Molecular Orbital Investigation of Various Reaction Pathways in Reaction of Ketones With Bromoform

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ABSTRACT: To elucidate the ring opening, nucleophilic reactions of dihaloepoxides the extensive calculations were done on a model system cyclohexanone–bromoform. In this reaction, the formation of dihaloepoxide is postulated as a key step that determines the distribution and stereochemistry of products. Every reaction scheme involves epoxide as a key intermediate (1). Three major products (2, 3, and 4) can be obtained, in principle, by three different competing reaction pathways. The calculations showed that all the pathways are exothermic. Reaction pathway 1 is most convenient, it does not include any intermediate, and its energy is not much affected by the polarity of the medium. In pathways 2 and 3, the calculations showed the intermediates having a largely carbocationic character on the spiro junction carbon atom. The step in which these intermediates are formed determines the reaction rate. Because of the polarity of intermediates in pathways 2 and 3, the base concentration and polarity of solvent determine the balance of reaction pathways and the product yield. © 2005 Wiley Periodicals, Inc. Int J Quantum Chem 106: 1323–1329, 2006

Key words: MNDO-PM3; reaction pathway; dihaloepoxides; bromoform

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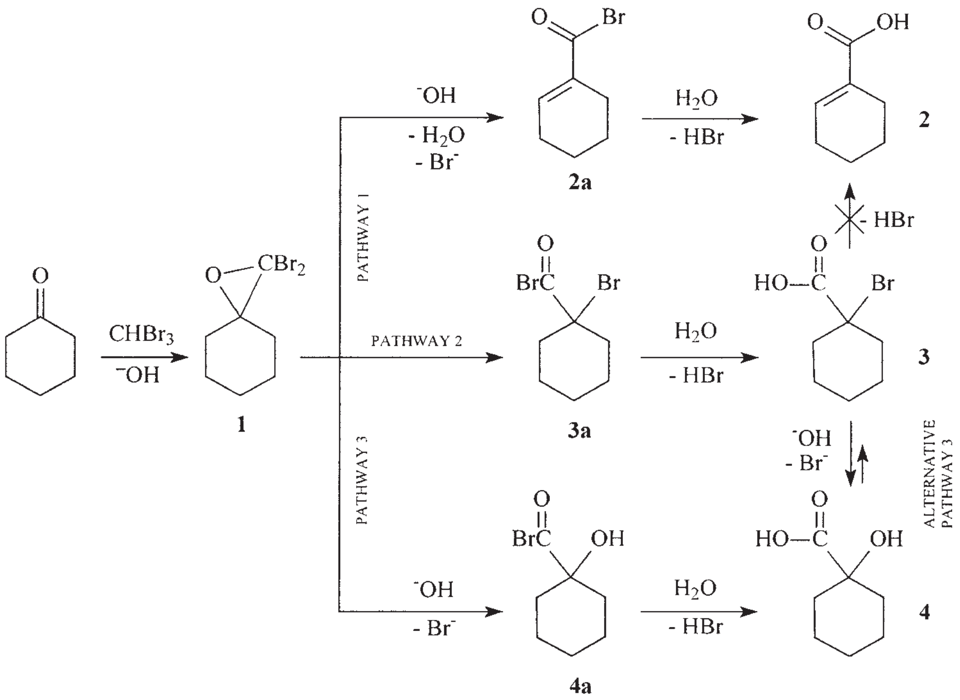

SCHEME 1. Reaction pathways for the studied reaction.

Introduction

Ring opening nucleophilic reactions of dihaloepoxides are important because of the large number of biologically active compounds affordable through these reactions [1–9]. One-pot reactions of aldehydes and ketones with chloroform, bromoform, or iodoform are particularly attractive [10–14]. 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 [15] and was widely accepted by other investigators [2–5, 10–14, 16, 17]. Whether the reaction is a free-radical one involving carbene intermediate, or an 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 [17–23]; however, these studies focused on the formation of dihaloepoxides and further metathesis was not studied in detail. In Ref. [23] the formation of single product was noted. Merz and Tomahogh [16] reported formation of three products emerging from dihaloepoxide intermediate. Our experimental study also showed the formation of at least three products [24]. In contrast, Ref. [17] presents an experimental study on the opening of dihaloepoxides with alkoxy nucleophiles, leading to different kinds of products, i.e., alkoxy acids.

To elucidate this reaction step, we have carried out extensive calculations on a model system, cyclohexanone–bromoform. We chose this model because of the many experimental data that is available for it. Most of them are obtained in the course of the optimization of the reaction in order to improve the yield [25]. An additional asset is a relative simplicity of the system, which is lacking the stereodiversity, and has a very low number of conformers.

The experimental investigation of the one-pot phase-transfer reaction of ketones with bromoform revealed that three final products are formed (2, 3, and 4). By fine-tuning the experimental conditions, the yield ratio of these products can be controlled.

Computational Details

In this work, the MNDO–PM3 method, which is known to be highly reliable for investigating the

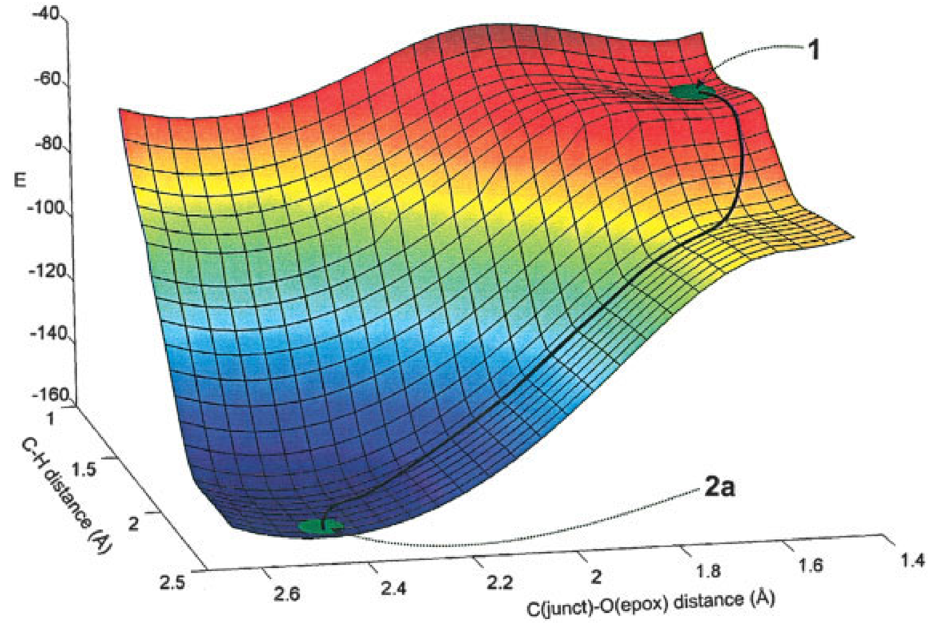

FIGURE 1. PES For pathway 1.

molecular properties of molecules, ions [26–34], and zwitterions [35], 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 [35, 36] and were saved as MOPAC input files for MNDO–PM3 semi-empirical calculations [28, 29]. The geometries of all molecular species, corresponding to the energy minima in vacuum, were optimized by the PM3 method. All were proved by vibrational analysis having all positive frequencies. The transition states for all reactions were explored using corresponding MOPAC facilities (TS, SADDLE).

Results and Discussion

Mechanistic consideration of the reaction of addition of bromoform on carbonyls is exemplified in Scheme 1, using cyclohexanone as the substrate. The three major products (2, 3, and 4) could be obtained, in principle, by three different reaction pathways.

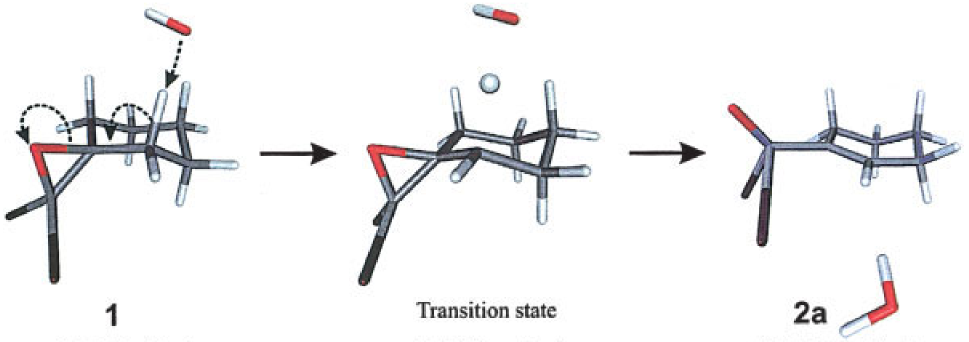

FIGURE 2. Structures of critical points on PES for pathway 1.

TABLE I

Reaction enthalpies, $\Delta\Delta H^0$, (kcal/mol), and activation energies, E_a, for various reaction pathways calculated by semi-empirical MNDO-PM3 method.*

	$\Delta\Delta H$ (kcal/mol)		$\Delta\Delta H^0$	E_a (kcal/mol)	
	Step 1	Step 2	(kcal/mol)	Step 1	Step 2
Pathway 1	109.069	—	109.069	1.537	—
Pathway 2	11.172	29.287	40.458	10.506	4.270
Pathway 3	25.388	74.339	99.728	4.559	5.561
Alternative pathway 2	43.037	—	43.037	21.803	—
Alternative pathway 3	11.352	108.271	119.623	8.488	7.519

* $\Delta\Delta H$ refers to partial reaction enthalpies when intermediates were involved (second and third columns).

Generally, every reaction scheme involves epoxide (1) as a key intermediate. In principle, any bond in a three-membered ring can be broken: one in the electrocyclic process and another in the nucleophilic substitution/elimination process. However, calculations proved that cleavage of the C—C bond is not likely to occur. (The electrocyclic opening of epoxide ring occurs only when nucleophilic reaction is suppressed by severe steric hindrance [38].)

Cleavage of both C—O bonds in epoxide was checked. Our calculations showed that the bond toward the CBr_2 group requires very high activation energy (>100 kcal/mol) to break. The other C—O bond, toward the cyclohexyl ring, appeared to be much easier to break and is subjected to further study.

Concerning the dehydrohalogenation 3→2, no experimental evidence hints that it could be concurrent to substitution (1→2a→2) at room temperature, and this particular transformation was not included in the computational study. Reactions of the hydrolysis of acyl bromides 2a, 3a, and 4a, to corresponding acids are trivial and were not subjected to computational study, too.

TABLE II

Experimental results on bromoform action to cyclohexanone in alkaline medium.

		Yield[a] (%)		
Reactant/Base	Solvent	2	3	4
$CHBr_3$ 4 eq. LiOH 20 eq.	*t*-Pent-OH, 4 ml H_2O, 1 ml	100	—	—
$CHBr_3$ 4 eq. KOH 18 eq.	*t*-Pent-OH, 9 ml THF, 1 ml	90	3	7
$CHBr_3$ 4 eq. KOH 18 eq.	*t*-Pent-OH, 5 ml H_2O, 1 ml	85	10	5
$CHBr_3$ 4 eq. KOH 20 eq.	*i*-PrOH, 1 ml H_2O, 1 ml	80	—	20

[a] Products ratio is determined from ^{13}C-NMR spectra.

The transformation of 1 to intermediate 2a goes without another intermediate. Potential energy surface (PES) for this reaction (Fig. 1) was obtained by systematic variation of two bond lengths: one is the already mentioned C—O bond (on the junction of two rings), and the other is the bond of the hydrogen next to the epoxy ring. The position of the OH^- ion (water in later phases of reaction) was partially restricted to avoid its wandering among various available neighboring hydrogen atoms. Structures referring to critical points on PES are given in Figure 2 and corresponding energy changes are given in Table I.

The structure of the transition state is established by vibrational analysis, showing one negative (imaginary) frequency. This reaction has an early transition state, having low activation energy. This is justified by the experimental results, which always give compound 2 as a main product of the reaction (Table II). The calculations reveal the developing of moderate negative charge in the transition state on the carbon from which the hydrogen has to be abstracted.

As shown in Table II, the distribution of products depends heavily on the solvent and base used. Experiments show the competition between pathway 1 and pathways 2 and 3. It is obvious that more polar medium endorse formation of products 3 and 4. This suggests that either a more polar transition state or some polar intermediates are involved.

Computational analysis of the pathway 2 was carried out by systematic variation of same C—O bond length as in other pathways, and of the dis-

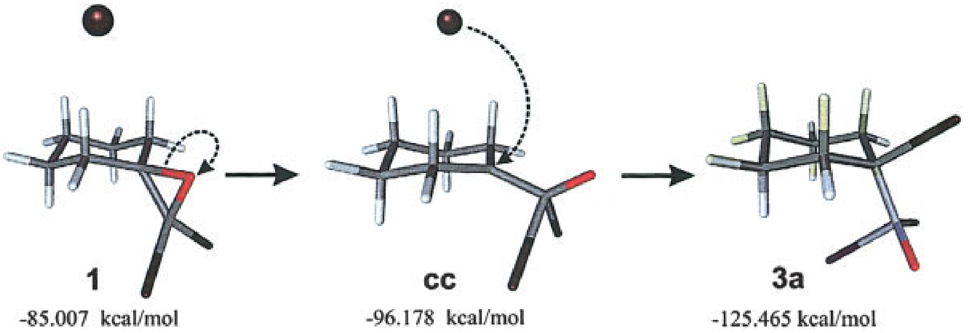

FIGURE 3. Structures of the critical points for pathway *2*.

tance between carbon on the ring junction and the attacking bromide ion (Fig. 3).

The PES for this pathway is shown on Figure 4. An unstable intermediate is found and is denoted cc. The charge distribution analysis shows that in this intermediate, a full positive charge is developed on the carbon involved in metathesis. The overall negative charge of this species is achieved by two negative charges located largely on attacking bromide and on (former) epoxy oxygen.

From Table I it can be seen that the activation energy for this pathway is much higher that for the pathway 1. As a corollary, it shouldn't be the preferred reaction path. In contrast, the reaction intermediate is highly (quadru)polar. This intermediate has an open epoxide ring, and a bond with attacking nucleophile is not yet formed. To check the polarity of substrate moiety of this intermediate, a single-point calculation of the corresponding structure, void of OH^- ion, or Br^- ion, was done. The calculation gives a dipole moment close to 10 D, and in the polar solvent it can be extraordinarily stabilized. According to the Hammond principle, the activation energy should be lowered in the po-

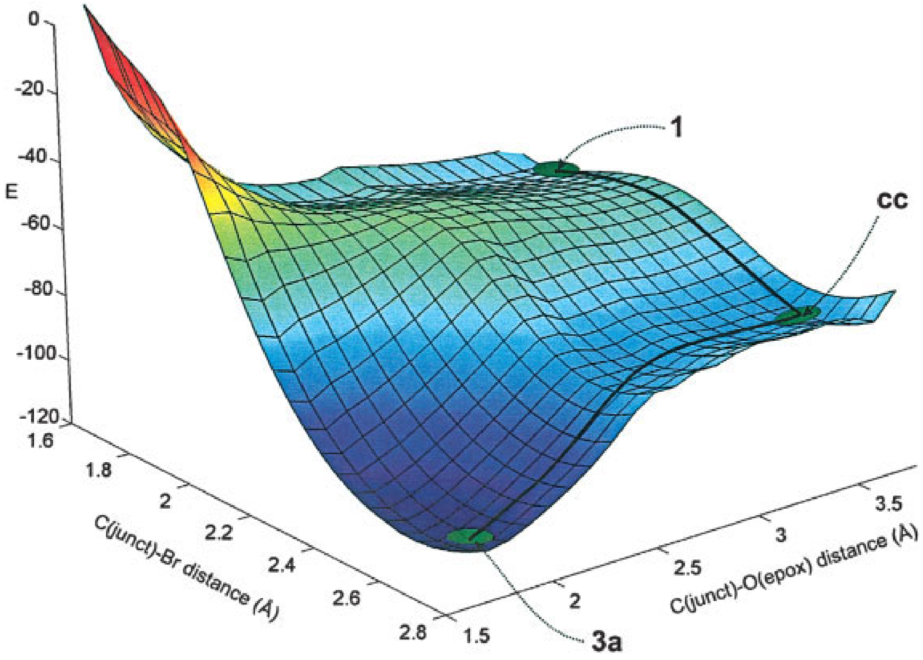

FIGURE 4. PES for pathway 2 (cc). Attack of bromide anion accompanied by epoxy ring opening (nucleophilic opening of epoxide). Intermediate has carbocationic center, and negative charges are located mostly on attacking bromide and oxygen.

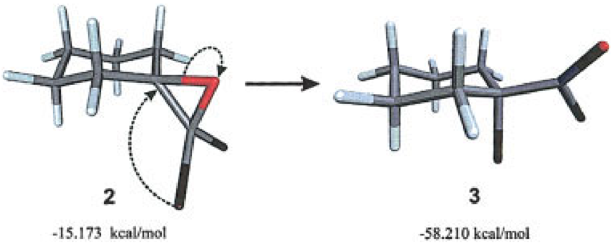

FIGURE 5. Alternative pathway 2. Rearrangement of dibromoepoxide in α-bromo acyl bromide.

lar medium, making this pathway competitive with pathway 1.

An (alternative) intramolecular variant of pathway 2 is given in Figure 5. A rearrangement of epoxide to α-bromo acyl bromide is the result of a 1,2-bromine shift accompanied with the opening of epoxy ring.

The PES for alternative pathway 2 does not show any intermediates, but it has the highest activation energy of all pathways studied. Therefore, it is unlikely that such intramolecular rearrangement could explain the formation of the compound 3.

In the reaction studied, there are two strong nucleophiles, Br^- and HO^- ions, which naturally invoke the third reaction pathway (Fig. 6).

There is a full analogy between pathways 2 and 3. A single difference is in attacking nucleophile (HO^- instead of Br^- ion). A very similar (quadru)polar intermediate ("cc", Figs. 3 and 6) is found, too. Again, highly polar intermediate could be stabilized in polar medium, rendering pathway 3 more probable.

Computational simulation of the substitution reaction of the hydroxyl ion with compound 3 shows that its transformation to compound 4 (alternative pathway 3) goes with modest activation energy. It involves an intermediate, which has a largely carbocationic character on the substitution center. This intermediate should be stabilized in the polar medium, making this process quite feasible. It could explain the lack of product 3 in the aqueous medium (last row in Table I). Inspection of Table II shows that this approach could be applied to rows 1, 3, and 4, and only the row (3) with the least share of water has some product 3.

Conclusions

The computational study of the metathesis of spiro-epoxy intermediate in the reaction of cyclohexanone with bromoform, in alkaline medium, confirmed the reliability of such mechanism. It renders these dihaloepoxides as well established (not only intuitively chosen) intermediates in reaction of ketones with bromoform. Three possible pathways for metathesis of the spiro-dibromoepoxy intermediate are studied, and all products were found to naturally emerge from it.

The calculations showed that all pathways are exothermic. Reaction pathway 1 is most convenient and does not include any intermediate. Because of the early transition state, a moderate polarization of bonds occurs, and its energy is not much affected by the polarity of the medium.

In pathways 2 and 3, calculations showed the intermediates having largely carbocationic character on the (initially) spiro junction carbon atom.

Both steps in reaction pathways 2 and 3 are highly exothermic, which makes the reaction prac-

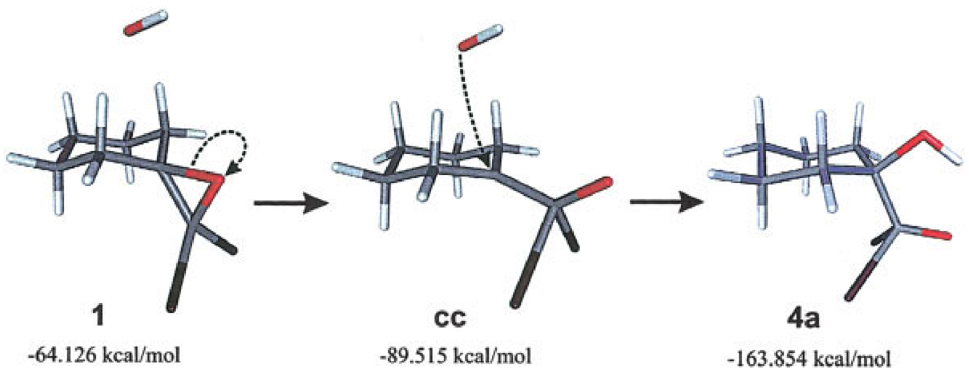

FIGURE 6. Reaction pathway 3 is completely analogous to pathway 2, but nucleophile is HO^- instead of Br^-, yielding α-hydroxy acyl bromide.

tically irreversible. This justifies the statement that the formation of carbocationic intermediates determines the reaction rate.

Because of the polarity of intermediates in pathways 2 and 3, the base concentration and polarity of solvent determine the balance of reaction pathways and the product yield. The alternative pathway 2 may enable the formation of species 3 in less polar solvents, and the alternative pathway 3 shows why species 3 is isolated in lower yields in aqueous medium.

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