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On the Effect of Tether Composition on *cis/trans* Selectivity in Intramolecular Diels–Alder Reactions

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Abstract: Intramolecular Diels–Alder (IMDA) transition structures (TSs) and energies have been computed at the B3LYP/6-31+G(d) and CBS-QB3 levels of theory for a series of 1,3,8-nonatrienes, $H_2C{=}CH{-}CH{=}CH{-}CH_2{-}X{-}Z{-}CH{=}CH_2$ [$-X-Z- = -CH_2-CH_2-$ (**1**); $-O-C(=O)-$ (**2**); $-CH_2-C(=O)-$ (**3**); $-O-CH_2-$ (**4**); $-NH-C(=O)-$ (**5**); $-S-C(=O)-$ (**6**); $-O-C(=S)-$ (**7**); $-NH-C(=S)-$ (**8**); $-S-C(=S)-$ (**9**)]. For each system studied (**1**–**9**), *cis*- and *trans*-TS isomers, corresponding, respectively, to *endo*- and *exo*-positioning of the $-C-X-Z-$ tether with respect to the diene, have been located and their relative energies (E_{rel}^{TS}) employed to predict the *cis/trans* IMDA product ratio. Although the E_{rel}^{TS} values are modest (typically $<3\,kJ\,mol^{-1}$), they follow a clear and systematic trend. Specifically, as the electronegativity of the tether group X is reduced (X=O → NH or S), the IMDA *cis* stereoselectivity diminishes. The predicted stereochemical reaction preferences are explained in terms of two opposing effects operating in the *cis*-TS, namely (1) unfavorable torsional (eclipsing) strain about the C4–C5 bond, that is caused by the $-C-X-C(=Y)-$ group's strong tendency to maintain local planarity; and (2) attractive electrostatic and secondary orbital interactions between the *endo*-(thio)carbonyl group, C=Y, and the diene. The former interaction predominates when X is weakly electronegative (X=N, S), while the latter is dominant when X is more strongly electronegative (X=O), or a methylene group (X=CH_2) which increases tether flexibility. These predictions hold up to experimental scrutiny, with synthetic IMDA reactions of **1**, **2**, **3**, and **4** (published work) and **5**, **6**, and **8** (this work) delivering ratios close to those calculated. The reactions of thioacrylate **5** and thioamide **8** represent the first examples of IMDA reactions with tethers of these types. Our results point to strategies for designing tethers, which lead to improved *cis/trans*-selectivities in IMDAs that are normally only weakly selective. Experimental verification of the validity of this claim comes in the form of fumaramide **14**, which undergoes a more *trans*-selective IMDA reaction than the corresponding ester tethered precursor **13**.

Keywords: cycloaddition · density functional calculations · diastereoselectivity · tether groups · transition structures

Introduction

The intramolecular Diels–Alder reaction (IMDA) offers an efficient, atom economic, and versatile solution to the problem of constructing multicyclic molecules.[1] The full potential of this important reaction will be realized only when the stereochemical outcome of IMDAs can be predicted and, hence, controlled experimentally. This goal remains elusive, notwithstanding recent significant progress towards delineating the various factors controlling IMDA stereochemistry.[2–18] In this paper, we explore, using density functional theory, the origin of *cis/trans* selectivity in IMDAs of 1,3,8-nonatrienes, **1**–**9**, possessing tethers that are three atoms long (Scheme 1). Given the experimental fact that IMDAs generally give kinetically controlled product distributions, the key to understanding *cis/trans* selectivity in these reac-

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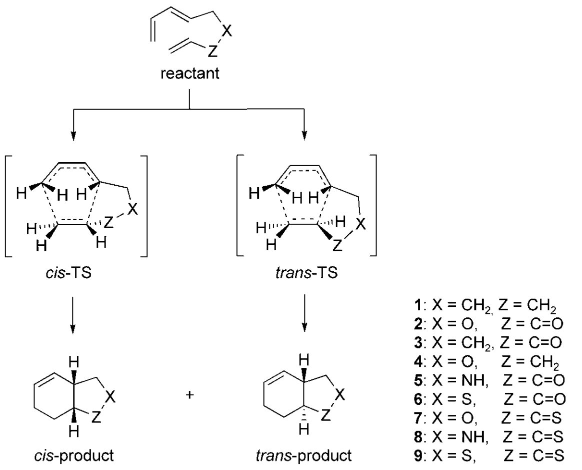


Scheme 1. IMDA reactions under scrutiny. Reactant trienes give rise to *cis* and *trans* fused bicyclic products from *cis* and *trans* TSs, respectively.

tions is to calculate and examine the IMDA transition structures (TSs) leading to the products (Table 1).

The origin of the *cis*/*trans* stereoselectivity[19] in the IMDA of the hydrocarbon 1,3,8-nonatriene[20] **1** has been previously elucidated by Houk et al.[21–23] In this paper, we focus primarily on IMDAs of the series of trienes **2**–**9**, with tethers possessing heteroatoms. Significantly, our results suggest that arguments used to explain the *cis*/*trans* selectivity in the IMDA of **1** are not applicable to reactant molecules with tethers containing either the ester or amide functionality, for example, **2**, **5**–**9**. This finding has enabled us to predict ways for improving *cis*/*trans* selectivity in IMDAs by judicious choice of tether composition.

Computational Details

All IMDA TSS associated with **1**–**9** were calculated using two methods: (a) the B3LYP functional[24] and the 6-31+G(d) basis set,[25,26] and (b) the multilevel CBS-QB3 method. Although B3LYP/6-31+G(d) is known to give acceptable relative energies and geometries of various DA TSs,[2–18,27,28] we found that it predicted an incorrect *cis/trans* selectivity in the IMDA reaction of the thiolacetate **6**. Consequently, in addition to the DFT calculations, we also used the more accurate (but computationally much more expensive) CBS-QB3 method,[29] a member of the complete basis set methods developed by Petersson et al.[29,30] The CBS-QB3 method uses a B3LYP/CBSB7 optimized geometry and frequencies together with CCSD(T), MP4SDQ, and MP2 single-point calculations and a CBS extrapolation to produce accurate energies. The CBS-QB3 method has recently been successfully applied in the investigation of DA reactions involving furan.[31] CBS-QB3 calculations were not carried out for **13** and **14** (Scheme 10), owing to their large size. It transpired that B3LYP/6-31+G(d) calculations on these two systems gave results in accord with experiment. Only B3LYP/6-31+G(d) calculations were carried out on the intermolecular TSs for **11** and **12** (Scheme 8) because this level of theory and CBS-QB3 gave similar results for the corresponding IMDA reactions of **2** and **7**. All calculations refer to the gas phase. In a previous study,[12] we have found that there is excellent agreement between gas phase B3LYP/6-31+G(d) predicted IMDA *cis*/*trans* ratios and the experimental ratios obtained using weakly polar solvents—which are the solvents of choice for carrying out IMDA reactions. Consequently, we ignore solvent effects in this study. Both *cis* and *trans* IMDA TSs were located for each molecule. Harmonic vibrational frequencies (at the same level of theory) were employed to characterize the TSs as first-order saddle points. The unscaled vibrational frequencies were also used to calculate the enthalpies and Gibbs free energies of the TSs at 298.15 K. Also reported are TS electronic energies at 0 K corrected for zero-point vibration energies (ZPE). *Cis/trans* product ratios were calculated from the Gibbs free energies of the TSs using the rate expression derived from standard transition state theory.[32] The *cis/trans* ratios listed in Table 2 refer to 298.15 K whereas those given in Scheme 2–7 and Scheme 9 were calculated using the experimental temperature.

The Gaussian 98[33] and 03[34] program packages were used throughout. Details of the structures (in Cartesian coordinate form) and energies of all computed TSs are given in the Supporting Information.

Results and Discussion

The numbering scheme for the atoms in the TSs is presented in Figure 1, together with definitions of salient geometrical parameters. Two types of asynchronicity characterize IMDA TSs, namely bond-forming asynchronicity, Δr_{as}, defined as the difference between the lengths of the peripheral (r_p) and internal (r_i) forming bond lengths, and the twist-mode asynchronicity, θ_{as},[21] which measures the extent of twisting of the dienophile double bond about the forming internal bond (Figure 1). Values of salient geometrical parameters for the various B3LYP/6-31+G(d) optimized TSs are presented in Table 1 (the B3LYP/6-31+G(d) and B3LYP/CBSB7 TS geometries are very similar to each other). Relative energies, enthalpies (H), and Gibbs free energies (G) between the *cis*

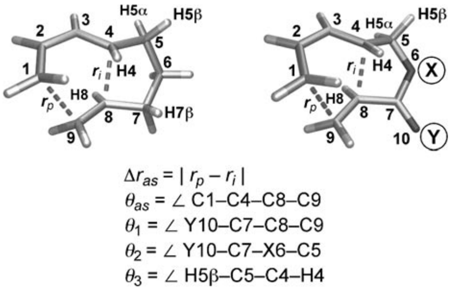


Figure 1. Schematic of IMDA transition structures (*cis* or *trans*) for **1**–**9** depicting the numbering schemes and relevant geometrical parameters.

Table 1. Salient IMDA TS (**1TS**–**9TS**) B3LYP/6-31+G(d) optimized geometrical parameters (Figure 1), including forming bond lengths r_i and r_p (Å), their difference Δr_{as} (Å), and key dihedral angles θ_{as}, θ_1, θ_2, and θ_3 (°).

TS	r_i	r_p	Δr_{as}	θ_{as}	θ_1	θ_2	θ_3
cis-**1TS**	2.346	2.162	−0.184	15.4	–	–	−40.3
trans-**1TS**	2.194	2.280	0.086	−12.7	–	–	−44.7
cis-**2TS**	2.226	2.310	0.084	5.9	−31.0	161.5	3.4
trans-**2TS**	2.159	2.355	0.196	−8.8	31.0	−162.3	−63.9
cis-**3TS**	2.478	2.083	−0.395	14.2	−14.8	101.5	−40.7
trans-**3TS**	2.317	2.192	−0.125	−4.8	15.2	−133.0	−66.9
cis-**4TS**	2.300	2.211	−0.089	16.8	–	–	−34.8
trans-**4TS**	2.152	2.347	0.195	−15.0	–	–	−46.5
cis-**5TS**	2.254	2.281	0.027	7.9	−33.5	158.6	−4.7
trans-**5TS**	2.176	2.323	0.147	−9.7	33.4	−160.4	−61.6
cis-**6TS**	2.310	2.232	−0.078	2.0	−23.0	152.9	2.8
trans-**6TS**	2.296	2.238	−0.058	−1.9	22.8	−154.6	−68.8
cis-**7TS**	2.266	2.284	0.018	4.5	−32.3	160.6	0.3
trans-**7TS**	2.212	2.310	0.098	−6.5	31.0	−160.5	−64.3
cis-**8TS**	2.291	2.267	−0.024	6.9	−37.0	162.5	−4.4
trans-**8TS**	2.228	2.290	0.062	−7.8	35.0	−161.5	−63.2
cis-**9TS**	2.400	2.175	−0.225	1.3	−25.3	149.4	–
trans-**9TS**	2.370	2.191	−0.179	0.0	25.0	−154.6	–

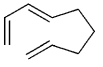
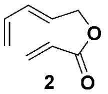
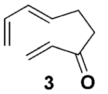
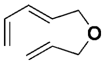
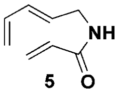
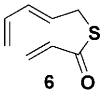
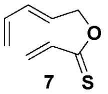
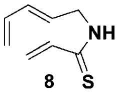
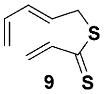
and *trans* TSs for each reaction ($Z_{rel}^{TS}=Z_{cis\text{-}TS}-Z_{trans\text{-}TS}$; $Z=E+\text{ZPE}$, H, G) are given in Table 2. Also given in Table 2 are *cis*/*trans* product ratios at 298.15 K. Perhaps not unexpectedly for structurally similar TSs, there is little difference between the E_{rel}^{TS}, H_{rel}^{TS}, and G_{rel}^{TS} values for each system studied. Thus, unless stated otherwise, the ensuing discussion refers to E_{rel}^{TS} values derived from the CBS-QB3 method.

Experimentally, the IMDA reaction of 1,3,8-nonatriene **1** gives a 75:25 ratio of *cis*/*trans* products at 190 °C in cyclohexane,[22] which was successfully reproduced computationally using HF/3-21G and hybrid QM-MM models.[23] Our CBS-QB3 and DFT calculations also correctly predict the predominant formation of *cis* adduct from the IMDA of **1**, with *cis*-**1TS** favored over the *trans*-**1TS** by 5.34 kJ mol^{-1}. The CBS-QB3 *cis/trans* ratio, calculated using the experimental temperature (190 °C), is in good agreement with the experimentally determined ratio (Scheme 2). Both *cis*-**1TS** and *trans*-**1TS** are only moderately asynchronous, with the forming peripheral bond slightly shorter than the forming internal bond ($\Delta r_{as}=-0.18$ Å) in *cis*-**1TS**, but longer than the internal bond in *cis*-**1TS** ($\Delta r_{as}=0.086$ Å; Scheme 2). As noted by Houk et al.,[21] both TSs exhibit marked twist-mode asynchronicity, amounting to 15° (*endo* twisting) and −13° (*exo* twisting) in *cis*-**1TS** and *trans*-**1TS**, respectively, which was attributed to the tendency of the dihedral angle C5−C4−C8−C7 in the developing 5-membered ring to be as close as possible to zero degrees. This theory was confirmed by optimizing the structure of cyclopentane in which one C−C bond length was frozen at 2.2 Å.[21,35]

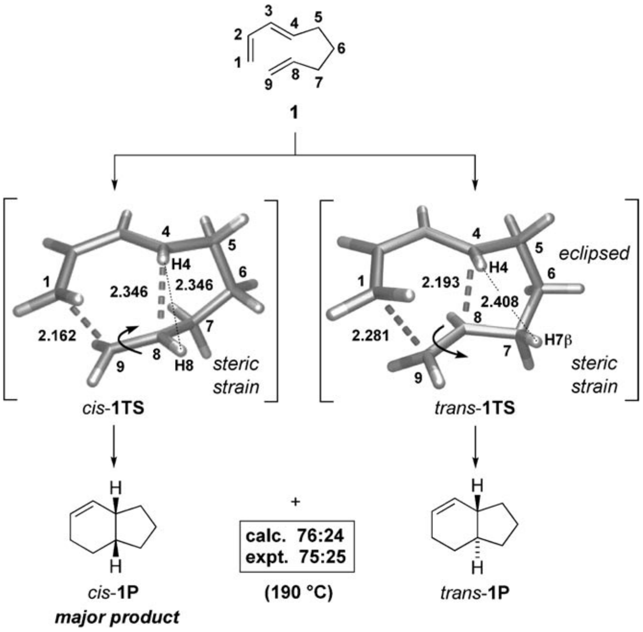
As proposed earlier, the origin of the *cis* selectivity in this reaction may be traced to the presence of an adverse steric interaction between H4 and H7β in the *trans* TS—they are 2.41 Å apart—which is absent in the corresponding *cis* TS.[21–23] In addition, *trans*-**1TS** experiences more torsional strain about the C5−C6 bond than does *cis*-**1TS**; the dihedral angles between the C5H and C6H bonds are approximately 17° in the former, compared to approximately 36° in the latter TS. These two unfavorable features of *trans*-**1TS** are evidently more energetically costly than the close contact between H4 and H8 in *cis*-**1TS** (2.35 Å). Within the context of this study, it is important to point out that both *cis*-**1TS** and *trans*-**1TS** are practically free of torsional strain about the C4−C5 bond, with θ_3 (Figure 1) ≈40° and 45°, respectively.

As in the case of **1**, the IMDA of acrylate **2** displays *cis* selectivity, but is weaker, with *cis*-**2TS** lying only 2.6 kJ mol^{-1} below *trans*-**2TS**. The CBS-QB3 *cis/trans* ratio at 180 °C is in accord with the experimental ratio[12] (Scheme 3). Unlike *trans*-**1TS**, there is no significant

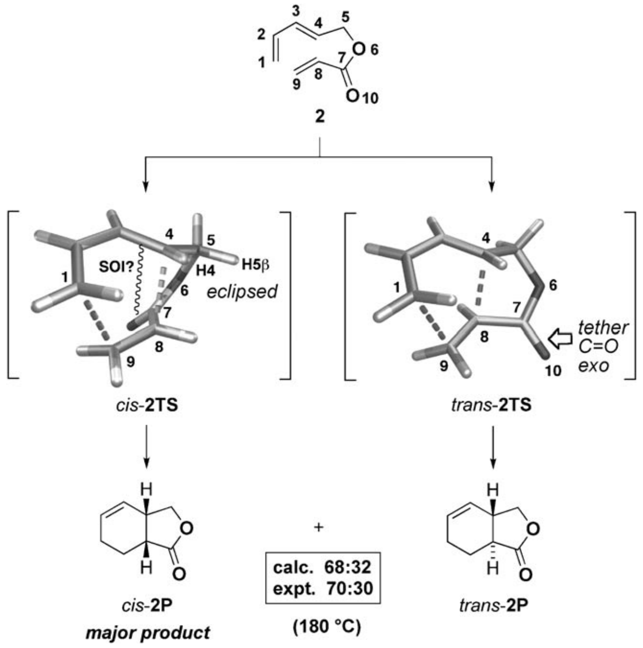
Table 2. ZPE-Corrected CBS-QB3 (B3LYP/6-31+G(d) values in parentheses) *cis*/*trans*-TS relative energies (E_{rel}^{TS})[a], enthalpies (H_{rel}^{TS})[a,b] and Gibbs free energies (G_{rel}^{TS})[a,b] kJ mol^{-1}, and *cis*/*trans* product ratios.[c]

Structure	E_{rel}^{TS}	H_{rel}^{TS}	G_{rel}^{TS}	*cis/trans*[b]
 **1**	−5.34 (−5.85)	−5.52 (−6.04)	−4.86 (−5.36)	*88*:12 (*90*:10)
 **2**	−2.62 (−1.88)	−2.51 (−1.75)	−2.77 (−2.06)	*75*:25 (*70*:30)
 **3**	−5.03 (−5.65)	−5.10 (−5.83)	−4.85 (−5.01)	*88*:12 (*88*:12)
 **4**	−5.67 (−6.42)	−6.12 (−6.81)	−4.38 (−5.59)	*78*:22 (*91*:9)
 **5**	0.66 (0.59)	0.82 (0.78)	0.39 (0.28)	46:*54* (47:*53*)
 **6**	0.11 (2.17)	0.26 (2.37)	−0.36 (1.63)	*54*:46 (34:*66*)
 **7**	−4.67 (−3.15)	−4.45 (−2.90)	−5.07 (−3.62)	*89*:11 (*81*:19)
 **8**	−1.30 (−0.71)	−1.05 (−0.41)	−1.67 (−1.19)	*66*:34 (*62*:38)
 **9**	−0.49 (2.10)	−0.24 (2.40)	−1.48 (0.96)	*64*:36 (40:*60*)

[a] $X_{rel}^{TS}=X_{cis\text{-}TS}-X_{trans\text{-}TS}$ (X=*E*, *H*, or *G*); a positive value indicates that the *trans*-TS is most stable. [b] At 1 bar pressure and 298.15 K. [c] Ratio (%*cis*)/(%*trans*) calculated from G_{rel}^{TS} values at 298.15 K.



Scheme 2. The *cis* and *trans* TSs for the IMDA reaction of **1** with the CBS-QB3 (at 190 °C) and experimental product distribution. Arrows show the direction of twisting of the dienophile about the C4–C8 pivot.



Scheme 3. The *cis* and *trans* TSs for the IMDA reaction of **2** with the CBS-QB3 (at 180 °C) and experimental product distribution.

transannular strain between the C4 and C7 groups in *trans*-**2TS**; H4 is 2.57 and 3.41 Å from C7 and O10, respectively, with the former distance being slightly larger than the sum of the van der Waals radii of a hydrogen and a carbon atom (Scheme 3).

Possible differences in conjugation in the *cis* and *trans* IMDA TSs for **2** cannot be responsible for the observed *cis* selectivity because the dihedral angle, θ_1, between the carbonyl group and the dienophile bond is the same (31°) in both TSs (Table 1). Likewise, the torsional angle about the O6–C7 bond, θ_2, is comparable (ca. 162°) in both TSs.

Intriguingly, the only obvious strain difference that we were able to identify is the presence of torsional strain in *cis*-**2TS**; in this TS, the conformation about the C4–C5 bond is unfavorably C–H/C–H eclipsed[36] with a 3.4° dihedral angle, θ_3, between the C5–H5β and C4–H4 bonds. In contrast, the C4–C5 bond in *cis*-**2TS** adopts the favored C–H/C–H staggered[36] conformation, with $\theta_3 \approx 64°$ (Table 1). Using pentadienyl formate **10** as a model for estimating torsional strain in *cis*-**2TS** and *trans*-**2TS** (Figure 2), the staggered conformation in *trans*-**2TS** is estimated to be approximately 2.5 kJ mol^{-1} more stable than the eclipsed conformation in *cis*-**2TS** (B3LYP/6-31+G(d)). Note that this model also takes into account repulsive interactions between C4 and C7 which are slightly larger in *trans*-**2TS** (C4–C7 separation 2.56 Å; C7–H4 separation 2.56 Å), than in *cis*-**2TS** (C4–C7 separation 2.61 Å; C7–H4 separation 3.29 Å).

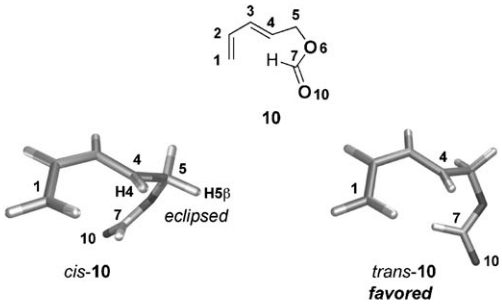
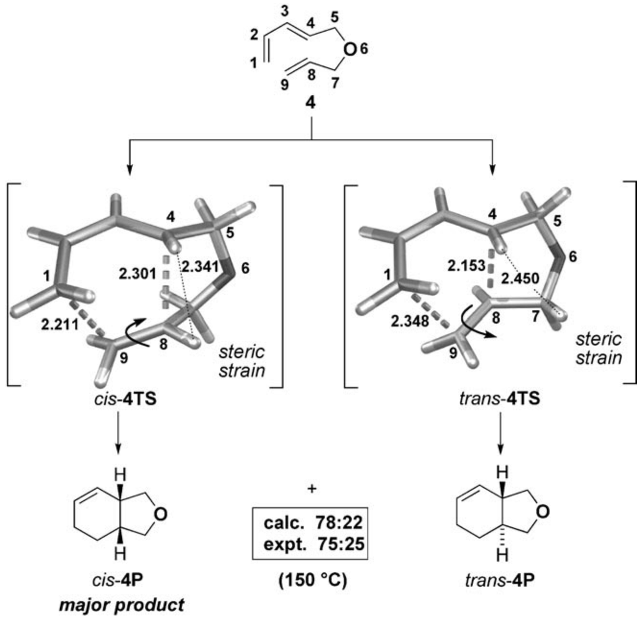


Figure 2. Models used to estimate the difference in the torsional strain about the C4–C5 bond in the *cis* and *trans* TSs of **2**.

The reason why the C4–C5 bond has an eclipsed conformation in *cis*-**2TS**, whereas it is staggered in *trans*-**1TS** arises from the resistance of an ester group to out-of-plane twisting about the alkoxy bond. Achievement of a staggered conformation about the C4–C5 bond in *cis*-**2TS** would require the TS dihedral angle θ_2 to be reduced from 162° to approximately 100°, and this is energetically too costly. In the case of *cis*-**1TS**, the flexible trimethylene tether is able to realize a staggered conformation about C4–C5 while, at the same time, maintaining a strain-free conformation within the tether. As to be expected, the staggered C4–C5 bond conformation is also found in the ketone *cis*-**3TS** ($\theta_3 = 40°$), in which O6 in *cis*-**2TS** is replaced by a methylene group, thereby restoring greater tether flexibility ($\theta_2 \approx 102°$), and also in the ether *cis*-**4TS** ($\theta_3 = 35°$), in which the conjugating tether carbonyl group is absent.

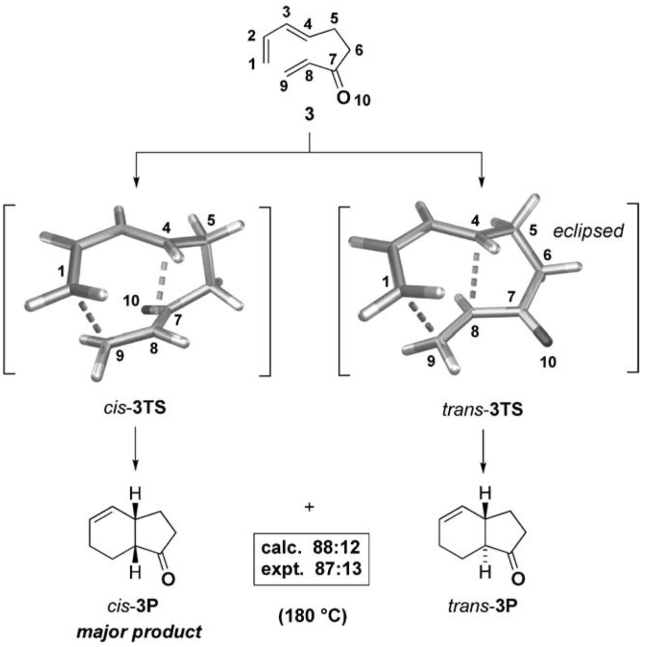
Combining the overall energetic preference of approximately 1.9 kJ mol^{-1} for *cis*-**2TS**, relative to *trans*-**2TS**, with the former's *unfavorable* C4–C5 torsional strain energy of approximately 2.5 kJ mol^{-1} suggests the presence of an additional, stabilizing, factor in *cis*-**2TS**, amounting to approximately 4.4 kJ mol^{-1}. We postulate that this factor is a stabilizing interaction between the diene and the tether carbonyl group, which occupies an *endo* disposition with respect to the diene moiety. This stabilizing interaction could arise either from secondary orbital interactions,[13,37] perhaps of the Singleton [4+3] kind,[38] between C4 and C7, or from electrostatic interactions between the dipole and quadrupole moments of the diene and carbonyl groups,[39] or from a combination of both types of interaction.[40,41] Our calculations on the IMDA TSs for **3**–**9**, in which the composition of the tether is varied, support this postulate, as will now be discussed.

The IMDA of ether **4** is *cis* selective and is similar to the trimethylene parent **1** in both experiment (*cis*/*trans* = 75:25 at 150 °C, no solvent)[42] and theory [$E_{\mathrm{rel}}^{\mathrm{TS}}$ (*trans*–*cis*) = 5.7 kJ mol^{-1}; *cis*/*trans* = 78:22 at 150 °C]. The geometries of TSs *cis*-**4TS** and *trans*-**4TS** (Scheme 4) are essentially identical to those of the parent trimethylene system, with minor (0.05–0.07 Å) differences in r_i and r_p resulting from the shorter tether C–O (1.43 Å) vs C–C (1.55 Å) bond distances.



Scheme 4. The *cis* and *trans* TSs for the IMDA reaction of **4** with the CBS-QB3 (at 150 °C) and experimental product distribution. Arrows show direction of twisting of dienophile about C4–C8 pivot.

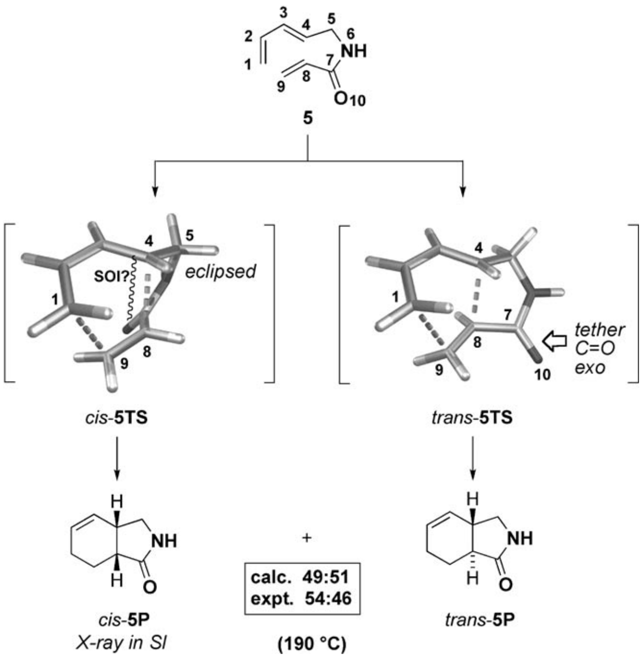
Theory predicts the IMDA of ketone **3** (*cis* selective by 5.0 kJ mol^{-1}; Table 2) to be 2.4 kJ mol^{-1} more *cis* selective than that for the acrylate **2**, which can be explained by noting that the unfavorable eclipsing about the C4–C5 bond in *cis*-**2TS** (Scheme 3) is absent in *cis*-**3TS** (Scheme 5), for reasons discussed previously. This torsional strain, estimated to be 2.5 kJ mol^{-1}, is comparable in magnitude to the predicted enhanced *cis* selectivity of approximately 2.4 kJ mol^{-1} for the IMDA of **3**, compared to that of **2**—resulting in a predicted *cis/trans* ratio of 88:12 at 180 °C (Scheme 5). The experimental *cis* IMDA selectivity of **3** (*cis*/*trans* = 87:13 at 180 °C in 1,2-dichlorobenzene)[43] is in very good agreement with this prediction.



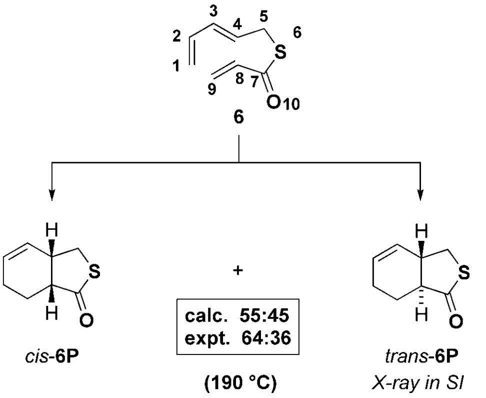
Scheme 5. The *cis* and *trans* TSs for the IMDA reaction of **3** with the CBS-QB3 (at 180 °C) and experimental product distribution.

As for the case of *cis*-**2TS**, the *cis* IMDA TSs for the remaining members of the series, **5**–**9**, all suffer the same degree of C4–C5 bond torsional strain. However, the tether carbonyl group in the acrylamide, **5**, is more electron rich and its LUMO is higher in energy than that in the acrylate, **2**, owing to the superior π-electron donating ability and the lower electronegativity of nitrogen, compared to oxygen. Thus, the B3LYP/6-31G(d) π* LUMO energy of formamide lies 0.7 eV above that of methyl formate and the carbonyl oxygen of the former is more negatively charged than the latter, by 0.03 electrons (natural population analysis). This will have the effect of reducing the stabilizing *endo* interaction between the carbonyl group and the diene moiety in *cis*-**5TS**, compared to *cis*-**2TS**. Indeed, we calculate an essentially stereo-random IMDA reaction for **5** (Scheme 6) and we have confirmed this prediction in the laboratory (*cis*/*trans* = 54:46, 190 °C, toluene).[44] Alternative explanations for the lack of stereoselectivity in the IMDA for **5**, based on geometric factors, seem unlikely because the geometries of *cis*-**5TS** and *cis*-**2TS** are very similar to each other (compare TSs from Scheme 3 and 6).

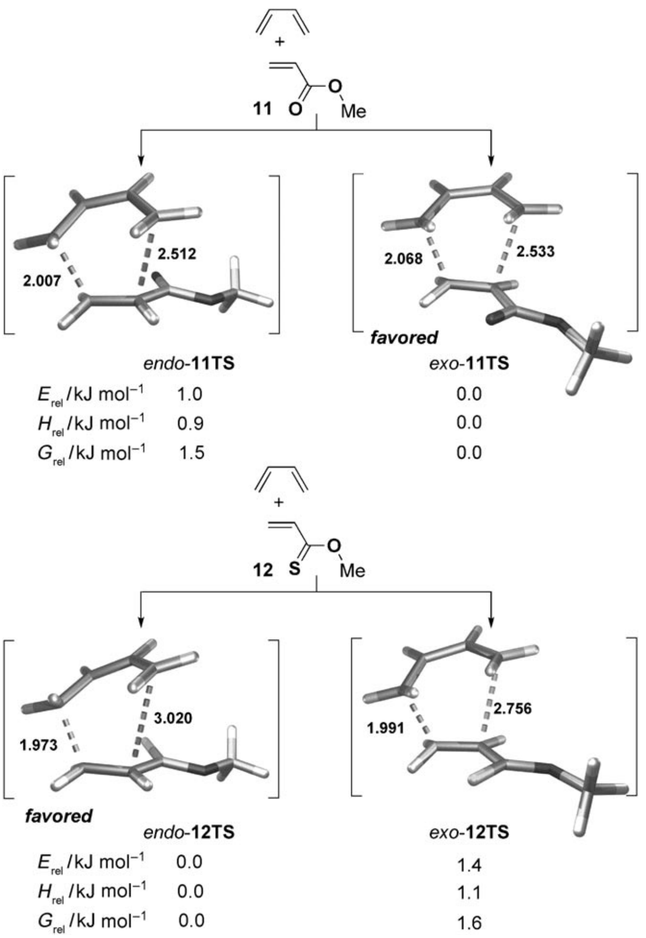
Presumably for similar reasons, the replacement of the ether oxygen of acrylate **2** with sulfur also diminishes the *cis* selectivity of the IMDA reaction, with thiolacrylate **6** (Scheme 7) calculated to give a *cis/trans* product ratio of 55:45 at 190 °C. Experimentally, this novel class of IMDA precursor, the dienophile of which was incorporated in masked form arising from the propensity for conjugate addition to acrylates by thiols,[45] delivered a product ratio gratifyingly close to the predicted value (*cis/trans* = 64:36, 190 °C,



Scheme 6. The *cis* and *trans* TSs for the IMDA reaction of **5** with the CBS-QB3 (at 190 °C) and experimental product distribution.



Scheme 7. The *cis* and *trans* TSs for the IMDA reaction of **6** with the CBS-QB3 (at 190 °C) and experimental product distribution.



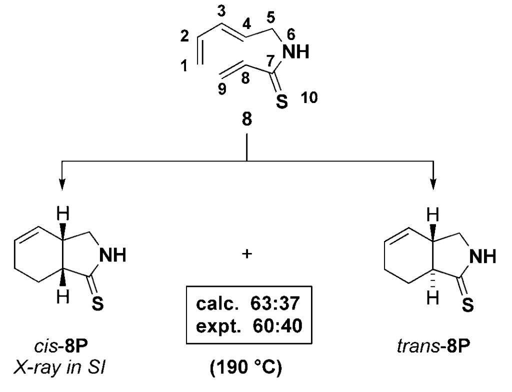
Scheme 8. B3LYP/6-31+G(d) fully-optimized TSs for the intermolecular Diels–Alder reactions of butadiene with methyl acrylate (top) and methyl thionoacrylate (bottom), together with ZPE-corrected relative energies (0 K), relative enthalpies (298.15 K), and relative Gibbs free energies (298.15 K) between the *endo* and *exo* TSs.

benzene). Simple DFT calculations incorrectly predict *trans* selectivity for this system (Table 2).

The IMDA reaction of the thionoacrylate **7**, is predicted to be 2 kJ mol^{-1} more *cis* selective than that for the acrylate, **2**, probably reflecting the greater propensity for the thiocarbonyl group to occupy the *endo* position of the diene, compared to the carbonyl group. For example, the B3LYP/6-31G(d) π* LUMO energy of methyl thionoformate is 1.6 eV lower than methyl formate which should provide stronger secondary orbital interactions between the diene and thiocarbonyl group, compared to those between the diene and the carbonyl group. This argument receives support from calculated *exo*/*endo* stereoselectivities in the *inter*molecular Diels–Alder reactions of methyl acrylate **11** and methyl thionoacrylate **12** with 1,3-butadiene (Scheme 8). Only the *s-cis* conformations of the dienophile esters were employed in the calculations because that is the conformation adopted by the carbonyl and thiocarbonyl groups in the IMDA TSs of **2** and **7**. Note that the *endo* (*exo*) stereochemistry for the intermolecular Diels–Alder TS corresponds to the *cis* (*trans*) stereochemistry in the IMDA reaction. The *exo*-**11TS** is favored by 1 kJ mol^{-1} using methyl acrylate as dienophile, whereas the *endo*-**12TS** is favored, by 1.4 kJ mol^{-1}, when the dienophile is switched to methyl thionoacrylate. Changing from carbonyl to thiocarbonyl in the acrylate group therefore enhances *endo* selectivity by approximately 2.5 kJ mol^{-1}. It might, at first sight, appear contradictory that the intermolecular DA reaction involving methyl acrylate is *exo* selective, whereas we are postulating that the origin of the observed *cis* selectivity in the IMDA of **2** arises from the carbonyl group's preference for the *endo* position. However, we note that the forming bond between the diene and the ester-bearing carbon atom in *endo*-**11TS** is appreciably longer (by 0.3 Å) than the internal developing bond in *endo*-**2TS**—secondary orbital interactions, which diminish exponentially with increasing inter-orbital separation, should be significantly weaker in the intermolecular TS than in the IMDA TS.

Parenthetically, we draw attention to the extraordinarily long developing "bond" —exceeding 3.0 Å— between the diene and the thionoester-bearing carbon atom in the intermolecular *endo*-**12TS** (Scheme 8). The degree of bond asynchronicity (>1 Å) in this TS is unusually high for a non-Lewis acid catalyzed DA reaction.[16,41a] The B3LYP/6-31+G(d) wavefunction for *endo*-**12TS** is stable with respect to all perturbations treated by the GAUSSIAN 03 program,[46] including relaxation of the wavefunction from restricted to unrestricted, thereby indicating insignificant biradical character in the wavefunction. Furthermore, an intrinsic reaction coordinate analysis failed to detect any intermediates. Consequently, *endo*-**12TS** represents a case of an extremely asynchronous but concerted DA reaction in which one of the developing bonds, at 3.0 Å in length, is barely a bond at all. Such a high degree of asynchronicity, while not uncommon in Lewis-acid-catalyzed DA reactions,[47] is unusual for an uncatalyzed DA reaction.[16]

As was found for the series of acrylate cognates, **2**, **5**, and **6**, the *cis* selectivity in the IMDAs of the thionoacrylate systems, **7**–**9**, becomes weaker with decreasing electronegativity of the group X in the tether $CH_2XC{=}S$. Thus, the IMDA reactions of thioacrylamide **8** and dithioester **9** are both predicted to be less *cis* selective than thionoacrylate **7** (Table 2). Experimental support for these predictions comes in the form of thioacrylamide **8** (Scheme 9), which undergoes an IMDA reaction with an experimental stereoselectivity (*cis/trans* = 60:40, 190 °C, toluene) similar to the calculated value (*cis/trans* = 63:37). Once again, this is the first experimental IMDA reaction involving this type of tether.[45]

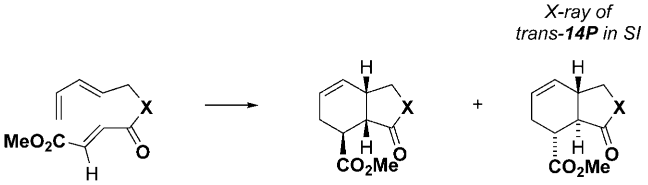


Scheme 9. The *cis* and *trans* TSs for the IMDA reaction of **8** with the CBS-QB3 (at 190 °C) and experimental product distribution.

Conclusions

The calculated *cis* and *trans* TS energy differences for the series of acrylate cognates, **2**, **5**–**9**, are only modest, lying within approximately 3 kJ mol^{-1}, but they do follow a systematic and explicable trend. Thus, as the electronegativity of the group X in the tether ($CH_2XC{=}Y$; Y=O, S) is reduced, the *cis* stereoselectivity of the IMDA reaction is diminished. We have explained this trend in terms of two opposing effects operating in the *cis* TSs, namely unfavorable eclipsing interactions about the C4−C5 bond and attractive interactions between the *endo* (thio)carbonyl group and the diene group (see Scheme 3, for example). The former interaction predominates when X is weakly electronegative (X=N, S), while the latter is dominant when X is more strongly electronegative (X=O). The origin of the aforementioned IMDA TS C4−C5 eclipsing interactions in our series arises from the C−X−C=Y group's strong tendency to achieve local planarity, resulting in significant stabilizing conjugation between an electron lone pair on X and the (thio)carbonyl group's π^* LUMO. This feature is absent in **1**, **3**, and **4**, where the tethers are sufficiently flexible that this torsional strain is avoided in their respective *cis* IMDA TSs.

Our results point to strategies for improving *cis*/*trans* selectivities in IMDAs that are only weakly selective. For example, experimentally, the IMDA of the 9-*E*-carbomethoxy acrylate **13** gives a *cis/trans* product ratio of 42:58 (110 °C, toluene),[12] which is reproduced by our B3LYP calculations (41:59), with an overall *trans* selectivity of only 0.7 kJ mol^{-1} (Scheme 10). Noting that the amide tether in **5** is predicted to be more *trans* selective than the ester tether in **2**, we predict greater *trans* selectivity in the IMDA of the 9-*E*-carbomethoxy acrylamide **14**, compared with that of the corresponding acrylate **13**. Indeed, our calculations (Scheme 10) predict stronger *trans* selectivity (3.2 kJ mol^{-1}) for the IMDA of the acrylamide **14**, compared to that for the acrylate **13** (0.7 kJ mol^{-1}), which translates into a *cis/trans* product ratio of 18:82 at 110 °C (cf. 48:52 for **3**). These predictions are borne out experimentally, with acrylamide **14** fur-



13: **X = O**	*cis*	*trans*
E_{rel} / kJ mol^{-1}	0.71 (42%)	0.0 (58%)
H_{rel} / kJ mol^{-1}	0.63 (44%)	0.0 (56%)
G_{rel} / kJ mol^{-1}	1.2 (41%)	0.0 (59%)
experiment (toluene, 110 °C, 205 h, 77% yield)	42%	58%
14: **X = NH**		
E_{rel} / kJ mol^{-1}	3.2 (22%)	0.0 (78%)
H_{rel} / kJ mol^{-1}	3.2 (22%)	0.0 (78%)
G_{rel} / kJ mol^{-1}	4.9 (18%)	0.0 (82%)
experiment (toluene, 110 °C, 42 h, 65% yield)	27%	73%

Scheme 10. B3LYP/6-31+G(d) ZPE-Corrected relative energies, relative enthalpies (110 °C), and relative Gibbs free energies (110 °C) between the *cis* and *trans* IMDA TSs of **13** and **14**, with the calculated and experimental product distribution.

nishing a *cis/trans* product ratio of 27:73 (110 °C, toluene).[48] While this example amounts to a modest improvement in *cis/trans* selectivity, we are confident that our model of the influence of tether composition on IMDA stereoselectivity will lead to the design of more effective tethers.

CCDC 689702, CCDC 689703, CCDC 689704, CCDC 689705 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

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