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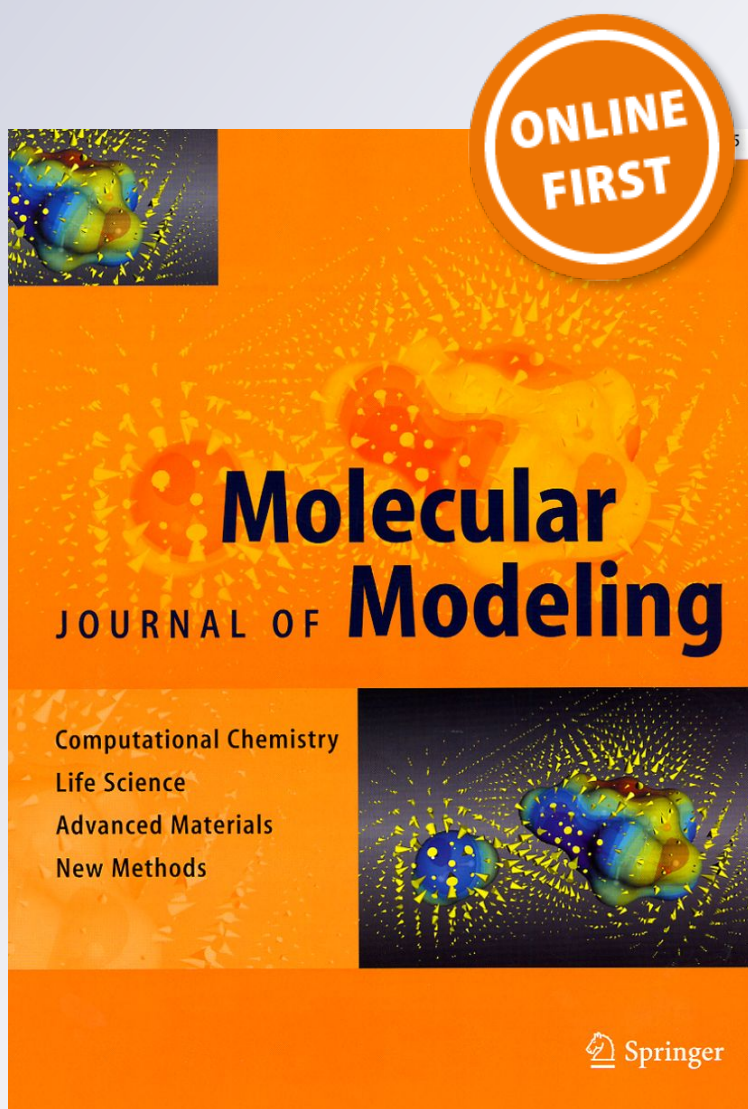
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Carbenic vs. ionic mechanistic pathway in reaction of cyclohexanone with bromoform

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Abstract The extensive computation study was done to elucidate the mechanism of formation dibromooxepoxide 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. Two mechanistic paths of reaction were investigated: the addition of dibromocarbene to carbonyl group of ketone, and the addition of tribromomethyl carbanion to the same (C=O) group. The mechanisms for the addition reactions of dibromocarbenes and tribromomethyl carbanions with cyclohexanone have been investigated using *ab initio* HF/6-311++G** and MP2/6-311+G* level of theory. Solvent effects on these reactions have been explored by calculations which included a continuum polarizable conductor model (CPCM) for the solvent (H₂O). The calculations showed that both mechanisms are possible and are exothermic, but have markedly different activation energies.

Keywords *Ab initio* calculations · Dibromocarbene · Dihaloepoxides · Reaction mechanisms · Tribromomethyl carbanion

Introduction

Nucleophilic ring opening reactions of dihaloepoxides are widely used to obtain the large number of biologically active compounds [1–4]. Particularly attractive are one-pot reactions of aldehydes and ketones with chloroform, bromoform, or iodoform [5–9]. In these reactions, the intermediate dihaloepoxides are considered to be a key factor in the shaping of products. The reactions of haloform compounds with aldehydes and ketones are already extensively studied, both experimentally and computationally [10–14].

While the cyclopropanation reactions involving carbenes have received much attention, there has been much less interest shown in cyclopropanation reactions involving carbanions. Hine (1950) [15] described kinetic and trapping experiments to demonstrate that the trichloromethyl carbanion is one of the intermediates formed during the generation of dichlorocarbene by the basic hydrolysis of chloroform. Hine and co-workers also demonstrated that CCl₂ carbene could be trapped by other chloride ion to yield trichloromethyl carbanions [16].

The mechanism of the cycloaddition between singlet dichlorocarbene and asymmetric π systems was not extensively studied [11, 13]. To our best knowledge, the reaction between the trihalomethyl carbanions and π systems having asymmetric charge distribution, has not been studied so far.

We have carried out extensive MO calculations on a model system, cyclohexanone-bromoform. We chose this model because of the many experimental data available for it. In our previous paper [12] we developed new one-pot synthesis of α,β -unsaturated and α -bromo carboxylic acids (Scheme 1), and most of the theoretical calculation data are obtained in the course of the efforts to define optimal reaction condition aiming to improve the yields in experimental

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work. An additional asset is the relative simplicity of the system, which is lacking the stereodiversity, and has a low number of conformers.

To examine the mechanisms of these reactions, we have undertaken a detailed investigation of the addition reactions of dibromocarbenes and tribromomethyl carbanions to cyclohexanone by using *ab initio* HF and MP2 calculations. The purpose of the present MO computational study was to identify the transition states for the reactions, and to carry out a vibrational analysis at these stationary points.

Through this work, we aimed to elucidate the factors that control the activation barriers for such addition reactions. We also aimed to further investigate the effects of solvent on the thermodynamic and kinetic properties of these reactions. It is well-known that solvent effects play an important role in determining reaction rates, equilibrium constants, and other quantities of chemical and biochemical processes. Our present study provides, too, some theoretical information about solvent effects on the reactions of this kind.

Computational details

Geometries, energies, and first- and second-order energy derivatives of all stationary points were fully optimized by restricted Hartree-Fock (RHF) method using 6-311++G** basis set, and second-order Møller-Plesset perturbation theory (MP2) [17] with 6-311+G* basis set using the GAUSSIAN 03 program suite [18]. Calculations of stationary points that may exist in triplet state have been done also with unrestricted approach (UHF and UMP2). Vibrational frequency calculations at the HF/6-311++G** and MP2/6-311+G* level of theory were used to characterize all the stationary points, as either minima (the number of imaginary frequencies (NIMAG=0) or transition states (NIMAG=1)). The relative energies are corrected for vibrational zero-point energies (ZPE, not scaled), and the transition states, both to the reactants and to the products direction in the reaction paths were checked by using the intrinsic reaction coordinate (IRC) [19].

To infer the effect of the H₂O solvent on the title reaction, the continuum polarizable conductor model (CPCM) [20] at HF/6-311++G** level was applied. The dielectric constant was assumed to be 78.4 for H₂O.

Results and discussion

In our previous paper [12] we reported an optimized, convenient synthesis of α,β -unsaturated and α -bromo carboxylic acids, by phase-transfer-catalyzed reactions of ketones with bromoform and aqueous lithium hydroxide in alcoholic solvent. The α,β -unsaturated carboxylic acids were obtained from corresponding cyclic or aromatic ketones. Bromo acids,

4-bromo-piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester and 4-bromo-piperidine-1,4-dicarboxylic acid monoethyl ester were obtained from 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester and 4-oxo-piperidine-1-carboxylic acid ethyl ester (Scheme 1).

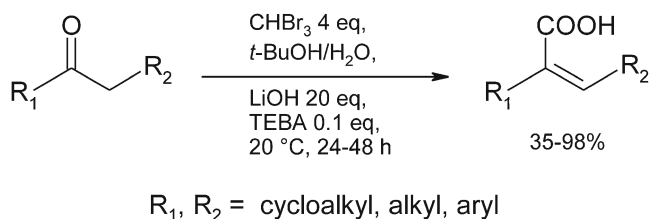
In this reaction the dibromoepoxide **2** is inferred as intermediate (see Scheme 2). The epoxide **2** could be obtained, in theory, by two different reaction mechanistic paths. The experimental results provide unambiguous evidence for asymmetric approach of carbene or carbanion to the carbonyl group, which is consistent with its polar nature.

The structures optimized by molecular-orbital calculations along the pathways (1 and 2) of cycloaddition reactions (Scheme 2), are almost the same at the HF/6-311++G** and at MP2/6-311+G* levels of theory. Considering the reliability of HF method in calculation of geometric parameters and the accuracy of MP2 method in energy calculation, the following discussions regarding energy and geometry parameters, are based on the results from MP2/6-311+G* and HF/6-311++G**, respectively.

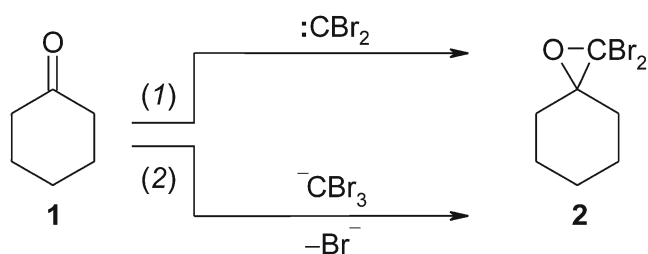
Mechanistic consideration of the addition reactions of singlet dibromocarbene and tribromomethyl carbanion on carbonyl are exemplified in Scheme 2, using cyclohexanone as the substrate.

Reaction of dibromocarbene with cyclohexanone

Computational analysis of the mechanism (1) was carried out by systematical variation of distance between center of carbonyl bond and the dibromocarbene carbon. In order to do a systematic study, the potential energy profiles of the investigated reaction were studied starting from two different geometric arrangements. The optimized stationary structures on the potential surfaces of the reaction are schematically shown in Fig. 1, where the atomic numbers are given for the key atoms. On the upper part of Fig. 1, the carbene was put in the plane of carbonyl group C(4)C(1)O (2) (atom numbering is given on the left side of the Fig. 1) (mechanistic path 1a), and distance from carbonyl oxygen was systematically changed. In the bottom part of Fig. 1, the carbene was put in the plane perpendicular to the plane of C=O group (mechanistic path 1b) and distance from carbonyl carbon is systematically changed.



Scheme 1 One-pot reaction of ketones with bromoform [12]



Scheme 2 Mechanistic pathways for the studied reaction

The present calculations indicate that the ground state of dibromocarbene is a singlet state that has lower energy than the triplet state by approximately 47.5 kJ mol⁻¹ at the MP2/6-311+G* level.

The selected bond parameters (bond length and bond angles) for the stationary structures are listed in Table 1. Corresponding energy changes referring to critical points on the potential energy surface are given in Table 2. In carbene mechanism, the favored approach of dibromocarbene from the distance is to the oxygen side of carbonyl group. It can be accounted for electrophilicity of carbene and the higher electron density at carbonyl oxygen.

Inspection of Fig. 1 reveals that the attack of the dibromocarbene carbon atom on the oxygen of the carbonyl group corresponds to the pathway (1a). As can be seen in Fig. 1, reaction (1a) consists of three steps: the first one is a barrier-free exothermic reaction of 12.87 kJ mol⁻¹, resulting

in the intermediate IM1a; the second step is the isomerization of IM1a to intermediate IM2a via TS1a with a barrier of 2.2 kJ mol⁻¹. Subsequently, IM2a isomerizes to product 2 via TS2a with 62.25 kJ mol⁻¹ barrier (this high value is obviously artifact, because of forcing the in-plane approach of reactants). The overall reaction energy is -260.72 kJ mol⁻¹, implying that the pathway (1a) is a thermodynamically feasible process. These values indicate that the attack of the carbene on the ketone has electrophilic selectivity for oxygen of carbonyl group.

Frontier molecular orbital (FMO) analysis has been successful in accounting for a range of addition reactions. Thus, the highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) energies of CBr₂ carbene and cyclohexanone are calculated for structures optimized at MP2/6-311+G* level of theory. Based on population analysis, in a small extent electrons from cyclohexanone have been transferred to atom C(3) in IM2a; i.e., the Mulliken charges on C(1), O(2) and C(3) are 0.457, -0.372 and 0.040, for the isolated reactants; and 0.412, 0.014 and -0.059 for IM2a. The NBO charges on C(1), O(2) and C(3) are 0.683, -0.646 and -0.153, respectively for the isolated reactants. For IM2a the corresponding NBO charges are 0.833, -0.595 and -0.245.

Because of the lack of higher symmetry, the genuine biradical intermediate could exist only as a triplet (Jahn-Teller principle). Additional calculation for IM2a as triplet biradical

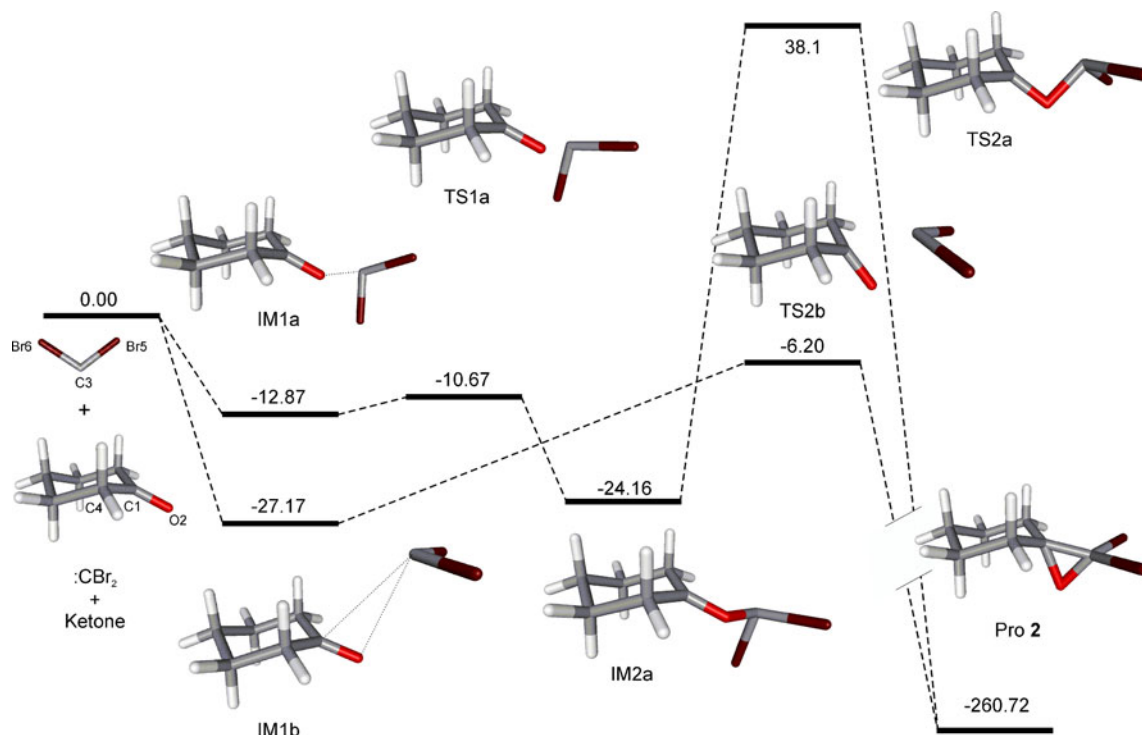


Fig. 1 Schematic energy diagram for the :CBr₂+cyclohexanone reaction, based on the theoretically calculated results of MP2/6-311+G* (in kJ mol⁻¹) and the equilibrium geometries of various species at the HF/6-311++G** level

Table 1 Calculated optimized geometry parameters for the stationary points of the reaction of dibromocarbene and tribromomethyl carbanion with cyclohexanone (corresponding structures are shown on Figs. 1 and 4)^a

Species	r C(1)-O(2)	r C(1)-C(3)	r O(2)-C(3)	r C(3)-Br(5)	A135	A235	A3214
Ketone + CBr ₂	1.189			1.875			
IM1a	1.191	3.823	3.017	1.878	101.7	93.0	-174.8
TS1a	1.212	2.627	1.775	1.946	97.3	98.1	-177.1
IM2a	1.223	2.453	1.586	1.993	121.3	99.3	-178.1
TS2a	1.264	2.102	1.550	1.957	122.4	101.5	119.5
IM1b	1.191	3.481	3.236	1.874	109.1	98.6	89.6
TS2b	1.244	1.995	1.951	1.905	117.0	99.6	100.3
Pro 2	1.428	1.466	1.350	1.930	122.5	116.3	112.1
Species	r C(1)-O(2)	r C(1)-C(3)	r O(2)-C(3)	r C(3)-Br(7)	A135	A235	A3214
Ketone + CBr ₃ ⁻	1.189			2.050			
TS1c	1.193	3.185	2.644	2.024	105.1	92.9	89.7
IM1c	1.241	2.398	1.509	6.154	103.3	100.0	-179.98
TS2c	1.291	2.082	1.470	5.896	119.2	104.5	121.6
IM1d	1.193	5.644	6.448	2.044	115.6	118.7	91.1
TS1d	1.251	1.916	2.569	2.010	109.4	145.8	113.5
IM2d	1.299	1.657	2.393	1.998	110.6	92.8	118.6
TS2d	1.330	1.547	2.068	2.547	118.0	99.1	116.3
Pro 2	1.455	1.461	1.343	5.493	122.7	116.1	112.3

^aAt the HF/6-311++G** level of theory, all distances are in angstroms and all angles are given in degrees

shows that this intermediate has about 32.06 kJ mol⁻¹ higher energy than IM2a singlet. From NBO analysis it can be seen that distribution of charge proves that IM2a mostly resembles a 1,3-dipole. The unrestricted approach gave the energy close to that of the restricted approach.

As shown in Fig. 2, the mechanism of the reaction (1a) could be explained with inspection of the frontier molecular orbitals. The combination of the HOMO orbital of C(1)-O(2) in cyclohexanone with the unoccupied 2p orbital (LUMO) of C(3) atom in carbene gives a donor-acceptor bond, forming a new three-membered ring (comprising C(3)C(1)O(2)) intermediate IM2a when carbene initially interacts with ketone. Formation of IM2a is an exothermic reaction. In the course of the reaction, carbene will rotate out of the plane of C(4)C(1)O

(2) in orientation perpendicular to it, and then the lone electron pair of carbene can overlap with π^* (LUMO) orbital of cyclohexanone. Accordingly, the addition reaction becomes completed.

In the much more convenient carbene mechanistic path (1b), dibromocarbene approaches to the carbonyl group in the plane which is perpendicular to the plane of that group (Figs. 3, and 1-bottom part). Path (1b) is completed by two steps: the intermediate IM1b is formed as a rather loose complex between the reactants, with an energy release of 27.17 kJ mol⁻¹, and then isomerizes to the product **2** via transition state TS2b with a barrier of 20.97 kJ mol⁻¹.

As can be seen from Table 1, the distances from C(3) to C(1) and to O(2) are 3.48, 3.24 Å in IM1b; and 1.99, 1.95 Å

Table 2 Relative energies^a (kJ mol⁻¹) for the reactions of dibromocarbene and tribromomethyl carbanion with cyclohexanone

Species	HF	HF-CPCM	MP2	Species	HF	HF-CPCM	MP2
Ketone + :CBr ₂	0	0	0	Ketone + CBr ₃ ⁻	0	0	0
IM1a	-6.80	0.77	-12.87	TS1c	46.37	41.15	77.35
TS1a	28.39	59.31	-10.67	IM1c	6.22	-9.54	15.56
IM2a	29.16	5.86	-24.16	TS2c	85.11	64.50	76.28
TS2a	97.10	128.01	38.10	IM1d	-30.69	-0.91	-66.66
IM1b	-6.35	-0.17	-27.17	TS1d	64.13	77.23	-51.16
TS2b	85.33	79.65	-6.20	IM2d	61.05	64.31	-84.95
				TS2d	104.89	110.84	-53.64
Pro	-152.25	-135.94	-260.72	Pro	-130.43	-151.20	-189.75

^a $E_R = E(\text{species}) - E(R1 + R2) + \Delta ZPE$; E , total energy of electronic structure; ZPE, zero-point energy correction

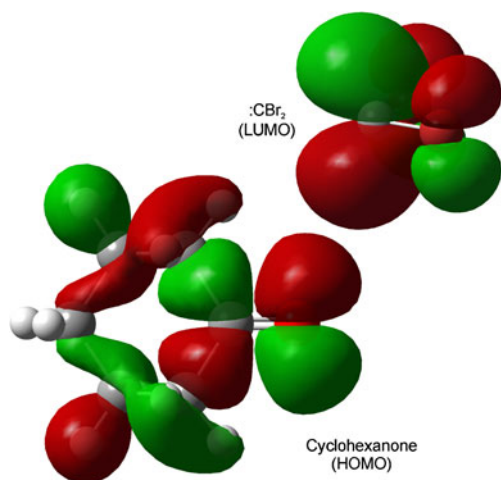
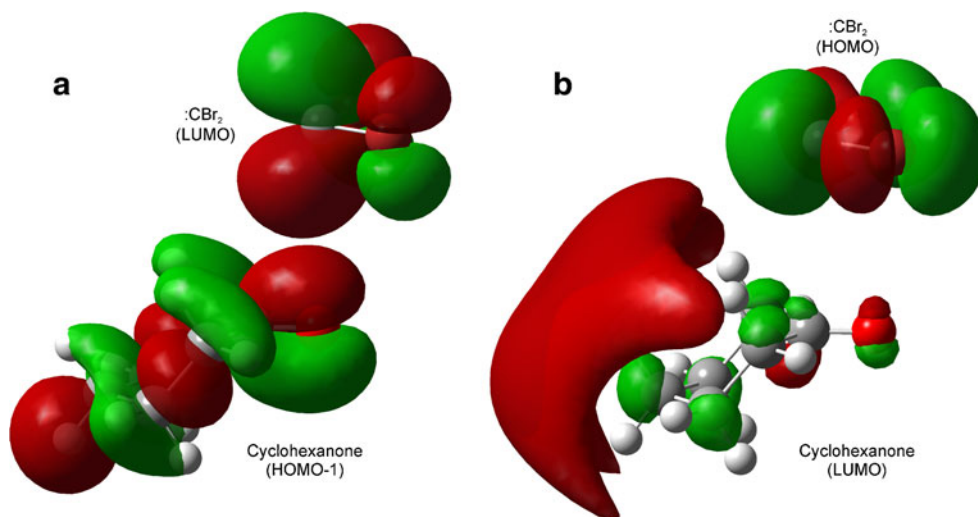


Fig. 2 Frontier molecular orbitals of :CBr₂ (LUMO) and cyclohexanone (HOMO), (Approach as in path *1a*)

in TS2b, respectively. The bond lengths of C(1)-O(2) bond in IM1b and TS2b are only slightly stretched (1.19 and 1.24 Å) as compared with the ketone. The unique imaginary frequency of the transition state TS1b is 564.2i cm⁻¹, and the transition state can, therefore, be affirmed as a genuine one. According to the calculation for the IRC of TS2b and the further optimization of primary IRC results, TS2b connects IM1b and product **2**.

As illustrated in Fig. 3, the formation mechanism of IM1b can be explained by frontier molecular orbital (MO) analysis. Two pairs of the orbital interaction exist between CBr₂ carbene and cyclohexanone: the empty 2*p* orbital of the CBr₂ carbene (LUMO) and the C=O π orbital (HOMO-1: the second highest occupied molecular orbital) of ketone (Fig. 3a), the C nonbonding electrons (σ) of CBr₂ carbene and the C=O π^* orbital (LUMO) of cyclohexanone (Fig. 3b).

Fig. 3 Frontier molecular orbitals interactions of :CBr₂ and cyclohexanone (Approach as in path *1b*)



The MP2 calculations show that the *p*- π orbital interaction is predominant, which can account for electrophilic behavior of the singlet CBr₂ carbene in the cycloaddition with cyclohexanone.

The free energy profiles for carbenic mechanistic paths *1a* and *1b* are added in the Supplementary (page S3). From the free energy profile it can be seen that carbenic mechanistic paths *1a* and *1b* have the free energies of activation for TS2a and TS2b 66.09 and 33.81 kJ mol⁻¹, but the overall activation barrier is approx. 44 kJ mol⁻¹ lower for mechanistic path (*1b*).

According to the above analysis, mechanistic path (*1b*) of carbene reaction (*1*) is the leading reaction channel for cycloaddition reaction between singlet dibromocarbene and cyclohexanone.

Reaction of tribromomethyl carbanion with cyclohexanone

Potential energy surface (PES) for ionic reaction 2 was obtained by systematic variation of distance between carbonyl bond and tribromomethyl carbanion. The potential energy profile and structures referring to critical points on PES of the reaction 2, are given in Fig. 4, where the atomic numbers are given for the key atoms (left side of Fig. 4). Two reaction paths are studied: approach of carbanion to carbonyl group targeting oxygen (2*c*) and targeting carbon (2*d*).

Reaction of tribromomethyl carbanion with cyclohexanone targeting oxygen of C=O

Chemical reasons usually disregard this mechanistic path, but we studied it to prove the possibility to generate carbene from carbanion.

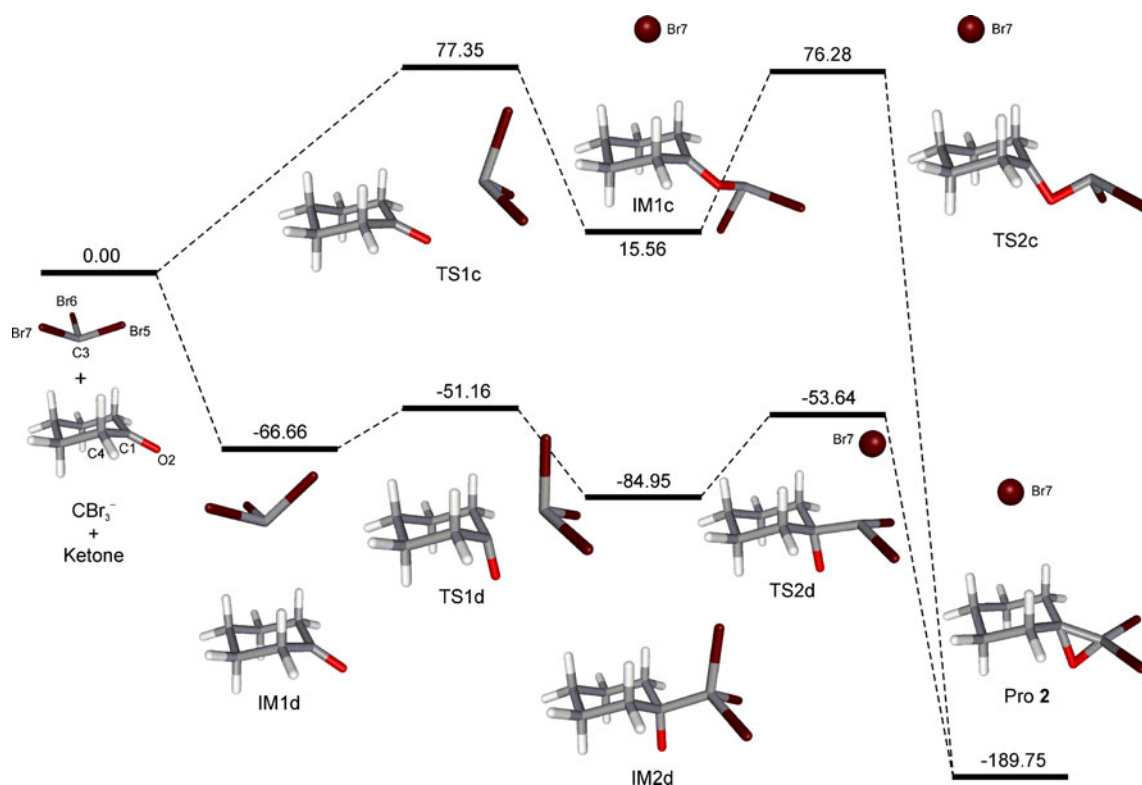


Fig. 4 Schematic energy diagram for the CBr_3^- + cyclohexanone reaction based on the theoretically calculated results of MP2/6-311+G* (in kJ mol^{-1}) and the equilibrium geometries of various species at the HF/6-311++G** level

When tribromomethyl carbanion approaches the oxygen atom of cyclohexanone, it forms an intermediate (IM1c) with cyclohexanone *via* TS1c, then IM1c isomerizes to product **2** *via* TS2c. The geometrical parameters for the intermediate IM1c, transition states (TS1c and TS2c), and product (**2**) in reaction (2c) are given in Table 1. Corresponding, relevant energy quantities are summarized in Table 2, from which can be seen that reaction (2c) involves two steps: in the first one tribromomethyl carbanion and cyclohexanone form IM1c *via* TS1c, for which the potential barrier is $77.35 \text{ kJ mol}^{-1}$; then IM1c isomerizes to product with a barrier of $60.72 \text{ kJ mol}^{-1}$. (The unique imaginary frequency of the transition state TS1c is $508.4i \text{ cm}^{-1}$, and IRC calculations confirmed that TS1c connects the corresponding reactants and intermediate IM1c). There are only relatively small structural changes going from the reactants to the transition state TS1c. This is a very early TS leading to intermediate IM1c. In this intermediate, there is an interaction between oxygen and dibromocarbene generated from tribromomethyl carbanion. Based on population analysis, electrons from cyclohexanone have been transferred in a small extent to atom C(3) in IM1c; *i.e.*, the Mulliken charges on C(1), O(2) and C(3) are 0.457, -0.372 and 0.040 , for the isolated reactants; and 0.094 , 0.144 and -0.014 for IM1c. For the isolated reactants the NBO charges on C(1), O(2)

and C(3) are 0.683 , -0.646 and -0.153 , respectively. For IM1c the corresponding NBO charges are 0.881 , -0.682 and -0.199 .

This intermediate is similar to the intermediate IM2a in carbene mechanism, and the mechanistic path (2c) proceeds by the mechanism which is analogous to carbenic mechanism (1a). Transition state TS2c, has forbiddingly high heat of formation, and renders the path 2c, unfavorable.

Reaction of tribromomethyl carbanion with cyclohexanone targeting carbon of $\text{C}=\text{O}$

Inspection of Fig. 4 shows that the attack between the carbon atoms of the tribromomethyl carbanion on C(1) of cyclohexanone will lead to a stepwise pathway yielding the addition product **2**. The rate-determining step is the addition of the nucleophile to give the alkoxy ion as intermediate. This step is followed by a relatively rapid loss of halide coupled with ring closure.

As can be seen in Fig. 4, reaction (2d) consists of three steps: the first one is a barrier-free exothermic reaction of $66.66 \text{ kJ mol}^{-1}$, resulting in the intermediate IM1d; the second step is the isomerization of IM1d to intermediate IM2d *via* TS1d with a barrier of $15.50 \text{ kJ mol}^{-1}$. Subsequently,

IM2d isomerizes to product **2** via TS2d with 31.31 kJ mol⁻¹ barrier.

In IM1d, the conformation of ketone is changed slightly compared with that in the isolated reactants. Intermediate IM1d leads to a very early TS1d with imaginary frequency of 197.8i cm⁻¹, (and IRC calculations confirmed TS to connect the IM1d and IM2d). From Table 1, we can see that the distances of C(1)-C(3), O(2)-C(3) are 1.66 and 2.39 Å and the distance of C(3)-Br(7) is 1.99 Å for the IM2d. Moreover, the C(1)-C(3)-Br(5) angles are close to a tetrahedral angle (110.6°), suggesting that the C(3) atom has essentially tetrahedral arrangement, and the distance of C(1)-O(2) (1.298 Å for the IM2d) is intermediate between single and double bond lengths for a CO bond. These changes in the bond angles and bond distances show that the C(3)-Br(7) bond will be cleaved and that the alkoxy intermediate will yield product **2** in one step through a ring closure TS (TS2d with only one imaginary frequency of 488.2i cm⁻¹, and IRC calculations confirmed that TS2d connects the corresponding reactant and product). As the reaction goes to the product, the C(3)-Br(7) bond is completely broken and the C(1)-C(3) and O(2)-C(3) single bonds become completely formed.

The energies of activation are 15.50 and 31.31 kJ mol⁻¹ for TS1d and TS2d, respectively, and the energy of reaction is -189.75 kJ mol⁻¹ for spiro-epoxide **2**.

The free energy profiles for ionic mechanistic paths *2c* and *2d* are added in the Supplementary (page S3). From them can be seen that ionic mechanistic paths *2c* and *2d* have the free energies of activation for final, cyclization step, (TS2c and TS2d) 57.72 and 30.65 kJ mol⁻¹. This final mechanistic step has similar energy demand as in carbene mechanism, but overall energy profile strongly prefers *2d* mechanistic path.

From the above description, the energetically most favorable mechanism of the reaction cyclohexanone with CBr₃⁻ is the addition path (*2d*), which has a negligible reaction barrier, and is in complete accord with experimental results [12].

From diagrams given on page S3, it is easily seen that in mechanistic path *2d*, all transition states and reaction intermediates are at lower energy levels than the starting reactants. By inspection of other diagrams (page S3), it is found that this is a unique situation. In other mechanistic paths (*2c*, *1a*, and *1b*) some (or all) transition states are richer in energy compared to reactants, and there must be a corresponding activation barrier for such reactions. From that reason the ionic mechanistic path *2d* is declared as barrierless.

Effects of solvent

The separated reactants, the transition states, intermediates and products were re-optimized at the HF/6-311++G** level, with effect of solvent included by employing the CPCM

model. The structures of the reactants and intermediates are closely similar in the gas phase and in water solution.

The C(1)-C(3) and C(1)-O(2) distances in TS1c and TS1d are a little increased with effects of solvent included in calculations, and in TS1a and TS1b are the same. The TS2 structures are changed toward the separated reactants due to effects of solvent. The C(1)-O(2) and C(3)-Br(7) distances in TS2c and TS2d are considerably increased by effects of solvent, which shows that the TS2 structures are changed toward the product due to effects of solvent. The interaction between solvent and solute has little influence on the structures of the other stationary points. This interaction, however, has a noticeable influence on the barrier heights. Solvent affects the activation barriers for radical reaction path (*1*) in higher extent than the activation barriers for ionic reaction path (*2*), which suggests a considerable polar character of transition states even in the radical path. Overall energy of reactions (*1*) and (*2*) in solvent (H₂O) are -135.94 and -151.2 kJ mol⁻¹, respectively. It is obvious that both cycloadditions of the singlet CBr₂ carbene and of CBr₃⁻, with cyclohexanone proceed very easily at room temperature in water solution, but the ionic path is practically barrierless, which is in accord with experimental findings [12].

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.

The interaction between solvent and solute has little influence on the structures of the stationary points, but has a noticeable influence on the barrier heights of the reactions. The calculations showed that both mechanisms are exothermic and possible, and reaction conditions may affect them to a large extent. Ionic mechanism is preferred in polar solvents and alkaline medium.

Hopefully, the present results may serve as a proxy for structural data in the study of the interactions between tribromomethyl carbanion and dibromocarbene with carbonyls.

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