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Thermolysis and photolysis of 2-ethyl-4-nitro-1 (2H)-isoquinolinium hydroperoxide

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The thermal and light-induced O – O bond breaking of 2-ethyl-4-nitro-1(2H)-isoquinolinium hydroperoxide (IQOOH) were studied using ¹H NMR, steady-state UV/vis spectroscopy, femtosecond UV/vis transient absorption (fs TA) and time-dependent density functional theory (TD DFT) calculations. Thermal O – O bond breaking occurs at room temperature to generate water and the corresponding amide. The rate of this reaction, $k = 5.4 \cdot 10^{-6} s^{-1}$, is higher than the analogous rates of simple alkyl and aryl hydroperoxides; however, the rate significantly decreases in the presence of small amounts of methanol. The calculated structure of the transition state suggests that the thermolysis is facilitated by a 1,2 proton shift. The photochemical process yields the same products, as confirmed using NMR and UV/vis spectroscopy. However, the quantum yield for the photolysis is low ($\Phi = 0.7\%$). Fs TA studies provide additional detail of the photochemical process and suggest that the S₁ state of IQOOH undergoes fast internal conversion to the ground state, and this process competes with the excited-state O – O bond breaking. This result was supported by the fact that the model compound IQOH exhibits similar excited-state decay lifetimes as IQOOH, which is assigned to the S₁ → S₀ internal conversion. Copyright © 2013 John Wiley & Sons, Ltd. Supporting information may be found in the online version of this paper.

Keywords: organic hydroperoxide; thermolysis; photolysis; pump probe spectroscopy

INTRODUCTION

Most organic peroxides are thermally and photochemically unstable, due to the presence of a weak oxygen–oxygen bond.^[1,2] The cleavage of the O-O bond in peroxides usually requires ~34 kcal/ mol of input energy, and this low bond strength is caused by the nonpolar character of the O-O bond (energies of polar bonds, such as those made of heteroatoms with sufficiently different electronegativities are larger than the energies of nonpolar bonds; for example, the bond energy of N-O bond is 53 kcal/mol, while the N-N bond energy is 38 kcal/mol)^[3] and destabilization of the O-Obond due to the repulsion by nonbonding electron pairs of the two oxygen atoms. Thus, the photochemical and thermal decomposition of organic peroxides is generally initiated by the cleavage of O-O bond to form oxygen-centered radicals, which undergo additional chemical reactions, such as hydrogen atom abstraction,^[4-6] β -scission,^[6] decarboxylation,^[7–9] rearrangements,^[10,11] and addition to multiple carbon-carbon bonds.^[12,13]

Organic hydroperoxides are formed and decomposed during the oxidation of organic compounds by molecular oxygen, which is the leading source of concern for the air stability of food, gasoline, plastics and other organic materials.^[14–18] For this reason, decomposition of organic hydroperoxides has been addressed in a large number of reports,^[19–26] all of which have clearly indicated the high complexity of the reaction mechanism. The decomposition usually begins with the O – O bond homolysis of the hydroperoxide, followed by a chain of reactions involving hydroxyl and alkoxyl radicals.^[18] The reaction mechanism, rates and product distribution are readily affected by experimental conditions, such as the concentration of the hydroperoxide,^[25] temperature,^[25,27] solvent^[28] and radical initiators^[21,28] or inhibitors.^[29–31]

The mechanism of hydroperoxide thermolysis is sensitive to the initial hydroperoxide concentration. At low concentrations, decomposition follows the first-order kinetics, while at higher concentrations the switch to a bimolecular mechanism occurs. Hydrogen-bonded hydroperoxide dimers are proposed to play an important role in the bimolecular mechanism.^[32,33] The solvent characteristics play a significant role in the decomposition of organic hydroperoxides. Specifically, the purity of the solvent^[19,25] is vital, since traces of strong acids and metallic complexes can catalyze the O – O bond breakage. Furthermore, the rate of thermolysis was found to be significantly higher in alcoholic and unsaturated solvents than in aromatic or chlorinated hydrocarbon solvents.^[28] These results are explained in terms of a radical forming, bimolecular solvent (SH)/hydroperoxide (ROOH) thermolysis of the type: $ROOH + SH \rightarrow RO^{-} + S^{-} + H_2O$. The presence of radical-forming substances can also lead to the suppression of the hydroperoxide decomposition, if the formed radicals S⁻ are chemically inert. These "antioxidants" are usually phenol and aniline derivatives and lead to a decrease of the hydroperoxide decomposition rates.^[29-31,34]

Hydroperoxides that exhibit a heteroatom in the α -position display a special type of reactivity, which is proposed to occur by the heterolytic O–O bond breaking in the presence of

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nucleophiles (S_N^2 mechanism).^[35] This polarization of the O – O bond enables the α -substituted hydroperoxides to incorporate atomic oxygen into organic substrates, such as amines, sulfides, alkenes, alcohols and ketones.^[36–42] The α -heteroatom is in most cases oxygen (as in α -hydroperoxyethers^[40] or peracids^[43,44]) or nitrogen (as in α -aminohydroperoxides^[40] or α -azo hydroperoxides^[36,45,46]), and, in some cases, the insertion of oxygen is believed to involve an intramolecular H-bond between the hydroperoxylic proton and the α -heteroatom.^[36,43,45,46] The oxygen insertion can also be made catalytic if the alpha-substituted hydroperoxide is obtained from iminium ions that reversibly form pseudobase intermediates.^[38,42,47–52]

This manuscript reports the room-temperature (RT) thermolysis of one such heterocyclic hydroperoxide, derived from the isoquinolinium ion derivative. In specific, as part of our ongoing interest in organocatalytic water oxidation by iminium ions, [53,54] the isoquinolinium hydroperoxide (IQOOH) was prepared (Fig. 1), and its thermal and photochemical behavior was studied using steady-state UV/vis and NMR spectroscopy, femtosecond transient absorption (fs TA) laser spectroscopy and density functional theory (DFT) calculations. It was found that IQOOH is, in aprotic solvents, less stable than other known hydroperoxides that lack the alpha heteroatom and that the O-O bond breaking in IOOOH occurs thermally at RT to yield 2-ethyl-4-nitro-1(2H)-isoquinolinone (IQ amide). Interestingly, the stability of IQOOH is significantly increased in the presence of small amounts of methanol, and the possible reasons for this stabilization effect are discussed. The photoinduced O - O bond breaking of IQOOH generates the same product, but with a surprisingly low quantum yield. These results are discussed in terms of a fast competing internal conversion to the IQOOH ground state via an S_1 - S_0 conical intersection.

EXPERIMENTAL PART

General methods

All starting compounds and solvents were purchased from Sigma-Aldrich and used as received. The thermal decomposition of IQOOH was studied at RT (298 K). Solvents used prior to kinetic measurements were carefully distilled several times over CaH₂. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 3 500 MHz system. MS-EI spectra were measured on Shimadzu GC-MS-Q5050A spectrometer.

SYNTHESIS

4-nitroisoquinoline

Synthesis of 4-nitroisoquinoline was described previously.^[55] Concentrated nitric acid (5 ml, 84 mmol, 70%) was slowly added to a solution of 10.0 g (77 mmol) of isoquinoline in 100 ml of acetic anhydride. The solution was heated at 80 °C for 12 h and then poured over 300 g of crushed ice. After neutralization

with concentrated aqueous ammonia, the resulting solution was extracted with chloroform (3 \times 150 ml). Combined extracts were washed with 1M HCl (4 \times 100 ml) and dried over anhydrous calcium chloride. After removal of the solvent under reduced pressure, the residue was dissolved in ether. Hydrogen-chloride gas was bubbled through the ethereal solution to precipitate 4-nitroisogunolinium chloride. The resulting precipitate was filtered and dissolved in distilled water. An aqueous solution of this salt was extracted with chloroform. The organic solution was dried over calcium chloride, and the solvent was evaporated in vacuo to give 0.73 g (5.4%) of 4-nitroisoquinoline. MS ESI⁺, m/z: found, 174; calculated for C₉H₆O₂N⁺₂, 174.16. ¹H NMR (300 MHz, CDCl₃) δ ppm: 9.46 (d, J = 0.8 Hz, 1H), 9.31 (s, 1H), 8.69 (dd, J = 8.7, 1.0 Hz, 1H), 8.15 (dt, J=8.2, 1.0 Hz, 1H), 7.99 (m, J=8.5, 7.0, 1.4 Hz, 1H), 7.80 (m, J = 8.1, 7.0, 1.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 158.0, 141.0, 137.4, 134.2, 129, 128.8, 128.3, 127.8, 122.5.

2-ethyl-4-nitroisoquinolinium tetrafluoroborate (IQ⁺)

IQ⁺ was prepared by a procedure similar to that described by Lorance *et al.*^[56] Triethyloxonium tetrafluoroborate (400 mg, 2.1 mmol) was added to a 20 ml solution of 4-nitroisoquinoline (290 mg, 1.7 mmol) in dichloromethane. Mixture was allowed to stir for 4 h at RT. The resulting precipitate was filtered and recrystallized from methanol to give 0.23 g (51%). MS ESI⁺, m/z: found, 203; calculated for C₁₁H₁₁O₂N⁺₂, 203.22. ¹H NMR (300 MHz, CD₃CN-d3), δ ppm: 9.87 (s, 1H), 9.35 (d, *J* = 1.3 Hz, 1H), 8.81 (d, *J* = 8.8 Hz, 1H), 8.61 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.48 (m, *J* = 8.5, 7.0, 1.3 Hz, 1H), 8.27 – 8.15 (m, 1H), 4.81 (q, *J* = 7.3 Hz, 2H), 1.71 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CD₃CN-d3) δ ppm: 153.88, 140.68, 133.61, 132.70, 131.90, 130.45, 129.10, 123.19, 117.78, 57.84, 15.19.

2-ethyl-4-nitro-1(2H)-isoquinolinium hydroperoxide (IQOOH)

Finely crushed urea-hydrogen peroxide tablets (7 g, 35% hydrogen peroxide, 72.06 mmol H₂O₂) were added to a 15 ml solution of IQ⁺ (0.6 g, 2.07 mmol) in methanol. The resulting mixture was wrapped with aluminum foil and stirred for 20 min at RT (298K) in the absence of light. Methanol was evaporated, and the remainder was purified by column chromatography using ethyl acetate/cy-clohexane mixture (3:2) as an eluent to give 0.14 g (30%) of IQOOH. MS MALDI⁺, m/z: found, 236; calculated for C₁₁H₁₂O₄N⁺₂, 236.22. ¹H NMR (300 MHz, CD₃CN-d3), δ ppm: 9.51 (d, *J* = 0.6 Hz, 1H), 8.67 (d, *J* = 1.2 Hz, 1H), 8.61 – 8.42 (m, 1H), 7.84 – 6.98 (m, 3H), 6.34 (d, *J* = 1.3 Hz, 1H), 4.30 – 3.37 (m, 2H), 1.40 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CD₃CN-d3) δ ppm: 146.78, 130.88, 129.70, 128.10, 127.67, 127.51, 123.99, 122.73, 91.22, 50.60, 14.86.

2-ethyl-4-nitro-1(2H)-isoquinolinone (IQ amide)

IQ amide was obtained by thermal decomposition of IQOOH (0.2 g, 0.86 mmol) in 25 ml of acetonitrile at RT for 10 days. The solvent was evaporated, and the residue was recrystallized from



(a) HNO₃, Ac₂O,100° C (6%); (b) Et₃O⁺BF₄⁻, CH₂Cl₂, RT (51%); (c) H₂O₂/urea, MeOH, RT (30%)



diethyl ether to give 0.08g (43%). MS ESI⁺, m/z: found, 219; calculated for $C_{11}H_{11}O_3N_2^+$, 218.21. ¹H NMR (300 MHz, CD₃CN-d3), δ ppm: 8.81 (s, 1H), 8.64 (m, *J*=8.5, 1.1, 0.6 Hz, 1H), 8.42 (m, *J*=8.1, 1.5, 0.6 Hz, 1H), 8.11 – 7.74 (m, 1H), 7.66 (m, *J*=8.2, 7.2, 1.1 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 1.38 (t, *J*=7.2 Hz, 3H).

Steady-state measurements

Absorption spectra were recorded on Varian Cary 100 BIO UV spectrometer in 1 cm pathlenght quartz cell. Fluorescence spectra were recorded on Edinburg Instruments Fluorimeter equipped with Xe900 lamp in 1 cm pathlenght quartz cell. Tris(2,2'-bipyridine) ruthenium bis(hexafluorophosphate) in acetonitrile ($\Phi = 0.059$) was used as a standard for fluorescence quantum yield.^[57] The solutions for fluorescence measurements were prepared with absorption of 0.1 at the excitation wavelength. FTIR spectra were collected using FTIR-8400S (Shimadzu).

RT thermolysis, photolysis and quantum yield experiments

The thermal bond breakage of IQOOH was performed using 1 ml of a 0.02 M solution of IQOOH in acetonitrile. The solution was kept at RT (298 K) in the absence of light until full decomposition was achieved. Light-induced bond breaking was carried out in a 4 ml quartz cuvette with a 0.02 M solution of IQOOH in acetonitrile. Radiation source was a 400 W Hg vapor quartz immersion lamp. A 400 nm short-pass colored glass filter was used to prevent irradiation above the desired wavelength. Dry ice was used to avoid thermal decomposition due to heat emitted from the lamp. Potassium ferrioxalate was used as a standard ($\Phi_{\rm S}$ = 1.14 at 405 nm) to measure the quantum yield of IQOOH photolysis ($\Phi_{\rm IQOOH}$).^[57,58]

TA measurements

The laser system for the ultrafast TA measurement was described previously.^[59] Briefly, the 800 nm laser pulses were produced at a 1 kHz repetition rate (fwhm = 110 fs) by a mode-locked Ti:sapphire laser (Hurricane, Spectra-Physics). The output from a Hurricane was split into pump (85%) and probe (10%) beams. The pump beam (800 nm) was sent into a second harmonic generator (Super Tripler, CSK) to obtain a 400 nm excitation source. The energy of the pump beam was 2 μ J/pulse. The probe beam was focused into a horizontally translated CaF₂ crystal for white light continuum generation between 350 and 800 nm. The flow cell (Starna Cell Inc. 45-Q-2, 0.9 ml volume with 2 mm pathlenght), pumped by a Fluid Metering RHSY Lab pump (Scientific Support Inc.), was used to prevent photodegradation of the sample. After passing through the cell, the continuum was coupled into an optical fiber and input into a CCD spectrograph (Ocean Optics, S2000). The data acquisition was achieved using in-house LabVIEW (National Instruments) software routines. The group velocity dispersion of the probe pulse was determined using nonresonant optical Kerr effect (OKE) measurements.^[60] Sample solutions were prepared at a concentration needed to have absorbance of A~0.8-1 at the excitation wavelength. Data processing and analysis was achieved as follows: (i) Chirp correction was determined using nonresonant OKE measurements. (ii) Noise was reduced using a singular value decomposition method (Matlab 7.1). (iii) Data were analyzed using SPECFIT/ 32[™] Global Analysis System (Spectrum Software Associates, MA, USA).

DFT calculations

All calculations were performed at the Ohio Supercomputer Center. Ground and transition state (TS) optimization of IQOOH in the gas phase were performed using Gaussian 09 software at the B3LYP/6-31 + G^{**} level^[61,62] The vibrational frequency calculations (B3LYP/6-31 + G^{**}) were used to confirm that all stationary points were energy minima (no imaginary vibrational frequencies). Difference density (DD) plots were generated from the computed electron densities of the ground and excited states (TD-B3LYP/6-31 + G^{**}) using Gaussian 09 with consideration of implicit solvation of acetonitrile (using the polarization continuum model, PCM).^[63–68]

RESULTS AND DISCUSSION

Model compound

This study investigates the behavior of a model hydroperoxide IQOOH derived from an isoquinolinium ion IQ⁺ (Fig. 1). The IQ⁺/IQOOH system exhibits the key characteristics similar to flavinium and other iminium ions found to catalytically insert oxygen atom into organic substrates,^[47–51] such as: (i) IQ⁺ reacts with H₂O₂ to generate IQOOH, which can potentially oxidize sulfides, amines and other organic substrates by a heterolytic O – O bond breakage (i.e. IQOOH + R₂S \rightarrow IQOH + R₂S = O); (ii) Since the IQOH pseudobase pKa value is 5.03,^[69] IQ⁺ can easily be regenerated from IQOH by the addition of a weak acid.

Even though this study does not address directly the catalytic oxidation reactions by IQOOH, it provides useful information regarding the O-O bond breaking pathways in these types of compounds. The hydroperoxide, IQOOH, was synthesized from isoquinoline 1 according to Fig. 1. The nitration of isoquinoline 1 to generate 4-nitroisoguinoline 2 was achieved using nitric acid and acetic anhydride according to the method described by Bunting et al.[55] Yield of 2 was low, at merely 6%, due to the lack of reactivity of the pyridine moiety of isoquinoline towards electrophilic aromatic substitution. Despite the low yield of this reaction, the nitration of isoquinoline was performed in order to increase the electrophilicity of the C1 atom in the ring and thus promote the formation of the hydroperoxide IQOOH. The N-alkylation of compound 2 using triethyl oxonium tetrafluoroborate generated N-ethyl-4-nitroisogunolinium salt (IQ⁺), which was further treated with $\mathrm{H_2O_2}$ to produce IQOOH.

RT thermolysis of IQOOH

The solution of IQOOH in deuterated acetonitrile was found to undergo thermal decomposition at RT (298K) within 4 days. The reaction was monitored using ¹H NMR spectroscopy (Fig. 2). The NMR spectrum of IQOOH (Fig. 2a) exhibits two characteristic peaks: a multiplet at 3.8 ppm corresponding to the two diastereotopic methylene protons of the N-ethyl group, and a singlet at 9.5 ppm corresponding to the proton of the hydroperoxy group. These peaks are diminished as a function of time (Fig. 2a and 2b), and the appearance of new signals at 7.8 and 8.4-8.8 ppm is observed. After RT thermolysis was completed, the product was isolated and characterized by ¹H NMR spectroscopy (Fig. 2c) as IQ amide (Fig. 3). IQ amide has specific NMR signals with chemical shifts at 4.15 ppm (quartet) due to H-atoms on carbon 1 and a singlet at 8.8 ppm due to the H-atom on carbon 6. Additional NMR peaks were observed, which are formed and diminished during the course of the reaction. These peaks do not correspond to the starting hydroperoxide or the IQ amide product and could belong to either the reaction intermediate or the unstable byproduct.

One possible mechanism for IQ amide formation involves the homolytic O - O bond breaking of IQOOH, followed by a hydrogen atom abstraction via hydroxyl radical: IQOOH \rightarrow IQO⁻ + ⁻OH \rightarrow IQ amide + H₂O. This mechanism is supported by the fact that the homolytic O-O bond scission is known to occur in many hydroperoxides.^[25,30,70,28] However, closer inspection of the reported rates of hydroperoxide thermolysis show that the O-O bond breaking usually occurs at a much slower rate than observed in this study. For example, Table 1 lists the first-order homolysis rates of several alkyl and aryl hydroperoxides calculated using the previously reported activation energies and pre-exponential factors.^[25,30] At RT, the calculated rates fall within the 10^{-16} -10⁻¹⁰ s⁻¹ ranges, suggesting that no observable decomposition of these compounds is observed at RT within the 4 days period. It is important to note that we performed careful purification of the solvent, to ensure that the traces of impurities, such as metal ions or acids, do not catalyze the observed reaction.

One possible cause for high IQOOH decomposition rate is that the presence of the α -nitrogen atom in IQOOH decreases its O – O bond dissociation energy (BDE), presumably by providing the extended delocalization of the spin density of IQO radicals. We used DFT at the B3LYP/6-31 + G** level to evaluate BDEs of IQOOH and several other hydroperoxides (Table 2). The calculated BDEs for MeOOH and tBuOOH are lower than the experimentally obtained values,^[71,72] and this effect was also observed previously by Bach *et al.*^[73] The BDE for IQOOH was found to be 35.7 kcal/mol. While this value is by 1 kcal/mol lower than the BDEs of alkyl hydroperoxides, it is not sufficient to explain the differences in the decomposition rates.

Previous reports have shown that, in some cases, the thermolysis of hydroperoxides occurs faster than expected based on their O–O bond dissociation energies.^[32,33] In these studies, the hydrogen-bonded hydroperoxide dimers were postulated to be involved in the homolysis step. To investigate the role of hydrogen-bonded dimer formation in the case of IQOOH, we investigated the effect of methanol on the rate of IQ amide formation. Due to its tendency to form hydrogen bonds, methanol is expected to break the hydroperoxide dimer and possibly



Figure 2. Changes in ¹H NMR spectra of 0.015 M IQOOH in CD_3CN after: a) 0 min; b) 34 h and c) 4 days of RT thermolysis



Figure 3. Formation of IQ amide upon RT thermolysis of IQOOH

slow down the RT thermolysis. This behavior was indeed observed, as shown in Fig. 4.

The progress of IQOOH RT thermolysis was studied in the absence (Fig. 4a) and presence (Fig. 4b) of methanol using UV/ vis absorption spectroscopy, by monitoring the disappearance of the IQOOH absorption band at $\lambda_{max} = 384$ nm and the growth of the IQ amide absorption at 360 nm. In the absence of methanol, significant amount of IQOOH converted into IQ amide within 28 h. In the presence of only 2% of methanol, the stability of IQOOH is significantly increased, and essentially no RT thermolysis is observed over the period of 5 days. Even though this preliminary study on methanol effect seems to support the presence of hydrogen-bonded dimers, the follow-up experiments have ruled this mechanism out. For example, the dimer mechanism should exhibit the second-order kinetics with respect to IQOOH concentration. To the contrary, the kinetic studies on IQOOH in acetonitrile (Fig. 5) suggest that the RT thermolysis is first order with respect to IQOOH concentration, with the rate constant of $k \sim 5.4 \cdot 10^{-6} \text{ s}^{-1}$. This value is significantly lower than the estimated RT rate constant for several other hydroperoxides (Table 1).

Table 1. Room temperature decomposition rates, frequencyfactors and activation energies of several hydroperoxides						
ROOH	A, s ⁻¹	E _a kcal/mol	k_{est} at $25^{\circ}Cs^{-1}$			
t-Bu ^a α-cumyl ^b n-octyl ^b decalyl ^b tetralin ^b	$\begin{array}{c} 1.0\cdot 10^{16}\\ 1.3\cdot 10^{11}\\ 1.0\cdot 10^{10}\\ 8.5\cdot 10^{13}\\ 1.3\cdot 10^{11} \end{array}$	43ª 29 ^b 26.9 ^b 32.1 ^b 29 ^b	$\begin{array}{c} 1.0 \cdot 10^{-16} \\ 1.0 \cdot 10^{-12} \\ 1.7 \cdot 10^{-10} \\ 1.0 \cdot 10^{-11} \\ 5.0 \cdot 10^{-13} \end{array}$			
^a Values obtained from reference ^[25] ^b Values obtained from reference. ^[30]						

Table 2. O-O Bond dissociation energies ΔH_{298} , Gibbs free
energies ΔG_{298} and standard entropies of formation ΔS_{298} (kcal/
mol) of several hydroperoxides, computed at B3LYP/6-31+G**
level of theory

ROOH	ΔH_{298} (experiment)	ΔH_{298}	ΔG_{298}	$\Delta \; S_{298}$
MeOOH t-BuOOH IQOOH	44.6 ^a 43.8 ^b	36.6 36.7 35.7	26.7 26.3 25.1	0.03 0.03 0.03

^a Values obtained from reference^[71]

^bValues obtained from reference^[72]. All values reported in kcal/mol. The frequencies were scaled by factor 0.9804 (thermal correction).

The lack of IQOOH dimers was also confirmed using ¹H NMR spectroscopy. Figure 6a represents the changes in NMR spectra of IQOOH upon addition of methanol. For comparison, Fig. 6b outlines the effect of methanol on IQOH, a model compound that generates hydrogen-bonded dimers. In case of IQOOH, the increase of methanol concentration only leads to a monotonous shift of OOH proton (proton 9) from 9.51 to 10.4 ppm as well as the broadening of the signal (Fig. 6a). The shift of the OOH proton to a higher frequency can be explained by intermolecular hydrogen bonding with methanol molecules. On the other hand, the effect of methanol on IQOH is much more prominent. Upon addition of methanol to IQOH, we observe the change in the chemical shifts of all protons and their coupling constants (Fig. 6b) that is indicative of the disassembly of IQOH dimers in the presence of methanol. If IQOOH were present in a similar dimer network, we would also expect the change in the coupling constants of all protons, similar to IQOH. Furthermore, the concentration-dependent NMR studies of IQOOH and IQOH (Fig. S1, Supporting Information) provide additional evidence of the absence of IQOOH hydrogen-bonded dimers and the presence of dimers in the case of IQOH. Based on these NMR and kinetic findings, we ruled out the possibility of hydrogenbonded IOOOH dimers formation in our studies.

In contrast to the low thermolysis rates observed with alkyl and aryl hydroperoxides, the hydroperoxides that contain α-heteroatoms exhibit significantly higher rates of thermolysis (for example, a flavin-based hydroperoxide exhibits the rate constant at RT of $1.3 \cdot 10^{-5} \text{ s}^{-1}$.^[74] In the presence of appropriate amines or sulfides, the oxygen-atom transfer from hydroperoxide to the substrate was found to occur,^[75–77] and the mechanism of this reaction is not well understood. It is proposed to involve a heterolytic O-O bond dissociation by an S_N2-type reaction of the type: $R_2S + R'OOH \rightarrow R_2SO + R'OH$. The role of the heteroatom in this chemistry is to polarize the O-O bond towards heterolysis. The support of the S_N2 mechanism is obtained in a study showing that the rate of oxygen transfer depends on the pKa value of the formed pseudobase R'OH.^[78] Given the structural similarities between IQOOH and the flavin hydroperoxide and the fact that the IQOH pKa value is 11.15^[69] (similar to flavin pseudobase, $pKa = 9.9^{[79]}$), we anticipated that IQOOH can perform similar oxygen atom transfer processes in the presence of suitable substrates. To confirm this behavior, we investigated a reaction between dimethyl sulfide and IQOOH (Fig. S2, Supporting Material). In addition to the formation of IQ amide due to the intramolecular

reaction, we observed the formation of pseudobase IQOH and the oxidized dimethyl sulfoxide. These results show that IQOOH also undergoes the oxygen-atom transfer reactions characteristic of other α -heteroatom hydroperoxides.

While an S_N2-type reaction can be proposed for a reaction between dimethyl sulfide and IQOOH, this type of chemistry cannot explain the observed intramolecular RT thermolysis of IQOOH to generate IQ amide and water. In this case, the nucleophile (hydride anion) would need to attack the oxygen atom via strained four-membered TS, which seems energetically demanding. Furthermore, the $S_N 2$ -type mechanism cannot explain the strong methanol effect observed for IQOOH RT thermolysis (Fig. 4b). To obtain a better mechanistic understanding of this low-barrier thermolysis, the TS was optimized at the UB3LYP/6-31 + G** level (Figure 7b). Surprisingly, we located the TS at only 1.11 kcal/mol above the IQOOH ground state, and the structure shows clearly that the C1 proton has shifted to the C9 position. This proton shift is likely facilitated by the electron donation from the nitrogen lone pair, as shown in Figure 7a. In addition to the proton shift, the O-O bond is significantly elongated (the TS bond length is 2.478 Å), while the weak C1–O bond is formed (TS bond length is 1.745 Å). Thus, a hemiacetal-type TS results, which further undergoes water elimination to generate the IQ amide, as illustrated in Figure 7a. Based on this calculation, we propose that the IQOOH



Figure 5. A first-order profile of the thermal decomposition of IQOOH solutions in acetonitrile at room temperature (298K): red (0.1 mM); blue (0.18 mM)



Figure 4. The changes in UV/vis absorption spectra of (a) 0.15 mM IQOOH in acetonitrile after 5 min (red), 2 (orange), 21 (green) and 28 h (maroon) and (b) 0.16 mM IQOOH in acetonitrile/methanol mixture (98:2) after 5 min (red), 1 (red), 2 (orange), 3 (green) and 5 days (maroon) at room temperature thermal decomposition. The blue dashed line represents the UV/vis spectrum of 0.1 mM IQ amide in acetonitrile



Figure 6. Changes in ¹H NMR spectra upon addition of methanol to: (a) 0.15 mM of IQOOH in CD₃CN; (b) 0.18 mM of IQOH in CD₃CN; (d)-dimer, (m)-monomer

thermolysis is facilitated by the presence of the adjacent nitrogen center, which, through conjugation with the aromatic moiety, serves as an internal base to abstract the C–H proton and facilitate the nucleophilic attack of C1 carbon at the distal oxygen center of the OOH moiety. This behavior would explain the discrepancy between the rates reported in Table 1 for several alkyl hydroperoxides and the rate of IQOOH RT thermolysis. It is possible that such a mechanism operates in catalytic oxidation reactions of nucleophiles by other hydroperoxides that exhibit a heteroatom in the α -position.

In light of this mechanism, the effect of methanol becomes clear: hydrogen bonding between methanol and the nitrogen center of IQOOH is expected to weaken the electron-donating ability of the nitrogen center, thus raising the barrier for the C1-H proton abstraction required to reach the TS in Figure 7. For example, it is interesting to compare the 1.11 kcal/mol activation energy of IQOOH with the barrier found in benzyl hydroperoxide. Benzyl hydroperoxide is structurally similar to IQOOH, but lacks the basic nitrogen site, and it requires 41.1 kcal/mol to undergo O–O bond scission and water elimination.^[80] This comparison shows that the presence of N-center in IQOOH drastically stabilizes the TS for thermolysis. The 1.11 kcal/mol barrier is very small, suggesting that the reaction likely occurs in multiple steps, with other TSs of higher energy. Additional computational studies are underway to fully characterize the reactivity of IQOOH.

Photolysis of IQOOH

Since RT thermolysis of IQOOH occurs at RT, we postulated that the O-O bond cleavage might occur with the investment of light energy as well. The UV/vis absorption and fluorescence



Figure 7. (a) Proposed mechanism for the formation of IQ amide upon RT thermolysis of IQOOH. (b) Calculated transition structure (two projections) for the 1,2-proton transfer of IQOOH at the UB3LYP/6-311 + G^{**} level

spectra of IQOOH (Fig. 8a) offer some support for the presence of photolysis: (i) the lowest energy absorption of IQOOH appears at 384 nm (3.23 eV), which is more than sufficient to break the O-O bond (calculated BDE is 1.55 eV, Table 1); (ii) the IQOOH fluorescence ($\lambda_{max} = 514$ nm) exhibits very low quantum yield $(\Phi = 5.4 \cdot 10^{-4})$, which is plausibly caused by the excited-state O-O bond cleavage of IQOOH. To perform the initial characterization of IQOOH excited states, time-dependent DFT (TD-DFT, B3LYP/6-31 + G**, PCM acetonitrile) was used to evaluate the first four singlet excited states of IQOOH. The DFT methodology reproduces the experimental findings to a satisfactory degree: (i) calculated ground-state vibrational frequencies match well with the experimental values, as shown in Fig. S3, Supporting Information; (ii) calculated electronic transition energies correlate well with the experimental UV/vis absorption spectrum, as shown in Figure 8a. Given this good correlation with the

experiment, the results of TD-DFT calculations were used to generate DD plots presented in Fig. 8b.

The DD plots show sections of the IQOOH molecular framework in which the electronic charge is depleted (red color) or accumulated (green color) upon excitation. One obvious observation that can be made from DD plots is that most of the charge redistribution involves the isoquinoline framework, while the O–O moiety exhibits only minor changes in the electron density redistribution upon excitation. The photolysis of peroxides usually occurs via $n \rightarrow \sigma^*$ transition,^[81] and this type of excited state should give rise to DD plots with large excited-state redistribution of electronic charge around the O–O group. On the contrary, the $S_1 \rightarrow S_0$ DD plot of IQOOH exhibits essentially $\pi \rightarrow \pi^*$ character with a certain degree of charge-transfer from the donating phenyl group to accepting nitro group. These results suggest that the Frank–Condon point of the S₁ state of IQOOH does



Figure 8. (a) Absorption (black) and emission (red) spectra of 0.12 mM IQOOH in acetonitrile. The IQOOH fluorescence quantum yield is $\Phi = 5.4 \cdot 10^{-4}$. Blue lines represent vertical excitation energies of IQOOH calculated using TD-B3LYP/6-31 + G^{**} level of theory (acetonitrile as a solvent using PCM model). Oscillator strength axis corresponds to calculated transitions; (b) Difference density plots calculated using time-dependent DFT methods (TD-B3LYP/6-31 + G^{**}; PCM acetonitrile). Isovalue: (0.001). Red color represents depletion, while green color represents accumulation of the electronic density in the excited state

not exhibit O-O bond dissociative character. However, these calculations do not address whether the O-O bond dissociation occurs during the vibrational relaxation of the IQOOH S₁ state.

To investigate whether IQOOH photolysis occurs, the irradiation of IQOOH at 400 nm was monitored using NMR, steady-state UV/vis spectroscopy and fs TA spectroscopy. The NMR spectra of photolyzed sample (Fig. 9) are similar to those collected during RT thermolysis: the peaks of IQOOH decrease in intensity after prolonged irradiation, with a concomitant growth of IQ amide peaks at 7.8 and 8.4–8.8 ppm (Fig. 9a–d).

However, the photolysis of IQ amide promotes the appearance of an additional product with singlets at 9.4 and 9.9 ppm, as well as a quartet at 4.81 ppm. This product was identified as isoquinolinium ion IQ⁺, whose NMR spectrum is shown in Fig. 9f. The mechanism of IQ⁺ formation is currently not known, but we postulate that it originates due to the shift in the IQOOH/IQ⁺ equilibrium (IQOOH + $H^+ \rightarrow IQ^+ + H_2O_2$) due to the release of a proton during the decomposition of IQO radical. We observed similar behavior during the electrochemical oxidation of pseudobases of flavinium ion, which have the pseudobase pKa value of 3.7.^[53] Since the IQOOH/IQ⁺ conversion is expected to occur at the pH = 5.03,^[69] the proton removal from IQO⁻ radical is likely to shift the IQOOH/IQ⁺ equilibrium and lead to the release of IQ⁺. Thus, the photochemical decomposition of IQOOH is clearly more complicated than the thermal process, presumably due to higher energy provided by the 400 nm photons, allowing for more possible reaction pathways.^[82]

The quantum yield for IQOOH photolysis was determined using potassium ferrioxalate as a standard.^[58] The UV/vis absorption spectroscopy was used to monitor the change in IQOOH concentration with irradiation time as the decrease of the 384 nm absorption band, while the formation of IQ amide was monitored using the growth of the 360 nm band (Fig. (10a)). The quantum yield for IQOOH photolysis in acetonitrile was determined to be only 0.7%, suggesting that the excited-state O - O bond breaking is not the major deactivation mechanism of IQOOH S₁ state. This finding was surprising given that some sort of nonradiative process must be the cause for the very low IQOOH fluorescence quantum yield (0.05%). The photolysis is even less efficient in methanol (0.15%, Fig. 10b), implying a possible role of hydrogen bonds on the photophysics/photochemistry of IQOOH.

The low quantum yield for IQOOH photolysis ($\Phi = 0.7\%$ in acetonitrile, Fig. 10a) and the low IQOOH fluorescence yield $(\Phi = 5.4 \cdot 10^{-4})$ in acetonitrile) raise the question of what is the process that causes deactivation of IQOOH and competes efficiently with the O-O bond breaking and fluorescence. To investigate this in more detail, we collected the fs TA spectra of IQOOH in acetonitrile (Fig. 11). Most of the transient signal decays within the initial 50 picoseconds, confirming that the excited IQOOH indeed undergoes a fast deactivation process. Three components are observed in TA spectra: (i) the initially formed transient (red trace in Fig. 11a), which has a lifetime of $\tau_1 = 0.8$ ps and consists of the ground-state bleach with $\lambda_{max} =$ 389 nm and a weak broad excited-state absorption band that covers the 400-800 nm region; (ii) the second transient with a strong absorption at 441 nm (pink trace, Fig. 11a), which is formed with a $\tau_1 = 0.8$ ps lifetime and decays with $\tau_2 = 8.6$ ps lifetime. The decay of this transient is associated with a blue shift of the absorption maximum, as can be seen by comparing the $\tau_1 = 1$ ps and $\tau_2 = 11$ ps spectra; (iii) The third transient at 438 nm is very weak (yellow trace, Fig. 11a), and exhibits long lifetime (remains unrecovered during the time window of our experiment, which is 1.6 ns).

This fast excited-state decay is consistent with the low fluorescence quantum yield of IQOOH. In addition, the ground-state bleach at 389 nm almost completely recovers within 1 ns, suggesting that no detectable photochemical process occurs, at least not the one with the formation of long-lived products. This is in turn consistent with the low photolysis quantum yield of IQOOH. Based on these experimental findings, two possible mechanisms for fast excited-state deactivation of IQOOH were proposed: (i) the bond break/form model, in which the O-O bond breaking from the S₁ state of IQOOH is followed by a fast recombination of IQO⁻ and OH⁻ radicals to regenerate the ground-state IQOOH. In accordance with this model, the observed τ_1 =0.8 ps lifetime can be assigned to the decay of IQOOH S₁ state and the rise of IQO⁻ radical signals due to O-O bond breakage (IQOOH* \rightarrow IQO⁻ + OH⁻), while the τ_2 = 8.6 ps component can be assigned to the recombination of the formed radicals to generate the S_0 state of IQOOH (IQO' + OH' \rightarrow IQOOH). The weak



Figure 9. Changes in ¹H NMR spectra of 0.02 M IQOOH in CD₃CN illustrating the light induced decomposition after (a) 0 min; (b) 45 min; (c) 90 min and (d) 150 min. The reference ¹H NMR spectra of IQ amide (0.02M in CD₃CN) and IQ⁺ (0.05 M in CD₃CN) are presented in graph e and f



Figure 10. The changes in UV/vis absorption during 400 nm photolysis of 0.18 mM IQOOH after 0 (red), 5 (orange), 15 (green), 25 (maroon), 35 (cyan) and 45 min (blue) of irradiation. The measurements were done in two solvents: (**a**) acetonitrile and (**b**) methanol. The pink dashed line in each graph represents the UV/vis absorption of IQ amide

long-lived transient with lifetime $\tau_3 > 3$ ns can be assigned to the fraction of radicals that escape the recombination and continue into the thermal reaction to generate IQ amide and water; (ii) the S_1/S_0 conical intersection model, according to which the S_1 state of IQOOH undergoes thermal S_1/S_0 deactivation. According to this model, the transient with $\tau_1 = 0.8$ ps lifetime can be assigned to $S_1 \rightarrow S_0$ internal conversion, the $\tau_2 = 8.6$ ps lifetime can be assigned to the vibrational cooling of S_0 state, while the long-lived $\tau_3 > 3$ ns component appears due to the slight red-shift of the IQOOH ground-state absorption spectrum in a solvent that has elevated temperature due to thermal equilibrium between IQOOH and the solvent.

To experimentally distinguish between the break/form and the conical intersection models, the photophysical behavior of a model compound IQOH was investigated (Fig. 12). The lack of O – O bond in IQOH restricts it from undergoing the break/ form deactivation mechanism. Interestingly, the TA spectra of IQOH are surprisingly similar to those of IQOOH, with an absorption band at 434 nm and the bleach at 395 nm (Fig. 12a). The signal dynamics exhibit three lifetimes ($\tau_1 = 0.8$ ps and $\tau_2 = 10$ ps, $\tau_3 > 3$ ns), which are very similar to the lifetimes observed in the case of IQOOH (Fig. 11). This large similarity between IQOOH and IQOH photophysics strongly implies that the O–O bond breaking is not involved in the fast excited-state deactivation of IQOOH. It was postulated that the S₁/S₀ conical

intersection model is valid, and the following mechanism for IQOOH photolysis is presented (Fig. 13): excitation of IQOOH at 400 nm generates "hot" S_1 state with π,π^* character. The short $\tau_1 = 0.8$ ps component is assigned to the $S_1 \rightarrow S_0$ internal conversion. This assignment is based on the fact that IQOH exhibits stimulated emission at 545 nm, which decays with the similar rate lifetime ($\tau_1 = 0.9$ ps). The vibrationally excited S₀ state further undergoes intramolecular (IVR) and intermolecular (VET) vibrational cooling with a $\tau_2 = 8.6$ ps lifetime. The $\tau_2 = 8.6$ ps lifetime is consistent with the IVR and VET lifetimes reported using IR-pump-UV/vis-probe experiments.^[83] The rate of IVR and VET must be significantly higher than the rate of O-O bond scission, causing only less than 1% of vibrationally excited S₀ population to form IQ amide. The nuclear coordinate that leads to this fast $S_1 \rightarrow S_0$ internal conversion of both IQOOH and IQOH is currently not known. It is interesting to note that we previously observed a very similar fast $S_1 \rightarrow S_0$ conversion in another hemiaminal, named EtFIOH (N(5)-ethyl-4a-hydroxyflavin, Fig. S4, Supporting information).^[84] In this study, we proposed that the excited-state deactivation occurs due to $S_1 \rightarrow S_0$ conical intersection reached via $sp^3 \rightarrow sp^2$ hybridization change of the N5 atom of the flavin moiety, followed by an out-of-plane distortion of the pyrimidine ring. It seems possible that this fast excited-state deactivation is general for other hemiaminal derivatives that are coupled with the aromatic units.





Figure 11. (a) TA spectra of 1 mM solution of IQOOH in acetonitrile after the 400 nm excitation pulse at -4.9 (**black**), 0 (**red**), 0.2 (**blue**), 0.5 (**dark cyan**), 1.0 (**pink**), 11 (**cyan**), 201 (**yellow**) and 301 ps (**green**) probe delays; (b) Dynamics of IQOOH transient absorption collected at 427 and 389 nm. Black lines represent fits obtained using the following lifetimes: $\tau_1 = 0.8$ ps, $\tau_2 = 8.6$ ps and $\tau_3 > 3$ ns

Figure 12. (a) TA spectra of 1 mM solution of IQOH in acetonitrile after the 400 nm excitation pulse at -1.1 (**black**), 0 (**red**), 0.2 (**blue**), 0.7 (**dark cyan**), 4.0 (**pink**), 10 (**cyan**), 20 (**orange**), 200 (**yellow**) and 1309 ps (**green**), respectively; (b) Decays dynamics of IQOOH transient absorption signals collected at 439 and 393 nm, respectively. The black lines correspond to fits obtained using the following lifetimes: $\tau_1 = 0.8$ ps, $\tau_2 = 10$ ps and $\tau_3 > 3$ ns; (c) structure of IQOH

Last, we investigated whether the variations in solvent polarity/viscosity can be used to manipulate the rate of nonradiative $S_1 \rightarrow S_0$ deactivation. Transient spectra of IQOOH in all solvents studied here are qualitatively similar (Fig. S5 and S6, Supporting Information), and the signal dynamics (Fig. 14 and Table 3) are not drastically affected by the solvent characteristics. In specific, the polarity study shows that dynamics at 427 nm consist of two components with lifetimes in the $\tau_1 = 0.5 - 1.0$ ps and $\tau_2 = 7.0 - 12.0$ ps ranges, while the viscosity study shows the presence of only one lifetime component that varies in the 3.5-4.5 ps range (Table 3). It appears that the most dominant difference occurs between the two sets of solvents; that is, when one switches from aprotic solvents (benzene, chloroform, etc.) to the range of protic solvents (methanol/ethylene-glycol mixtures). These results suggest that the protic solvent-induced changes in hydrogen bonding patterns of IQOOH cause the $S_1 \rightarrow S_0$ conversion to occur faster than in aprotic solvent. This increased rate of deactivation in turn additionally reduces the guantum yield for photolysis (from 0.7% in CH₃CN to 0.15% in methanol, Fig. 8).

CONCLUSION

The RT thermolysis and photolysis of IQOOH were found to lead to the formation of water and the corresponding amide, IQ amide. The rate of thermal decomposition of IQOOH at RT is significantly higher than that of typical alkyl and aryl hydroperoxides, even though the calculated bond dissociation energies are similar. Surprisingly, this rate is greatly inhibited in the presence of small amounts of methanol. Based on the TS structure calculated using DFT, we propose that the RT thermolysis in IQOOH is facilitated by the C1–C9 proton shift. In the presence of methanol, the proton shift is less likely to occur, as the basicity of the nitrogen center is reduced due to the hydrogen bonding with methanol. The photochemical decomposition proceeds with a very low quantum yield.



Figure 13. Proposed mechanism of IQOOH photolysis



Figure 14. Decay dynamics of 1 mM solution of IQOOH monitored at (a) 440 nm in ethylene glycol/methanol mixtures with relative viscosities: 3.8 (red); 7.4 (blue); 12 (dark yellow) and 20.8 (whine). (b) 427 nm in the polar solvents: benzene (red); dichloromethane (blue); acetonitrile (dark yellow); and dimethylsulfoxide (wine)

Table	3.	Lifetimes	of	components	observed	in	transient
absorp	tior	n measure	mei	nts of IQOOH	in different	t so	lvents

Viscosity			Polarity			
MeOH:EG molar fraction	η/mPa ·s ^[85]	τ/ps	Solvent	Diel. constant ^[86]	τ_1/ps	τ_2/ps
1:1	3.8	3.9	Benzene	2.31	1.0	9.0
0.3:0.7	7.4	3.5	CH_2CI_2	9.08	1.0	12.0
0.15:0.85	12.0	3.7	CH₃CN	37.5	0.8	8.0
0:1	20.8	4.3	DMSO	46.68	0.5	7.0

Fs TA measurements reveal that the excited-state dynamics of IQOOH are very similar to the model compound IQOH. Since IQOH cannot undergo O–O bond breakage, it was proposed that the surprising photostability of IQOOH could be ascribed to the fast S_1/S_0 thermal deactivation.

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