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MOLECULAR ORBITAL INVESTIGATION OF POSSIBLE MECHANISTIC PATHS IN REACTION OF CYCLOHEXANONE WITH BROMOFORM

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Abstract
The extensive calculations were done to elucidate the mechanism of formation dibromoepoxide from cyclohexanone and bromoform. In this reaction, the formation of dihaloepoxide 2 is postulated as a key step that determines the distribution and stereochemistry of products. Every reaction scheme involves epoxide as a key intermediate. Two reaction mechanisms were investigated: the addition of tribromomethyl carbanion to carbonyl group of ketone and the addition of dibromocarbene to the same (C=O) group. The mechanisms for these two reactions have been theoretically studied using a semi-empirical MNDO-PM3 method. The calculations showed that both mechanisms are possible and exothermic.

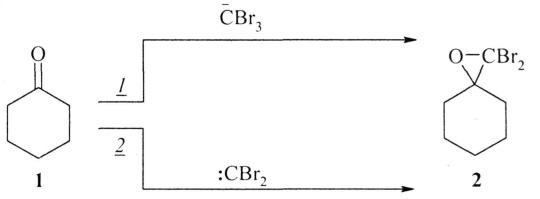
Introduction
Ring opening nucleophilic reactions of dihaloepoxides are important because of the large number of biologically active compounds affordable through these reactions [1,2]. One-pot reactions of aldehydes and ketones with chloroform, bromoform, or iodoform are particularly attractive [3,4]. In these reactions, the intermediate dihaloepoxides could not be isolated but, nevertheless, they are considered a key factor in the shaping of products. The formation of intermediate dihaloepoxides was proposed in 1940 by Jacobs [5] and was widely accepted by other investigators [3,4]. Whether the reaction is a free-radical one involving carbene intermediate, or is ionic one involving trihalocarbinol, the formation of dihaloepoxide is postulated as a key step in determining the distribution and stereochemistry of products. Many investigators have studied the reactions of haloform compounds with aldehydes and ketones, both experimentally and computationally [6,7,8]. We have carried out extensive calculations on a model system, cyclohexanone– bromoform. We chose this model because of the many experimental data available for it. Most of them are obtained in the course of the optimization of the reaction in order to improve the yield [6]. An additional asset is a relative simplicity of the system, which is lacking the stereodiversity, and has a very low number of conformers.

Computational Details
In this work, the MNDO–PM3 method, which is known to be highly reliable for investigating the molecular properties of molecules, ions, and zwitterions , was used. The MOPAC program package, version 7.01, was used. The initial structures of the compounds were generated by PC MODEL, version 4.0 (Serrene Software Box, Bloomington, IN, USA), which involves an MMX force field and were saved

as MOPAC input files for MNDO–PM3 semi-empirical calculations [9]. The geometries of all molecular species, corresponding to the energy minima in vacuum, were optimized by the PM3 method. The transition states for all reactions were explored using corresponding MOPAC facilities (TS, SADDLE).

Results and Discussion

Mechanistic consideration of the reactions of addition of tribromomethyl carbanion and dibromocarbene on carbonyl are exemplified in Scheme 1, using cyclohexanone as the substrate.



Scheme 1. Mechanistic pathways for the studied reaction.

The epoxide **2** could be obtained, in principle, by two different reaction mechanisms. The results provide unambiguous evidence of the asymmetric approach of carbanion or carbene to the carbonyl group.

Potential energy surface (PES) for ionic reaction *1* was obtained by systematic variation of distance between carbonyl bond and tribromomethyl carbanion. Corresponding energy changes referring to critical points on PES are given in Table 1. Two reaction paths are possible: approach of carbanion to carbonyl group targeting carbon (*1a*) and targeting oxygen (*1b*). Our calculations showed that the ionic mechanism has activation enthalpies 21.068 and 27.497 kcal/mol, for pathway *1a* and pathway *1b*, respectively.

Computational analysis of the mechanism *2* was carried out by systematic variation of distance between centre of carbonyl bond and the dibromocarbene. In carbene mechanism the favored attack of dibromocarbene is to oxygen side of carbonyl group. The activation enthalpy for this reaction is 0.338 kcal/mol.

Table 1. Reaction and activation enthalpies, (ΔH_r and $\Delta H^{\#}$), for various reaction pathways calculated by semi-empirical MNDO-PM3 method.

	ΔH_r (kcal/mol)			$\Delta H^{\#}$ (kcal/mol)		
	Step 1*	Step 2*		Step 1*	Step 2*	
1a	-14.980	26.098	11.119	16.766	6.088	21.068
1b	-15.910	27.029	11.119	23.451	11.587	27.497
2	26.136	31.701	57.837	0.338	17.376	0.338

* Step 1 denotes transformation of reactants to intermediate; Step 2 denotes transformation of intermediate to products. Third and sixth column contain overall reaction/activation enthalpies

From Table 1 can be seen that the activation enthalpy for pathway *1* is much higher than that for the pathway *2*.

Conclusions

The computational study of the formation of spiro-epoxy intermediate **2** in the reaction of cyclohexanone **1** with bromoform, in alkaline medium, confirmed the reliability of ionic mechanism. It renders these dihaloepoxides as well established intermediates in reaction of ketones with bromoform. Two possible mechanisms for the formation of the spiro-dibromoepoxy intermediate are studied. The calculations showed that both mechanisms are exothermic and possible, and reaction conditions may affect them in a large extent. Ionic mechanism is preferred in polar solvents and alkaline medium.

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