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Authors
He, CQ
Chen, TQ
Patel, A
et al.

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Distortion, Tether, and Entropy Effects on Transannular Diels–Alder Cycloaddition Reactions of 10–18-Membered Rings

Cyndi Qixin He,† Tiffany Q. Chen,† Ashay Patel,† Sedef Karabiyikoglu,† Craig A. Merlic,*‡ and K. N. Houk*†‡

†Department of Chemistry and Biochemistry and ‡Department of Chemical and Biochemical Engineering, University of California, Los Angeles, California 90095, United States

Supporting Information

ABSTRACT: Density functional theory calculations were performed on a set of 13 transannular Diels–Alder (TADA) reactions with 10–18-membered rings. The results were compared with those for bimolecular and intramolecular Diels–Alder reactions in order to investigate the controlling factors of the high TADA reactivities. The effects of tether length, heteroatoms, and alkynyl dienophiles on reactivity were analyzed. We found a correlation between tether length and reactivity, specifically with 12-membered macrocycles undergoing cycloaddition most readily. Furthermore, modifying 12-membered macrocycles by heteroatom substitution and utilizing alkynyl dienophiles enhances the reaction rates up to 105-fold.

INTRODUCTION

The Diels–Alder reaction has been widely employed in organic synthesis to construct six-membered carbocyclic compounds since its discovery in 1928.1 The prototypical Diels–Alder reaction of butadiene and ethene is very slow, but it is accelerated by appropriate substitution to confer nucleophilic and electrophilic character on the diene and dienophile, or vice versa.2–4 Intramolecular Diels–Alder reactions, which have been well studied both experimentally and computationally, exhibit higher reaction rates due to the minimization of entropic penalties by linking the reacting moieties in a single molecule.5,6

Transannular Diels–Alder (TADA) reactions are particularly interesting, because the macrocyclic reactants are often found to undergo Diels–Alder reactions rapidly under exceptionally mild conditions even below room temperature.7 Furthermore, they are effective in giving rise to tricyclic molecules with predictable stereochemistry at the ring junctions, which can serve as the structural backbone for a wide range of natural products.8

The greatest challenge for successful transannular reactions is to synthesize the requisite macrocycles efficiently. Deslongchamps and co-workers were the first to report methods to prepare macrocyclic substrates in the early 1990s, utilizing a Pd(0) catalyst to prepare 10–14-membered rings.9–11 In 2013, Merlic and co-workers developed a new method to synthesize a range of cyclic trienes and dienynes by Pd(II)-catalyzed macrocyclizations (Scheme 1).12,13 This method enables the synthesis of a broad range of macrocycles that contain diene and dienophile joined by two tethers.

Scheme 2 shows six TADA reactions of macrocycles reported earlier.12 The macrocycles in eqs 1–3a are 12-membered rings with cis-alkenyl, trans-alkenyl, and alkynyl dienophiles; the macrocycle in eq 3b also contains an alkynyl dienophile, and the oxygen atoms are replaced by nitrogen atoms in the tethers.

None of the 12-membered macrocycles were isolable and instead directly gave the tricyclic cycloaddition products in high yields (Scheme 2 eqs 1–3). The 14-membered substrates such as macrocycles 7 and 9 in eqs 4 and 5 were less reactive and could be isolated and characterized. The 14-membered hydrocarbon macrocycle underwent a TADA reaction readily to form the corresponding [6,6,6]-fused tricyclic product. The TADA reaction was not observed to give the [5,6,7]-fused tricyclic product with unsymmetrical macrocycle 9 (eq 5).

Macrocycles 1 and 7 gave endo and exo isomers, respectively.

More recent results on a series of dioxa macrocycles featuring a diene and an alkyne dienophile showed that the length of the oxygen-containing tethers dramatically influences TADA reactivities (Scheme 3). With the exception of the 12-membered macrocycle 5a, the remaining macrocycles were isolable. As the ring size increases, the reactivities decrease markedly. The largest 18-membered macrocycle does not

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We studied the energetics and transition structures of this series of TADA reactions in order to delineate the origins of the reactivities and stereoselectivities.

■ METHODS

Optimizations and frequency calculations were computed using the B3LYP density functional theory with the 6-31+G(d,p) basis set implemented in Gaussian 09 Revision D.01. The D2 version of Grimme’s dispersion model was used to correct for dispersion energies in the calculations. Single-point energies were calculated at the M06-2X level using the 6-311+G(d,p) basis set. While B3LYP provides accurate optimized geometries, it overestimates reaction barriers for pericyclic reactions. Performing single-point energy calculations with M06-2X on B3LYP optimized structures gives results in better agreement with experimental data without resorting to higher levels of theory. All stationary points were verified as minima or first-order saddle points by a vibrational frequency analysis. All of the free energies are reported in kcal/mol for 1 atm and at 298.15 K.

Conformational searches were carried out with MacroModel from Schrödinger using MMFF with an energy window of 20 kcal/mol. The 10 lowest energy conformers were optimized with B3LYP-D2/6-31+G(d,p) to locate the global minimum for each reaction. Conformations of transition structures are sampled by constrained searches. All graphics on optimized structures were generated with CYLview.

■ RESULTS AND DISCUSSION

The computed barriers (ΔG‡) for experimental results shown in Scheme 2 for six TADA reactions (eqs 1–5) are given in Table 1. The barriers for 12-membered substrates (eqs 1–3b) are below 20 kcal/mol and thus are expected to be reactive at room temperature. This is consistent with the experimental observation that 12-membered substrates were not isolable under the conditions in which they were generated. Macrocycle 7 (eq 4) undergoes a TADA reaction with a computed barrier of 27.2 kcal/mol in benzene at 334 K and 26.7 kcal/mol in the gas phase at room temperature, which is in good agreement with the experimental barrier of 26.1 kcal/mol. Macrocycle 9 in eq 5 has a high computed barrier of at least 30 kcal/mol and does not undergo a TADA reaction. Overall, our initial computational results are consistent with the experimental observations.

There are two diastereomeric transition states for the TADA reaction of macrocycle 1, and the energy difference between the endo and the exo pathways is 3.4 kcal/mol in favor of the endo transition state. This is consistent with the stereoselectivity observed experimentally. The forming five-membered rings in all of the transition structures adopt envelope conformations exclusively (Figure 1). The stereochemistry is explained by the lower energy of the cis-ring junctions in the endo transition state. This preference is more pronounced in the product, and no work has been done on how the types of atoms in the macrocycles modulate reactivities.15–17

12-membered macrocycles were not isolated. Yields are for two steps from the macrocyclization of the acyclic diboronates.

Yield is for two steps from the macrocyclization of the acyclic dienynyl diboronate.

\( \Delta G^\ddagger \) for experimental results shown in Scheme 2.

Table 1. Computed Activation Free Energies and Stereoselectivities

<table>
<thead>
<tr>
<th>Scheme 2. Experimental Data on TADA Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scheme 3. Experimental Data on a Series of TADA Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

| 
| 11040 DOI: 10.1021/acs.joc.5b02288 J. Org. Chem. 2015, 80, 11039−11047 |
the cis-fused [5,6,5]-tricycle is 12.8 kcal/mol lower in energy than the trans-fused tricycle.

The stereoselectivities of TADA reactions of 14-membered macrocycles have been studied theoretically and experimentally by Deslongchamps and co-workers. For the TADA reaction of the 14-membered macrocycle 7, the 6-membered rings formed by the tethers preferentially adopt chair conformations (Figure 2). Transition structures with more than one boat conformation (for details, see the Supporting Information) are at least 3.1 kcal/mol less stable than the chair–boat–chair conformers. The computed energy difference between endo and exo transition states is 2.0 kcal/mol in favor of the exo pathway. Although both transition states adopt chair–boat–chair conformations, there are steric clashes between the carbonyl oxygen atoms of the axial methyl esters and the diene hydrogens in the endo transition state, as revealed by view 2 in Figure 2. These steric clashes are not found in the exo transition state.

To further understand the differences in reactivities among the transannular Diels–Alder reactions, we compared these results to those for simple models. We first studied a series of four bimolecular and six intramolecular Diels–Alder reactions (Tables 2 and 3). These substrates were chosen because they share the same diene and dienophile moieties with the transannular substrates. The two common motifs, namely the triene and the dienyne, are color coded in blue and red, respectively.

Table 2 shows four bimolecular reactions varying in the dienophile (alkenyl versus alkynyl) and in the extent of substitution of the reactive component (hydrogen versus methyl group). Their energetics are also given in Table 2. The common theme in bimolecular Diels–Alder reactions is their large $-T\Delta S^\ddagger$ terms (12–16 kcal/mol). For the unsubstituted substrates 17/18 and 23/18, which only differ in the dienophile, the activation barriers of 34.4 and 33.3 kcal/mol, respectively, are similar. When a methyl group is added to each end of the reactive component, the barriers are substantially lower. However, the transition structures of the endo pathways are less stable than those of the exo pathways, resulting in a larger $-T\Delta S^\ddagger$ term for the endo pathway.

Table 3. Computed Activation Parameters for Model Intramolecular Diels–Alder Reactions

$^a$Energies are calculated at the M06-2X/6-311+G(d,p)//B3LYP-D2/6-31+G(d,p) level and are reported in kcal/mol in the gas phase.

Although both transition states adopt chair–boat–chair conformations, there are steric clashes between the carbonyl oxygen atoms of the axial methyl esters and the diene hydrogens in the endo transition state, as revealed by view 2 in Figure 2. These steric clashes are not found in the exo transition state.

Figure 1. Endo and exo transition structures of the TADA reaction of 1 to 2.

Figure 2. Endo and exo transition structures of the TADA reaction of 7 to 8.
higher (40.6 and 44.4 kcal/mol) due to steric hindrance in the transition states. The reaction with the alkylnyl dienophile is enthalpically less favorable, which is well-known experimentally.\textsuperscript{14,21} For the reaction with 20/21, the \textit{endo} transition state is 2.3 kcal/mol more stable than the \textit{exo} state. 

The six intramolecular reactions and their energetics are shown in Table 3. Both the hydrocarbon and the oxadienynic series are shown. The substrates within each series vary in the length of the tether. In general, their entropy terms are approximately 10 kcal/mol lower than those of the bimolecular reactions. The great decrease in the entropy term from 12-16 kcal/mol to 3-5 kcal/mol is consistent with the reduced translational and rotational entropy cost of unimolecular processes relative to bimolecular reactions. The intramolecular reactions have activation enthalpies that are higher than those of the bimolecular reactions depending on the tether length. The increase in reactivities of intramolecular Diels–Alder reactions is entropy-controlled.

We have modeled 13 TADA reactions to systematically investigate the factors controlling their reactivities (Scheme 4). They are designed to model the effects of tether length, alkenyl versus alkylnyl dienophile, and the types of atoms in the tethers.

To quantify how tether length, types of atoms, and types of dienophile affect activation enthalpies in TADA reactions, we used a modified variant of the distortion-interaction model to analyze these transannular cycloadditions. The distortion-interaction model was developed to study bimolecular reactions but has been applied to intramolecular cycloadditions.\textsuperscript{23-26} The activation energy, \( \Delta E^\text{fi} \), is dissected into two parts, namely the distortion energy \( \Delta E^\text{tether} \) and the interaction energy \( \Delta E^\text{app} \): \( \Delta E^\text{fi} = \Delta E^\text{tether} + \Delta E^\text{app} \). \( \Delta E^\text{tether} \) is defined as the total energy required to distort the diene and dienophile from the reactant geometry to the transition state geometry for methylated references between \( \Delta E^\text{fi} \) and \( \Delta E^\text{app} \) suggests there is strain carried by the methyl groups, which come close in the transition structure. For the intramolecular reactions, the total distortion energies of the diene and the dienophile are higher than those of the parent bimolecular reactions. In addition, the tethers are also strained in the transition states (\( \Delta E^\text{fi} > \Delta E^\text{app} > 0 \)). Given that, substrate 35, with less tether strain, is more reactive.

\textbf{(1). Tether Length.} Scheme 4 shows 13 model TADA reactions that were investigated in this work. We first analyze two series that demonstrate how ring size influences TADA reactivity. The energetics are summarized in Tables 5 and 6. For reactions with diastereomeric (\textit{endo} versus \textit{exo}) pathways, the lowest values are shown. The series of hydrocarbon macrocycles in Table 5 ranges from 10- to 16-membered rings, and the dioxa macrocyclic series in Table 6 ranges from 12- to 18-membered rings. For the series of dioxa macrocycles, we compare our computational predictions with Merlic’s experimental results. The computed barrier of 28.0 kcal/mol for the reaction with 11 is in good agreement with the experimentally measured barrier of 27.0 kcal/mol.

In both series, the 12-membered macrocyclic substrates have the lowest activation barriers. The 12-membered hydrocarbon 41 has an activation free energy of 20.4 kcal/mol, while the
dioxa analogue 5a has a barrier of only 12.6 kcal/mol. Both substrates form [5,6,5]-fused tricyclic products. Note that while the activation entropies range from 1 to 3 kcal/mol for all reactions, the activation enthalpies for the 12-membered substrates are considerably lower than those of most larger substrates, which is thus responsible for the rate enhancement.

The 10-membered and 14-membered substrates are also reactive at ambient or slightly elevated temperatures, with a barrier range of 23–28 kcal/mol. Macrocycles of 16 atoms or more do not undergo the TADA reaction readily. The computed barriers for the dioxa macrocycles 5a, 11, 13, and 15 correspond well with the experimental yields and reaction conditions. Figure 3 shows the computed lowest energy transition structures for both model series.

The distortion-interaction analysis for bimolecular and intramolecular Diels–Alder reactions was given in Table 4. We now present similar results for the TADA reactions. Table 7 compares trienic macrocycles 39, 41, 43, and 45 to the prototypical bimolecular reaction between 2-butene (20) and 2,4-hexadiene (21). For all cases, there are two factors governing the reactivities of TADA reactions: the total distortion energy of the reactive components and the tether strain change from the reactant to the transition state geometry.
(both indicated in green). All TADA reactions here have increased tether strain in the transition states, which shows that the tethers contribute negatively to reactivities ($ΔE^+ - ΔE^\text{app} = ΔE^+_{\text{d,tether}} > 0$). The reaction of 39 has the highest tether strain, because two four-membered rings are formed in the product. The reaction of 43 has the least tether strain, as two cyclohexane rings are formed in the most stable chair conformation. Despite this, the reaction of 43 is not the most facile. The TADA reaction of 41 is the most facile in the series because it has the lowest total distortion energy and a reasonable tether strain of 7.1 kcal/mol. For the reactions of 5a, 11, 13, and 15, respectively. The dienyne has activation free energies of 21.2 and 15.7 kcal/mol, respectively. The dienyne 47, the oxygen-containing 5a, and the nitrogen-containing 5b have activation free energies of 14.2, 12.6, and 12.2 kcal/mol, respectively. We calculate that for 12-membered macrocycles, replacing carbon atoms with heteroatoms such as oxygen and nitrogen increases the reaction rate by 10–1000-fold (Table 9).

Table 8. Distortion-Interaction Analysis on TADA Reactions 5a and 11–15

<table>
<thead>
<tr>
<th>reaction</th>
<th>BMDA-21/25</th>
<th>5a ($n = 1$)</th>
<th>11 ($n = 2$)</th>
<th>13 ($n = 3$)</th>
<th>15 ($n = 4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ΔE^+_{\text{d,tether}}$</td>
<td>16.7</td>
<td>13.7</td>
<td>12.6</td>
<td>13.6</td>
<td>15.9</td>
</tr>
<tr>
<td>$ΔE^+_{\text{d,tether}}$</td>
<td>18.6</td>
<td>9.4</td>
<td>22.1</td>
<td>17.2</td>
<td>26.9</td>
</tr>
<tr>
<td>$ΔE^+_{\text{dist}}$</td>
<td>35.3</td>
<td>23.1</td>
<td>34.8</td>
<td>30.7</td>
<td>42.8</td>
</tr>
<tr>
<td>$ΔE^+_d$</td>
<td>$-12.0$</td>
<td>$-7.3$</td>
<td>$-12.7$</td>
<td>$-7.9$</td>
<td>$-12.7$</td>
</tr>
<tr>
<td>$ΔE^+_{\text{app}}$</td>
<td>28.5</td>
<td>11.8</td>
<td>26.4</td>
<td>37.7</td>
<td>40.0</td>
</tr>
<tr>
<td>$ΔE^+_{\text{d,tether}}$</td>
<td>5.3</td>
<td>$-4.1$</td>
<td>4.3</td>
<td>14.9</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Values are given in kcal/mol.

The unsymmetrical 13-membered macrocycle should show reactivity between those of the 12-membered and 14-membered macrocycles. Indeed, the trinuclear 13-membered macrocycle is predicted to undergo a TADA reaction via the endo pathway with a barrier of 21.9 kcal/mol (for details, see the Supporting Information).

Table 9. Activation Parameters of Two Series of Modeled Reactions To Demonstrate the Effect of Heteroatoms in 12-Membered Macrocycles on TADA Reactivity

| 41-$\text{endo}$-TS | 19.6 | 1.6 | 21.2 |
| 1-$\text{endo}$-TS | 14.4 | 1.3 | 15.7 |

$ΔH^\text{a}$, $ΔS^\text{a}$, and $ΔG^\text{a}$ are the activation enthalpy, entropy, and free energy, respectively. The unsymmetrical 13-membered macrocycle should show reactivity between those of the 12-membered and 14-membered macrocycles. Indeed, the trinuclear 13-membered macrocycle is predicted to undergo a TADA reaction via the endo pathway with a barrier of 21.9 kcal/mol (for details, see the Supporting Information).
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Table 10 shows the distortion-interaction analysis for the two series of TADA reactions. As X changes from a carbon atom to a heteroatom, the decrease in the total distortion of the diene and the dienophile is accompanied by a decrease of favorable interaction between the two reactive parts with comparable magnitudes (2–3 kcal/mol). However, the distortion of the tether is greatly reduced (2–5.6 kcal/mol) when the heteroatom is part of the ring. The incorporation of heteroatoms enhances TADA reaction rates by reducing the distortion of the tethers built up in the transition states.

Table 10. Distortion-Interaction Analysis Explaining the High Reactivities with Heteroatoms in 12-Membered Macrocycles

<table>
<thead>
<tr>
<th></th>
<th>( \Delta E^\ddagger )</th>
<th>( \Delta E^\ddagger_{\text{tether}} )</th>
<th>( \Delta E^\ddagger_{\text{total}} )</th>
<th>( \Delta G^\ddagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-endo-TS</td>
<td>20.2</td>
<td>21.0</td>
<td>-7.9</td>
<td>7.1</td>
</tr>
<tr>
<td>41 alkene</td>
<td>( \text{43 alkene} )</td>
<td>( \text{49 alkene} )</td>
<td>( \text{43 alkene} )</td>
<td>( \text{49 alkene} )</td>
</tr>
<tr>
<td>47-endo-TS</td>
<td>15.1</td>
<td>19.3</td>
<td>-5.7</td>
<td>1.5</td>
</tr>
<tr>
<td>47 alkene</td>
<td>( \text{5a-TS} )</td>
<td>( \text{5b-TS} )</td>
<td>( \text{5a-TS} )</td>
<td>( \text{5b-TS} )</td>
</tr>
<tr>
<td>47 alkene</td>
<td>14.0</td>
<td>26.0</td>
<td>-10.2</td>
<td>-1.8</td>
</tr>
<tr>
<td>5a-TS</td>
<td>11.8</td>
<td>23.1</td>
<td>-7.3</td>
<td>-4.1</td>
</tr>
<tr>
<td>5a-TS</td>
<td>12.1</td>
<td>23.5</td>
<td>-7.6</td>
<td>-3.8</td>
</tr>
</tbody>
</table>

Values are given in kcal/mol.

Table 11. Activation Parameters of Alkene vs Alkyne 14-Membered Macrocycles

Table 11 compares the activation parameters for the TADA reactions of the alkene and the alkyne 14-membered macrocycles. The barrier for the alkyne-containing macrocycle is much higher than that for the alkene-containing macrocycle, as expected (31.8 versus 22.6 kcal/mol). The distortion-interaction analysis shows that the distortions for both the reactive components and the tethers are higher in the alkyne macrocycle (Table 12).

For 12-membered macrocycles, macrocycles with a trans-alkene dienophile are roughly 100-fold less reactive than those with a cis-alkene, in accord with literature examples (Table 13). However, substrates possessing alkyne dienophiles are 10^2–10^3-fold more reactive than those involving cis-alkene dienophiles. Table 14 shows that although distortions of the reactive parts of macrocycles 47 and 5a are higher, which is expected for alkyne dienophiles, the distortions of the tethers are significantly lower by 5–9 kcal/mol in comparison to their cis-alkene dienophile counterparts (41 and 1). This is because the 12-membered cyclodienyne has more strain release than 12-membered cycloatriene in the cycloaddition transition state.

The rate enhancement with alkyne dienophiles and/or heteroatoms in 12-membered macrocycles summarized in Figure 4 is an exception rather than a general trend. For larger macrocycles, the rate enhancements were not observed. The effect of alkyne dienophiles in larger rings resembles that for the bimolecular and intramolecular Diels–Alder reactions, decreasing reactivity.

Table 12. Distortion-Interaction Analysis for Two TADA Reactions of 14-Membered Macrocycles

<table>
<thead>
<tr>
<th></th>
<th>( \Delta E^\ddagger )</th>
<th>( \Delta E^\ddagger_{\text{tether}} )</th>
<th>( \Delta E^\ddagger_{\text{total}} )</th>
<th>( \Delta G^\ddagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)-43-exo-TS</td>
<td>20.4</td>
<td>2.2</td>
<td>22.6</td>
<td>31.8</td>
</tr>
<tr>
<td>43 alkene</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
</tr>
<tr>
<td>49-TS</td>
<td>30.1</td>
<td>1.7</td>
<td>31.8</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Values are given in kcal/mol.

Table 13. Activation Parameters of Two Series of Modeled Reactions To Demonstrate the Effect of Dienophile Types in 12-Membered Macrocycles on TADA Reactivity

<table>
<thead>
<tr>
<th></th>
<th>( \Delta E^\ddagger )</th>
<th>( \Delta E^\ddagger_{\text{tether}} )</th>
<th>( \Delta E^\ddagger_{\text{total}} )</th>
<th>( \Delta G^\ddagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-endo-TS</td>
<td>19.6</td>
<td>1.3</td>
<td>21.2</td>
<td>15.7</td>
</tr>
<tr>
<td>41 alkene</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
</tr>
<tr>
<td>47-TS</td>
<td>12.6</td>
<td>1.6</td>
<td>14.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Values are given in kcal/mol.

Table 14. Distortion-Interaction Analysis Explaining the High Reactivities for Alkyne-Containing 12-Membered Macrocycles

<table>
<thead>
<tr>
<th></th>
<th>( \Delta E^\ddagger )</th>
<th>( \Delta E^\ddagger_{\text{tether}} )</th>
<th>( \Delta E^\ddagger_{\text{total}} )</th>
<th>( \Delta G^\ddagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-endo-TS</td>
<td>20.2</td>
<td>21.0</td>
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<td>7.1</td>
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<tr>
<td>41 alkene</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
<td>( \text{47 alkene} )</td>
<td>( \text{49 alkene} )</td>
</tr>
<tr>
<td>47-TS</td>
<td>14.0</td>
<td>26.0</td>
<td>-10.2</td>
<td>-1.8</td>
</tr>
<tr>
<td>1-endo-TS</td>
<td>15.1</td>
<td>19.3</td>
<td>-5.7</td>
<td>1.5</td>
</tr>
<tr>
<td>1 alkene</td>
<td>( \text{3-TS} )</td>
<td>( \text{5-TS} )</td>
<td>( \text{3-TS} )</td>
<td>( \text{5-TS} )</td>
</tr>
<tr>
<td>3-TS</td>
<td>16.3</td>
<td>24.0</td>
<td>-8.0</td>
<td>0.3</td>
</tr>
<tr>
<td>5a-TS</td>
<td>11.8</td>
<td>23.1</td>
<td>-7.3</td>
<td>-4.1</td>
</tr>
</tbody>
</table>

Values are given in kcal/mol.
CONCLUSIONS

The reactivities of macrocyclic trienes and dienynes in TADA reactions have been systematically investigated. The most reactive TADA substrates benefit from two factors: lowering of the distortion energies of the diene and dienophile in comparison to bimolecular and intramolecular reactions due to the linking tethers and strain release of the tethers in the transition structures. Among the macrocycles we studied, 12-membered rings undergo the most facile TADA reactions due to favorable enthalpy. Within 12-membered rings, the presence of heteroatoms in the tethers and alkynyl dienophiles increases the reactivities by up to 5 orders of magnitude relative to the all hydrocarbon trienic macrocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02288.

Complete sets of TSs for the TADA reactions carried out experimentally (TS-1, 3, 5, 7, 9) and for the model bimolecular (TS-17/18, TS-20/21, TS-23/18, and TS-25/21), intramolecular (TS-27, 29, 31, 33, 35, 37), and transannular (TS-39, 41, 43, 45, 47, 49, 51) Diels–Alder reactions, conformers of 7-exo-TS, and Cartesian coordinates and thermodynamic parameters (inhartree) of all stationary points (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail for C.A.M.: merlic@chem.ucla.edu.

*E-mail for K.N.H.: houk@chem.ucla.edu.

Notes

The authors declare no competing financial interest.

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