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ARTICLE

Photosensitized selective semi-oxidation of tetrahydroisoquinoline: A singlet oxygen path‡

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Selective semi-oxidation of tetrahydroisoquinoline (THIQ) leads to a valuable dihydroisoquinoline (DHIQ) derivative via singlet oxygen photooxidation process. Typical photosensitisers (i.e., Ru complexes) can activate the reaction even under heterogeneous conditions that facilitate catalyst separation and reusability. In contrast to DHIQ, THIQ acts as an efficient singlet oxygen quencher driving the reaction selectivity. The reaction can also be facilitated by semiconductor catalysts such as MoCo@GW, a glass wool-based catalyst that is easy to separate and reuse and compatible with flow photochemistry. Its role is to mediate the formation of isoquinoline (IQ) and thus an *in situ* generated singlet oxygen catalyst. Laser flash photolysis with NIR detection provides proof of the singlet oxygen mechanism proposed and rate constants for the key steps that mediate the oxidation.

Dedicated to Dr. Silvia Braslavsky as her amazing journey through science brings her to a memorable landmark

Introduction

Reactions that involve partial hydrogenation or de-hydrogenation present selectivity challenges due to catalytic processes that tend to proceed to completion; for example, we recently reported on the reduction of alkynes, where it is easy to proceed completely to the alkane, but difficult to stop "half way" at the alkene.[1, 2] In the case of oxidations, a similar characteristic is common, for example the overoxidation of 1,2,3,4-tetrahydroisoquinoline (THIQ) to yield isoquinoline (IQ) is common, while stopping at the semi-oxidation product – dihydroquinoline (DHIQ) is challenging and requires highly selective catalysts. This is reflected in commercial pricing, where DHIQ is 70 times more expensive than THIQ and 200 times more expensive than IQ.[3] The possibility of carrying out these selective transformations with reusable catalysts and utilising molecular oxygen constitute a preferred sustainable pathway. Badu-Tawiah et al.[4] have recently reported on the photocatalytic aerobic dehydrogenation of tetrahydroquinolines (THQ) and THIQ derivatives. While they recognise THIQ oxidation is frequently incomplete, they attribute this unusual reactivity to the hyper-conjugation of the molecule and use N-substituted derivatives to achieve full oxidation. Contrasting reports suggest the formation of singlet oxygen under photocatalytic conditions can be either detrimental[5] or essential[6] when considering aerobic oxidation of N-substituted THIQ to their corresponding isoquinoline derivatives. In this work, we show singlet oxygen is essential for the dehydrogenation of THIQ and that the oxidation process is stalled until minimal concentrations of IQ are generated *in situ* during the reaction, driving selectivity towards the semi-oxidation product DHIQ.

Oxidation of THIQ with visible light showed an induction delay before the reaction starts. Using different solvents with different oxygen solubility affected the reaction delay time, and experiments with deuterated methanols with various singlet oxygen lifetimes suggested the involvement of singlet oxygen in this reaction. Further experiments with laser flash photolysis were a confirmation on the main role of singlet oxygen in THIQ oxidation.

The mechanistic studies shown here test a recently introduced photocatalyst based on glass wool as an inexpensive, widely available catalyst support that with adequate surface modification can provide physical or chemical affinity towards numerous catalytic materials.[7, 8] In this research heterogeneous and homogeneous catalysts were used. For heterogeneous a

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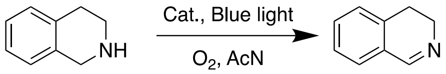
Supplementary information includes details of catalyst preparation and characterization, XPS data and additional conversion/selectivity graphs.

newly designed molybdenum disulfide-cobalt semiconductor catalyst (MoCo@GW) and a modified Ru(bpy)$_3$Cl$_2$ (RuB@GW}, both supported on glass wool, were selected, while a homogeneous catalyst, commercial Ru(bpy)$_3$Cl$_2$, was also tested. Remarkably, these catalysts allow for selective photooxidation to dihydroisoquinoline (DHIQ), avoiding common overoxidation to isoquinoline (IQ), under oxygen atmosphere, room temperature, and visible light irradiation.



Scheme 1. Selective oxidation of THIQ to DHIQ catalysed by supported Ru@GW, MoCo@GW or soluble Ru(bpy)$_3$Cl$_2$. When no catalyst is added the reaction shows a prolongued induction period until catalyst is generated *in situ.*

The reaction was performed under blue light excitation (wavelength centred at ~450 nm) and an oxygen atmosphere. For catalytic experiments 50 mg of the heterogeneous catalyst were used. Kinetic studies show a long induction period for the reaction to start; for example, under an irradiance of ≤6 Wcm^{-2}, it takes as long as 90 minutes to achieve the first 10% conversion, followed by a dramatic acceleration of the partial oxidation to DHIQ (*vide infra*). Given the high value-added for DHIQ we decided to undertake a mechanistic study of this semi-oxidation step and the parameters that control the rate, initial delay, and selectivity of the process. Our studies show that MoCo@GW can perform single electron transfer (SET) reactions (even if inefficiently) that can get the oxidation started and eventually produce enough IQ that can accelerate the reaction through efficient singlet oxygen mechanisms. While alternative direct photosensitization to generate singlet oxygen (e.g., with soluble Ru(bpy)$_3$Cl$_2$) allows a delay-free oxidation process, the use of MoCo@GW has the advantage of being readily removable from the reaction media and also potentially compatible with flow photocatalysis.

We combine catalyst characterization and bench studies with laser flash photolysis which under a variety of conditions – including near infrared detection – lead to compelling kinetic information showing the role of singlet oxygen in the advanced stages of the reaction and lead to information enabling the reduction or elimination of the initial reaction delay.

Experimental

See ESI for additional information on experimental conditions, sources of materials and spectroscopic and analytical conditions.

Conditions of irradiation

The standard conditions for reaction involved 67 mg of THIQ (0.125 M) in 4 mL of acetonitrile, irradiated with ≤ 6 Wcm^{-2} of LED light centered at ~450 nm (LEDi, Luzchem online standards for LED Illuminator with FWHM 23 nm) under O$_2$ atmosphere with air cooled samples maintained at ~23 °C. A detailed spectroscopic analysis of this light source reveals that it contains 0.02% of light below 400 nm.

Laser flash photolysis and NIR detection

The laser flash photolysis experiments were performed using a Surelite Nd-YAG laser 355 nm (~10-20 mJ/pulse) in a customized LFP-111 laser-flash photolysis (LFP) system (Luzchem Inc., Ottawa, Canada) and 1×1 cm^2 or 0.7 x 0.7 cm^2 LFP cuvettes from Luzchem. Samples had an absorbance of ~0.3 at the laser wavelength.

Time resolved singlet oxygen luminescence measurements were conducted using the same laser system as above and were detected at right angles using a Hamamatsu photomultiplier tube sensitive in the near-IR. The signal was captured and digitized using a Tektronix 2440 transient digitizer part of the customized Luzchem laser flash photolysis system. Singlet oxygen measurements were made with the detector monochromator set at 1270 nm, where Singlet oxygen has an emission peak, with samples having absorbances at 355 nm in the range of 0.1 - 0.4.

Synthesis and characterization of MoCo@GW catalyst

Initial requirements for the active species attachment have implied the activation of the non-silanized glass wool with a source of amino- groups given by (3-aminopropyl)-triethoxysilane (APTES) treatment. The catalyst was then synthesized by treating glass wool with 3.5 %wt of Mo and a 5.4 %wt Co load. Metallic species were grafted (chemisorption) to the APTES@GW fibers using a photochemical method. Briefly, proper amounts of Mo and Co precursors were mixed with the photoinitiator Irgacure 907 (I-907) in a flask using acetonitrile as reaction solvent. This initiator can undergo Norrish type I cleavage upon UVA excitation generating radical species that can reduce the metal cations, also improving the attachment of cobalt oxide (CoO$_x$) nanoparticles to the Mo layered matrix. Mo and Co proportions were determined by ICP-OES analysis (Table S1). Additionally, through comparisons with the only Mo (Mo@GW) and only Co (Co@GW), control catalysts, we found that mix of both Mo and Co (MoCo@GW) is more efficient than the single metal catalysts. This synergistic effect of Co and Mo, as has also been reported by others.[9] Scanning electron microscopy (SEM) allowed us to observe the particles and a similar distribution of Mo and Co determined by EDS analyses on fibers; images of the complete fibers show that cobalt centers are located in the same area as the molybdenum structures (Figure S1). The oxidation states of Mo 3d and Co 2p were determined by X-ray photoelectron spectroscopy (XPS), with a mixture of Mo^{4+}, Mo^{6+} and Co^{2+} being observed (Figure S2).

Results and Discussion

Experiments without catalyst

The selective oxidation of THIQ was studied under different conditions. In the absence of any catalyst, THIQ solutions in acetonitrile are stable under dark conditions. The system also shows minimal changes for at least two hours under visible light (λ = 450 nm) irradiation. Prolonged irradiation leads to small conversions to DHIQ (10 % after 370 min), after which the reaction accelerates and reaches a conversion rate of 0.51% per minute near the inflexion point, see Figure 1. The reaction reaches 90% selectivity towards DHIQ [i.e.,100 x DHIQ/(DHIQ + IQ)] at 50% conversion and remains at 82% selectivity at 98.5% conversion. The drastic acceleration of the reaction shown in Figure 1 suggests a slow *in situ* formation of efficient catalytic species within the reaction, which were further analysed by LFP (see below). Notably, the reaction performs poorly in air and does not proceed under an inert atmosphere (Figure S3).

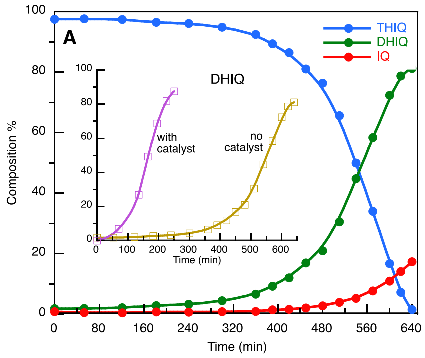


Figure 1: Evolution of the semi-oxidation of THIQ (0.125 M) in AcN under Blue LEDi (~450 nm) irradiation and O_2 atmosphere in the absence of catalyst and (inset) a comparison of DHIQ formation when the catalyst is MoCo@GW.

Close analysis of the reaction evolution experiments indicate that the maximum conversion rate, as measured at the inflexion point in the THIQ curve, coincided with the presence of small (≤2%) formation of IQ. To better understand the role of IQ in the selective oxidation of THIQ, we performed a series of experiments introducing small quantities of IQ at different reaction times (Figure S4). Addition of 4 %mol equivalents of IQ at the start of the reaction reduced the initial delay (to 10% conversion) from 370 to 210 minutes. Effect of addition of 4 %mol DIQ was less than IQ addition. Further, adding 0.5 mL of a completed reaction to a 4 mL fresh sample reduced the delay to 35 minutes, doubling the conversion rate (figure S4).

Another way to test the effect of pre-irradiation is to add THIQ when the reaction is almost completed as illustrated in Figure 2, where THIQ was added after 600 minutes. Notice that no delay is detectable after the addition of THIQ, suggesting that the solution was “ready” to proceed with the photocatalytic process.

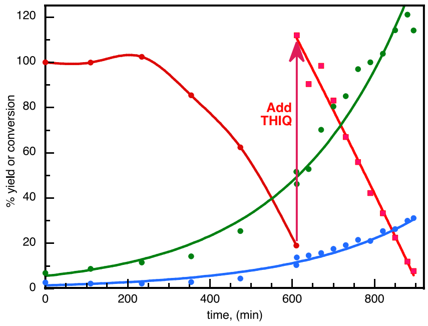


Figure 2: THIQ oxidation reaction evolution over time under conditions described in Figure 1, followed by addition of THIQ (to reach 0.125 M) at 611 minutes. Notice that after addition of THIQ = red, DHIQ = green and IQ = blue follow a smooth growth curve, while consumption of THIQ occurs without delay. Selectivity was 79% after 900 minutes.

Solvent effects

The reaction conditions shown in Figure 1 were used to test different solvents, namely acetonitrile, hexane (Hx), and methanol (MeOH). The solvents were selected based on their different oxygen solubility (Hx > Acetonitrile > MeOH) and polarity (dielectric constant: Hx < Acetonitrile ~ MeOH) or ET(30) values (Hx < MeOH < Acetonitrile).[10] This suggests that less efficient singlet oxygen generation leads to a less favorable reaction; while not compelling evidence for singlet oxygen mediation, it was enough to led us to explore this possibility. Figure 3 shows that methanol is the least efficient solvent because of the long initial delay and the low rate of THIQ consumption, effectively almost 5 times slower than in acetonitrile. This led us to suspect that singlet oxygen could be mediating the late stages (post initial delay) of the oxidation of THIQ. To test this possibility, we substituted methanol for CD_3OD, as deuteration is known to enhance dramatically the lifetime of singlet oxygen.[11] As illustrated in Figure 3, CD_3OD causes a significant acceleration of the overall process, as expected for singlet oxygen reactions, reflecting that THIQ reactions will be favoured if the lifetime of singlet oxygen is enhanced.[11] The effect for CH_3OD (not shown) is minor, reflecting a minor $^1O_2$ lifetime enhancement.

As a further test of the singlet oxygen hypothesis, we added NaN_3 to the system, as N_3^- is a well-known singlet oxygen scavenger.[12] This led to a small slow-down of the reaction (figure S7). The usual extensive effect of azide is probably attenuated by the fact that THIQ is itself an excellent singlet oxygen scavenger. On the other hand adding $Ru(bpy)_3Cl_2$ as a singlet oxygen sensitizer to the THIQ showed a reaction without any delay Figure S5.

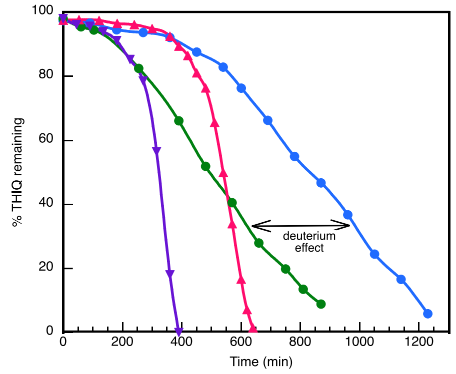


Figure 3: Consumption of THIQ as a function of time in various solvents: Purple triangles = hexane, pink triangles = acetonitrile, blue circles = methanol and green circles = methanol-d₄. Note that methanol-d₄ accelerates the reaction by ~ 360 minutes.

Mechanistic studies

As the next step we decided to examine the possible role of singlet oxygen making its generation independent of the THIQ system. For this purpose, we used $Ru(bpy)_3Cl_2$ as a commercially available sensitizer, using 355 nm laser pulses for excitation and monitoring the emission from singlet oxygen in acetonitrile at 1270 nm. The lifetime in the absence of quencher was ~80 μs (τ_0), which is consistent with literature reports for singlet oxygen in acetonitrile.[13, 14] The lifetimes were reduced in the presence of THIQ, as illustrated in the inset in Figure 4. A plot of the rate constant for decay (k_d) as a function of the THIQ concentration (equation 1) leads to a quenching rate constant of 2.63 x 10^7 $M^{-1}s^{-1}$.

$$k_d = \tau^{-1} = \tau_0^{-1} + k_q[THIQ] \qquad (1)$$

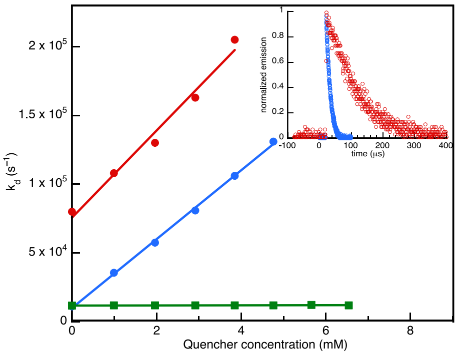


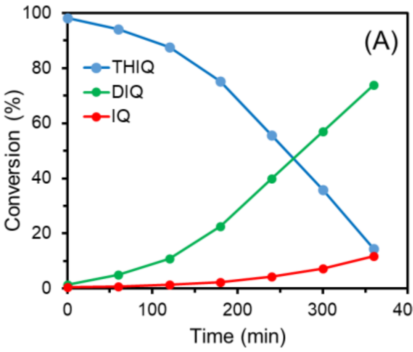
Figure 4: Quenching plots for singlet oxygen in acetonitrile. Blue and red points for THIQ with $Ru(bpy)_3Cl_2$ and IQ as sensitizers, respectively. Green points are for DHIQ as quencher, with $Ru(bpy)_3Cl_2$ as sensitizer. No significant quenching is observed for DHIQ. Inset: decay traces for singlet oxygen emission (monitored at 1270 nm) in the absence (red) and presence of 0.0029 M THIQ (blue). For long lifetimes (red data) it is necessary to attenuate the signal to obtain more reliable lifetimes.

As discussed before, the presence of IQ can accelerate the oxidation of THIQ (Figure 2). To understand this apparent *in situ* catalytic effect, we explored the potential formation of singlet oxygen using IQ as sensitiser. The experiment needed to be performed at a rather high IQ concentration that led to a reduction of singlet oxygen lifetimes; however, the identification of the emitter was unequivocal and the rate constant for THIQ quenching was the same as in $Ru(bpy)_3Cl_2$ experiments. What is more, similar $Ru(bpy)_3Cl_2$ experiments with DHIQ as a quencher revealed that singlet oxygen quenching by DHIQ is at least 1000 times slower than by THIQ (Figure 4), an observation that is key to the high discrimination towards selective oxidation observed in our work.

Heterogeneous Catalysts

We tried several catalysts to test the oxidation dynamics without affecting the selectivity. While the experiments above show that singlet oxygen generators can greatly enhance the kinetics of THIQ to DHIQ conversion with minimal loss of selectivity, it would be desirable to avoid soluble catalysts that add steps to the post-reaction separation and purification processes. For this purpose, we tested if the ruthenium catalysis could be performed by a heterogeneous catalyst also capable of generation of singlet oxygen but being amenable for easy removal after use. We have previously developed glass-grafted ruthenium catalysts, among them the $[Ru(bpy)_2dppa](PF_6)_2$ loaded onto glass wool (RuB@GW).[8] As shown in Figure 5A, irradiation of RuB@GW confirmed the conversion of THIQ to DHIQ without an extended initial delay, in reasonable time (that could be adjusted with light intensity) and with excellent selectivity.

The same reaction conditions were assayed in the presence of 50 mg of MoCo@GW and the initial delay was shortened to ~80 min for 10% conversion and the rate at the inflexion point increased to 0.82% per minute. At 90% conversion (225 min) the selectivity was still 90%, Figure 5B and S9. As a control experiment for using a bimetallic catalyst, we prepared Mo@GW, Co@GW, and APTES@GW and ran the experiment with the same conditions (Figure S6). The results confirmed the synergistic effect between Mo and Co in improving catalytic role in oxidation reaction.[15, 16]



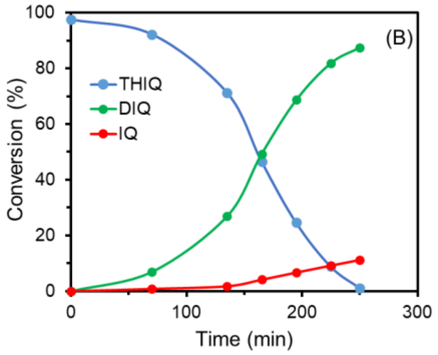


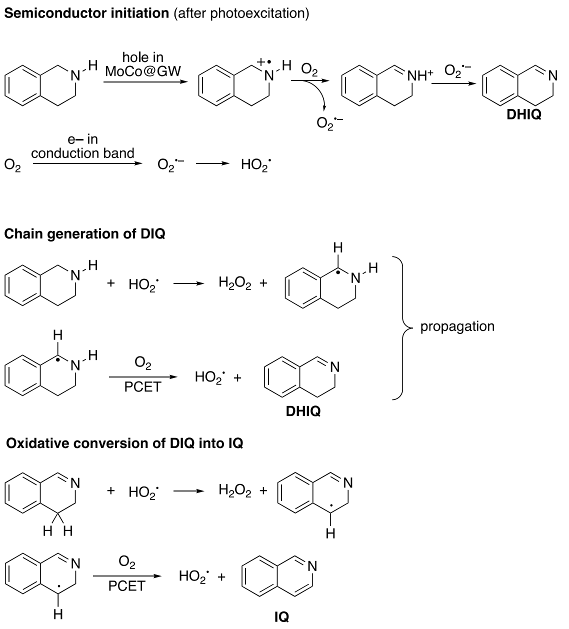
Figure 5: THIQ oxidation reaction evolution over time under visible light irradiation in the presence of (A) RuB@GW and (B) MoCo@GW. Conditions: THIQ (0.125 M), acetonitrile, O_2 atmosphere, λ= 450 nm (≤ 6 W cm^{-2}). THIQ in blue, DHIQ in green and IQ in red.

Mechanistic analysis

There are two aspects to the oxidative generation of DHIQ from THIQ. One is straightforward and is the singlet oxygen mediated oxidation. With a quenching rate constant of 2.6 x 10^7 $M^{-1}s^{-1}$ THIQ is a favoured target for singlet oxygen reaction. Further, the fact that DHIQ is a poor singlet oxygen target, with its reaction at least 1000 times slower than for THIQ is the cause of the high selectivity that helps the oxidation to stop "halfway" rather than proceed to IQ.

The second aspect is the initiation of the process in the absence of added singlet oxygen sensitizers. Since in all cases singlet oxygen is the dominant reaction mechanism, in the cases with no sensitiser added, or with MoCo@GW as a pre-catalyst we require a route for the *in-situ* generation of a singlet oxygen sensitizer, with the simplest explanation (and confirmed by chromatographic analysis) is the formation of IQ. For the no-catalyst system, nearly 6 hours delay under strong irradiation is required to form minimum amount of IQ. It is hard to identify a source, although it is hardly surprising that some oxidation takes place, noting also that once some IQ is generated it can support further oxidation.In addition, as much as 0.7% IQ may be present in the initial reaction mix.

The presence of MoCo@GW greatly reduces the delay. We propose that the formation of IQ in this case is also mediated by DHIQ which is an excellent target for HOO• radicals (given the presence of benzylic hydrogens),[17] with DHIQ formed by the mechanisms of Scheme 2.



Scheme 2: Semiconductor based mechanisms for the formation of DHIQ, a precursor for IQ under semiconductor mediated oxidation.

The complexity of Scheme 2 is entirely related to the need to add or generate *in situ* a good singlet oxygen sensitizer; once this has been achieved the singlet oxygen oxidation takes over and ensures the excellent selectivity towards DHIQ. In fact, the mechanism of Scheme 2, which enables the initial formation of IQ, would not be anticipated to provide the selectivity towards DHIQ that is at the centre of this report.

Conclusions

For the series THIQ. DHIQ and IQ, the most valuable one is DHIQ, largely reflecting that both for catalytic oxidations and reductions, stopping "halfway" is difficult. Catalysts that utilize molecular oxygen are highly desirable as they enable sustainable pathways, more so if they are heterogeneous catalysts, easy to recover and suitable or adaptable flow chemistry.

In the case of THIQ the dramatic difference in reactivity towards singlet oxygen between THIQ and DHIQ (≤1000) enables exceptional selectivity which is maintained even at very high conversion.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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