the triene features a “concave-up” boat that forces the C3–C4 bond into the plane of pseudoequatorial C–H bond (Figure 1 and 2), introducing eclipsing strain as well as allylic strain between the C3 substituent and the pseudoequatorial hydrogen.

Remote stereinduction in this manifold is only possible because the triene adopts one of two well-defined, clearly distinguishable boat-like geometries (i.e., “concave up” or “concave down”) at the transition state. These boat-like transition states have rigid geometries that do not distort easily since the boat arrangement of the triene maximizes orbital overlap²² within the cyclic array of p orbitals, while conforming to the rules of orbital symmetry. Overlays of the triene portions of **TS4a_β**–**TS4f_β** confirm this recalcitrance towards distortion as the triene geometries are conserved throughout the series of trienes, even for **TS4e_β** (R = TMS) and **TS4f_β** (R = *t*Bu).

Conclusions

We have explored the torquoselective 6π electrocyclizations of a series of isoquinoline-derived trienes containing variation at the 3-position of the triene experimentally and computationally. For the six trienes examined, there is a qualitative agreement between theory and experiment. The observed diastereoselectivities for this series of trienes is sensitive to substitution at the C3 position of the triene. Trienes bearing moderately bulky substituents like methyl or methyl ester at this position undergo the 6π electrocyclization reaction with the greatest levels of diastereoselectivity, whereas trienes with more bulky C3 substituents like R = TMS or R = *t*Bu undergo a much less stereoselective ring closing. Our results also illustrate that the conformation of the piperidine ring (C-ring) in conjunction with the strict geometric requirements of the triene at the transition state are responsible for the relay of stereochemical information from a distal stereogenic center to the forming stereocenter six atoms away. Allylic strain in the β transition states explains the observed preference for the α diastereomer in this series of electrocyclizations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Top and front views of the α and β disrotatory transition states of the electrocyclic reactions of triene **4**, optimized using M06-2X/6-31+G(d,p) *in vacuo*.

Figure 3. Top and front views of the α and β disrotatory transition states of the electrocyclic reaction of triene **4b** optimized using M06-2X/6-31+G(d,p) *in vacuo*. Note the *S*-phenyl group is made transparent for clarity where necessary.

Figure 4. Top and back views of the α and β disrotatory transition states of the electrocyclic reaction of triene **4d** optimized using M06-2X/6-31+G(d,p) *in vacuo*.

thermally allowed

disrotatory
ring closure

thermally forbidden

conrotatory
ring closure

Scheme 1.

Disrotatory and Conrotatory Modes for the Electrocyclic Ring Closure of 1,3,5-hexatriene

Scheme 2.
The Two Disrotatory Modes of Electrocyclization of a Chiral Hexatriene

Scheme 3.

1,6 Stereinduction in a 6 π Electrocyclization Approach to Reserpine Alkaloids

Scheme 4. Synthesis of Key Enynes 3a–f^aSee Supporting Information for details.

Scheme 5.
The Six Model Systems Examined Computationally

Table 1

Synthesis of Trienes and Experimental Diastereoselectivities of Electrocyclizations.

enyne (R)	A-value (kcal/mol)	6 π product (dr) ^{a,b,c}

3a (H)	0	5a (3.5:1)
3b (SPh)	0.8	5b (6.7:1)
3c (CO ₂ Me)	1.3	5c (15.7:1)
3d (Me)	1.7	5d (13.3:1)

^aFor entries 3 and 5 the electrocyclization product was isolated directly from the cross-coupling reaction without isolation of the triene. All other products were generated by subsequent heating of the isolated triene at 120 °C in xylenes.

^bDiastereomeric ratios determined by ^1H NMR.

^cRelative configuration of the new stereogenic center assigned by analogy to a crystal structure of a pentacyclic reserpine precursor (see SI).¹⁶

Table 2

A-Values of C3 Substituents, Computed $\Delta\Delta H^\ddagger$ and $\Delta\Delta G^\ddagger$, and Experimental $\Delta\Delta G^\ddagger$ and Values

triene (R)	A Value ^a	Comp. ^b $\Delta H^\ddagger$ ($\Delta G^\ddagger$) ^a	Comp. ^b $\Delta\Delta H^\ddagger$ ($\Delta\Delta G^\ddagger$) ^a	Comp. ^c $\Delta\Delta H^\ddagger$ ($\Delta\Delta G^\ddagger$) ^a	Expt. $\Delta\Delta G^\ddagger$ ^a
4a (H)	0	29.1 (30.2)	0.8 (0.8)	1.0 (1.0)	1.0
4b (SPh)	0.8	28.8 (29.4)	-0.3 (0.1)	0.3 (0.8)	1.5
4c (CO ₂ Me)	1.2	26.1 (27.2)	1.6 (1.4)	1.6 (1.4)	1.9
4d (Me)	1.7	27.8 (28.8)	2.3 (2.4)	2.4 (2.5)	2.0
4e (TMS)	2.4	25.8 (26.9)	1.2 (1.3)	1.5 (1.6)	1.0
4f (tBu)	>4.5	25.7 (26.8)	-0.2 (-0.7)	-0.1 (-0.7)	0.9

^aValues in kcal/mol.

^bGas phase M06-2X/6-31+G(d,p) energies.

^cGas phase M06-2X/def2-TZVPP//M06-2X/6-31+G(d,p) energies.