

Why a Proximity-Induced Diels–Alder Reaction Is So Fast

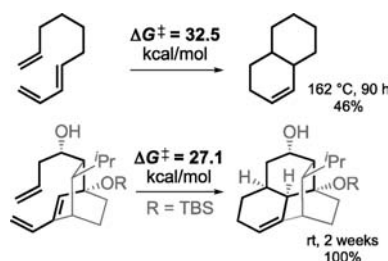
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ABSTRACT

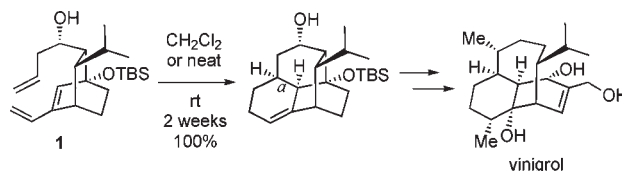


Unlike normal Diels–Alder reactions of acyclic alkadienes with alkenes, the vinylbicyclo[2.2.2]octene employed in the Baran total synthesis of vinigrol undergoes a quantitative Diels–Alder reaction with a tethered alkene at room temperature. Density functional theory calculations reveal that this unprecedented reactivity originates from a combination of preorganization, diene strain, and tether stabilization.

The Diels–Alder cycloaddition has been a transformative reaction in organic synthesis, and new aspects of this 1950 Nobel Prize-winning reaction continue to emerge. A recent total synthesis of the diterpene vinigrol features a “remarkable proximity-induced” Diels–Alder reaction as a key step.^{1,2} The intramolecular Diels–Alder reaction of **1** (Scheme 1) occurs quantitatively at room temperature, while normal Diels–Alder reactions of acyclic alkadienes with alkenes require temperatures of nearly 200 °C; even the intramolecular reaction of **2** (Scheme 2) occurs readily only above 170 °C.^{3,4} A related intramolecular Diels–Alder approach to the vinigrol ring system was developed by Barriault,⁵ although in this case a carbonyl group in

conjugation with the dienophile enabled the cycloaddition to be catalyzed by Lewis acids.

Scheme 1. A Proximity-Induced Diels–Alder Reaction in the Total Synthesis of Vinigrol^{1,2}



What is the origin of the acceleration? Why does proximity produce acceleration? Is the rate acceleration due to an activation entropy increase, strain release, or some other factor? We have determined and quantified the factors leading to this acceleration.

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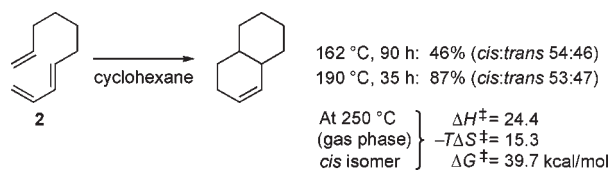
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Scheme 2. Intramolecular Diels–Alder Reaction of a Decatriene^{3,4}



Calculations involved B3LYP/6-31G(d) optimizations,⁶ followed by M06-2X/6-311+G(d,p) single points⁷ and estimates of solvation energies with CPCM.⁸ The conclusions that follow are independent of the exact computational method used.⁹

Compound **1** was modeled by the OTMS analogue, **3**, but was otherwise complete. Figure 1 shows the calculated transition structures for the intramolecular Diels–Alder reactions of **2** and **3**. Activation parameters measured for the reaction of **2** are $\Delta H^\ddagger = 24.4$ kcal/mol and $\Delta S^\ddagger = -29.3$ eu at 250 °C.⁴ The computed value of ΔH^\ddagger calculated from the lowest-energy conformer of **2** (23.7 kcal/mol) is about the same as the experimental value. The entropy term from one conformer is somewhat too positive ($\Delta S^\ddagger = -18.5$ eu), but when the entropy is calculated from all low-energy conformers (see Supporting Information), the value becomes -26.0 eu, very close to the experimental value. For **3**, the solution-phase ΔG^\ddagger at 25 °C (27.1 kcal/mol) corresponds well with the observed reaction time of approximately two weeks at room temperature.

The bicyclic framework of **3** enforces similar constraints on the alignment of the reacting groups as does the simple acyclic tether in **2** but eliminates two rotational degrees of freedom. The forming bond lengths in **TS3** are within 0.03 Å of the values in **TS2**, and both TSs show small deviations from the ideal distance of 2.27 Å found in the synchronous parent Diels–Alder reaction of butadiene with ethylene.¹⁰ Experimentally, the Diels–Alder reaction of **1** affords *cis* stereochemistry at the newly formed ring junction (bond *a*, Scheme 1) as determined by X-ray crystallography, while the reaction of **2** displays a small *cis* selectivity.¹¹ In both **TS2** and **TS3**, the tether ring adopts a six-membered chair conformation with little torsional strain (most dihedrals are $60 \pm 8^\circ$).

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(11) The isomeric intramolecular Diels–Alder reaction of **2** leading to the *trans* product is reported to be disfavored by $\Delta\Delta H^\ddagger = 0.15$ kcal/mol and $\Delta\Delta G^\ddagger = 0.03$ kcal/mol at 250 °C (ref 4). The calculated values of ΔH^\ddagger and ΔG^\ddagger for formation of the *trans* isomer in the gas phase at 250 °C are 24.1 and 37.2 kcal/mol, respectively.

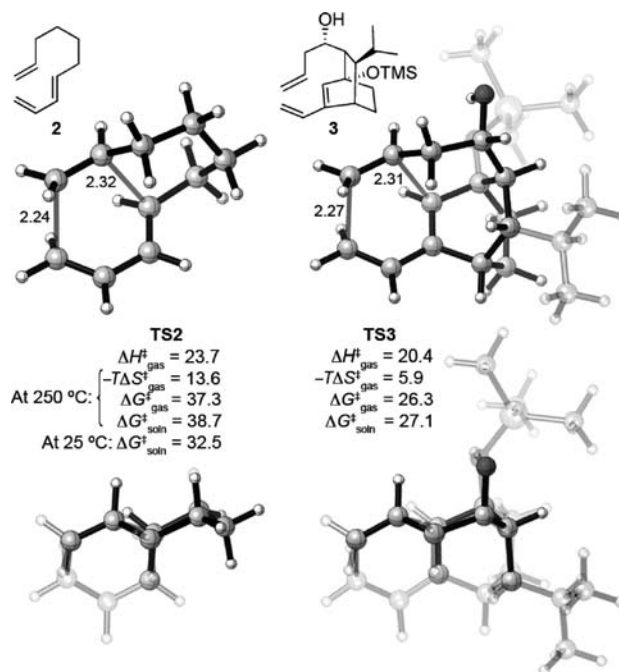


Figure 1. Transition structures for intramolecular Diels–Alder reactions of **2** and **3**. The lower views illustrate the chair conformation of the six-membered ring formed by the tether. Activation energies (kcal/mol) are reported at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level (solution values are in CH_2Cl_2). Data are reported at 25 °C, except where noted. Bond lengths in Å.

Overall, the intramolecular Diels–Alder reaction of **3** is favored over **2** by 5.4 kcal/mol at 25 °C ($\Delta\Delta G^\ddagger$). Solvation accounts for 0.7 kcal/mol of this difference, while the activation entropy term $-T\Delta S^\ddagger_{\text{gas}}$ accounts for a further 1.5 kcal/mol, including a 0.5 kcal/mol difference from conformational entropies due to the smaller degree of conformational flexibility in **3** compared to **2**. To identify the structural features giving rise to the remaining 3.2 kcal/mol stabilization of **TS3**, we designed an intramolecular version of the Distortion/Interaction model of reactivity.¹² The analysis is shown in Figure 2. Activation barriers for the intramolecular Diels–Alder reactions of **2**, **3**, and the related species **4** and **5** were dissected into components representing the distortions (E_{dist}^\ddagger) present in three different parts of the molecule—diene, dienophile, and tether—along with the effects of the appended functional groups in **3**. Model diene, dienophile, and tether fragments were constructed by deleting extraneous portions of the structure, replacing the deleted atoms with an H-atom at a distance of 1.09 Å; these H-atoms are represented by the gray spheres in Figure 2. Estimates of the interaction

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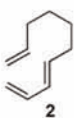



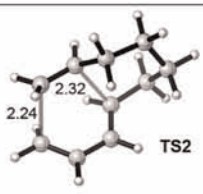
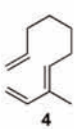



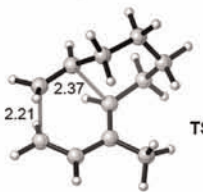




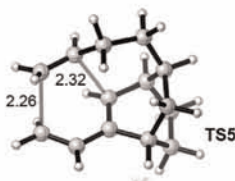
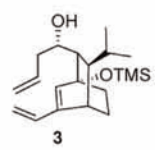


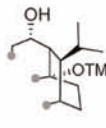
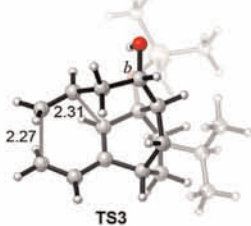

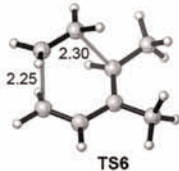
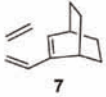
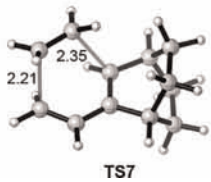
reactant	ΔG^\ddagger	ΔH^\ddagger	$-T\Delta S^\ddagger$	model diene	E_{dist}^\ddagger (diene)	model dienophile	E_{dist}^\ddagger (dienophile)	model tether	E_{dist}^\ddagger (tether)	
	29.2	23.7	5.5		21.6		11.3		0.8	
	30.7	24.9	5.8		21.7		11.8		1.0	
	26.9	22.3	4.6		20.1		10.9		0.5	
	24.9	20.4	4.5		18.7		10.4		-3.2	
	ΔG^\ddagger 35.2	ΔH^\ddagger 20.8	$-T\Delta S^\ddagger$ 14.4	E_{int}^\ddagger -9.0						
	ΔG^\ddagger 34.9	ΔH^\ddagger 20.2	$-T\Delta S^\ddagger$ 14.7	E_{int}^\ddagger -9.7						

Figure 2. Analysis of factors contributing to acceleration of the intramolecular Diels–Alder reaction of **3**. Along with the overall values of ΔG^\ddagger , ΔH^\ddagger , and $-T\Delta S^\ddagger$ in the gas phase at 25 °C (excluding conformational entropy) are given the energies required to distort different fragments of each reactant to the transition-state geometry ($\Delta E_{\text{dist}}^\ddagger$). To obtain the model dienes, dienophiles, and tethers shown, the remainder of the structure was deleted and replaced with an H atom at a distance of 1.09 Å. Added hydrogen atoms are indicated by the gray spheres. Energies (kcal/mol) are reported at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level in the gas phase. Bond lengths in Å.

energy¹² (E_{int}^\ddagger) between the diene and dienophile in the transition states were obtained from the model intermolecular Diels–Alder reactions of **6** and **7**.

Comparison of **2** and **4** indicates that the presence of a 3-alkyl group slightly increases the activation barrier. However, incorporation of the diene into the bicyclic ring system (**4**→**5**) lowers ΔG^\ddagger by 3.8 kcal/mol. The rigid bicyclic framework provides a more favorable entropy term; $-T\Delta S^\ddagger$ is reduced by 1.2 kcal/mol on going from **4** to **5**. The total distortion energy of **TS5** is 3.0 kcal/mol smaller than that of **TS4**, and the largest difference (1.6 kcal/mol) is seen in the diene distortion. This results from the fact that strained cycloalkenes are easier to distort

to the pyramidalized TS geometry.¹³ As a substrate for cycloaddition reactions, the C=C bond of bicyclo[2.2.2]octene has previously been shown to be 5–90 times more reactive than the C=C bond of cyclohexene.¹⁴

The additional functionality present in **3** (OH, OTMS, and *i*Pr) contributes 2.0 kcal/mol to the rate acceleration (**5**→**3**). These substituent effects are largely enthalpic. Reduced tether strain is the primary contributor. The tether in the functionalized reactant **3** is more highly strained than that in the unsubstituted analogue **5** due to steric repulsion between the *i*Pr group and the

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proton on the carbon labeled *b*. In the corresponding TS, this element of strain is relieved and the tether is also stabilized by an O–H···O hydrogen bond between the secondary hydroxyl and OTMS groups that is not present in the reactant.

In summary, the “remarkable proximity-induced” Diels–Alder reaction in the reported^{1,2} total synthesis of vinigrol has been analyzed through density functional theory calculations. The rigid bicyclo[2.2.2]octene-based diene present in **1** lowers the Diels–Alder activation energy by 5.4 kcal/mol compared with the acyclic analogue, **2**. Distortions of both the diene and dienophile in the bicyclo[2.2.2]octene-based TS are 1–3 kcal/mol smaller than those for the acyclic system, while the tether contributes 4 kcal/mol to the rate acceleration through a combination of strain relief and hydrogen bond formation in the transition state. This method of delineation of factors underlying reactivity may prove to be useful in the design of other construction reactions leading to polycyclic, fused ring systems under mild conditions.

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Supporting Information Available. Calculated geometries and energies, calculations of conformational entropy, B3LYP/6-31G(d) activation barriers and distortion/interaction analyses, and a complete citation for ref 9. This material is available free of charge via the Internet at <http://pubs.acs.org>. The authors declare no competing financial interest.

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