Research Paper Medical Science

Substituent Effect on Cyclohexane Ring: A Theoretical Study

Dr. Nityagopal Mondal | Assistant Professor of Chemistry Siliguri B.Ed. College

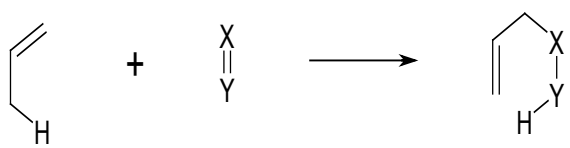
KEYWORDS

Introduction:
Normally cyclohexane molecules remain in chair conformation. Thermodynamic calculations have shown that at 25°C only one molecule in a thousand will be in boat form. Besides the chair and boat conformation a cyclohexane molecules assumes twist Boat conformation (Fig.-1).



1. **Equatorial bonds (those pointing sideways, denoted by 'e' [blue]**
2. **Axial bonds (those pointing up or down, denoted by 'a' [red]**

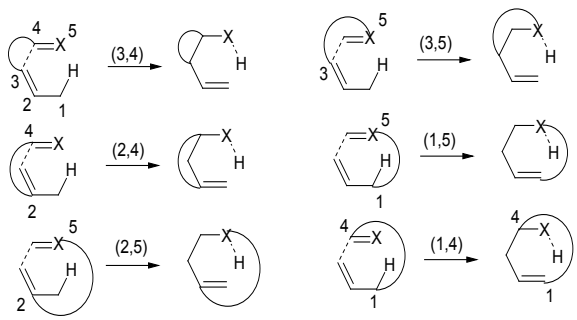
Ene reactions



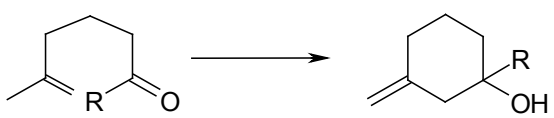
ene enophile

ene : alkene, alkyne, allene, arene
X=Y : C=C, C=O, C=N, C=S, O=O, N=N.

Scheme-1
Classification of ene reaction



Scheme-2
Substituent effect in Type-II or (2, 4) ene cyclization



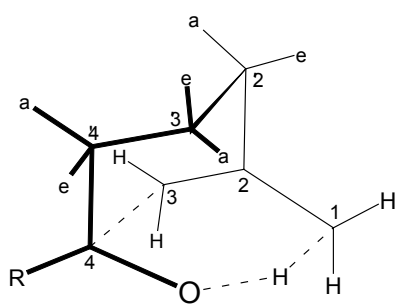
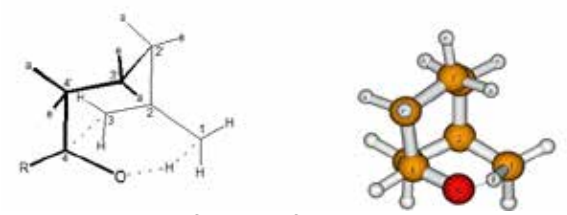


Fig.2.

TS of (2, 4) ene cyclization
The general form of the transition structure is shown in Fig.2. The numbering scheme of the atoms, involved in the reaction center, follows the notation of Mikami and Shimizu[118]. The connecting carbon atoms of the ene and enophile moiety at 2 and 4 positions are designated by 2', 3' and 4'. The axial and equatorial orientation of bonds in the forming cyclohexane ring are indicated by 'a' and 'e' respectively.

Substituted TSs have been constructed by placing methyl or methoxy group at 2', 3' or 4' position in axial or equatorial orientation on the cyclic transition structure (Fig.3)

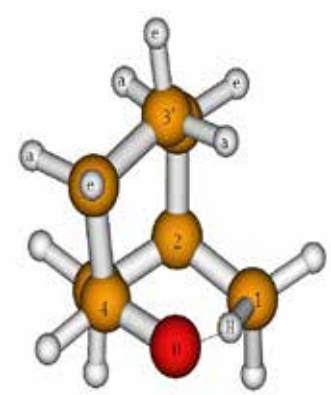


Skeletal diagram of the TS of Type-II ene cyclisation. The forming ring is in chair conformation. (b) Ball and stick model of the TS (R=H), viewed along the forming 4C-3C bond.

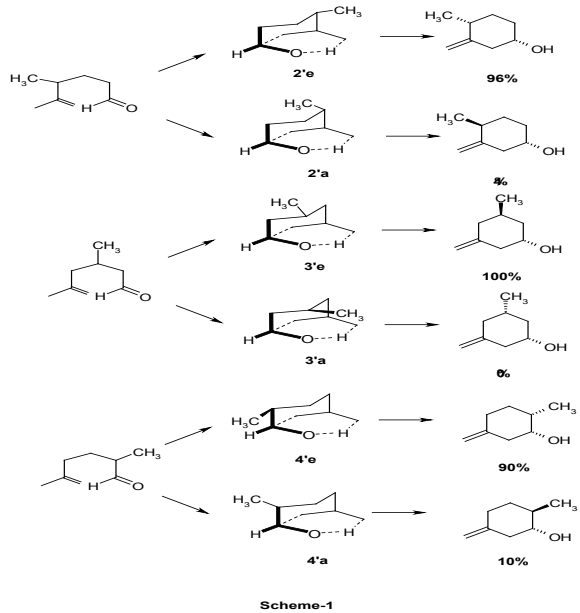
Among various possible conformers, originated from methoxy substituent, we have considered the TSs of lowest energy for our analysis. Relative energies of all these structures are gathered in Table -1

Nature of carbonyl enophile in TS	*Orientation of the substituent (axial /equatorial)*	*Methyl (CH_3) substituent at*			*Methoxy (OCH_3) substituent at*		
		2'	*3'*	*4'*	*2'*	*3'*	*4'*
Aldehyde (R=H)	a	1.16[a] (1.26)[b] **1.18[c] (1.28)[d]**	3.31 (2.80) **3.31 (2.81)**	2.27 (2.03) **2.19 (1.90)**	0.06 (0.11) **0.00 (0.07) -sc[e]**	2.38 (1.91) **2.48 (2.02) -sc**	0.00 (0.00) **0.00 (0.00) ±ap**
	e	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.04 (0.00) +sc**	0.00 (0.00) **0.00 (0.00) +sc**	5.23 (3.87) **5.17 (3.85) +sc**
Ketone (R=CH_3)	a	1.15 (1.24) **1.18 (1.25)**	3.46 (3.17) **3.47 (3.12)**	2.88 (2.61) **2.85 (2.49)**	0.08 (0.04) **0.00 (0.02) -sc**	2.53 (1.67) **2.66 (1.74) -sc**	0.00 (0.00) **0.00 (0.00) ±ap**
	e	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.00 (0.00)**	0.00 (0.00) **0.02 (0.00) +sc**	0.00 (0.00) **0.00 (0.00) +sc**	4.47 (2.95) **4.35 (2.91) +sc**

[a]HF/6-31G*
[b]B3LYP/6-31G*//HF/6-31G*
[c]HF/6-31G**
[d]B3LYP/6-31G**//HF/6-31G**



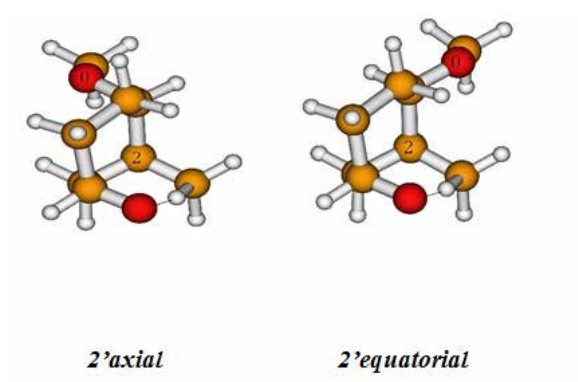
It is evident that for aldehyde and ketone enophile, the axial isomers of methyl substituted TS show a higher relative energy than the corresponding equatorial one. Reported experimental observations summarized in Scheme-3, also shows that the major diastereomeric products are generated from equatorially substituted TS. This means that the alkyl (methyl) substituent always prefers the equatorial position rather than the axial one.



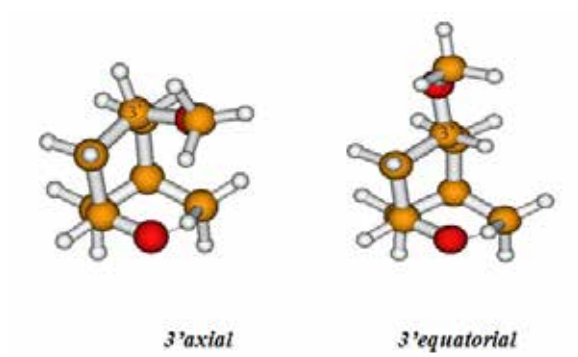
Scheme-1

I. Johnston, J,a. Kwass, R.B.Beal, b.B. Snider, J.Org.Chem. 52 (1987) 5419

Methoxy substituted TS



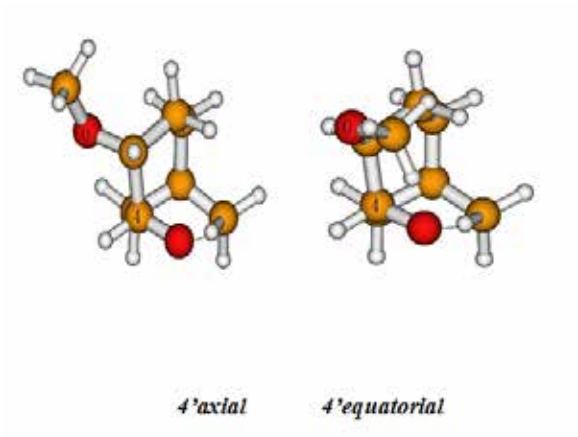
Methoxy substituted TS



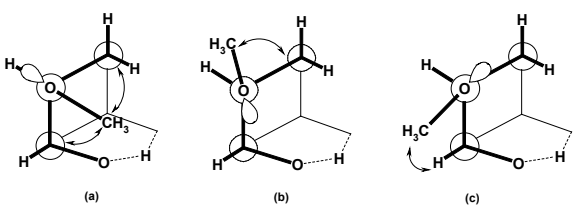
However the stability order of the axial/equatorial isomers of methoxy derivatives, as shown in Table-1, depends on the location of the substituent on the connecting carbon chain. At 3' position it favours the equatorial direction, however, when placed at 4' position, the same group prefers to orient axially. At 2' position both axial and equatorial orientations are equally favourable as both of them show almost the same energy.

The model structures of TSs with methoxy substituent in favourable orientation for aldehydic enophile are shown in Fig.4.

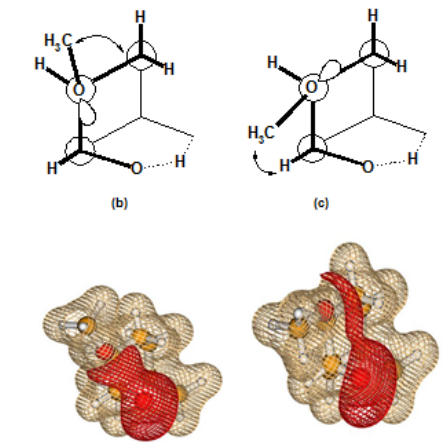
Methoxy substituted TS



A close observation to the conformation of TS also shows that the methoxy group at 4′ position in equatorial isomer adopts a +sc conformation in its stable orientation (Fig.). This conformer suffers from two butane gauche interactions (Fig.), which appears to make it sterically congested than the other two possible conformers in ±ap and –sc orientations (b & c in Fig.5).



Newman projection along O (methoxy)-C (cyclohexane) bond of the TS with 4′-methoxy substituent in equatorial position. Conformer (b) and (c) suffer from one butane-gauche interaction whereas conformer (a) suffers from two such interactions. However the latter two conformers suffer from a strong electrostatic interaction due to the unfavourable orientation of the oxygen lone pair with respect to the lone pair of the carbonyl oxygen of enophile and this fact is quite evident from the isosurface plot of electrostatic potential for these conformers, as shown in Fig.6



(a) Two equatorial conformers of TS with methoxy substituent at 4′-position. These structures are sterically favourable over the +sc conformer (Fig.), however energetically unfavourable due to lone-pair lone-pair interaction. (b) Isosurface plot of electrostatic potential. The red surface indicates the negative electrostatic potential originated due to the lone pair around the two oxygen atom.

Conclusions

- The above discussion for the substituent arrangement on the forming cyclohexane ring in a ene reaction reveals that not all substituents behave in a similar way. Oxygenated substituent (e.g. methoxy group) prefers to occupy axial orientation when placed at 4′ position. The favorable orientation of the substituents in TS determines the overall stereochemistry of the reaction.
- It is my believe that the above information will provide some useful guideline to an experimental chemist to determine the stable transition structure for a sunstituted ene cyclization.

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