Transition structures of intramolecular ene reactions in the presence of activating substituents: a theoretical study

Gourab Kanti Das

Department of Chemistry, Visva-Bharati, Santiniketan-731235, West Bengal, India

Received (in Cambridge) 1st February 1999, Accepted 27th May 1999

Transition states of intramolecular ene reactions in the presence of an activating substituent were studied by an AM1 approximation to calculate the proportion of various diastereomeric products. The predicted diastereoselectivity for the formation of a five membered ring containing chiral and/or achiral centres was found to be in good agreement with the reported experimental observations.

An intramolecular ene reaction for the formation of an alicyclic ring is a useful tool in organic synthesis.[1–3] The presence of an activating substituent in the reactant usually reduces the reaction temperature and increases the possibility of controlling the stereoselectivity.[4] Various models have been proposed[5–7] to predict the stereoselectivity of this reaction for the formation of a five membered ring. The most modified model proposed by Houk *et al.*,[7] predicts successfully the ratio of the diastereomeric products formed in the case of unactivated reactants. But the model is inadequate in the case of activated enophiles.[7] This is due to the assumption of a rigid transition state, and the predictions using this differ greatly from what is experimentally observed. This discrepancy clearly indicates that the actual transition state is relatively flexible.

In this paper the transition states (TSs) of suitable examples of intramolecular ene reactions with activating substituents have been investigated using a semi-empirical quantum mechanical method. Of the two most popular semi-empirical methods, AM1[8] gives more realistic energies[9] whereas PM3[10] predicts more reliable structures.[9] As our prediction of product ratios is based on the relative energies of the TSs, we adopted AM1 for all calculations. In the first part of this paper reactions involving an achiral reactant have been studied, and in the latter part, reactions with a reactant containing a chiral centre have been investigated. The latter case also demonstrates the effect of steric factors in controlling the stereoselectivity.

Computational methods

Semi-empirical MO calculations were performed using the AM1[8] Hamiltonian. Full geometry optimisation was carried out using the MOPAC 7 program,[11] and each species was characterised as corresponding to a saddle point on the energy hypersurface by means of vibrational analysis: a transition state possesses only a single imaginary vibrational frequency.

Results and discussion

Fig. 1 shows the Newman projection of the transition structure for the ene reaction of ethene with propene.[7] There are four ways of adding an achiral tether to this structure to build transition states of an intramolecular ene reaction (Fig. 1). Two transition structures (with binding modes 1 and 3) result in a *cis* cycloalkane product while the other two (with binding modes 2 and 4) lead to a *trans* product. As all these transition structures are chiral, another four enantiomeric transition structures exist along with these two. Out of the four transition structures resulting from the four binding modes with an achiral tether we have characterised only three (Fig. 2). The failure to observe a TS with binding mode 4 is probably due to the non-existence of such a TS because of the large dihedral angle between the forming C–C bond. Our observation shows that the energy of the three characterised TSs with binding modes 1, 2 and 3 largely depends on the size of the dihedral angles, *α*, *β* or *γ* (Fig. 1). The presence of a chiral centre on the tether (*e.g.* due to the group R^5 in Fig. 2) creates another three diastereo-

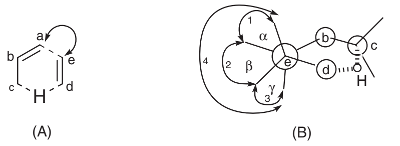


Fig. 1 Transition structure for the ene reaction of ethene with propene. In the Newman projection (**B**) the curly arrows represent the possible binding modes of the tether to convert this transition structure to an intramolecular ene reaction transition structure.

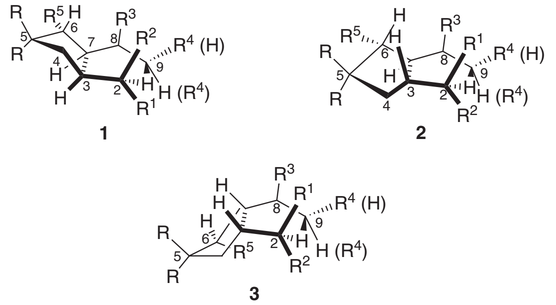


Fig. 2 Three transition structures out of four possible binding modes. **1** and **3** form the *cis* product while **2** forms the *trans* product.

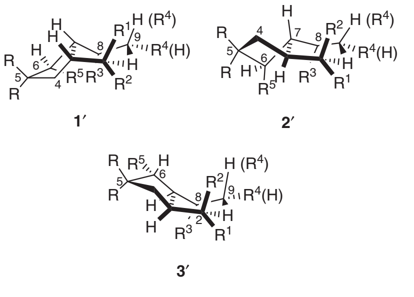


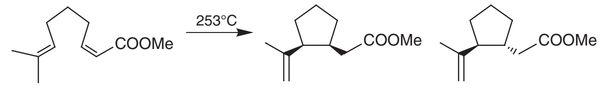
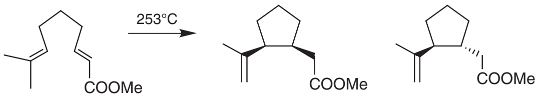
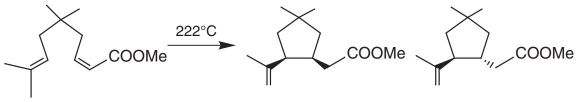
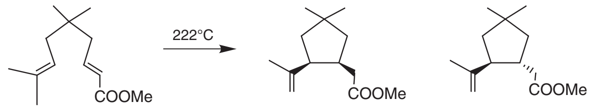
Fig. 3 Three other possible transition structures, diastereomeric with the structures of Fig. 2 due to the presence of a chiral centre at C-6. When $R^5 = H$, these three will be the enantiomers of the transition structures of Fig. 2.

meric TSs (Fig. 3), which have also been characterised in our second case.

TSs for the ene reactions with an achiral tether

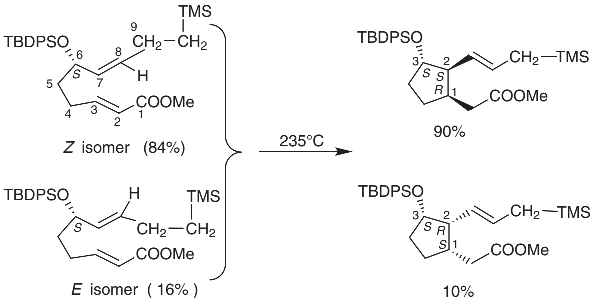
The first cases studied are the ene reactions of methyl 8-methylnona-2,7-dienoate and methyl 5,5,8-trimethylnona-2,7-dienoate (Table 1). The energies and the possible products derived from the possible TSs are shown in Table 2. In both reactions the *cis* product is possible from TSs **1** and **3** (Fig. 1), whereas a *trans* product is formed from TS **2**. The calculated ratios of the products were determined from a Boltzmann distribution based on the relative energies of all possible TSs and the temperature at which the reaction takes place. Experimentally both *cis* and *trans* isomers are isolated,[12] and their proportions (Table 1) are in better agreement with the prediction from the AM1 method than with the prediction from the rigid MM2 Houk model.[7] It is quite interesting to note that the ratio of *cis* and *trans* products in the *E* isomer is greater than the ratio in the case of the *Z* isomer. This may be explained on the basis of the β values of the transition structures (Table 2). In both the reactions the β angle of the TS **2**, forming the *trans* product, is smaller for the *Z* isomer than that for the *E* isomer (Table 2). This indicates that when the orientation of the ester group (activating group) is *trans* to the tether (*i.e.*, *E* isomer) the reactant results in a TS with a relatively large β value to produce the *trans* isomer of the alicyclic ring. As a large β value increases the strain in the TS with binding mode 2, we may conclude that the formation of the *trans* product in the *E* isomer is more difficult than in the *Z* isomer. The presence of a dimethyl group (R = CH_3) makes the tether more bulky and increases the steric interaction with other atoms directly connected to the reaction centre in TSs **1** and **3**. For this the formation of the *trans* product from TS **2** is more favoured in reactions (3) and (4) than in reactions (1) and (2) (Table 1). This effect is supported by AM1 calculations as well as experimental observations (Table 1). It should be noted that during this prediction one should pay attention to the magnitude of the difference in the relative energies of the TSs because if the two structures differ by 1 kcal mol^{-1} their calculated ordering is sometimes unreliable.[9]

Table 1 Intramolecular ene reaction with 1,6-diene containing an activated enophile

	cis	*trans*
(1) 		
Exp.[9]	43%	57%
MM2[7]	99%	1%
AM1	62%	38%
(2) 		
Exp.[9]	76%	24%
MM2[7]	100%	0%
AM1	89%	11%
(3) 		
Exp.[9]	40%	60%
MM2[7]	98%	2%
AM1	53%	47%
(4) 		
Exp.[9]	72%	28%
MM2[7]	100%	0%
AM1	83%	17%

TSs for the ene reaction with a tether containing a chiral centre

In our second case we have investigated the cyclisation of a mixture of methyl (6*S*,2*E*,7*Z*)-10-(trimethylsilyl)-6-(*tert*-butyldiphenylsilyloxy)deca-2,7-dienoate and methyl (6*S*,2*E*,7*E*)-10-(trimethylsilyl)-6-(*tert*-butyldiphenylsilyloxy)deca-2,7-dienoate (Scheme 1), the experimental result of which was reported by Sarkar *et al.*[13] This reaction was found to create three chiral



Scheme 1

Table 2 Heat of formation (HOF) and relative energies (kcal mol^{-1}) of transition structures for the intramolecular ene reaction of 1,6-dienes with an activated enophile (Table 1)

Reactant	TS (Fig. 2)	β/°	HOF/ kcal mol^{-1}	Relative energies/ kcal mol^{-1}	Product (Table 1)
(1) Methyl (2*Z*)-8-methylnona-2,7-dienoate	**1**	88.9	−47.3	0.0	*cis*
R = R^1 = R^4 = R^5 = H;[a]	**2**	42.2	−47.0	0.3	*trans*
R^2 = COOMe; R^3 = Me	**3**	82.9	−45.8	1.5	*cis*
(2) Methyl (2*E*)-8-methylnona-2,7-dienoate	**1**	83.6	−48.9	0.0	*cis*
R = R^2 = R^4 = R^5 = H;	**2**	43.4	−47.1	1.8	*trans*
R^1 = COOMe; R^3 = Me	**3**	94.9	−47.9	1.0	*cis*
(3) Methyl (2*Z*)-5,5,8-trimethylnona-2,7-dienoate	**1**	85.6	−55.1	0.1	*cis*
R = R^3 = Me; R^1 = R^4 = R^5 = H;	**2**	43.0	−55.2	0.0	*trans*
R^2 = COOMe	**3**	81.0	−53.7	1.5	*cis*
(4) Methyl (2*E*)-5,5,8-trimethylnona-2,7-dienoate	**1**	84.6	−56.7	0.0	*cis*
R = R^3 = Me; R^2 = R^4 = R^5 = H;	**2**	44.2	−55.4	1.3	*trans*
R^1 = COOMe	**3**	95.5	−55.6	1.1	*cis*

[a] Designation of R's is for TS in Fig. 2.

centres with a high degree of diastereoselectivity. The authors noted the inadequacy of the Houk model and adopted the Oppolzer model in an attempt to rationalise the high stereoselectivities observed in the ene cyclisation. Though some of the facts have been explained, the stereoselectivity can not be totally rationalised qualitatively or quantitatively by this model.

The substituent at the 6 position of the actual reactant may take various conformational arrangements in the TS. To avoid this complexity we have replaced the *tert*-butyldiphenylsilyloxy (TBDPSO) (Scheme 1) with a trimethylsilyloxy group in our TS models (R^5 in Fig. 2). As this group creates a chiral centre on the tether, three additional diastereomeric TSs (Fig. 3) along with the former three (Fig. 2) can exist. Again in all these TSs, R^4 and H on C-9 may interchange their positions due to conformational isomerisation in the reactant, and another set of six TSs is possible. All these TSs along with their energies and the configuration of the products are presented in Table 3. '**a**' and '**b**' indicate isomeric structures where R^4 and H at C-9 interchange their positions ('**b**' isomers are indicated by placing R^4 in parentheses in Fig. 2 and Fig. 3).

TSs from the (7*E*)-isomer of Scheme 1. The possible TSs from *E*-isomers are **1**, **1′**, **2** and **2′** (Table 3, Fig. 2 and Fig. 3). The high relative energy of **2** and **2′** (both **a** and **b**) makes them unsuitable for product formation (*i.e.* they will not make any effective contribution to product formation at the reaction temperature). This is primarily due to *β* angle strain. **1b** and **1′b** show high energy for the steric interaction between R^1 and R^4 which are at the same side of the reaction plane. However, an additional steric strain between R^5 and R^3 in **1′b** makes it unsuitable to be a product forming TS. The steric strain is reflected by its high relative energy (3.2 kcal mol^{-1}). To investigate the mode of variation of relative energy with the size of the group at R^5 we have substituted it with other groups in the TSs which contribute in product formation (**1a**, **1b** and **1′a**), and have calculated their relative energies with respect to the stable transition state (Table 4). The nature of the variation of the relative energy with the nature of the group clearly shows that it passes through a maximum for the -OCH_3 group and then diminishes. This is probably due to some other interactions in TS **1a**, which is effective when R^5 is larger than -OCH_3. This makes the heat of formation (HOF) of **1a** higher and simultaneously causes the reduction of the relative energy of **1′a**. The relative energy of **1b** is almost insensitive to the variation in size of the R^5 group as expected.

TSs from the (7*Z*)-isomer of Scheme 1. Possible TSs from the *Z*-isomer are **3** and **3′** (both **a** and **b**) (Fig. 2 and Fig. 3). The high relative energies of **3** (**a** and **b**) and **3′b** (Table 3) are

Table 3 Energies and heat of formation (HOF) of the possible TSs (Figs. 2 and 3) and configurations of products formed from them for the reaction of Scheme 1 (R = R^2 = R^3 = H; R^1 = COOMe; R^4 = CH_2-TMS; R^5 = O-TMS)

TS (Fig. 2 and Fig. 3)	HOF/ kcal mol^{-1}	Relative energy	Configuration of the product (Scheme 1)
For *E*-isomer			
1a[a]	−182.9	0	1*R*,2*S*,3*S*
1b[a]	−180.6	2.3	1*R*,2*S*,3*S*
1′a	−182.1	0.8	1*S*,2*R*,3*S*
1′b	−179.7	3.2	1*S*,2*R*,3*S*
2a	−179.2	3.7	1*S*,2*S*,3*S*
2b	−176.9	6.0	1*S*,2*S*,3*S*
2′a	−178.3	4.6	1*R*,2*R*,3*S*
2′b	−176.0	6.9	1*R*,2*R*,3*S*
For *Z*-isomer			
3a	−177.8	2	1*S*,2*R*,3*S*
3b	−171.0	8.8	1*S*,2*R*,3*S*
3′a	−179.8	0	1*R*,2*S*,3*S*
3′b	−176.3	3.5	1*R*,2*S*,3*S*

[a] '**a**' and '**b**' indicate the isomeric TSs where R^4 and H in Fig. 2 and Fig. 3 interchange their positions.

Table 5 Intramolecular ene reaction with unactivated octa-1,6-diene

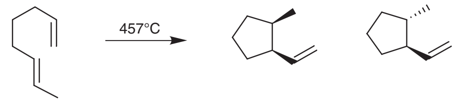
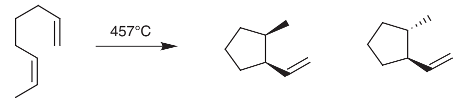
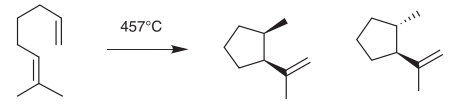
	cis	*trans*
(1) 		
Exp.[14]	100%	0%
MM2[7]	99%	1%
AM1	91%	9%
(2) 		
Exp.[14]	100%	0%
MM2[7]	100%	0%
AM1	100%	0%
(3) 		
Exp.[14]	100%	0%
MM2[7]	99%	1%
AM1	90%	10%

Table 4 Heat of formation (HOF) and relative energies (both in kcal mol^{-1}) of product forming TSs (Figs. 2 and 3) when R^5 is substituted with various groups (R = R^2 = R^3 = H; R^1 = COOMe; R^4 = -CH_2-TMS)

$R^5 \rightarrow$	H		-OH		-OCH_3		-O-$C(CH_3)_3$		-O-$Si(CH_3)_3$	
TS	HOF	Relative energy	HOF	Relative energy	HOF	Relative energy	HOF	Relative energy	HOF	Relative energy
For *E*-isomer										
1a	−90.5	0	−133.2	0	−128.4	0	−139.2	0	−182.9	0
1b	−88.2	2.3	−130.9	2.3	−126.0	2.4	−136.9	2.3	−180.6	2.3
1′a	−90.5	0	−132.3	0.9	−127.3	1.1	−138.2	1.0	−182.1	0.8
For *Z*-isomer										
3a	−88.3	0	−128.6	1.5	−123.3	1.9	−134.6	1.9	−177.8	2
3′a	−88.3	0	−130.1	0	−124.2	0	−136.5	0	−179.8	0

Table 6 HOF and relative energies of TSs for the intramolecular ene reaction of 1,6-dienes without any activating enophile (Table 5)

Reactant	TS (Fig. 2)	β/°	HOF/ kcal mol^{-1}	Relative energies/ kcal mol^{-1}	Product (Table 5)
1) *trans*-octa-1,6-diene	**1**	93.2	45.5	0	*cis*
$R = R^1 = R^2 = R^3 = R^4 = R^5 = H$	**2**	49.7	48.9	3.4	*trans*
2) *cis*-octa-1,6-diene	**3**	96.3	47.1	—	*cis*
$R = R^1 = R^2 = R^3 = R^4 = R^5 = H$					
3) 7-methylocta-1,6-diene	**1**	89.4	39.3	0	*cis*
$R = R^1 = R^2 = R^4 = R^5 = H; R^3 = CH_3$	**2**	49.2	41.8	2.5	*trans*
	3	95.0	40.0	0.7	*cis*

attributed to the steric strain created by R^4 and/or R^5 with other hydrogens at C-9. TS **3′a** shows minimum energy as R^4 and R^5 are far away from each other. When both R^4 and R^5 are large groups the interaction between them in **3b** is severe, resulting in a high energy TS. This makes **3b** unsuitable to be a product forming TS. Here also the variation of relative energy with the change in size of the group R^5 has been studied only in the case of product forming isomers (*i.e.* **3a** and **3′a**) (Table 4). When R^5 is replaced with hydrogen **3a** and **3′a** are enantiomers and their heats of formations are the same (Table 4). With an increase in the size of the substituent, the relative energy of **3a** increases, and at the same time reduces the possibility of formation of product with a 1*S*,2*R*,3*S* configuration (Scheme 1).

On the basis of the relative energies of the TSs the computed results show that from a mixture of *E* and *Z* isomers in a 16:84 proportion, only two isomeric products with (1*R*,2*S*,3*S*) and (1*S*,2*R*,3*S*) configurations may be formed at 235 °C, and the ratio of them is 85:15. From this predicted ratio and the effect of substituents at R^5 on stereoselectivity (Table 4) it is evident that if R^5 is substituted with TBDPSO (which is bulkier than -O-TMS) the theoretical ratio of the product will be close to the experimentally observed one (90:10, Scheme 1).[13]

TSs for the unactivated intramolecular ene reactions

Our study of the TSs of the ene reaction of octa-1,6-diene (*cis* and *trans*) and its 7-methyl derivative revealed that the AM1 predicted stereoselectivity (Tables 5 and 6) is not as accurate as the prediction of the MM2 restricted model. In the case of reactions (1) and (3) (Table 5) the proportion of *trans* product has been overestimated to some extent. This indicates that for an unactivated ene reaction the flexibility is not as much as that predicted by AM1.

The above discussion for the prediction of the product ratio in an activated intramolecular ene reaction reveals that a semi-empirical technique with an AM1 Hamiltonian may be used as a guideline to predict the stereoselectivity before performing the experiment. Selection of an appropriate substituent at the appropriate position may also be used to attain a high degree of stereoselectivity.

Acknowledgements

The author thanks CSIR, New Delhi, India for a Research Associateship. The author also thanks Dr D. Bhattacharyya, Biophysics Division, Saha Institute of Nuclear Physics (SINP), Belgachia, Calcutta, Professor B. P. Das and Dr D. N. Chowdhury, Department of Chemistry, Visva-Bharati, Santiniketan, India for their help.

References

1 (*a*) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 556; (*b*) W. Oppolzer, K. K. Mahalanabis and K. Battig, *Helv. Chim. Acta*, 1977, **60**, 2388; (*c*) W. Oppolzer, C. Robbiani and K. Battig, *Helv. Chim. Acta*, 1980, **63**, 2015; (*d*) W. Oppolzer and K. Battig, *Tetrahedron Lett.*, 1982, 4669.

2 W. Carruthers, in *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990, Chapter 5.

3 (*a*) T. K. Sarkar, B. K. Ghorai, S. K. Nandy and B. Mukherjee, *Tetrahedron Lett.*, 1994, **35**, 6903; (*b*) T. K. Sarkar, B. K. Ghorai, S. K. Nandy, B. Mukherjee and A. Banerji, *J. Org. Chem.*, 1997, **35**, 6903; (*c*) T. K. Sarkar, B. Mukherjee and S. K. Ghosh, *Tetrahedron*, 1998, **54**, 3243.

4 (*a*) B. B. Snider, *Acc. Chem. Res.*, 1980, **13**, 426; (*b*) B. B. Snider and E. A. Deutsch, *J. Org. Chem.*, 1982, **47**, 745; (*c*) L. F. Tietze and Y. Beifuß, *Synthesis*, 1988, 359; (*d*) K. Maruoka, Y. Hoshino, T. Shirasaka and H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 3967.

5 W. Oppolzer and C. Robbiani, *Helv. Chim. Acta*, 1980, **63**, 2010.

6 R. J. Loncharich and K. N. Houk, *J. Am. Chem. Soc.*, 1987, **109**, 6947.

7 B. E. Thomas IV, R. J. Loncharich and K. N. Houk, *J. Org. Chem.*, 1992, **57**, 1354.

8 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

9 N. T. Anh, G. Frison, A. Solladie-Cavallo and P. Metzner, *Tetrahedron*, 1998, **54**, 12841.

10 J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.

11 J. J. P. Stewart, *J. Comput. Aided Mol. Des.*, 1990, **4**, 1.

12 S. K. Ghosh and T. K. Sarkar, *Tetrahedron Lett.*, 1986, **27**, 525.

13 T. K. Sarkar, B. Mukherjee and S. K. Ghosh, *Tetrahedron*, 1998, **54**, 3243.

14 W. D. Huntsman, V. C. Solomon and D. Eros, *J. Am. Chem. Soc.*, 1958, **80**, 5455.

Paper 9/00831D