SHORT PAPER

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Effect of chirality on the diastereoselectivity of intramolecular ene reaction: a theoretical study†

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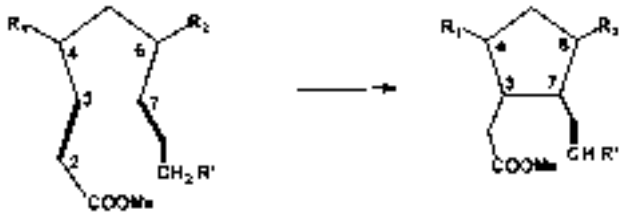
The effect of a preloaded chiral centre on the energies of the transition states in an intramolecular ene reaction has been studied by the AM1 semiempirical method. The stereoselectivity has also been predicted on the basis of the energies of transition states.

Keywords: chirality, diasteroselectivity, intramolecular ene reaction

The intramolecular ene reaction is a useful tool in the preparation of an alicyclic ring in synthetic organic chemistry.[1,2] The presence of an activating substituent in the reactant makes the reaction occur at low temperature.[3] It is possible to control the stereoselectivity of this reaction by introducing a chiral centre in the reactant.[3] Many theoretical studies have already been published on this reaction.[4] Our previous theoretical study reveals that the AM1 model[5] of semiempirical approach is suitable to predict the stereoselectivity.[6] In that paper, we reported 12 possible transition states (TSs) for a synthetically useful reaction shown in Scheme 1 (R_1=H; R_2=OTMS; R′=CH_2-TMS) where a substituent was placed at C-6 carbon atom. The six transition structures as shown in Fig.1, generate another six transition structures when R′ and H on C-9 carbon atom interchange their positions. Among these 12 TSs, it was found that many are energetically unfavourable and the energies predicted by the AM1 semiempirical technique are consistent with the experimentally obtained ratio of products.



Scheme 1

Here we report the effect of a substituent at C-4 (R_1) carbon of the transition state on the stereoselectivity in comparison to the effect created by C-6 substituent.

Computational methods

Semiempirical MO calculations were performed using the AM1 Hamiltonian.[5] Geometry optimisation was performed using the MOPAC 7 program,[7] and each species was characterised as corresponding to a saddle point on the energy hypersurface by means of vibrational analysis.

Results and discussion

Table 1 represents the energy and the configuration of the products derived from the possible 12 TSs for the ene cyclisation of the (4R)-4-methoxy and (6S)-6-methoxy derivative of methyl-2E-10(trimethylsilyl)-deca-2,7-dienoate (Scheme 1). ‘a’ And ‘b’ indicate isomeric structures where R′ and H at C-9 (Fig.1)

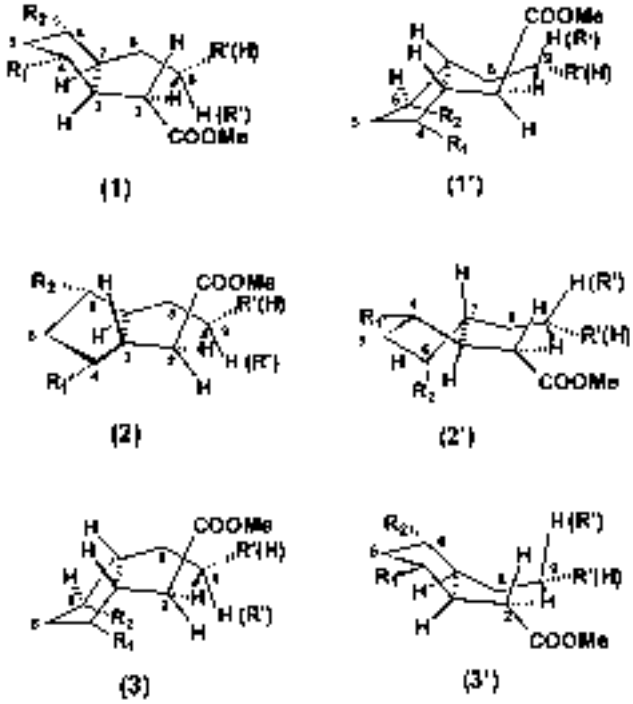


Fig 1 Possible six diastereomeric transition structures for the ene reaction of Scheme 1. Other six structures may be generated by interchanging the positions of R′ and H at the C-9 carbon atom.

interchange their positions (‘b’ isomers are indicated by placing R′ in parenthesis). The 7*E* isomer of each reactant generates eight possible TSs while the 7′*Z* isomer is able to form only four TSs. The reaction creates three chiral centres with a possibility of diastereoselectivity. The substituent OCH_3 group, placed at the 4 or 6 position, has been chosen for its prominent effect on stereoselectivity as found theoretically in our previous report.[6] Table 2 shows the configurations and product ratios obtained from a Boltzmann distribution based on the relative energies of all possible TSs and the temperature (253°C) as reported by Sarkar *et al.* for a similar reaction.[2]

Table 2 shows that the two groups at C-3 and C-7 (*vide* Scheme 1 for numbering in the product according to the numbering in the reactant) at the cyclopentane moity of the product always try to orient in *cis* configuration with each other. In the major products, the substituent R_1 or R_2 orients itself in the *trans* position with respect to these groups. It is evident that the substituent R_1 or R_2 prohibits the other two groups, attached at C-3 and C-7, taking their positions on the same side of the plane of the cyclopentane ring where the former group is placed. In the case of the E-isomer the stereoselectivities produced by R_1 and

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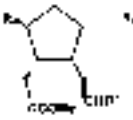
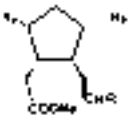
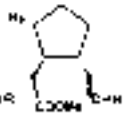
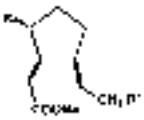
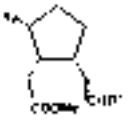
Table 1 Heat of formation (H.O.F.) and relative energies of the possible TSs (Fig. 1) and configuration of products formed from them for the reactions in Scheme 1 (R′=CH_2-TMS)

TS (Fig.1)	Reaction 1 (R_1=H; R_2=OCH_3)			Reaction 2 (R_1=OCH_3; R_2=H)		
	H.O.F (kcal/mol)	Relative energy (kcal/mol)	Configuration of the product H.O.F	H.O.F (kcal/mol)	Relative energy (kcal/mol)	Configuration of the product
For 7*E* isomer of the reactant						
1a	–128.4	0.0	3R6S7S	–127.1	0.0	3R4R7S
1b	–126.0	2.4	3R6S7S	–124.2	2.9	3R4R7S
1′a	–127.3	1.1	3S6S7R	–125.8	1.3	3S4R7R
1′b	–124.9	3.5	3S6S7R	–123.7	3.4	3S4R7R
2a	–124.3	4.1	3S6S7S	–123.5	3.6	3S4R7S
2b	–121.9	6.5	3S6S7S	–121.1	6.1	3S4R7S
2′a	–123.7	4.7	3R6S7R	–123.0	4.1	3R4R7R
2′b	–121.4	7.0	3R6S7	–120.7	6.4	3R4R7R
For 7*Z* isomer of the reactant						
3a	–123.3	1.9	3S6S7R	–124.3	0.9	3S4R7R
3b	–116.6	8.6	3S6S7R	–119.4	5.8	3S4R7R
3′a	–125.2	0.0	3R6S7S	–125.2	0.0	3R4R7S
3′b	–120.9	4.3	3R6S7S	–120.2	5.0	3R4R7S

Table 2 Intramolecular ene reaction of Scheme 1 with chirality placed at C-4 or C-6

Reactant	Predicted products and their percentages		
Reaction-1			
			 Other
E-isomer	~74%	~25%	<2%
			
Z-isomer	~87%	~13%	
Reaction-2			
			  
E-isomer	74.5%	22%	~2% ~1%
			
Z-isomer	71%	29%	

R_2 are nearly similar. However, for the *Z*-isomer the presence of R_2 makes the reaction more stereoselective than that induced by R_1. This effect can be explained if we scrutinise the structures and energies of the 'product forming transition states' (1a and 1′a for *E* isomer and 3a and 3′a for *Z*-isomer). In the case of the *E*-isomer the difference between the energies of the product forming transition states 1a and 1′a is same for both substituents R_1 and R_2 (Table 1). But for the *Z*-isomer the R_2 substituent in the 3a transition structure interacts strongly with the groups at the adjacent carbon atoms, making it a high energy species (relative energy is 1.9 kcal as shown in Table 1). This increases the selectivity for the 3′a structure as a product forming TS. On the other hand R_1 group, being placed at distant zone, is unable to interact strongly with other groups in the 3a transition structure and fails to make it a high energy species (relative energy is 0.9 kcal). Accordingly product selectivity is lost to some extent. All other TSs derived from the structure 2 and 2′ (Fig. 1) show high energy, primarily due to β angle strain,[6] for which the scarcity of the products with the *trans* oriented substituents at C-3 and C-7 is observed. It should also 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 their calculated ordering is sometimes unreliable.[8] However our previous success[6] for the prediction of the correct product ratio prompt us to make a similar hypothesis here.

In conclusion it may be predicted that the chirality at C-4 (due to R_1) or C-6 (due to R_2) of the reactant in reaction 1 and 2 (Table 2) results in similar stereoselectivity for the 7*E* isomer. However, for the 7*Z* isomer, chirality at the 6-position induces more stereoselectivity than that at the 4-position. The results given in Table 2 may help a synthetic organic chemist to develop a synthetic strategy using the stereoselective intramolecular ene reaction for the preparation of a particular stereoisomer of a cyclopentane derivative.

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