A DFT Study on Formation of Bisaryl Oxime Ether from Benzaldehyde and Phenoxyamine

Guilei Wang, Yue Chen, Aiguo Zhong, Hongguang Du, and Ming Lei*
Institute of Materia Medica, School of Science, Beijing University of Chemical Technology, Beijing, 100029, P. R. China

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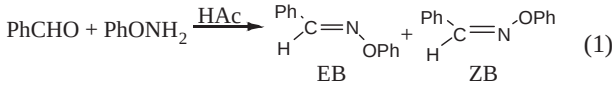
A theoretical study on the formation mechanism of bisaryl oxime ether from benzaldehyde and phenoxyamine at the B3LYP/6-31++G** level indicates that the water-assisted acid-catalyzed mechanism is more favorable than that in neutral conditions. Intermolecular interactions between monomers of E and Z producing stereoisomers are predicted to play an important role in their stabilities.

Oxime ethers are important compounds due to their potential application in bioorganic and medicinal chemistry.[1] Recently, bisaryl oxime ethers have been reported as active inhibitors preventing tranthyretin from forming amyloid fibrils.[2,3] Benzaldehyde *O*-phenyloxime is the smallest form among bisaryl oxime ethers, which are prepared by the reaction between aryloxyamine and arylaldehyde in acetic acid solution as shown in eq 1. Two-stereoisomer forms about the imine linkage are possible in theory, but in reality only the EB (E isomer) has been detected in experiments. Such a phenomenon was also confirmed by NMR and UV studies reported by S. Johnson et al. and G. Karabatsos et al.[4–6]



(1)

Different conformations of oxime ethers may show different biological activities.[7,8] The formation of hydrazone was investigated in detail to show that the E structure is slightly more energetically favorable than the Z isomer.[8] Because the structure of oxime is similar to that of hydrazone, this work will discuss the stability difference between EB and ZB conformers from a mechanistic viewpoint.

All of calculations were performed at the B3LYP/6-31++G** level of theory with Gaussian 03 software.[9,10] The transition states (TSs) were confirmed by only one imaginary frequency.

Figure 1A is a neutral mechanism without acid (path 1) and Figure 1B shows direct and water-assisted mechanisms of acid-catalyzed bisaryloxime ether formation (path 2 and path 3). In path 1, phenoxyamine directly attacks the carbonyl group of benzaldehyde to produce the product passing an intermediate (INT) and two TSs (TS1 and TS2). The first step from R to INT is a hydrogen transfer (TS1) from N8 to the carbonyl oxygen atom linking with C7. INT produces the final product via dehydration (TS2) in the second step. In path 2, acetic acid interacts with the benzaldehyde oxygen atom at first, then the protonated benzaldehyde is attacked by the lone electron pair of phenoxyamine, and the protonated product is formed via an intermediate (INT1) and a TS (TSH) accompanied by the elimination of water. It is a downhill process in the first step from RH to INT1 where no transition state is found.

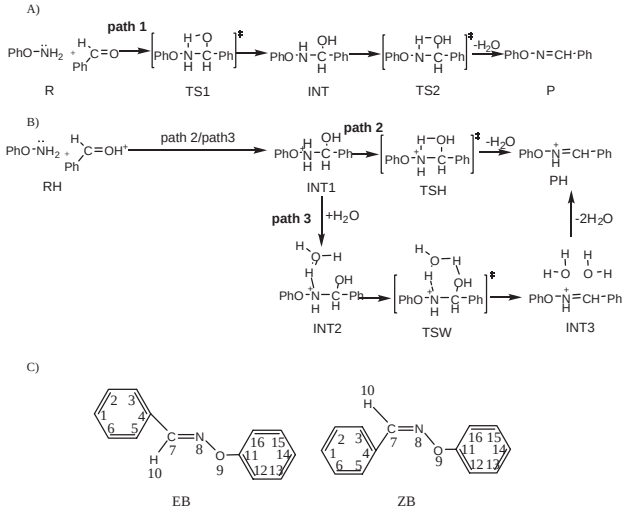


Figure 1. (A) The proposed neutral mechanism (path 1), direct acid-catalyzed mechanism (path 2), and water-assisted acid-catalyzed mechanism (path 3) for the formation of bisaryl oxime ether. (B) Atom numbering of EB and ZB.

As shown in Figure 2, in path 2, the barrier to form EB and ZB is 30.8 and 33.6 kcal/mol, respectively, whereas in path 1, the barrier is 43.2 and 45.3 kcal/mol, respectively. The barrier height of the former mechanism is found to be lower than that of the latter by 12.4 kcal/mol for EB formation and 11.6 kcal/mol for ZB formation, indicating that the acid-catalyzed mechanism is more favorable than the neutral mechanism. However, the barrier is still energetically too high. Here, another alternative path has been explored taking into account the role of water during hydrogen transfer and H_2O elimination. Such a path can be conceived to proceed via an mechanism which involves (1) formation of INT2 and (2) synchronous diproton transfer. The water-assisted mechanism is found as path 3 in Figure 1, where the O atom of water firstly forms a hydrogen bond (HBond) with the N–H bond of the intermediate INT1. The step of R $\rightarrow$ INT1 $\rightarrow$ INT2 is equivalent to the step from R to INT2 directly because INT2 could be formed via an interaction of protonated water (H_3O^+) with the benzaldehyde. The hydrogen of the N–H bond is then transferred to water, a hydrogen atom of water transferred to the O atom of the O–H bond simultaneously in the step from INT1 to INT2. The protonated products are reached via TSW accompanied by the elimination of two water molecules. In three pathways, the elimination of water is rate-determining step. In path 3, the barrier height is 14.7 kcal/mol for PH_{EB} and 15.5 kcal/mol for PH_{ZB}, respectively. Compared with paths 1 and 2, the barrier height is much lower, implying that the water-assisted acid-catalyzed mechanism is more favorable than the other two pathways.

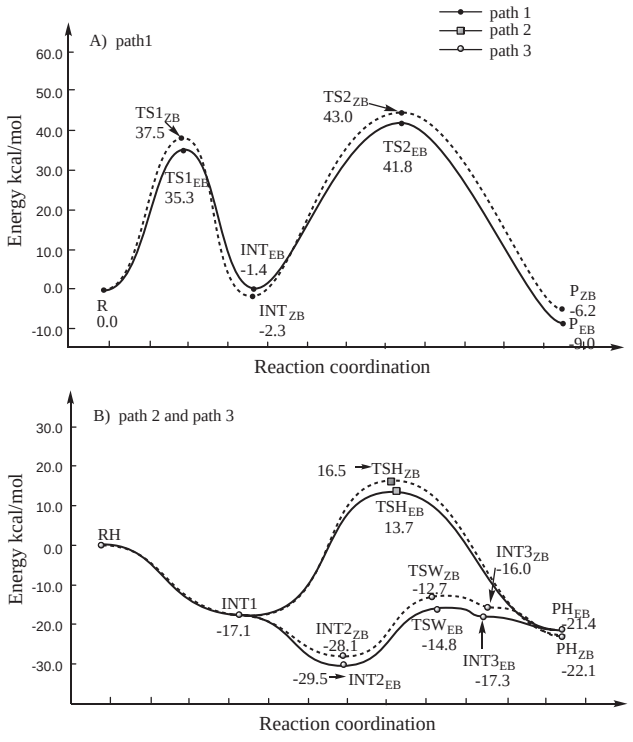


Figure 2. (A) Energy profiles of neutral mechanism (path 1). (B) Energy profiles of the direct acid-catalyzed mechanism (path 2) and the water-assisted acid-catalyzed mechanism (path 3). Solid lines represent those of E isomers, and dotted lines represent those of Z isomers. Energies include zero point energies (ZPEs).

In the three pathways without exception the formation barrier of EB is a little lower than that of ZB. The relatively lower barrier for the EB formation can be explained by their structure parameters. The atom labels of the product are given in Figure 1C and the structure parameters are given in supplemental Table S1.[14] The bond lengths of C_4–C_7, C_7–N_8, N_8–O_9, and O_9–C_{11} bonds of EB are almost equal to those of ZB. Both EB and ZB have C_s symmetry with phenyl and phenyloxyl in the plane. The C_7–N_8 bond length for EB and ZB is 1.283 and 1.288 Å, respectively, which is longer than that of a normal C=N bond (a normal bond length is 1.27 Å). This implies that there exists electron delocalization on π electrons. The C_4–C_7 bond for EB and ZB is 1.460 and 1.469 Å, and the O_9–C_{11} bond is 1.384 and 1.387 Å, respectively. They are shorter than normal C–C and C–O bonds (normal C–C and C–O bond lengths are 1.54 and 1.43 Å). This is due to the different conformation between phenyl and C_7–N_8 bond. Meanwhile, $\angle C_4C_7N_8$ and $\angle C_7N_8O_9$ of EB are different from those of ZB. $\angle C_4C_7N_8$ of ZB is drastically larger than that of EB by 13 degrees because of the steric repulsion between the phenyl group and the lone electron pair of the phenyloxyl oxygen.[11,12] The details of structural changes along the three pathways are shown in supplemental Figures S1–S3.[14]

Meanwhile, the barrier differences between PH_{EB} and PH_{ZB} are only 2.8 kcal/mol in path 2 and 0.8 kcal/mol in path 3 (see Figure 2B). Although it implies that the formation of the EB is easier than ZB, it is also not enough to elucidate that EB is the only stereoisomer from experiments. The possible reason accounting for only EB existing in experiments should be related to the π stacking between phenyl groups and hydrogen bonds between N atom and phenyloxyl oxygen atom. A dimer structure is proposed to be a basic unit in the crystal structure.[13]

In summary, the reaction mechanisms of phenoxyamine with benzaldehyde in the presence of acetic acid and in neutral conditions were studied using DFT method. The water-assisted acid-catalyzed mechanism is more favorable than the direct acid-catalyzed and neutral mechanism. These results are consistent with the experimental data in the condensed phase. The stability difference between EB and ZB might be not only related to the kinetic factors but also likely related to the stability of oligomers formed by corresponding monomers.

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14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

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