The mechanism of rearrangement process in styrene based iodohydrin via deiodination pathway

Abul Kalam Biswas*

Department of Chemistry, Mahishadal Raj College, West Bengal, India-721628

*Email: amikalamfeb@gmail.com

Abstract: *Deiodination of styrene based vicinal iodohydrins with the hypobromous acid derived from acid activated bromate/bromide couple and simultaneous 1,2 migration of a phenyl group or hydrogen atom has been reported. The semipinacol rearrangements observed with styrene based vicinal iodohydrins are however dependent on the substrates examined. DFT study has been performed to investigate the semipinacol rearrangement processes of styrene based vicinal iodohydrins. The preference for the phenyl migration in 2-iodo-1-phenylethanol (1a) and in other substrates 2a was predicted with B3LYP/6-31G* level of theory in both ground state and transition state calculations. The dramatic difference in the preference of migration of hydrogen atom of 3a was predicted with DFT calculations in agreement with the observed results. It is to note that the (RS) configuration of 3a showed the hydrogen migration is preferred over the phenyl migration. The preference of hydrogen migration over phenyl migration in this case is due to the intramolecular hydrogen bonding interaction between the hydroxyl group and the carbonyl oxygen of the ester moiety. However, the (RR) configuration of 3a showed the phenyl migration as observed with substrates 1a-2a. The DFT calculations shed the light on the importance of the configuration of substrates to achieve the desired products in such cases.*

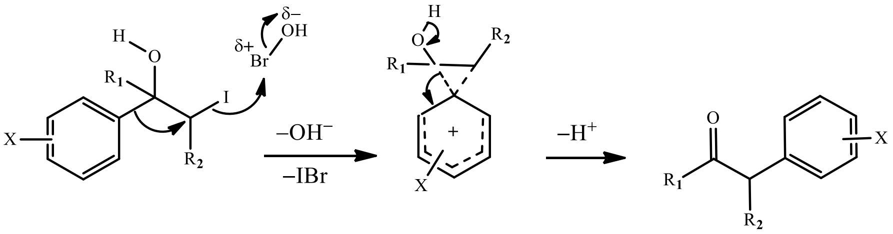
Keywords: *semipinacol rearrangement; iodohydrin; DFT calculations; migratory aptitude*

1. Introduction:

The pinacol-pinacolone rearrangement is an important acid catalyzed process in organic synthesis.[1] It is used for the preparation of aldehydes or ketones from the rearrangement of vicinal-diols. This rearrangement process involves the formation of carbocations.[1] The structure, stability of such carbocations is important for the formation of rearranged products.[2] The formation of carbocation in the rearrangement process can compete with the migratory aptitudes of the groups. In general, it is found that the migratory aptitude is in the order Ph > Me_3C > $MeCH_2$ > Me > H. However, in the rearrangement of the compound 2-methyl-1,1-diphenylpropanediol [$Ph_2C(OH)C(OH)Me_2$], the less prior migratory aptitude methyl group migrates compared to the phenyl group, because the reaction is governed by the formation of more stable initial carbocation.[3] The disadvantages of this rearrangement process are the excess of Lewis acids required for the completion of the reaction,[4] poor regio- and dia-stereoselectivity and unpredictable side reactions.[5] To overcome such drawbacks of pinacol-pinacolone rearrangement, analogous semipinacol rearrangements have been reported.[6] In 1923, the first semipinacol rearrangement was reported by Tiffeneau[7] in which the desired carbocations can be formed.

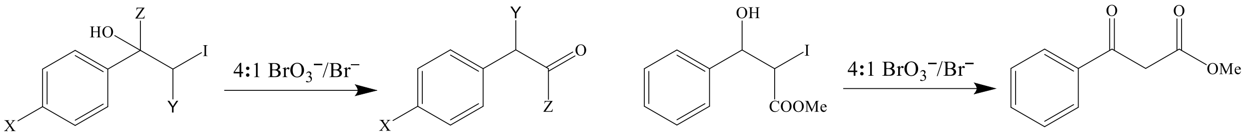
All types of reported semipinacol rearrangements are closely associated with pinacol-pinacolone rearrangement process.[8] Most of them proceeds through the formation of a carbocation and 1,2-migration of a C-C or C-H bond yields a carbonyl compound.[9] The most important advantage of semipinacol rearrangement is that a number of methods and reagent other than 1,2-diols can be used to produce the carbocations. Moreover, the reactions can be carried out in acidic, basic and neutral conditions depending on the nature of the substrate.[9] Recently, Agrawal and Ghosh reported the bromate/bromide couple at 0-10°C with acid activation for the deiodination of styrene-based vicinal iodohydrins.[10] A series of styrene-based vicinal iodohydrins was studied, which yields the corresponding carbonyl compounds. The plausible pathway to deiodinate the styrene-based vicinal iodohydrins with the hypobromous acid (HOBr) derived from bromate/bromide couple is shown in the Scheme 1.[10]

Scheme 1. Deiodination of iodohydrins with the hypobromous acid derived from acid activated bromate/bromide couple process.



The rearranged carbonyl products in these reactions generally show that the higher migratory aptitude of the phenyl group prefers to migrate than that of the hydrogen atom. However, in entry **3a**, the least migratory aptitude group prefers to migrate to yield the keto ester compound.[10] In the present article, we have investigated the rearrangement products of these reactions computationally. Density functional calculations (DFT) at B3LYP/6-31G* level was employed to determine the transition state and ground state geometries in each case. The computational study revealed the change in the migratory aptitude of the groups in specific cases (Scheme 2).

Scheme 2



1a X=H, Y=H, Z=H
2a X=Me, Y=H, Z=H

1b X=H, Y=H, Z=H
2b X=Me, Y=H, Z=H

3a

3b

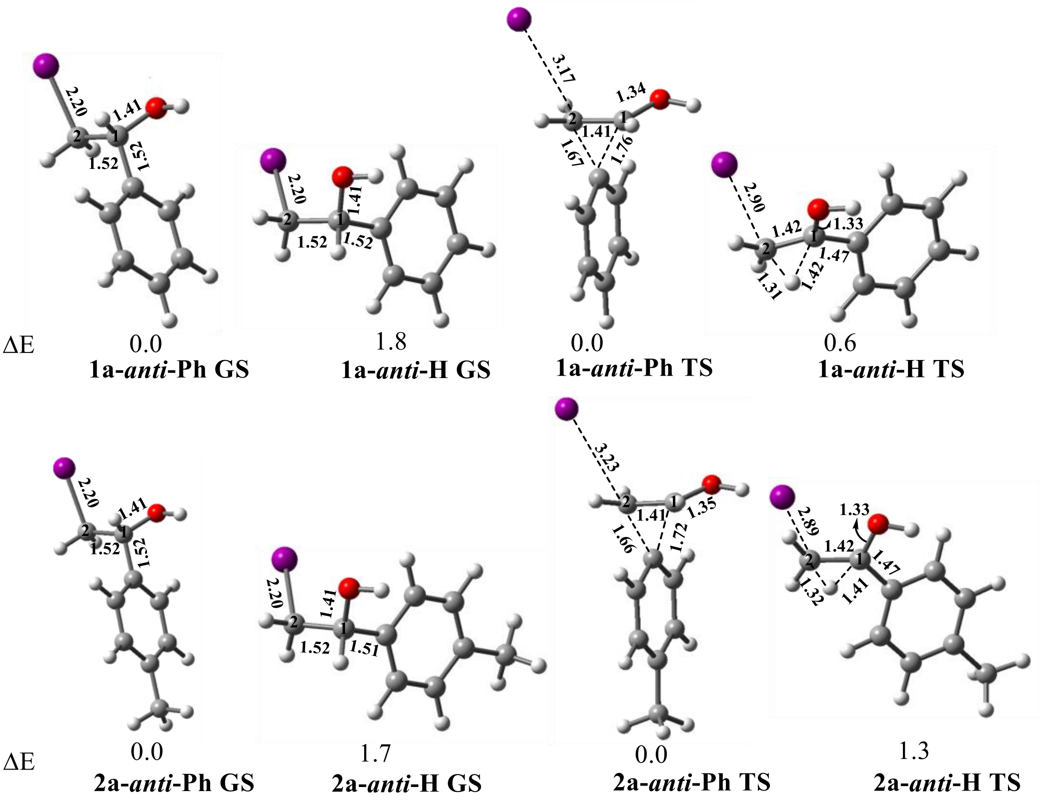
2. Computational Methods:

All calculations were performed with density functional theory (DFT) using Becke's three-parameter exchange functional with the correlation functional of Lee, Yang, and Parr (B3LYP).[11,12] The geometries were fully optimized using 6-31G* basis set[13] for hydrogen, carbon, oxygen, chlorine, bromine and DGDZVP basis set employed for iodine by using The ORCA 3.0.3.

3. Results and Discussions:

In semipinacol rearrangement, the heterosubstituted alcohols form the carbonyl compounds in acidic or basic conditions. The leaving groups varies from halogen atoms (Cl, Br, I), to tosylate, or a thioxy group attached with the electrophilic carbon center.[9] The 1,2 migration of the alkyl, aryl or hydrogen group occurs with the loss of the leaving group in this rearrangement process. Generally, the migratory aptitude of the groups determines the rearranged products.

Recently the semipinacol rearrangement of styrene-based vicinal iodohydrin was examined experimentally.[10] In this rearrangement process, abstraction of the leaving group I^- with the hypobromous acid, yields the IBr[10,14] and 1,2 migration of phenyl group takes place as shown in Scheme 2. We have not considered the interaction of the leaving group with HOBr in our computational study. Presumably, such approximation would not influence the results on the semipinacol rearrangement in these studied systems. We have initially considered the different possible configurations of the parent molecules (Scheme 3). The lowest energy conformation of the parent molecules are calculated with B3LYP/6-31G* level of theory. **1a** and **2a** possess only one chiral center, whereas two chiral centers are present in **3a**, respectively (Scheme 3). The ground state energy calculations of entry **1a** showed that the phenyl group antiperiplanar to iodine atom (**1a**-*anti*-Ph GS) is 1.8 kcal/mol more stable than the corresponding H atom antiperiplanar to I atom (**1a**-*anti*-H GS) (Figure 1). The phenyl group susbtitued with the methyl group at *para* position **2a** (**2a**-*anti*-Ph GS) also showed the similar trend in the ground state stability of configurational isomers as observed with **1a** (**1a**-*anti*-Ph GS) (Figure 1).



ΔE 0.0 1.8 0.0 0.6

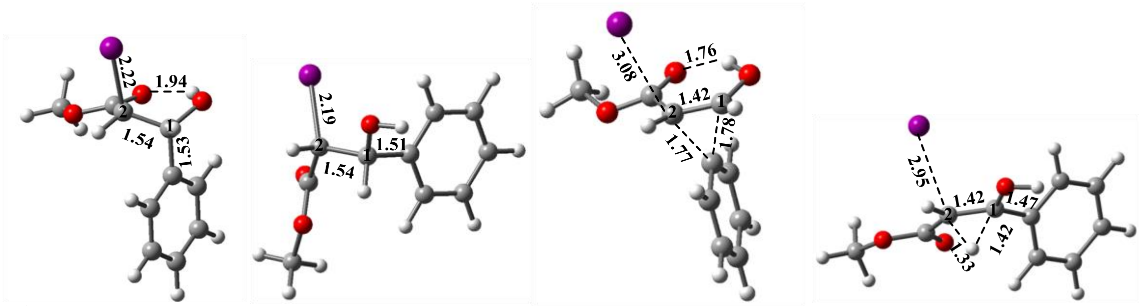
1a-*anti*-Ph GS **1a-*anti*-H GS** **1a-*anti*-Ph TS** **1a-*anti*-H TS**

ΔE 0.0 1.7 0.0 1.3

2a-*anti*-Ph GS **2a-*anti*-H GS** **2a-*anti*-Ph TS** **2a-*anti*-H TS**

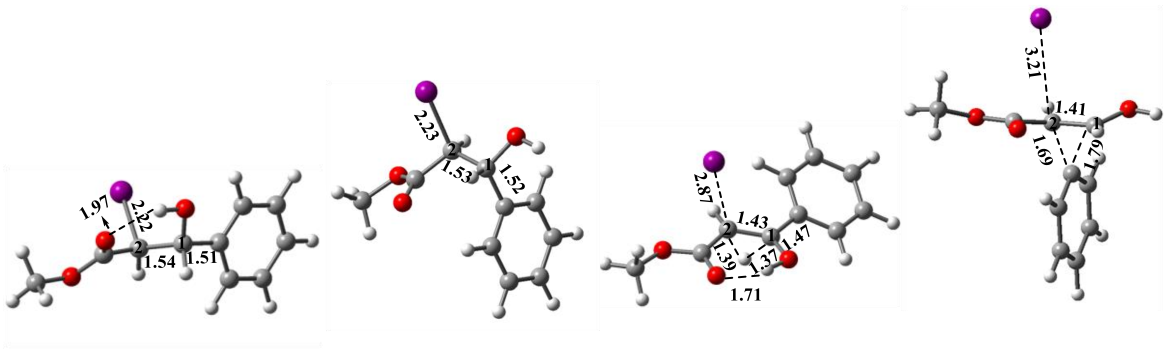
Figure 1. The optimized ground state, transition state geometries and relative energies (ΔE) are shown for systems **1a** & **2a**. [Gray = carbon; Red = oxygen; White = hydrogen; Purple = iodine]

Going from ground state calculations to the transition state calculations, the leaving group I^- moves away from the substrate molecule (**1a**-*anti*-Ph TS) and the phenyl group simultaneously undergoes 1,2 migration (Figure 1). In this transition state structure, the migratory phenyl group provides the anchimeric assistance to the leaving iodide ion.[15] The formation of a carbocation intermediate was not observed on the potential energy surface of this reaction and hence the migration of the phenyl group is concerted with the departure of the leaving group.



ΔE 0.0] 7.4 0.0 12.9

3a-*RR*-*anti*-Ph GS **3a-*RR*-*anti*-H GS** **3a-*RR*-*anti*-Ph TS** **3a-*RR*-*anti*-H TS**



ΔE 0.0 2.2 0.0 10.8

3a-*RS*-*anti*-H GS **3a-*RS*-*anti*-Ph GS** **3a-*RS*-*anti*-H TS** **3a-*RS*-*anti*-Ph TS**

Figure 2. The optimized ground state, transition state geometries and relative energies (ΔE) are shown for systems 3**a**. [Gray = carbon; Red = oxygen; White = hydrogen; Purple = iodine]

In the transition state of **1a**, the phenyl group antiperiplanar to the leaving I^- (**1a**-*anti*-Ph TS) is 0.6 kcal/mol more stable than the corresponding transition state, where the hydrogen atom is antiperiplanar to the leaving I^- (**1a**-*anti*-H TS) (Figure 1). In the transition state of **1a** (**1a**-*anti*-Ph TS), the bond distance of the C-I bond is 3.17 Å which is much longer than the C-I bond distance in the corresponding ground state geometry 2.20 Å (**1a**-*anti*-Ph GS) (Figure 1). The migration of the phenyl group in the transition state is slightly asymmetrical in nature as the distance obtained for Ph-C_1 and Ph-C_2 is 1.76 Å and 1.67 Å, respectively (Figure 1). The formation of carbocation during the migration of the phenyl group is stabilized by the resonance effect. The resonance effect is observed with the shortening of O-C_1 and C_1-C_2 bond lengths in the transition state of **1a**-*anti*-Ph TS compared to the corresponding ground state structure (**1a**-*anti*-Ph GS) (Figure 1). This phenomenon is also observed in the transition state structure of hydrogen atom antiperiplanar to the leaving I^- (**1a**-*anti*-H TS) (Figure 1). Further, the additional stabilization might also come from the π-donating ability of the phenyl group to stabilize the formation of carbocation in the transition state (**1a**-*anti*-Ph TS), which is absent in the case of **1a**-*anti*-H TS. The reactant **2a** also showed that the phenyl group antiperiplanar to the leaving I^- (**2a**-*anti*-Ph TS) is 1.3 kcal/mol more stable than the corresponding H atom antiperiplanar to I^- (**2a**-*anti*-H TS) in the transition state calculations, which corroborates the experimental results (Figure 1).[10]

Turning to the substrate molecules with 2 chiral centers **3a**, the ground state and transition state structures have been calculated with B3LYP/6-31G* level of theory. These molecules can yield two different products depending upon the configurations they possess. The intramolecular hydrogen bonding interaction was also observed for **3a** (*RS*) configuration (Figure 2). Because of the presence of strong intramolecular hydrogen bonding in the ground state, the hydrogen atom antiperiplanar to the leaving iodine atom (**3a**-*RS*-*anti*-H GS) was 2.2 kcal/mol more stable than the phenyl group antiperiplanar to the leaving iodine atom (**3a**-*RS*-*anti*-Ph GS). This effect was prevalent in the transition state calculations, where the antiperiplanar hydrogen atom (**3a**-*RS*-*anti*-H TS) was found to be 10.8 kcal/mol stable than phenyl group antiperiplanar to the leaving I^- (**3a**-*RS*-*anti*-Ph TS) (Figure 2). Hence, the observed product should be a keto ester (**3b**) rather than an aldehyde, which is corroborated by the experimental results (Scheme 3). The **3a** (*RR*) configuration showed the preference for the migration of the phenyl group than the hydrogen atom as observed in other cases (**1a**-**2a)**. Therefore, it appears that the experiments were carried out with the (*RS*) configuration of **3a**.[10]

4. Conclusion:

We have computationally examined an interesting reaction involving halonium ion-assisted deiodination of styrene based iodohydrins with semipinacol rearrangement processes. 2-iodo-1-phenylethanol (**1a**) undergoes the rearrangement process with the migration of the phenyl group and forms phenyl acetaldehyde (**1b**). Our ground state and transition state calculations support the migration of the Ph group over the hydrogen atom in this case. The computed transition state energy difference was found to be 0.6 kcal/mol in favor of phenyl migration to form phenyl acetaldehyde (**1b**). Iodohydrin of **2a** also showed that the phenyl migration is preferred over the hydrogen and methyl migration respectively, which supports the experimental observations. Iodohydrin of methyl cinnamate (**3a**) has two chiral centers and can yield two different products depending upon the configurations it possess. The (*RS*) configuration of **3a** showed that the hydrogen migration is preferred over the phenyl migration in both the ground state and transition state calculations.

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