SHORT PAPER

J. Chem. Research (S), 2003, 588-590

Study on first reported (2,5) ene cyclisation: does it really follow a concerted pathway?†

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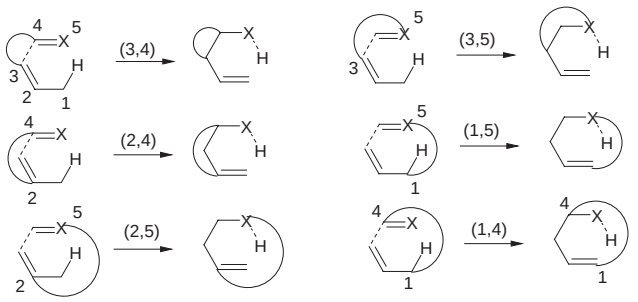
Theoretical calculation reveals that the reported (2,5) ene cyclization reaction follows a stepwise pathway, which results in a thermodynamically less stable compound through intramolecular proton abstraction; the presence of an external molecule, capable of abstracting a proton, directs the reaction to form thermodynamically more stable compound as a major product.

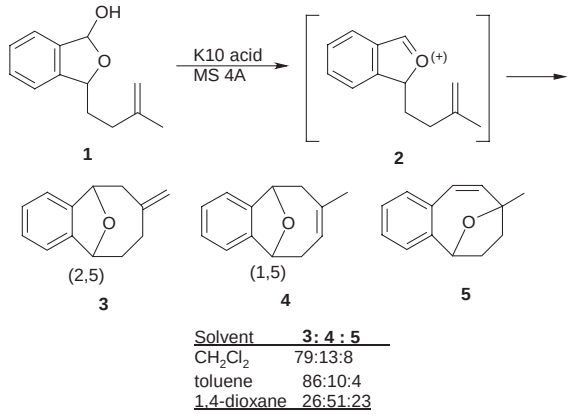
Keywords: (2,5) ene reaction, *ab initio*, semiempirical

The intramolecular ene reaction, a useful tool in synthetic organic chemistry, may be classified in six different categories (Scheme 1)[1,2] depending on the binding site of the tether to the atoms of the basic reactants.



Scheme 1

Among these categories, the first (2,5) ene cyclisation, which involves the oxonium ion as the enophile component (**2,** Scheme 2) was reported by Ohmura *et al.*[3]



Solvent	3 : 4 : 5
CH_2Cl_2	79:13:8
toluene	86:10:4
1,4-dioxane	26:51:23

Scheme 2

They showed that lactol **1**, when treated with montmorillonite K10 (a solid heterogeneous acid catalyst) in toluene at room temperature in the presence of molecular sieves 4A (MS4A), affords the (2,5) ene product **3**, along with the 1,5 ene type product **4** and the isomerised product **5**. It was also observed that the selectivity for (2,5) ene cyclisation depends critically on the solvent. Use of dichloromethane or toluene as the solvent shows a high selectivity for the (2,5) ene product (Scheme 2). However, the selectivity is decreased to give mainly the (1,5) ene product **4**, in 1,4-dioxane solution. It was also found that the catalytic activity of K10 is sensitive to its water content. Very low water content gives a poor yield. This clearly shows that its acid sites are derived from the water molecules coordinated to the cations on the framework of the clay[4]. Dependence of the catalytic activity of K10 on water content clearly reveals that the catalyst and MS4A sieves act on the reactant **1** to generate the oxonium ion, **2**. The process of cyclisation occurs spontaneously to generate **3, 4** and **5**. PM3 calculations show that the presence of a terminal double bond in **3** makes it a less stable product than the other two. However, formation of this product, in major amount, led the authors to suggest a concerted pathway among various ones for this reaction (Scheme 3). However, the stability of a major product cannot always be a true indicator of the nature of the pathway (whether concerted or stepwise). Moreover the concerted pathway of this reaction cannot explain the decrease in the formation of the product **3** due to the use of dioxane as a reaction medium (Scheme 2). For proper understanding of the pathway of this reaction, it is necessary to investigate the favorable transition structures of this reaction, selecting one on the basis of its energy requirement. Literature shows a number of theoretical studies on the ene reaction[5]. Among these, the (3,4) intramolecular ene process is well documented. This report deals with theoretical investigation on the pathway of the reported (2,5) intramolecular ene reaction.

Computational methods

All structures were optimised at the restricted Hartree-Fock (RHF) level using 3-21G* basis set of *ab initio*[6] calculation and single point energy was calculated at RHF/631G* and B3LYP/631G* level. GAMESS software was used for these calculations. AM1 and PM3 semiempirical[7,8] methods were also used to calculate the energies. All gas phase transition structures (TSs) were characterised by frequency analysis. The reactants and products were tested by IRC calculation. The bond lengths, shown in various figures, are of the optimised geometries obtained by *ab initio* calculations.

Results and discussion

We followed the reaction by searching the transition structures of both concerted and stepwise paths as shown in Scheme 3.

All our attempts for searching a transition structure (TS) for a concerted reaction, in which transfer of hydrogen to the oxonium ion and C–C bond formation occurs simultaneously, failed. Such failure, to obtain a TS, reveals that most probably the reaction does not follow this pathway. In the stepwise pathway the first step involves C–C bond formation (Scheme 3). For this step our search results in two TSs (TS1a and TS1b in Fig.1).

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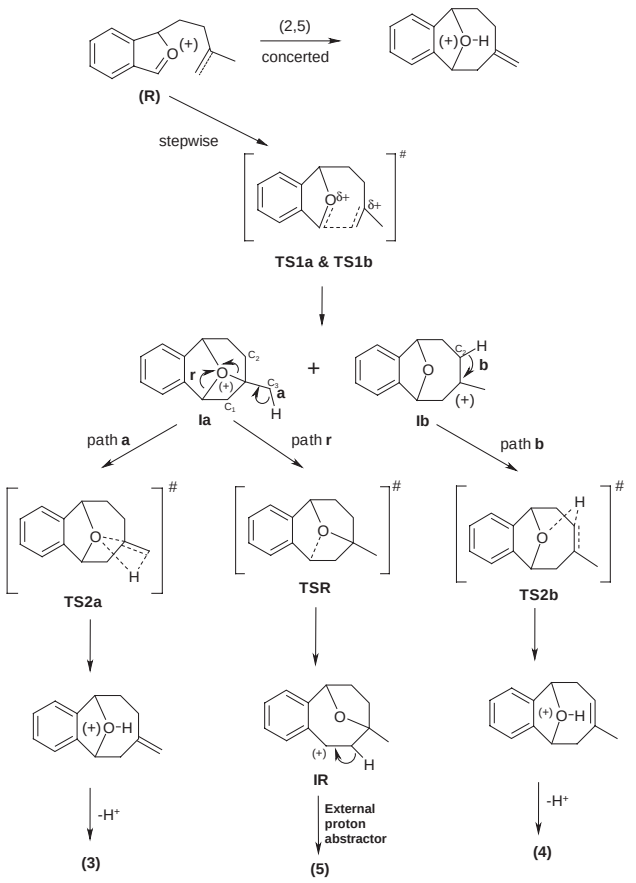
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 3

The conformation of TS1a, where methyl group (C_3) and phenyl ring are opposite to each other around the forming ring, is similar to a boat conformation. However, the TS1b, which is similar to a chair-like conformation, shows these two groups facing at the same side of the forming ring. In TS1a, the methyl group and oxygen are very close to each other, while they are far apart in TS1b. The relative energies, of all the transition states, calculated using various standard basis sets, are shown in Table 1. The higher energy of TS1b, indicates that TS1a is more favourable than TS1b. This higher energy of TS1b may be due to the steric hindrance between the methyl and phenyl group, positioned at the same side of the forming ring.

IRC calculation, followed by optimisation, shows that an oxetane like intermediate **Ia** is formed from TS**1a**, whereas TS**1b** generates a carbocation intermediate **Ib** (Scheme 3 and Fig.2). It should be mentioned here that semiempirical methods generate an alternative form of carbocation instead of **Ia** as a stable intermediate. However, in another report of amine catalysed aldol condensation in an ene type process, Bahmanyar and Houk[10], show the formation of an oxetane intermediate and on the basis of this report we rely on the results obtained by *ab initio* calculation.

Formation of any product **(3, 4** or **5**) from these intermediates should pass through some proton elimination (and possibly an rearrangement process). Proper scrutiny of the structure of **Ia** (Fig.2) revealed that the methyl group (C_3) is in close proximity to the oxygen atom and this oxygen atom may serve to abstract a proton from the methyl group (path a in Scheme 3) giving a stable protonated double bonded cyclic molecule. By following this process the system may lead to the product **3**. With this view we searched path a (Scheme 3) and the proton transfer transition state TS2a (Fig.3) was

Table 1 Relative energies (kcal/mol) with respect to initial reactant for all the transition states and intermediates (Figs 1–4)

Species	RHF/3-21G*	RHF/6-31G*// RHF/3-21G*	B3LYP/6-31G*// RHF/3-21G*	AM1[7]	PM3[8]
TS for the first step of the reaction					
TS1a	6.96	16.84	9.68	9.52	11.34
TS1b	8.76	17.6	10.39	9.55	12.38
Intermediate after the first step					
Ia	-24.47	-4.96	-4.20	-2.14	1.47
Ib	0.48	9.94	12.15	-2.16	4.59
TS for the second step of the reaction					
TS2a	15.37	35.14	25.10	21.88	23.91
TSR	2.28	13.84	12.23	5.13	9.36
TS2b	55.03	77.77	56.25	47.26	50.71

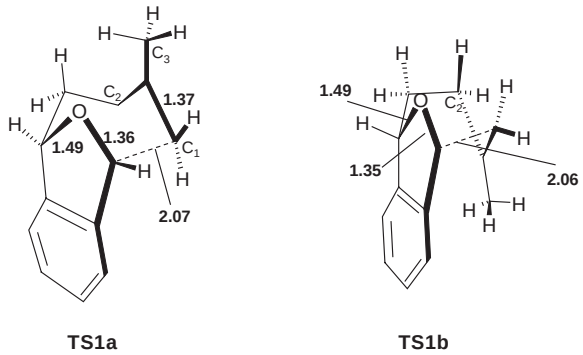


Fig. 1. Transition structures for the first step in stepwise pathway of reaction as shown in Scheme 3. Dotted lines show the forming bonds. Bond lengths are shown in Angstrom units.

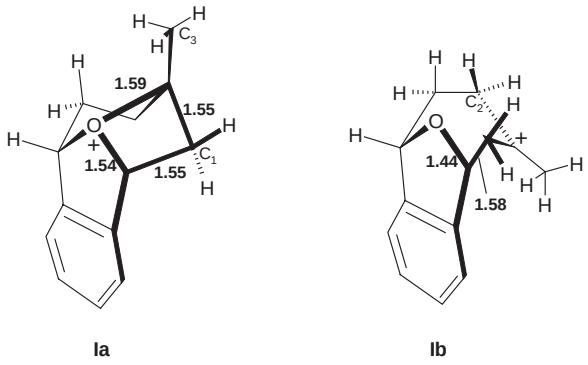


Fig. 2. Intermediate obtained after the first step of the reaction.

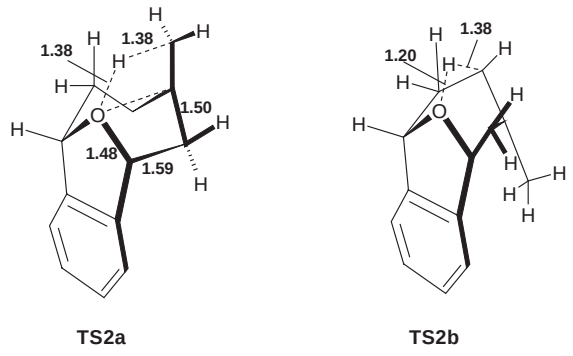


Fig. 3. Transition structures for the second step in stepwise pathway for intramolecular proton transfer. Dotted lines indicate the cleavage or formation of bonds.

found. The relative energies are shown in Table 1. We did not find other transition state, which can transfer other proton intramolecularly, to generate a different product from **Ia**.

In another pathway **Ia** may result in the rearranged product **5** by the cleavage of C–O bond. We have shown it as path r in Scheme 3. Our search resulted in transition state TSR and intermediate IR corresponding to this cleavage step (Fig.4).

The intermediate IR, formed from the TSR, can be stabilised by the elimination of a proton (Scheme 3). Scrutiny of the structure IR (Fig.4) reveals that the hydrogens of methylene group (C_1), next to carbocation centre, are not suitably oriented for intramolecular transfer to internal oxygen. So product **5** must have to be formed by the assistance of some external proton abstractor. This indicates that absence of any suitable proton abstractor in the environment directs the reaction to follow path a from intermediate **Ia** which results the precursor of **3** by internal abstraction of proton (Scheme 3).

We examined the intermediate **Ib** (Scheme 3 and Fig.2) in a similar way for intramolecular proton transfer reaction and it was revealed that the spatial arrangement of hydrogen attached to the C_2 methylene group is suitable for intramolecular proton transfer to oxygen (path b in Scheme 3) and this process leads to the product **4**. The transition state corresponding to this pathway was characterised and is shown here as TS-2b (Fig.3). Relative energies, as shown in Table 1, indicate that a higher energy is required to generate this transition state than that needed for TS2a from intermediate Ia (path a) in the overall reaction. This suggests that so long as we consider the intramolecular proton abstraction process, 'path a' is more energetically favourable than 'path b'. Quantitative estimation using Boltzmann distribution revealed that at the reaction temperature the intramolecular proton transfer by 'path a' is almost 100% favourable. Hence it suggests that in dichloromethane or toluene medium (non oxygenated medium), where intramolecular proton transfer is the only possible pathway for proton abstraction reaction, path a is favourable and compound **3** is the only expected product. If an external molecule, capable of abstracting a proton, is present, like 1,4-dioxane, the reaction may furnish the highly substituted product **4** or the rearranged product **5** by the pathway as shown in Fig. 5.

This conclusion is in good agreement to the reported observation as summarised in Scheme 2. The formation of **4** and **5** in small proportion in dichloromethane or toluene is probably due to the participation of the oxygen atom as a proton abstractor, present in the product ether or water bound catalyst. The involvement of an external proton-abstracting molecule in the formation of **4** and **5** can also be supported by the fact that in all conditions the percentage of **4** to **5** is almost constant (~2:1). The favourable formation of **4** among these two is probably due to the facile access of the external proton abstractor to the proton of C_2 with less steric effect.

The authors thank UGC, New Delhi, India, for providing financial assistance for the research work.

Received 18 December 2002; accepted 16 May 2003
Paper 02/1690

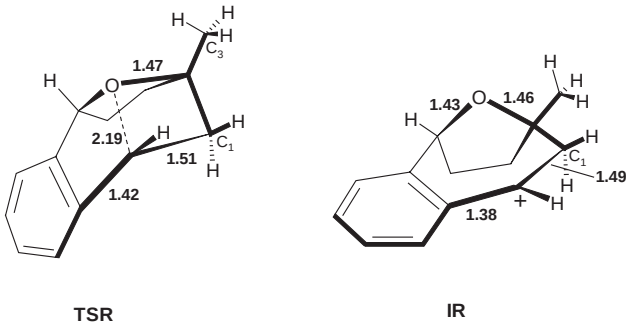


Fig. 4. Transition structure and intermediate for path r (Scheme 3).

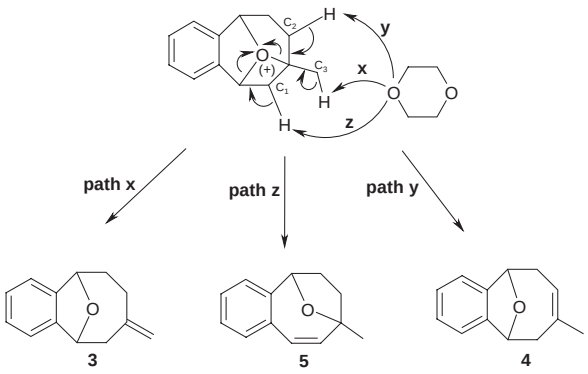


Fig. 5. Presence of proton abstracting solvent favours intermolecular proton transfer.

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