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Revising the Role of a Dioxirane as an Intermediate in the Uncatalyzed Hydroperoxidation of Cyclohexanone in Water

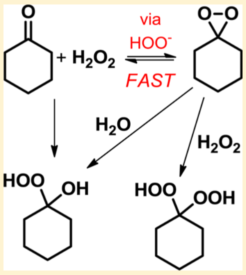
Elena Rozhko,[†] Stefania Solmi,[†] Fabrizio Cavani,[†] Angelo Albini,[‡] Paolo Righi,*[,†] and Davide Ravelli*[,‡]

[†]Department of Industrial Chemistry "Toso Montanari" Alma Mater Studiorum, University of Bologna, Viale del Risorgimento 4, 40136 Bologna, Italy

[‡]PhotoGreen Lab, Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy

Supporting Information

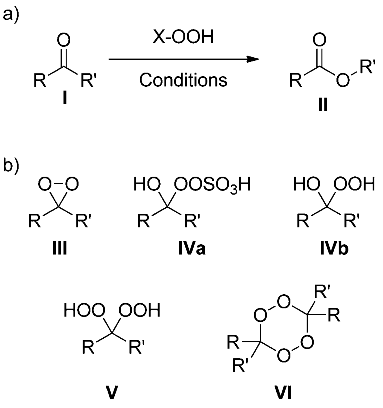
ABSTRACT: The mechanism of the oxidation of cyclohexanone with an aqueous solution of hydrogen peroxide has been investigated. Experiments revealed the preliminary formation of an intermediate, identified as cyclohexylidene dioxirane, in equilibrium with the ketone, followed by formation of 1-hydroperoxycyclohexanol (Criegee adduct). Computational analysis with explicit inclusion of up to two water molecules rationalized the formation of the dioxirane intermediate via addition of the hydroperoxide anion to the ketone and revealed that this species is not involved in the formation of the Criegee adduct. The direct addition of hydrogen peroxide to the ketone is predicted to be favored over hydrolysis of the dioxirane, the latter in competition with ring opening to carbonyl oxide followed by hydration. However, dioxirane may account for the formation of the bis-hydroperoxide derivative.



INTRODUCTION

Intermediates in oxygen transfer reactions have been the subject of intensive research and some controversy, in particular, for the role of dioxiranes.[1] Apart from that case, such species have not often been considered. An important exception is the versatile Baeyer–Villiger (BV) oxidation, largely used in organic synthesis, particularly for the preparation of pharmaceuticals, such as antibiotics, steroids, and pheromones, as well as of fine chemicals and intermediates for the chemical industry.[2,3] The reaction consists of the oxidation of a carbonyl group (**I**) to give an ester (**II**) via insertion of oxygen from a peroxyl derivative (X–OOH; Scheme 1a). *m*-Chloroperoxybenzoic acid, peroxytrifluoroacetic acid, peroxybenzoic acid, and peroxyacetic acid are typically used as the reagent, but hydrogen peroxide and *tert*-butyl hydroperoxide have also been used. In comparison with peroxyacids, which are often explosive and form carboxylic acid as co-product at any rate, the cheaper and safer hydrogen peroxide in the presence of a catalyst is obviously advantageous (higher content of active oxygen, water as the only co-product).

Scheme 1. (a) Baeyer–Villiger Oxidation of Ketones to Esters and (b) Proposed Intermediates Involved in the Process



For the mechanism, Baeyer and Villiger proposed a dioxirane (**III** in Scheme 1b) as an intermediate in the original paper,[2] while Criegee suggested the involvement of perester **IVa**.[4] Later, von Doering and Dorfman excluded the formation of a dioxirane in the BV oxidation with peroxybenzoic acid,[5] while Curci and co-workers claimed its involvement when the bis(trimethylsilyl) derivative of peroxymonosulfuric acid (H_2SO_5, Caro's acid) was used as the oxidant.[6] However, NMR analysis showed that dioxiranes survived only a few minutes at low temperature (from −20 to −10 °C, depending on the actual structure) in chloroform.[7]

The convenience of the hydrogen peroxide choice fostered several recent investigations, with particular regard to the role of intermediates and the mechanism. Thus, cyclohexanone was reported to react with H_2O_2 and give the Criegee adduct 1-hydroperoxycyclohexanol (**IVb**; R = R′ = $-(CH_2)_5-$) at room temperature[8a] as well as ε-caprolactone at 90 °C in the presence of a heterogeneous catalyst (Sn-zeolite beta) in dioxane.[8b]

Further products formed from ketones and hydrogen peroxide included 1,1-dihydroperoxycyclohexane (from cyclohexanone; **V**) as well as other cyclic bis-hydroperoxides.[9] The same derivatives were also prepared by ozonolysis of vinyl ethers in the presence of H_2O_2[10] or by reaction of ketals with

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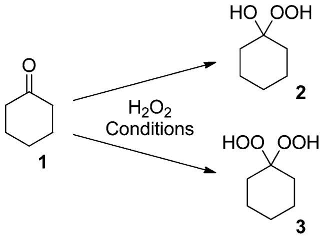
hydrogen peroxide in the presence of tungstic acid[11] or in anhydrous ether under BF_3 catalysis.[12] Condensation of bishydroperoxides leading to dihydroperoxydicycloalkyl peroxides and tetraoxadispiroalkanes (**VI**) or ozonides was also reported.[13−15]

The formation of the Criegee adduct (**IV**) from ketone (**I**) and the ensuing rearrangement of **IV** to the final ester (**II**) has been analyzed computationally,[16−19] while, to the best of our knowledge, the involvement of dioxiranes (**III**) has never been considered.

In view of the general interest for mild oxidations, it appeared worthwhile to establish the precise role, if any, of the dioxirane and the relation among the intermediates involved, as we report in the following through a combined experimental/computational investigation for the paradigmatic case of the noncatalyzed reaction between cyclohexanone (**1**) and aqueous hydrogen peroxide (Scheme 2).

Scheme 2. Process Investigated in the Present Work



■ COMPUTATIONAL DETAILS

All of the simulations have been carried out with the Gaussian 09 software.[20] Reactants, intermediates, transition state structures, and products have been initially optimized having recourse to density functional theory (DFT), viz. adopting the B3LYP functional[21] and the standard 6-31G(d,p) basis set in the gas phase. To confirm the nature of the stationary points, vibrational frequencies (in the harmonic approximation) have been calculated for all of the optimized structures at the same level of theory as geometry optimizations, and it was verified that local minima had only real frequencies, while transition states (TSs) were identified by the presence of a single imaginary frequency corresponding to the expected motion along the reaction coordinate. Unscaled results from the frequency calculations have been used to compute zero-point energies and their thermal corrections, enabling the calculation of the Gibbs free energy of the system considered.

For each reacting situation, a systematic investigation on all the possible conformations has been carried out by running several constrained optimizations. In most cases, the conformers differed for the arrangement of the O−H groups not involved in the reaction. However, since the difference in energy of these conformers was small (in most cases, a few kcal mol^{-1}), only the most stable conformation has been considered for further work.

In each case, the most stable conformation has been used as the starting point for a refinement at a higher level of theory, viz. using the composite method CBS-QB3[22] in the gas phase. The CBS-QB3 approach is part of the so-called "complete basis set" (CBS) methods of Petersson and co-workers for computing very accurate energies.

With both levels of theory (DFT and CBS-QB3), Gibbs free energies (G) obtained in vacuo have been corrected by adding the ΔG of solvation, calculated as recommended by the Gaussian 09 software, viz. by using the SMD model[23] by Truhlar and co-workers at the B3LYP/6-31G(d,p) level of theory.

The computed enthalpy, entropy, and Gibbs free energy were converted from the 1 atm standard state into the standard state of molar concentration (ideal mixture at 1 mol L^{-1} and 1 atm) in order to allow a direct comparison with the experimental results in water solution. Thus, the contribution $RT \ln R'T$, where R' is the value of R in L atm K^{-1} mol^{-1} had to be added to the Gibbs free energy term.[24] This contribution always cancels out unless a process where a molecularity change (Δn) between reagents and products occurs. Accordingly, this contribution should be written as $\Delta nRT \ln R'T$. As an example, in the reaction $A + B \rightarrow C$, $\Delta n = -1$ and the contribution will be $-RT \ln R'T$ (−1.90 kcal mol^{-1} at 298.150 K).

Importantly, the DFT level of theory has only been adopted for preliminary and screening purposes, while all the Gibbs free energy data reported in the text do refer to the CBS-QB3 level of theory, also including the solvent effect (named "SMD-CBS-QB3").

■ RESULTS AND DISCUSSION

Experimental Studies. Cyclohexanone **1** (98 mg, 1 mmol; 1.85 M) was dissolved in water (100 μL) and then was treated with 3 molar equiv of H_2O_2 in aqueous solution (30%; 340 μL, 3 mmol). Monitoring by ESI-MS revealed that the Criegee adduct **2** (peak + Na^+, m/z = 155) was formed immediately after mixing the reagents and increased with time. A further peak compatible with cyclohexylidene dioxirane (hereafter termed **4**) structure (m/z = 115) was formed, but there were no oligomeric compounds. After 2 h, at the end of the reaction, the aqueous reaction mixture was extracted with 0.8 mL of $CDCl_3$. The organic phase was then separated with the aid of a membrane phase separator, and its analysis by NMR showed the formation of the Criegee adduct **2** only (Figure S1 in Supporting Information).[8a]

2,2,6,6-Tetradeuterocyclohexanone (**1**-d_4) gave the corresponding ESI-MS peaks for **2**-d_4 and **4**-d_4 and followed a practically identical kinetics (see Figure S2), thus supporting that α-H atoms were not involved in the rate-determining step of the reaction. The experimental activation energy was measured to be 14 ± 2 kcal mol^{-1} in both cases.

A second set of experiments was run directly in a NMR tube on the 1-^{13}C-cyclohexanone (**1**-^{13}C; see the corresponding C NMR spectrum in Figure S3; peak at 220 ppm)/H_2O_2 system by recording ^{13}C NMR spectra at regular intervals at 50 °C in D_2O (with ≈0.1 M **1**-^{13}C starting concentration and all other parameters unchanged with respect to batch experiments; no effect due to the concentration change, except for a slower reaction). A new compound was formed within the 5 min required for recording the first spectrum (see inset in Figure 1 and Figure S4 for details). This showed signals conserving the cyclohexanone symmetry and very close to those reported for cyclohexylidene dioxirane at low temperature.[7] NMR spectra were run at regular intervals over 24 h (see Figure S5) and showed that, after "immediate" initial fast formation of the dioxirane (**4**-^{13}C; peak at 103 ppm), the Criegee adduct (**2**-^{13}C; peak at 110 ppm) was formed in several hours. Separate integration of the ^{13}C-enriched peaks at 220, 110, and 103 ppm evidenced (Figure 1) that starting cyclohexanone and dioxirane were initially in a ratio of about 1:1 and that this ratio was

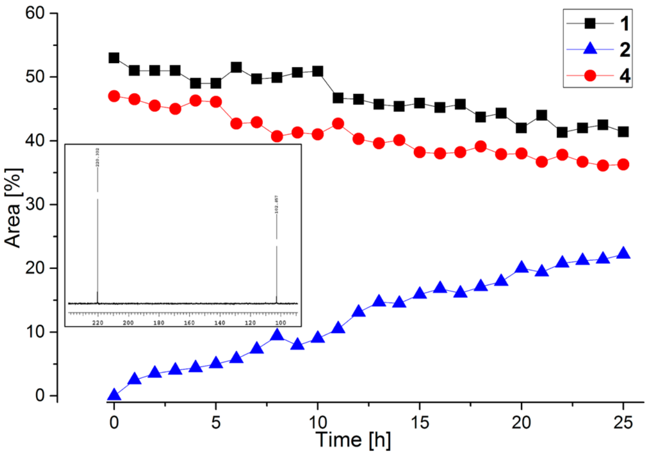


Figure 1. Relative amounts of starting cyclohexanone (**1**-^{13}C), Criegee adduct (**2**-^{13}C), and dioxirane (**4**-^{13}C), as determined from integration of the corresponding ^{13}C signals. Inset: Partial spectrum registered immediately after adding hydrogen peroxide (only ^{13}C-enriched carbon portion shown).

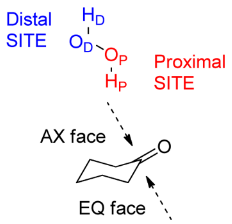
maintained throughout, while the Criegee adduct increased steadily.

That **4** was an intermediate on the way to **2** contrasted, however, with the purported instability of the dioxirane, reported not to survive longer than a few minutes in $CDCl_3$ at room temperature.[7] We confirmed this finding, as outlined in the Supporting Information (see section 1.1), and showed that in $CDCl_3$ the dioxirane either reverted back to starting **1** or was destroyed in a few minutes. We found, however, that it was stabilized by the water environment, and NMR monitoring showed that it remained unchanged for as long as 2 days.

Computational Study. These findings demanded a computational study on the role of **4** and its relation to **2** and **3**, as summarized below (values at the SMD-CBS-QB3 level of theory are reported throughout).

Dioxirane 4 Formation. Theoretical simulations predicted that dioxirane formation from cyclohexanone was a slightly endergonic process, with an associated Gibbs free energy change of +1.64 kcal mol^{-1}. In this and other cases (see below), attack to non-equivalent faces of the carbonyl group in the chairlike configuration of **1**, viz. axial ("AX") and equatorial ("EQ"; see Scheme 3), was considered. A realistic scenario was obtained by incorporating explicitly a network of water molecules (in the role of proton relays) in the optimization of the reacting system[18] and then including the solvent effect (as an implicit model) via single-point calculations.

Scheme 3. Different Modes of Approach to the Cyclohexanone Molecule Considered in the Present Study and the Labeling Adopted for the Hydrogen Peroxide Molecule



The first situation examined was indicated as "N-0", where N stands for neutral (only noncharged species involved) and "0" identifies the number of water molecules included explicitly into the optimization (see Figures 2 and 3a for details). In this model, the proximal oxygen (O_P; red color in Scheme 3) became linked to the carbonyl group, giving the dioxirane, while the distal oxygen (O_D; blue) and H_P (red) gave the co-product of the reaction, viz. a water molecule. This process occurred with an activation Gibbs free energy (ΔG^*) of more than 50 kcal mol^{-1}, independently from the trajectory adopted.

The inclusion of an explicit water molecule (Figure 2; pathway "N-1") resulted in the formation of dioxirane through a five-membered cyclic transition state. However, ΔG^* remained >50 kcal mol^{-1} in this case, and the same held for "N-2" pathway (Figure 2), with an activation Gibbs free energy around 45 kcal mol^{-1}. As apparent from Figure 2, the geometric parameters of these three TSs vary little from each other, with the bonds involved in dioxirane formation, viz. the two C−O bonds and the O−O bond, comprised in a narrow range (<0.1 Å difference). The situation including two molecules of water was then examined by considering different arrangements of the reacting cluster, with a water molecule acting in the role of proton relay (as in pathway N-1) and the other coordinated via hydrogen bonding to either the distal (N-2D pathway) or the carbonyl oxygen (N-2C pathway). Activation Gibbs free energies consistently around 50 kcal mol^{-1} were again obtained.

Hydrogen peroxide is slightly more acidic than water (reported pK_a value at 25 °C of 11.6)[25] and is partially dissociated in the reaction mixture, so that a non-negligible amount of the hydroperoxide anion is present in solution. Thus, the reaction of cyclohexanone with HOO^- to give the dioxirane, hereafter termed as "anionic pathway" and indicated as "A", was likewise considered. This process was slightly more endergonic with respect to the neutral case (+ 7.73 kcal mol^{-1}). First, we examined whether this reaction occurred either via a two-step mechanism, involving the initial nucleophilic addition of the anion to the carbonyl to give a tetrahedral intermediate (the 1-hydroperoxycyclohexanolate anion) later evolving into the product, or in a single step. However, any effort to locate such a structure was unsuccessful, and only a sort of loose complex was found, the energy of which was close to the sum of the energies of cyclohexanone and hydroperoxide anion alone (data not shown).

Adopting the same approach as above, we devised several scenarios and found that this process occurs with a markedly lower activation Gibbs free energy with respect to the neutral paths described above. Thus, path "A-0" (see Figures 2 and 3b for details) showed activation Gibbs free energies of ca. 19 and 25 kcal mol^{-1} for the axial and the equatorial trajectories, respectively. Introducing a molecule of water did not lead to a cyclic TS, but we checked the effect of coordination of the distal oxygen, where the most important structural changes were occurring (pathway "A-1"). This caused a further decrease of ΔG^*, with both AX ad EQ pathways dropping to ca. 14 kcal mol^{-1}. For the geometric aspect, it is worth noting that the TSs belonging to the anionic pathway more resemble the situation of the final products (late TS), where this feature is slightly more pronounced in the A-0 path than in the A-1 one (see Figure 2).

As expected when large complexes are considered (e.g., the TSs pertaining to the "2" classes) as well as with charged species, the energy of both complexed reagents and products was much higher than the sum of isolated compounds (see

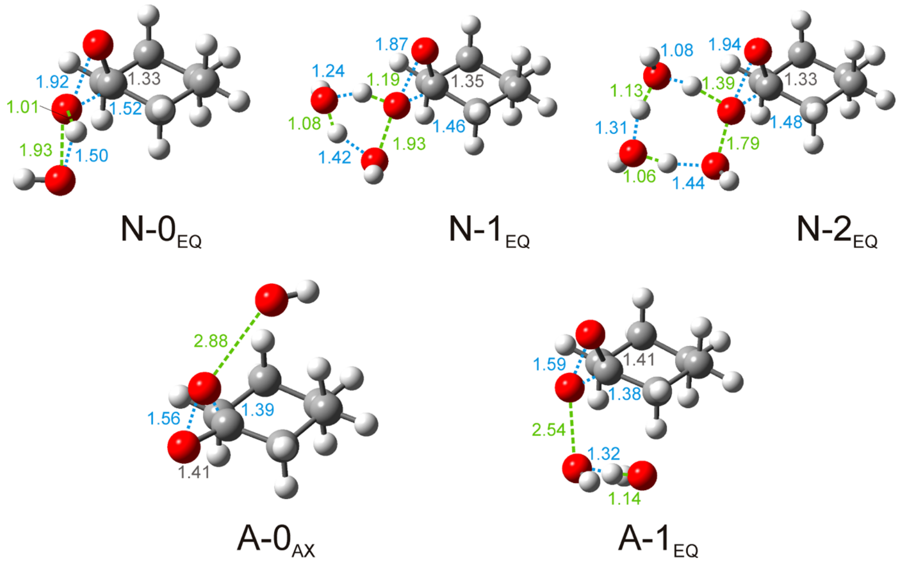


Figure 2. Optimized transition state structures for selected reacting situations describing the formation of the dioxirane intermediate. The bonds depicted with a blue dotted line and a green dashed line represent, respectively, those bonds formed and broken during the process. The corresponding bond lengths are reported (in Å), adopting the same color coding; the length of the C−O bond of the original carbonyl group is likewise reported in gray color.

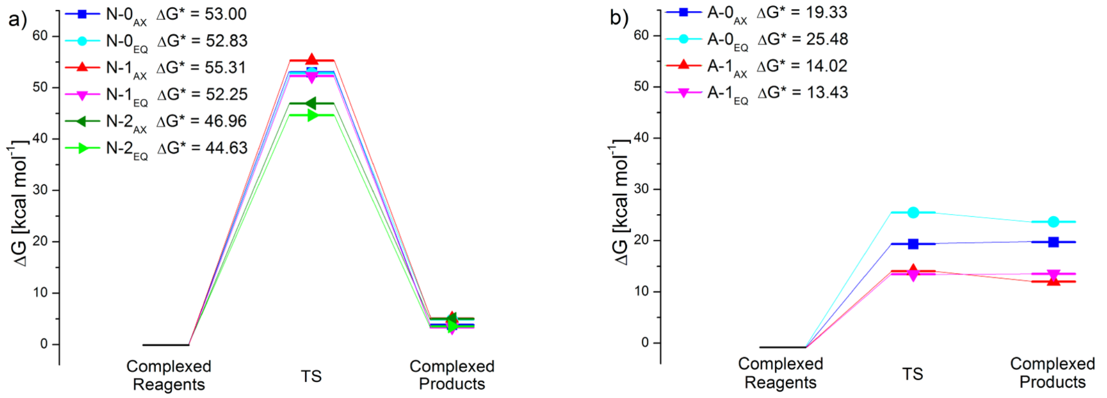


Figure 3. Energy profile at the SMD-CBS-QB3 level for the pathways: (a) “N” and (b) “A”. In each case, the energy of complexed reagents has been taken as the zero-point of the energy scale. Further notice that pathways N-2D and N-2C have been omitted for clarity (see Table 1).

Table 1), but these contributions canceled out in the calculation of ΔG* values.

Criegee Adduct **2** *Formation.* Next, the formation of the Criegee adduct was considered. This may be formed either from the starting ketone **1** or from the dioxirane intermediate **4**. Both processes are slightly exergonic, −0.94 and −2.57 kcal mol^{-1}, respectively. Formation of the Criegee adduct **2** from cyclohexanone **1** (pathway “K”) can be described as the formal addition of a molecule of hydrogen peroxide to the carbonyl moiety.

The uncatalyzed pathway (“K-0” path; already reported in the literature)[19c] occurs with an activation Gibbs free energy around 40 kcal mol^{-1}, with the axial trajectory favored by ca. 2 kcal mol^{-1} over the equatorial one. By contrast, the inclusion of one (K-1) or two (K-2) molecules of water resulted in the location of the sought for cyclic transition states, with activation Gibbs free energies around 29 and 23 kcal mol^{-1}, respectively, when considering the most favorable trajectories (see Figure 4a). The corresponding anionic pathway involving the hydroperoxide anion was not investigated because this would have involved the same (already excluded) anionic intermediate 1-hydroperoxycyclohexanolate (see above for details).

For the conversion of dioxirane **4** to the Criegee adduct **2** (pathway “D”), this involved the hydrolysis of the three-membered ring that could occur via cleavage of either the O−O or one of the two (non-equivalent) C−O bonds of the dioxirane moiety. As in the case of cyclohexanone, the usual AX/EQ dichotomy has been confronted also with this intermediate (see Scheme 3). For the O−O cleavage pathway, we found several TSs (the corresponding pathways have been named as “D^{O}”), but none of them pertained to the direct process (no TS D^{O}-0 structure found). On the other hand, the corresponding structures including one or two molecules of water acting as proton relays ranked activation Gibbs free energies around 48 and 34 kcal mol^{-1}, respectively. This supported the role of water in facilitating this rearrangement (see Figure 4b).

In contrast, all the attempts to identify a similar process involving the cleavage of either of the C−O bonds in the dioxirane moiety failed because the system evolved toward the formation of a carbonyl oxide intermediate (named **5**; this

Table 1. Selected Calculated Parameters for the Reacting Situations Described in the Text[a]

	Gibbs free energy (G), [kcal mol^{-1}]			
reacting situation	complexed reagents	TS	complexed products	ΔG^{*b} [kcal mol^{-1}]
N-0$_{\mathrm{AX}}$	3.02	56.02	6.84	53.00
N-0$_{\mathrm{EQ}}$	1.90	54.73	6.76	52.83
N-1$_{\mathrm{AX}}$	7.42	62.73	12.47	55.31
N-1$_{\mathrm{EQ}}$	9.04	61.29	12.37	52.25
N-2$_{\mathrm{AX}}$	13.89	60.85	18.89	46.96
N-2$_{\mathrm{EQ}}$	14.14	58.77	17.67	44.63
N-2D$_{\mathrm{AX}}$	13.26	68.32	19.12	55.06
N-2D$_{\mathrm{EQ}}$	14.17	67.89	20.73	53.72
N-2C$_{\mathrm{AX}}$	13.76	66.25	18.14	52.49
N-2C$_{\mathrm{EQ}}$	14.75	64.72	18.03	49.97
A-0$_{\mathrm{AX}}$	14.99	34.32	34.70	19.33
A-0$_{\mathrm{EQ}}$	9.73	35.21	33.40	25.48
A-1$_{\mathrm{AX}}$	19.30	33.32	31.29	14.02
A-1$_{\mathrm{EQ}}$	16.39	29.82	29.90	13.34
K-0$_{\mathrm{AX}}$	2.73	42.52		39.79
K-0$_{\mathrm{EQ}}$	1.89	43.49		41.60
K-1$_{\mathrm{AX}}$	7.44	36.87	5.70	29.43
K-1$_{\mathrm{EQ}}$	8.27	36.96	5.82	28.69
K-2$_{\mathrm{AX}}$	12.93	36.37	10.55	23.44
K-2$_{\mathrm{EQ}}$	12.12	35.61	10.14	23.49
D$^{\mathrm{O}}$-1$_{\mathrm{AX}}$	12.06	59.94	4.29	47.88
D$^{\mathrm{O}}$-1$_{\mathrm{EQ}}$	11.06	59.55	4.34	48.49
D$^{\mathrm{O}}$-2$_{\mathrm{AX}}$	17.68	52.91	14.20	35.23
D$^{\mathrm{O}}$-2$_{\mathrm{EQ}}$	16.96	50.44	9.93	33.48
D$^{\mathrm{C}}_{\mathrm{AX}}$		36.87	16.66	36.87
D$^{\mathrm{C}}_{\mathrm{EQ}}$		36.62	16.66	36.62
D$^{\mathrm{C2}}$-0$_{\mathrm{AX}}$	4.02	18.16	−19.06	14.14
D$^{\mathrm{C2}}$-0$_{\mathrm{EQ}}$	4.07	18.38	−19.16	14.31
D$^{\mathrm{C2}}$-1$_{\mathrm{AX}}$	8.75	19.38	−13.55	10.63
D$^{\mathrm{C2}}$-1$_{\mathrm{EQ}}$	8.92	18.99	−13.75	10.07
D$^{\mathrm{C2}}$-2$_{\mathrm{AX}}$	13.62	26.76	−10.22	13.14
D$^{\mathrm{C2}}$-2$_{\mathrm{EQ}}$	14.18	24.86	−10.22	10.68

[a] A more comprehensive list is available in Supporting Information Table S1. Gibbs free energies at the SMD-CBS-QB3 level of theory have been reported. In each case, the sum of the Gibbs free energies of the involved reagents has been taken as the zero-point of the energy scale. [b] ΔG^* values have been calculated by taking the difference between the energy of TS and the corresponding complexed reagents.

pathway is hereafter termed as "D$^{\mathrm{C}}$"). Again, both the axial and the equatorial pathways describing **5** formation occurred with activation Gibbs free energies around 37 kcal mol^{-1}. The carbonyl oxide, a valence isomer of the dioxirane, underwent hydration to give the Criegee adduct **2** with very low activation Gibbs free energies (around 10 kcal mol^{-1} in the most favorable case; see the reacting situations labeled with "D$^{\mathrm{C2}}$" in Table 1).

Bis-hydroperoxide 3 Formation. Finally, the formation of the α,α-bis-hydroperoxide (**3**) has been considered. Kinetic considerations support that **3** does not arise from the ketone since this would involve addition of two H_2O_2 molecules at the same time, a kinetically unlikely process, but rather from the dioxirane (pathway "D$^{\mathrm{B}}$"; exergonic with a $\Delta G = -8.54$ kcal mol^{-1}). However, any attempt to depict either the O−O or the dioxirane C−O bond cleavage in the presence of hydrogen peroxide and variable amounts of water molecules (from 0 to 2) failed. It appeared likely that the course of this reaction was similar to that observed for the Criegee adduct; that is, it involved the carbonyl oxide intermediate **5**, which further underwent addition of a hydrogen peroxide molecule to give the final bis-hydroperoxide (however, this step, named D$^{\mathrm{C3}}$, was not investigated in detail).

Summarizing the Mechanism. A plausible reaction mechanism supported by both theoretical simulations and experimental data is reported in Scheme 4. For dioxirane **4** formation, two different paths can take place, viz. addition of neutral H_2O_2 or its anionic form HOO^- to cyclohexanone **1**. Under the present reaction conditions, the equilibrium between the hydrogen peroxide molecule and the hydroperoxide anion (concentration estimated ca. 4×10^{-6} M under the present conditions) can be safely considered fast, due to the aqueous environment facilitating proton exchange. Accordingly, the observed reactivity can be rationalized via the Curtin−Hammett principle,[26] that is, by considering the difference in energy of the representative transition states. Thus, dioxirane results from a kind of nucleophilic addition onto the carbonyl by the hydroperoxide anion (Scheme 4, path A). The huge activation Gibbs free energy observed for the corresponding addition of neutral hydrogen peroxide (path N) militates against the direct intervention of such species in the reaction ($k_A \gg k_N$). Calculations likewise excluded the formation of the 1-hydroperoxycyclohexanolate anion. The coincidence between the experimental activation energy for cyclohexanone consumption (ca. 14 kcal mol^{-1}) and the calculated activation

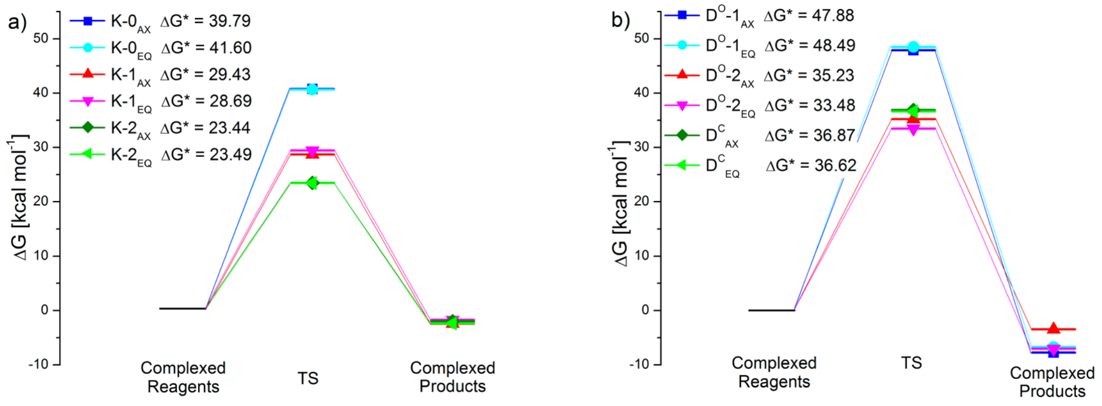
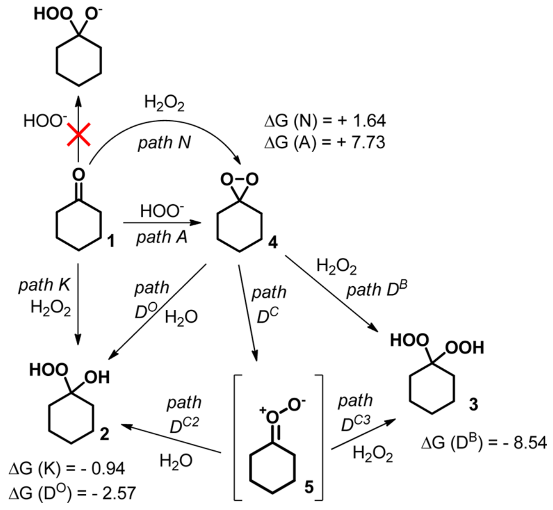


Figure 4. Energy profile at the SMD-CBS-QB3 level for the pathways: (a) "K" and (b) "D". In each case, the energy of complexed reagents has been taken as the zero-point of the energy scale (see Table 1).

Scheme 4. Proposed Reaction Mechanism[a]



[a] The energy changes (ΔG; expressed in kcal mol^{-1}) for selected pathways at the SMD-CBS-QB3 level of theory have been likewise reported.

Gibbs free energy for addition of the hydroperoxide anion to cyclohexanone further supports the present proposal.

Experiments suggest that dioxirane **4** and starting ketone **1** are in fast equilibrium with each other (**1**/**4** ratio slightly >1), and both of them may be responsible for the formation of the Criegee adduct. Indeed, theoretical calculations support that addition of hydrogen peroxide to the ketone (path K) is more favored than hydrolysis of the dioxirane intermediate. If operating, dioxirane hydrolysis may occur directly through O−O bond cleavage (path D^O) or involve a further intermediate, viz. the carbonyl oxide **5**, through C−O bond cleavage (path D^C) and ensuing (facile) addition of water (path D^{C2}). Thus, considering that the ΔG^* values for paths D^O and D^C (the rate-determining step on the way from **1** to **2** through **5**) are similar (in the 33 to 37 kcal mol^{-1} range), the conversion of **4** to **2** may occur through either of them, with the first slightly favored over the latter. By contrast, the ΔG^* value for path K is approximately 10 kcal mol^{-1} lower (around 23 kcal mol^{-1}), indicating that the formation of **2** occurs preferentially from **1** and not from **4**, that is, $k_K \gg k_{D^O} > k_{D^C}$.

Formation of the bis-hydroperoxide presumably involves again the dioxirane, likewise via the carbonyl oxide, then undergoing addition of hydrogen peroxide (via paths D^C, D^{C3}), while no evidence was found for the direct reaction of dioxirane with H_2O_2 (path D^B). The involvement of a carbonyl oxide (also called "Criegee intermediate" in the literature, as opposed to "Criegee adduct" **2**)[27] in the present reacting system also finds support from the literature since ozonolysis of vinyl ethers in the presence of H_2O_2,[10] where the involvement of a carbonyl oxide intermediate is generally accepted, leads to the same geminal bis-hydroperoxides proposed here.

The experimental data presented above also allowed us to exclude mechanisms different from that depicted in Scheme 4, such as radical reactions via $HO^\bullet$ or $HOO^\bullet$[28] since deuterium atoms in α do not affect the kinetics[29] and are conserved in the Criegee adduct formed from **1**-d_4.

CONCLUSIONS

In conclusion, the present work strongly supports the involvement of cyclohexylidene dioxirane in the hydroperoxidation of cyclohexanone with hydrogen peroxide in water. This is the first formed intermediate that is in fast equilibrium with the starting ketone. The computational analysis fully supports this hypothesis and provides a scenario in excellent agreement with experimental data. The demonstration that the hydroperoxide anion (not hydrogen peroxide) is involved in dioxirane formation suggests that this mechanism is operative only in neutral and/or basic conditions. Another important aspect is the reaction medium because water is apparently required to stabilize the dioxirane.

This mechanism can be easily adapted to rationalize the formation of all of the intermediates reported in Scheme 1b because dioxirane could act as a sort of reservoir of "oxidized" ketone and may be involved in the formation of oligomeric species, formally arising via addition of several hydrogen peroxide molecules to the starting ketone and ensuing condensation (e.g., species **V**, **VI**, and higher homologues). By contrast, since the formation of Criegee adduct **2** occurs directly from **1**, the parallel pathway through dioxirane **4** actually slows the formation of **2**. The scenario may be different, however, under catalyzed conditions, where the present mechanistic evidence may help in the search for a catalyst, which should be tailored in order to intercept the dioxirane intermediate.

EXPERIMENTAL SECTION

Typical Conditions for Batch Reactions. In a 10 mL Pyrex reactor equipped with screw stopper, a mixture of 100 μL of H_2O, 3 mmol 30% H_2O_2 (340 μL), and 1 mmol cyclohexanone (98 mg) was dropped in. The resulting mixture was then stirred at 50 °C for 2 h.

Experimental Details. Cyclohexanone, 2,2,6,6-tetradeuterocyclohexanone (98 atom % D), and 1-^{13}C-cyclohexanone (99 atom % ^{13}C) were commercially available and used as received.

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or at 600 and 150 MHz, respectively, at 25 °C, except where otherwise noted. Chemical shifts (δ) for ^{1}H and ^{13}C are given in parts per million relative to residual signals of the solvents. $CDCl_3$ was passed over a short pad of alumina before use.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure for attempted dioxirane isolation and full details about computational data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00861.

AUTHOR INFORMATION

Corresponding Authors

*Tel: +39 051 2093640. E-mail: paolo.righi@unibo.it.
*Fax: +39 0382 987323. Tel: +39 0382 987198. E-mail: davide.ravelli@unipv.it.

Notes

The authors declare no competing financial interest.

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