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New insights into the *endo–exo* stereoselectivity of the intramolecular Diels-Alder reaction of 1,3,8-nonatrienes†

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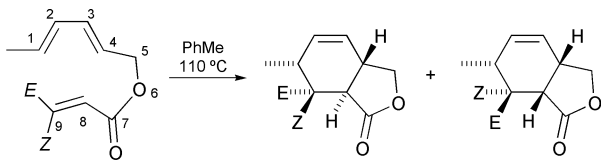
B3LYP/6-31G(d) theory predicts the experimental *endo–exo* selectivity of intramolecular Diels-Alder reactions of C9-substituted 1,3,8-nonatrienes: the reactions are concerted but the transition structures are remarkably asynchronous.

The intramolecular Diels-Alder (IMDA) cycloaddition is a strategy-level reaction in synthesis[1] that is being viewed increasingly as a biosynthetic event.[2] If this process is to reach its optimum synthetic potential and be fully understood in its biological setting, the stereochemical outcome of IMDA reactions must be more readily predicted and understood. *Exo* and *endo* transition structures (TSs) have been located for the prototype 1,3,8-nonatriene and 1,3,9-decatriene IMDA reactions at the HF/3-21G level of theory.[3,4] These structures were used to construct empirical force field models for a wide range of IMDA reactions.[5] While this hybrid quantum mechanics–molecular mechanics model reproduces many experimentally determined diastereoselectivities with remarkable accuracy, terminally activated 1,3,8-nonatrienes in which the dienophile activating group is disposed in a *Z*-orientation are predicted to form *cis*-fused bicyclic cycloadducts when, in fact, the *trans*-fused stereoisomer is the major observed product.[5]

In studies directed towards unearthing the reasons for the *exo* preference‡ of IMDA reactions of terminally activated 1,3,8-nonatrienes, we have examined the intramolecular cycloadditions of **1**, **2** and several related compounds using B3LYP/6-31G(d) theory. Thus, *exo* and *endo* TSs for nine related systems have been located at a higher level of theory than in any previous investigation into IMDA reactions. Our results confirm the asymmetric stretch–twist asynchronous transition state model proposed for 1,3,8-nonatriene IMDA reactions,[6] reveal hidden TS features and shed new light on their *endo–exo* preferences.

To confirm the experimental *exo* preference of terminally activated trienes, two IMDA precursors differing only in dienophile geometry were prepared and cyclised.[7] Triene precursors **1** and **2** (Fig. 1)§ were prepared by esterification of 2,4-hexadien-1-ol with maleic anhydride–diazomethane[8] and methyl fumaroyl chloride[9] respectively. Thermolysis of the *Z*-dienophile precursor **1** in dilute toluene solution at 110 °C was complete within 2 h to afford a 79 : 21 mixture of *exo* and *endo* stereoisomers. Intramolecular cycloaddition of *E*-dienophile precursor **2** proceeded more slowly to afford a 65 : 35 mixture of *exo* and *endo* stereoisomers, again in good yield. The *exo* preference of the IMDA reaction of both **1** and **2**, and the increased *exo* selectivity of the *Z*-dienophile precursor are mirrored in the trimethylene tether series.[10] That these thermal intramolecular cycloadditions are under kinetic control was demonstrated by subjecting pure samples of each of the

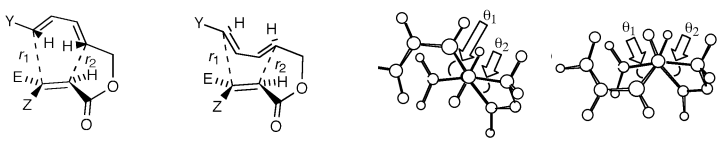


1 (*E* = H, *Z* = CO_2Me; 2h, 79%) **3** *exo* 79:21 **4** *endo*
2 (*E* = CO_2Me, *Z* = H; 23h, 85%) **5** *exo* 65:35 **6** *endo*

Fig. 1 *Exo*-selective IMDA reactions of **1** and **2**.

† Electronic supplementary information (ESI) available: final optimised coordinates for stationary points in all transition structures. See http://www.rsc/org/suppdata/cc/b0/b006483l/

Table 1 B3LYP/6-31G(d) *exo–endo* IMDA TS energy differences and predicted ratios, TS partial bond lengths and dihedrals



	Substituents					*exo*		*endo*		*exo*		*endo*	
Entry	Y	Z	E	ΔE^a	*exo–endo*[b]	r_1	r_2	r_1	r_2	θ_1	θ_2	θ_1	θ_2
1	H	H	H	1.3	40:60	2.357	2.165	2.314	2.230	61.7	44.6	42.6	42.4
2	H	NH_2	H	−7.0	90:10	2.654	1.875	2.551	1.956	70.8	37.5	40.4	38.8
3	H	H	NH_2	1.25	40:60	2.629	1.944	2.460	2.051	58.4	44.6	47.2	43.9
4	H	CN	H	−7.9	92:8	2.634	1.985	2.477	2.084	70.8	35.5	41.6	36.8
5	H	H	CN	1.3	40:60	2.549	2.035	2.477	2.092	63.6	43.2	45.3	42.6
6	H	CO_2Me	H	−9.7	95:5	2.676	1.994	2.558	2.055	73.8	33.0	34.7	30.0
7	H	H	CO_2Me	−0.79	56:44	2.543	2.036	2.472	2.098	62.8	42.5	45.3	41.5
8	Me	CO_2Me	H	−10.7	97:3	2.741	1.972	2.631	2.004	73.6	32.9	34.7	29.6
9	Me	H	CO_2Me	−0.57	55:45	2.678	1.957	2.581	2.016	64.3	41.2	46.4	40.8

[a] $E(exo) - E(endo)$, kJ mol^{-1}. [b] Boltzmann populations from ΔE values (plus zpe correction) at 110 °C.

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stereoisomers **3**–**6** to the cycloaddition reaction conditions. In each case, no isomerisation was observed.

Table 1 presents data for fully optimised B3LYP/6-31G(d) *endo* and *exo* IMDA TSs¶ of related ester-linked 1,3,8-nonatrienes.‖ An *endo* selective IMDA reaction is predicted for the parent acrylate derivative (Table 1, entry 1).** The calculations correctly predict the qualitative trends in *exo*–*endo* selectivity for **1** and **2**, *i.e.* strong *exo* selectivity for **1** (entry 8) and less so for **2** (entry 9). Three important conclusions may be drawn from the data of Table 1: (1) For C9-substituted trienes, the *exo*–*endo* selectivity is strongly dependent on the *E*–*Z* stereochemistry of the dienophile. Thus, *Z*-dienophiles (entries 2, 4, 6 and 8) are predicted to be significantly *exo* selective, while the *E*-dienophiles exhibit either a less pronounced shift towards the *exo* product (entries 7 and 9) or no change (entries 3 and 5). The presence of a terminal diene substituent (Y) has a negligible effect upon this preference (compare entries 6 *vs.* 8; 7 *vs.* 9). (2) In stark contrast to IMDA reactions of C1-substituted trienes,[11] the *exo*–*endo* selectivity is scarcely affected by the electronic demands of the C9-substituent (compare data for NH_2 *vs.* CN or CO_2Me). (3) All TSs display substantial bond forming asynchronicity which is particularly pronounced for the C9-substituted systems. In all cases the developing *internal* bond is more advanced than the developing *peripheral* bond, as indicated by the difference between their lengths, Δr ($= r_2 - r_1$): upon introduction of a C9 substituent (either *E* or *Z*), Δr increases from 0.19 Å (entry 1) to 0.51–0.77 Å, for the *exo* TSs, and from 0.08 Å to 0.37–0.63 Å, for the *endo* TSs. The large Δr values for the substituted systems is mainly due to much longer developing peripheral bonds in these TSs, with r_2 becoming as long as 2.74 Å (entry 8, *exo* TS).††

Our calculations support the Houk twist-asynchronous model[1,4,5,6] for explaining the influence of C9-substituents on the stereochemistry of IMDA reactions. In this model, applied to a trimethylene tether,[6] attention is focussed on strain in the developing cyclopentane ring in the IMDA TS. This strain is alleviated by reducing the magnitude of the C5–C4–C8–C7 dihedral angle θ_2 which may be achieved by twisting the TS about the C4–C8 bond such that C9 rotates in the *exo* (*outside*)[6] direction for the *exo* TS, and in the *endo* (*inside*)[6] direction for the *endo* TS. For a C9-substituted triene, this twisting is more facile for the *exo* TS than for the *endo* TS, since *endo* twisting in the *endo* TS probably leads to increased Pauli overlap repulsion‡‡ between the C9-substituent and the diene. The θ_1 (C3–C4–C8–C9 dihedral angle) values for the *Z*-substituted systems are consistent with this conjecture, with θ_1 displaying a large *exo* twist of 9–12° for the *exo* TSs, but a smaller *endo* twist of 1–8° for the *endo* TSs, relative to the unsubstituted system.

In contrast, the enhanced twist-asynchronicity seen in the *Z*-substituent TSs is absent in the corresponding *E*-substituent TSs since the θ_1 values for these TSs are similar to that for the unsubstituted TS (entry 1). This lack of enhanced twist asynchronicity is consistent with the reduced *exo* selectivity calculated for the *E*-substituted systems, compared to the corresponding *Z*-substituent series. What is the origin of this reduced *exo* preference for *E*-substituted nonatrienes?

Fig. 2 shows the *exo* and *endo* TSs for the parent acrylate compound (Table 1, entry 1), as viewed from the developing *peripheral* (C1–C9) bond. The preferred direction of asynchronous twist of the dienophile about the shorter *internal* (C4–C8) bond is depicted by a curved arrow. The approximate direction of the π electron density surface vector of the diene is depicted by solid arrows. The position of C9 substituents are indicated by *E* and *Z*.

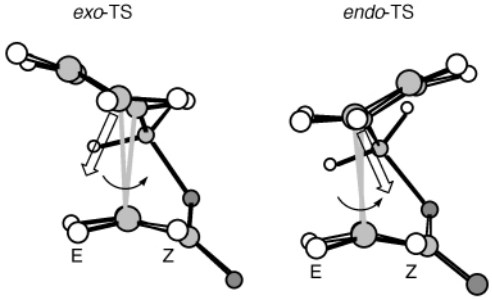

Fig. 2 Fully optimised B3LYP/6-31G(d) *exo* and *endo* TSs for the parent acrylate (Table 1, entry 1). See main text for key to arrows.

In the *exo* TS, preferred *exo* twisting of the dienophile about the C4–C8 axis moves the *Z*-substituent further from the diene, thereby reducing diene–substituent overlap repulsion. In contrast, preferred *endo* twisting in the *endo* TS moves the *Z*-group further into the diene region and overlap repulsion should increase, but slightly (because of the canting of the diene plane with respect to the dienophile). These effects combine to give strong *exo* selectivity for *Z*-substituted systems. For the *E*-substituted systems, *exo* twisting in the *exo* TS brings the substituent closer to the π electron density (once again, due to the canting of the diene), resulting in increased overlap repulsion. This outcome occurs also for preferred *endo* twisting in the *endo* TS. Consequently, on the basis of our refined Houk twist-asynchronicity model, reduced *exo*–*endo* selectivity is *expected* for *E*-substituted nonatrienes.

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Notes and references

‡ In intramolecular Diels-Alder reactions, we use the terms *endo* and *exo* to describe the orientation of the dienophile tether connection with respect to the diene. An *endo* orientation of the dienophile tether 'substituent' affords the *cis*-fused bicycle; an *exo* orientation of the dienophile tether furnishes the *trans*-fused cycloadduct.

§ For ease of comparison between the all-carbon prototype and other derivatives (such as the substituted esters described here), 1,3,8-nonatriene numbering is retained throughout.

¶ For entries 6–9, two discrete orientations of the terminal ester group with respect to the dienophile C=C bond are possible, namely s-*cis*- and s-*trans*. Both s-*cis* and s-*trans* TSs gave similar *exo*:*endo* product ratios and only data for the slightly lower energy s-*cis* TSs are given in Table 1.

‖ All TSs were fully optimised and characterised by B3LYP/6-31G(d) harmonic frequency calculations.

** Our B3LYP6-31G(d) calculations correctly predict predominant *endo* selectivity for the IMDA reaction of the trimethylene tether analogue of entry 1 (Table 1): the calculated *endo*:*exo* ratio is 83:17, compared to the experimentally observed value of 69:31.[3]

†† IRC calculations carried out on several substituted systems depicted in Table 1 show that these IMDA reactions are concerted, notwithstanding their marked asynchronicity.

‡‡ Electrostatic repulsion and secondary orbital overlap effects may also play a role.

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