A density functional theory study of π-facial stereoselectivity in intramolecular Diels–Alder reactions†

Michael N. Paddon-Row*[a] and Michael S. Sherburn[b]

[a] *School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia. E-mail: m.paddonrow@unsw.edu.au*
[b] *School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia*

Received (in Cambridge, UK) 8th August 2000, Accepted 27th September 2000
First published as an Advance Article on the web 31st October 2000

B3LYP/6-31G(d) theory has been used to construct a transition structure model which correctly accounts for the observed π-diastereofacial selectivity in intramolecular Diels-Alder reactions induced by allylic substituents attached to the diene.

In addition to the extraordinary number of synthetic studies reported on the intramolecular Diels-Alder (IMDA) reaction,[1] there is growing interest in its stereochemical interpretation by computational methods.[2] The stereochemical outcome of IMDA reactions is complicated by *endo–exo*- and π-facial attributes, factors which allow up to four stereoisomeric products for each concerted process. We recently reported some of the first examples of IMDA reactions in which the stereocontrolling group is at the terminus of the diene (Fig. 1).[3] Whilst *exo* cycloadducts were formed exclusively in all cases, the level of π-diastereofacial selectivity was tuned by altering the substituents at the allylic stereocentre (C*) of **1**. The source of the *exo* preference of this general class of IMDA reactions was discussed in the previous communication.[4] Herein we explain our observed *π-facial* selectivities using transition structure (TS) models based on B3LYP/6-31G(d) theory, which has been shown to give good descriptions of TSs for the intermolecular Diels-Alder reaction.[5]

The origin of the observed π-facial selectivity in the IMDA reaction of **1** (Fig. 1), in terms of identifying the preferred disposition of the allylic substituents R, X and H among the *inside* (*in*), *anti* (*an*), or *outside* (*ou*) positions in TS **7** (Fig. 2), was investigated by carrying out B3LYP/6-31G(d) density functional theory calculations on the TSs for the IMDA reaction of **4**, which serves as a good simulacrum of **1**. In addition to the three conformations about the C1–C* bond, three conformations about the allylic C*–O bond and s-*cis*–s-*trans* orientations of the C9–CO_2CH_3 bond are possible (see **8**, Fig. 2). Thus, in principle, there are 18 diastereomeric TSs for *each* diastereomeric *exo* cycloadduct, **5** and **6**.‡ Two sets of six fully optimised lowest energy TSs associated with the different C1–C* conformations **7** were located, one set with the *Z*-ester adopting the s-*cis* conformation and the other with the *Z*-ester group in the s-*trans* conformation.

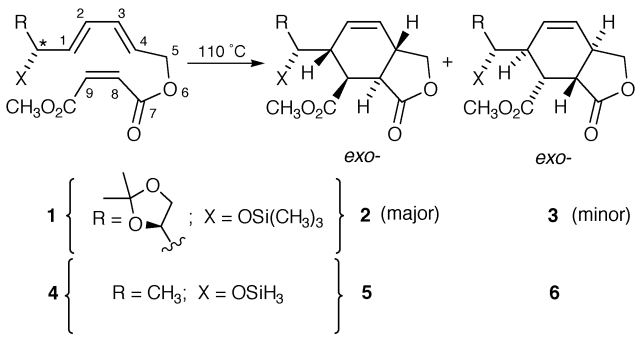

Fig. 1 The reported IMDA reaction (**1** → **2** + **3**) and the reaction under scrutinity by DFT (**4** → **5** + **6**).

† Electronic supplementary information (ESI) available: final optimised coordinates for stationary points in all transition structures. See http://www.rsc/org/suppdata/cc/b0/b006486f/

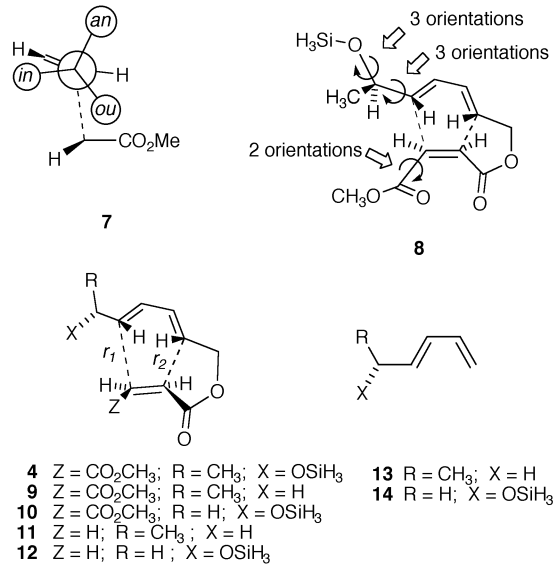

Fig. 2 Positioning of substituents in the IMDA TSs of **4** (**7** and **8**) and structures under investigation (**4**, **9**–**14**).

The relative energies, together with B3LYP/6-31G(d) zpe corrections, of the six diastereomeric TSs **4a**–**4f** for the IMDA reaction of **4**, in which the *Z*-ester adopts the s-*cis* conformation, are given in Table 1 and the profiles of the structures are shown

Table 1 B3LYP/6-31G(d) relative energies (kJ mol^{-1})[a]

Structure	*in*	*an*	*ou*	E_{rel}
4a[b]	$OSiH_3$	CH_3	H	0.0 (0.0)
4b[b]	H	$OSiH_3$	CH_3	4.0 (4.2)
4c[b]	CH_3	H	$OSiH_3$	14.5 (14.6)
4d[b]	$OSiH_3$	H	CH_3	4.8 (4.6)
4e[b]	CH_3	$OSiH_3$	H	10.5 (11.3)
4f[b]	H	CH_3	$OSiH_3$	5.55 (5.4)
9a[c]	H	CH_3	H	0.0 (0.0)
9b[c]	H	H	CH_3	5.4 (5.5)
9c[c]	CH_3	H	H	2.3 (2.0)
10a[c]	$OSiH_3$	H	H	0.0 (0.0)
10b[c]	H	$OSiH_3$	H	5.9 (6.8)
10c[c]	H	H	$OSiH_3$	12.6 (12.7)
11a	H	CH_3	H	0.0 (0.0)
11b	H	H	CH_3	4.5 (3.9)
11c	CH_3	H	H	4.3 (4.1)
12a	$OSiH_3$	H	H	0.0 (0.0)
12b	H	$OSiH_3$	H	2.2 (3.15)
12c	H	H	$OSiH_3$	2.1 (1.75)

[a] Relative energies corrected for zero point energy in parentheses. [b] s-*cis* ester conformation. [c] s-*trans* ester conformation.

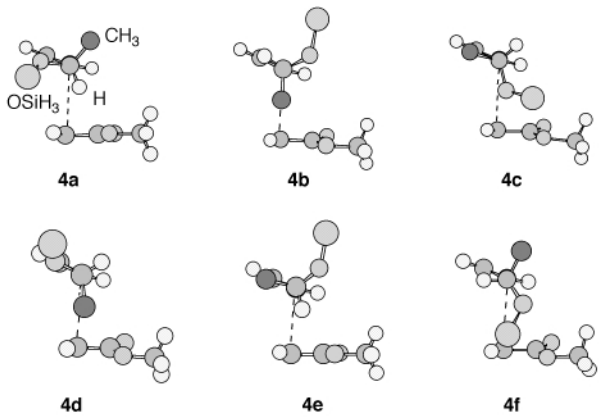

Fig. 3 The six TSs located for the IMDA reaction of **4**, as viewed down the C1–C4 axis (*cf.* **7**, Fig. 2). The developing *peripheral* C1–C9 bond is shown as a dashed line. Tether atoms are omitted for clarity.

in Fig. 3. The other set of six TSs associated with the s-*trans* conformation of the *Z*-ester are slightly higher in energy, by 2.5–6.0 kJ mol^{-1}, with respect to their corresponding s-*cis* congeners. In all other respects, the two sets of TSs show similar trends and so, unless stated otherwise, the following discussion refers to the *s-cis* set of TSs. The following five important points emerge from this study: (1) The lowest energy TS is **4a**, in which the silyloxy group adopts the *inside* position and the methyl group the *anti* position. This TS leads to formation of **5**, possessing the same configuration as **2**, the observed major product. The same major product is predicted from analysis of the TSs associated with the *Z*-ester adopting the s-*trans* conformation. (2) The three TSs **4a**–**4c** give **5**, whereas the three TSs **4d**–**4f** give the minor product **6** having the same configuration as the observed minor adduct **3**. A Boltzmann analysis of the two sets of conformations at 110 °C, including zpe corrections, gives a predicted product distribution of **5**:**6** = 74:26. A similar analysis carried out on the two sets of three TSs associated with the s-*trans Z*-ester conformations predicts a product distribution of **5**:**6** = 81:19. These analyses are in very good qualitative agreement with the experimental product distribution of **2**:**3** = 82:18 for the IMDA reaction of **1** (refluxing toluene) and provide compelling evidence in support of the reliability of our theoretical model. (3) The preferences of the methyl and silyloxy groups for the *anti* and the *inside* positions, respectively, in the lowest energy TS **4a** are a consequence of their respective innate tendencies to adopt these positions, irrespective of the presence of the other substituent. This conclusion is borne out by the calculations on **9** and **10**, each of which contains only one of these substituents. Thus, the most favourable TS for **9** is **9a**, with methyl in the *anti* position, and that for **10** is **10a**, with silyloxy in the *inside* position. The same trend is found for **11** and **12** in which the C9-ester substituent is absent, thereby demonstrating that the presence of this group is not required for inducing the conformational preferences of the methyl and silyloxy groups in these systems.§ (4) Inspection of the profiles of the TSs **4a**–**4f** (Fig. 3) reveals that the allylic substituents show little staggering about the forming *peripheral* bond (r_2) that is normally characteristic of additions to allylic systems.[6] Indeed, the C1–C* conformations in these TSs are essentially the same as those for isolated allylic ethers, with one substituent eclipsing the double bond.[7] This is hardly a surprising finding, given the extended length of the developing *peripheral* bond[4] (the *peripheral* bond length reaches a peak at 2.93 Å for **4d**). Model B3LYP/6-31G(d) calculations on the planar 1-ethyl-s-*cis*-butadiene **13**¶ show that the staggered conformer is favoured over the eclipsed conformer by 2.7 kJ mol^{-1}, which is similar to the energetic preference of the *anti* conformation over the *inside* conformation in the TSs for both **9** and **11**. In contrast, the calculations for **14** demonstrate that the eclipsed conformation is favoured over the staggered conformation by 2.7 kJ mol^{-1}, in reasonable agreement with the results for the TSs for **10** and **12**. (5) Our model for the favoured TS for IMDA reactions, in which the silyloxy group adopts the *inside* position and the alkyl group the *anti* position, is reminiscent of that proposed for *intermolecular* 1,3-dipolar cycloadditions of nitrile oxides to chiral allylic ethers.[6,8]

In conclusion, our model may be used to predict the degree of π-facial selectivity of IMDA reactions with substituents at the allylic position of the diene. The preferred TS, with the C* alkyl substituent *anti* and RO group *inside*, will be further favoured energetically by increasing the size of the alkyl group, for steric reasons, and by increasing the electron density at the oxygen atom of the RO group, for electrostatic reasons. The *inside* preference for the RO group may arise from an attractive electrostatic interaction between the oxygen atom and the hydrogen atom at C2. This would explain why greater π-facial selectivity is observed in IMDA reactions of silyl ethers (*e.g.* **1**) than the corresponding alcohol (Fig. 1; X = OH).[3] Our calculations predict even stronger selectivity for a metal alkoxide (Fig. 1; X = OM).

The authors thank the Australian Research Council for the award of a Senior Research Fellowship (to MNP-R) and a project grant (to MSS) and the New South Wales Centre for Parallel Computing for allocation of CPU time (to MNP-R).

Notes and references

‡ Cycloadducts **5** and **6** result from dienophile approach from below and above the plane of the diene respectively to enantiomerically pure **4**. For simplicity, the π-facial selectivity of this IMDA reaction was evaluated computationally by locating IMDA TSs for dienophile approach to the lower face of the diene for each enantiomer of **4**: *cf.* S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, 1991, 327.

§ With the exception of **4c**, the energetic ordering of the TSs calculated for **4a**–**4f** may be correctly deduced from the monosubstituted allylic systems **9** and **10** by simply adding the relative energies of the various pairs of TSs.

¶ The butadiene moiety in **4a**–**4f** is only *ca.* 5° off planarity.

1 Reviews: D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; W. R. Roush, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 513.

2 M. K. Diederich and F.-G. Klarner, *J. Am. Chem. Soc.*, 1998, **120**, 6212; M. K. Diederich, F.-G. Klarner, B. R. Beno, K. N. Houk, H. Senderowitz and W. C. Still, *J. Am. Chem. Soc.*, 1997, **119**, 10 255; L. Raimondi, F. K. Brown, J. Gonzalez and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 4796; F. K. Brown, U. C. Singh, P. A. Kollman, L. Raimondi, K. N. Houk and C. W. Bock, *J. Org. Chem.*, 1992, **57**, 4862; F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2297.

3 M. J. Lilly and M. S. Sherburn, *Chem. Commun.*, 1997, 687.

4 M. J. Lilly, M. N. Paddon-Row, M. S. Sherburn and C. I. Turner, *Chem. Commun.*, 2000, 2213.

5 O. Wiest and K. N. Houk, *Top. Curr. Chem.*, 1996, **183**, 1.

6 K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science*, 1986, **231**, 1108.

7 B. W. Gung, M. A. Wolf and Z. Zhu, *J. Org. Chem.*, 1993, **58**, 3350.

8 K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880.