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Theoretical Study on Z/E Selectivity in the Oximation of α-Haloacetophenones

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A theoretical study on the selectivity in oximation reaction of α-haloacetophenones was carried out. The calculations were performed by molecular mechanics (MM+) and semiempirical (AM1 and PM3) methods. A conformational search considering the torsional angles was made using the HyperChem program and the lowest energy conformations of (Z)- and (E)-α-haloacetophenone oximes were subject to optimization by AM1 and PM3 methods. The (Z)-stereoisomers were found as the most stable structures by these different methods. Thus, the stereoselectivity, observed experimentally for (Z)-oxime formation in the oximation of α-haloacetophenones arises from the more stability of (Z)-stereoisomers. According to this data the (Z)-stereoisomer prefers the lower energy state when compared to (E)-stereoisomer, indicated that the (Z)-stereoisomer should be preferentially obtained from oximation of α-haloacetophenones, in good agreement with experimental results.

Key Words: α-Haloacetophenone oxime, (Z)- and (E)-Isomers, Selectivity, Theoretical calculations.

INTRODUCTION

Oximes are extensively used as preferred derivatives for purification and characterization of carbonyl compounds[1,2]. The highly stable and readily prepared oxime derivatives play an important role in synthetic organic chemistry as protecting group and selectively α-activating groups and for preparation of amides *via* Beckman rearrengement and synthesis of heterocycles[3-7].

α-Haloketoximes are good building blocks in organic synthesis[8-12]. Several methods are available for the preparation of α-haloketoximes and α-haloaldoximes. These include the reduction of nitro olefins with zinc chloride, the reaction of an olefins with nitrosyl chloride and the direct

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oximation of α-halocarbonyls[13]. However, the synthesis and stereochemistry of (E)- and (Z)-α-haloacetophenone oximes have been much studied[13-17]. 2-Bromoacetophenone oxime was recorded by Korten and Scholl[17] to obtained in the treatment of 2-bromoacetophenone with 3 equivalent of hydroxylamine hydrochloride in methanol. Some substituted 2-haloacetophenone oximes were prepared by reported procedure[18]. NMR-studies and X-ray crystallography reveals that in the oximation reaction of α-haloacetophenones (Fig. 1), the major products have (Z)-stereochemistry and N-O and C-CH_2 bonds are *syn*[14-16]. The oxime geometry play a crucial role in many chemical and biochemical processes and therefore, has also been the subject of interest in theoretical studies.

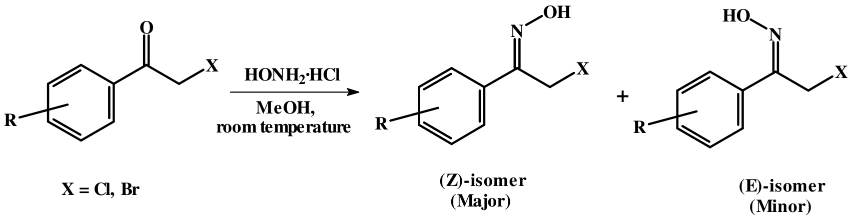


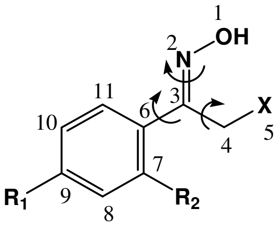
Fig. 1

In this paper, molecular modeling was used to characterize selectivity in the oximation of α-haloacetophenones and conformational properties of (Z)- and (E)-α-haloacetophenone oximes.

EXPERIMENTAL

Computational analysis: The calculations were performed by molecular mechanics (MM+) and semiempirical (AM1 and PM3) methods[19-22] using the HyperChem ver. 7 software package[23]. The selected compounds **1a-e** (Table-1) were built within HyperChem and bond angles and lengths were optimized with the Polak-Ribiere method. The flexibility of the moieties connecting to oxime group permit to assume many different conformatins. In all calculations the molecular conformations were determined by principal torsion angles $\tau_1(O_1\text{-}N_2\text{-}C_3\text{-}C_4)$ which define the position of the oxime moiety, τ_2 $(N_2\text{-}C_3\text{-}C_4\text{-}X_5)$ and τ_3 $(C_4\text{-}C_3\text{-}C_6\text{-}C_7)$ (Table-1). A general procedure of multiconformational search has been used only for MM procedure method. That consists in studying the energy variation according to the variation of the dihedral angle by rotational increments of 5°. Torsion angles were defined by clockwise rotation around the appropriate bonds and molecular geometries were obtained after the lowest molecular energy minimization. Secondly, the more stable conformations of (E)- and (Z)-stereoisomers were subjected to optimization at the semiempirical AM1 and PM3 levels.

TABLE-1
SELECTED COMPOUNDS AND TORSION ANGLES FOR CONFORMATIONAL ANALYSIS

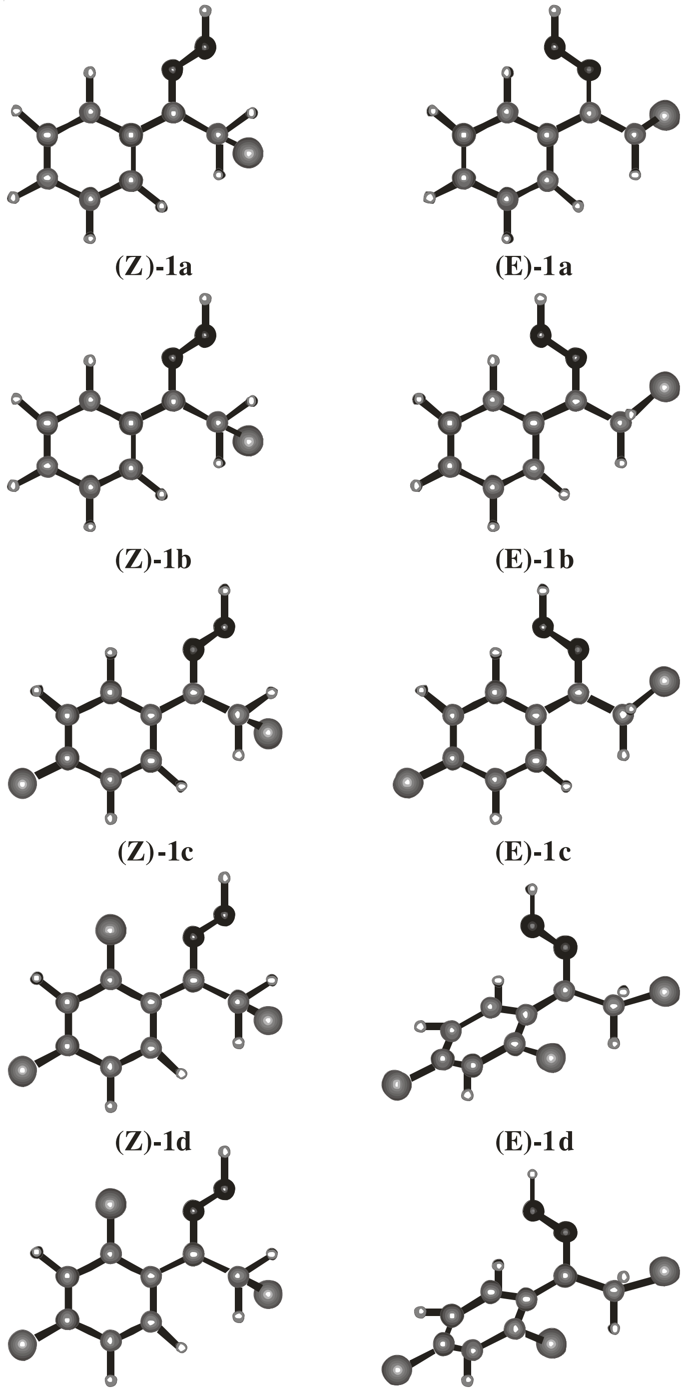


$\tau_1 = O_1\text{-}N_2\text{-}C_3\text{-}C_4$; $\tau_2 = N_2\text{-}C_3\text{-}C_4\text{-}X_5$; $\tau_3 = C_4\text{-}C_3\text{-}C_6\text{-}C_7$

Compound	X	R_1	R_2
1a	Br	H	H
1b	Cl	H	H
1c	Cl	Cl	H
1d	Br	Cl	Cl
1e	Cl	Cl	Cl

RESULTS AND DISCUSSION

The present studies have been focused on two points, *i.e.*, (i) the search for the most stable stereoisomer of α-haloacetophenone oximes and (ii) the influence of oxime geometry on the conformational features of the compounds **1a-e**. Although limited theoretical study on stability of oxime stereoisomers have been performed, it was thought that it could have been useful to determine the possibility of Z and E isomers obtained from synthesis by conformational analysis studies. The molecular conformations of compounds were determined by principal torsion angles τ_1, τ_2 and τ_3 which define the position of the oxime towards (E)- and (Z)-isomers, flexibility of phenyl ring and halomethyl residue, respectively. The conformational analysis produced two energetically low energy conformers belonging to (Z)- and (E)-isomers. Always, every lowest-energy conformation was resubmitted to final optimization by AM1 and PM3. Their optimized geometry and related energies are illustrated in Table-2 and Fig. 2. (E)- and (Z)-isomers show different stability by molecular mechanics calculations. In general, (Z)-isomers are more stable than (E)-isomers by 4.55-6.14 kcal/mol. Moreover, the calculated heats of formation (Table-2) reveal (Z)-isomers as the more stable one. In this case AM1 method found (Z)-isomers to be 0.82-1.52 kcal/mol more stable than (E)-isomers, while PM3 method found (Z)-isomers 1.76-3.42 kcal/mol more stable than (E)-isomers. The instability of (E)-configuration compared with (Z)-configuration may be due to the repulsion interaction. Although a planar



(Z)-1a **(E)-1a**

(Z)-1b **(E)-1b**

(Z)-1c **(E)-1c**

(Z)-1d **(E)-1d**

(Z)-1e **(E)-1e**

Fig. 2.

TABLE-2
POTENTIAL ENERGY (MM) AND ENTHALPIES OF FORMATION (AM1 AND PM3) OF LOWEST-ENERGY CONFORMATIONS FOR (*Z*)- AND (*E*)- (**1a-e**)

Compounds	Energy (kcal/mol)			τ_1	τ_2	τ_3
	MM	AM1	PM3			
(*Z*)-1a	2.91	66.32	70.01	0.19	95.22	-177.90
(*E*)-1a	7.46	67.36	71.77	174.78	-83.72	166.24
(*Z*)-1b	2.98	54.07	58.41	-0.29	-92.86	176.65
(*E*)-1b	7.75	55.16	60.71	-173.02	-33.27	-162.91
(*Z*)-1c	3.40	47.37	51.97	-0.30	-93.43	176.77
(*E*)-1c	8.17	48.52	54.39	-172.90	-34.00	-162.70
(*Z*)-1d	9.32	58.18	59.88	1.29	91.64	-174.64
(*E*)-1d	15.46	59.70	63.30	171.08	52.77	-30.64
(*Z*)-1e	9.77	45.61	48.09	1.77	88.67	-172.23
(*E*)-1e	15.31	46.43	51.28	171.18	50.42	-30.19

conformation may be favoured in these molecules by an electron-delocalization effect, the steric effect between the hydrogen or chloro-substitution on the phenyl ring and the hydroxy moiety of oxime seems to prevent its complete planar geometry.

For the isomers of compounds studied, the torsion angles in the moieties connecting to oxime group are defined dependent on the configuration of oxime. According to the optimized geometry in (Z)-isomers, the phenyl ring and imino moiety are nearly coplanar. In (E)-isomers the geometry of phenyl ring and imino moiety are twist structure because of the steric repulsion of hydrogen or 2-chloro- substitution on phenyl ring and the OH of oxime moiety. As shown in Fig. 2, the incorporation of chloro-substituent in 2-position of phenyl ring experiences a large steric hindrance, which induces a large torsion of molecules. As shown in Fig. 2, the α-halo group and imino moiety are twisted in (E)-isomers and are perpendicular in (Z)-isomers. This difference may be due to the repulsion arising from α-halo atom *syn* to the oxime double bond and hydroxy group of oxime in (Z)-isomers.

Therefore, the geometries obtained for the different oximes is result of both an energetic gain obtained by stabilization of the π system in a planar structure and different geometrical considerations: (i) steric repulsion between the lone pair of the N atom and the hydrogen or chlorine atom hold by the phenyl ring in (Z)-isomers (ii) steric repulsion between OH of oxime and hydrogen or chlorine atom on phenyl ring in (E)-isomers

(iii) electronic repulsion arising from lone pairs of electrons on the halogen atom *syn* to the oxime double bond and the oxime π-electrons including a lone pair of electrons on the nitrogen atom in (E)-isomers or hydroxy group in (Z)-isomers.

In conclusion, the molecular mechanics and semiempirical energy levels of the derivatives obtained from HyperChem molecular modeling program indicated a difference between the (Z)- and (E)-isomer of the derivatives. According to this data the (Z)-isomer prefers the lower energy state when compared to (E)-isomer, indicated that the (Z)-isomer should be obtained preferentially in the synthesis.

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