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<th>Journal:</th>
<th>RSC Advances</th>
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<tr>
<td>Manuscript ID</td>
<td>RA-ART-09-2015-020100.R1</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Paper</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>28-Oct-2015</td>
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</tbody>
</table>
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| Subject area & keyword: | Physical organic < Organic |
Photo-induced proton coupled electron transfer from a benzophenone ‘antenna’ to an isoindoline nitroxide

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The current study reports the synthesis and properties of a novel isoindoline nitroxide containing a benzophenone chromophore fused into the carbon framework. When exposed to UV light, rather than undergoing traditional benzophenone photochemical pathways, the presence of the nitroxide enables an energy transfer process whereby the nitroxide enters an excited state which induces an efficient hydrogen atom transfer from unactivated alkanes.

Introduction

Proton-coupled electron transfer (PCET) is of critical importance to a range of chemical and biological processes. From the oxidation and combustion of hydrocarbons to energy storage, enzyme-driven transformations, ultrafast relaxation of UV-irradiated DNA, and the quintessential examples of photosynthesis and respiration, PCET has widespread impact across materials and biology. PCET involves the transfer of a proton and an electron to or from acceptor substrate orbitals. Formally, the process can occur in a step-wise manner (whereby the proton and electron transfer sequentially, in either order) or the transfer can occur simultaneously, relative to periods of coupled vibrations. A prominent example of the concerted process is hydrogen atom transfer (HAT) which is central to free radical related processes.

Photochemically derived HAT processes provide a number of advantages over thermally driven systems. Both spatial and temporal control over photochemical processes are readily achieved by variation of the location, duration and intensity of UV exposure. The most well-known example of a molecule that undergoes a photo-induced HAT is benzophenone (see Scheme 1), which undergoes HAT from its excited triplet state with remarkable efficiency. The driving force of subsequent HAT reactions from the excited triplet state is the electron deficiency of the ketyl oxygen. HAT allows the ketyl oxygen to complete its half-filled orbital and in so doing generate a stabilized ketyl radical capable of further radical reactions. In deoxygenated solutions these reactions typically involve reactions of the HAT derived radical species such as those originating from the hydrogen atom donor, or, dimerization of ketyl radicals through well-established pinacol chemistry.

Nitroxides are stable, kinetically persistent free radicals that have been the subject of extensive research over the last 40 years. Also known as aminoxyl or nitroxyl radicals, the interest in these compounds arises from the range of remarkable physical and chemical properties that they possess, several of which parallel those found in less stable free radical compounds (e.g. reaction at diffusion controlled rates with carbon, sulfur, phosphorus and nitrogen centred radicals) and while others are unique to this class of molecules (e.g. the ability to undergo one electron redox processes).
These properties explain why nitroxides have found applications in a wide variety of fields, including controlled free radical polymerization, biological and material-based antioxidants and electron paramagnetic resonance (EPR) spectroscopy. In addition, nitroxides possess the ability to undergo HAT from a hydrogen donor to produce the corresponding hydroxylamine (which is able to readily undergo re-oxidation under normal atmosphere to the parent nitroxide). HAT to a nitroxide has also been able to be achieved photochemically from less activated hydrogen sources (See Scheme 2). The radical produced from the donor source is subsequently scavenged by a second nitroxide to produce an alkoxyamine derivative. Generally, in order to achieve such HAT for the nitroxide, high energy light and prolonged exposure times are required. For piperidine-based nitroxides (e.g. TEMPO) such harsh conditions can lead to significant α-cleavage, eventual loss of NO and alkene formation. Isoindoline nitroxides however, show a much greater photo-chemical stability and have been shown to undergo rapid and clean hydrogen abstraction of unactivated hydrocarbons, albeit still with excitation by high energy light. Nitroxides have also been successfully employed as profluorescent probes whereby the nitroxide acts as an efficient fluorescence quencher when covalently linked to a chromophore. Fluorescence quenching mechanisms associated with nitroxide radicals have been described as involving photo-induced electron-transfer and electron-exchange quenching processes.  

Aliaga recently demonstrated that efficient quenching is achieved via a strong intercalation interaction between the frontier orbitals of the fluorophore and the SOMO of the nitroxide radical, allowing for a spin exchange between it and the LUMO of the excited fluorophore, leading to non-radiative relaxation. This interaction is distance dependent and more effective when the chromophore is conjugatively linked to the nitroxide.  

Herein, we demonstrate an extension of the profluorescent nitroxide concept, with the rapid and efficient quenching of the excited state of a benzophenone chromophore by a highly proximate isoindoline nitroxide moiety. This quenching leads in turn to unique PCET chemistry involving the nitroxide unit. Notably, in the presence of the nitroxide radical, the benzophenone does not appear to undertake any of the typical photochemical HAT reactions of excited state carbonyls as no pinacol-type products were detected. In this instance the benzophenone chromophore acts instead as an “antenna” whereby the energy absorbed by the benzophenone is efficiently transferred within the molecule to give an excited state nitroxide that is produced under much milder photolysis conditions than have been previously reported.

**Results and discussion**

Benzophenone was chosen as the target chromophore as it has been previously employed for intermolecular photosensitization of a range of substrates. Typically this chemistry involves excitation of the n-π* transition of benzophenone, centered ca. 350 nm, from which the long-lived excited triplet state is reached. In the case of the benzophenone derivative 11, the energy of this efficient n-π* transition matches the n-π* absorption band of the nitroxide that converts it to a more reactive species, able to undergo HAT chemistry. Therefore benzophenone represents an ideal moiety to act as an “antennae” chromophore within the molecule and impart novel reactivity to the nitroxide component. As isoindoline nitroxides also possess stability advantages over other nitroxides in photochemical reactions, the incorporation of this fused aryl ring isoindoline nitroxide was a key driver in the synthetic design of the target 11.

Incorporating this aryl ring into both the chromophore and nitroxide components delivers two advantages. Firstly, the fused carbon-carbon skeleton gives a much more robust linkage between the chromophore and the nitroxide unit, as compared to ester or amide linkages, limiting the potential for scission and subsequent separation of the two moieties. Secondly, as with profluorescent nitroxides, transfer of excited state energy is inherently distance dependent, incorporating the isoindoline nitroxide structure within the benzophenone moiety minimises the distance between the two groups. The synthetic approach employed is shown in Scheme 3. Starting with the previously synthesised 5-bromo-2-methoxy-1,1,3,3-tetramethylisoindoline (8) which can be achieved in 5 steps in 19% yield starting from phthalic anhydride, the diphenyl alcohol core was incorporated by lithiation and quenching with benzaldehyde. Oxidation of the benzylic alcohol to the corresponding ketone with PCC then afforded the desired benzophenone chromophore. Deprotection of the nitroxide moiety was then undertaken with MCPBA furnishing the target compound in good overall yield (82% over three steps). The absorbance spectrum of 11 in cyclohexane (see SI) shows the characteristic bands centred at 250 nm and 350 nm corresponding to π-π* and n-π* transitions respectively.
Figure 1 Comparison of UV-Vis absorbance at 347 nm of 1 (red) vs 11 (black) during photolysis in argon (solid circles) or air (unfilled circles).

Figure 2 EPR signal strength as a function of photo-irradiation time of a solution of 11 in cyclohexane under an argon atmosphere (solid markers). Unfilled markers indicate the signal recorded after the sample had been exposed to PbO₂ as a mild oxidant. This indicates the presence of hydroxylamine within the solution.

In comparison to the absorbance spectrum of benzophenone (1), there was no notable shift in either of the absorbance bands for compound 11, indicating that the incorporation of the nitroxide moiety has little effect on the overall absorbance of the molecule. Upon illumination of a deoxygenated solution of 11 in cyclohexane with UVB light, a reduction in the peak absorbance at 350 nm, corresponding to the carbonyl moiety, was observed with increasing irradiation time.

Complete disappearance of this signal was achieved after 25 minutes of irradiation (Figure 1). In contrast to this, irradiation of benzophenone (1) under the same conditions led to complete loss of the starting material in less than 10 minutes. This result demonstrates that much less of the carbonyl of 11 is transformed despite more energy absorption over a longer period of time. When the same samples are photolysed under aerated conditions the difference becomes more marked.

Benzophenone (1) shows a slight retardation in reaction rate, which is expected. Literature shows this to be due to oxygen quenching the excited state in competition with the dimerization reaction to give the pinacol product. In contrast, irradiation of compound 11 in the presence of oxygen shows very little change in the carbonyl absorbance, with over 90% of the initial absorbance retained after 40 minutes of irradiation. A sample of 11 in an argon atmosphere was also investigated by Electron Paramagnetic Resonance (EPR) spectroscopy (as shown in Figure 2) as a function of irradiation time. The rate of loss of the EPR signal arising from the nitroxide 11 following irradiation occurred faster than the observed change in the UV-Vis spectrum associated with reaction at the carbonyl moiety. Notably, when these inert atmosphere irradiated samples were exposed to atmospheric oxygen or treated with a mild oxidant (PbO₂) and then re-examined by EPR, a partial recovery of the nitroxide signal was observed. This result is indicative of the presence of hydroxylamine 12. A compositional analysis of the irradiated sample was also undertaken using high-performance liquid chromatography/mass spectrometry (HPLC/MS). Thus a sample of 11 in cyclohexane under an argon atmosphere was irradiated, samples removed periodically and analysed using HPLC/MS. The chromatograms obtained following detection at 254 nm are shown in Figure 3 (see the SI for the full MS for each peak). Each major component within these chromatograms could be readily assigned based on the obtained MS results data as well as preparative scale isolation and characterisation (see the SI for full characterisation details). Prior to irradiation, the starting material 11 was the only component observed. After 5 minutes irradiation, less than 40% of compound 11 remained and two new prominent peaks appeared the hydroxylamine 12 and the cyclohexylalkoxyamine 14. A larger amount of the starting material 11 was present at this stage of the analysis compared
Scheme 4. Proposed reaction pathway when 11 is photo-irradiated in cyclohexane

with the other in situ studies as 12 is not stable and readily reverts to 11 when exposed to oxygen during HPLC/MS sample preparation and analysis. It is important to note that at this stage no products related to the reaction of the excited state benzophenone moiety could be detected. As irradiation continued, the yield of the oxidatively stable 14 continued to increase and, matching this increase, products where reaction had occurred at the carbonyl began to appear. There was also an increase (at early retention times) of a number of oxidized products (with the main contributors being identified as cyclohexanol, cyclohexanone and dicyclohexyl ether via analysis employing Gas chromatography coupled mass spectroscopy (GC-MS). After 20 minutes irradiation, there was less than 5% of the nitroxide starting material present and none of the hydroxylamine could be detected. All of the major products detected relate to various cyclohexylalkoxyamine derivatives (14, 16 and 17 account for ca. 9, 10 and 75% of the observed UV signal respectively). At no stage could any compounds be detected that arise from reaction at the carbonyl and which also contain either a hydroxylamine or nitroxide (which could be formed via oxidation of the hydroxylamine species).

Based on these results, the proposed photochemical reaction pathway for 11 is shown in Scheme 4. UV light is absorbed by the benzophenone chromophore where there is an internal energy transfer to the nitroxide moiety leading to 11*. In this state the nitroxide then undergoes rapid HAT with the solvent yielding 12 and a cyclohexyl radical 13. Hydroxylamine 12 will cycle to reform the nitroxide 11 either by oxidation with molecular oxygen or from HAT self-exchange or back-transfer with 13. Radical 13 can also undergo various side-reactions (e.g. HAT, dimerization, oxidation with oxygen) or it can be efficiently scavenged by another molecule of 11 to yield the alkoxyamine adduct 14. Once the free spin is removed from the molecule and it enters a photo-excited state (14*), internal energy transfer is no longer possible and typical benzophenone excited state chemistry returns. This leads to HAT from the solvent to the excited carbonyl of 14 yielding the ketyl radical intermediate 15. Here two termination reactions are possible: reaction with 13 to yield the alkylated product 16 or reaction with another equivalent of 15 to yield the pinacol dimer analogue 17. In this system, the proximate nitroxide moiety is acting as an efficient quencher of the excited state of the benzophenone moiety. The nitroxide must be converted to a diamagnetic species before reactivation of the benzophenone photochemical pathways can occur. This demonstrates that rather than simply dissipating energy through non-radiative pathways (such as through vibrational loss as occurs with profluorescent nitroxides), the nitroxide moiety is raised to an excited energetic state where it becomes a potent hydrogen abstractor, even of unactivated alkanes such as the solvent used in these studies. This phenomenon becomes important to consider when using profluorescent nitroxides as probe molecules under prolonged periods of photo-irradiation or with high intensity laser irradiation in fluorescence microscopy where photobleaching can be a complication.
Conclusions

The synthesis of an isoindoline nitroxide containing a benzophenone moiety fused to the carbon framework was described. When photo-irradiation of this compound was undertaken, none of the photochemistry that is traditionally associated with the benzophenone chromophore was observed to occur. Instead the benzophenone acted as an antenna with energy being transferred to the nitroxide moiety. This process gives an excited state nitroxide, capable of undergoing HAT from non-activated alkanes, under much milder conditions and more efficiently than have previously been reported.

Acknowledgements

We gratefully acknowledge financial support from the, the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology (CE 0561607), and the Ian Potter Foundation. J.M. and L.W. also thank the Australian Government for postgraduate research scholarships.

Notes and references

† Experimental Procedures

Synthesis of 5-Hydroxy(phenyl)methyl-2-methoxy-1,1,3,3-tetramethylisoindoline (9)

A solution of 5-bromo-2-methoxy-1,1,3,3-tetramethylisoindoline (8) (1.00 g, 3.52 mmol, 1.0 eq.) in THF (50 mL) was cooled to -78 °C and placed under an inert atmosphere of argon. To this solution was added n-butyllithium (1.6 M in n-hexanes) (2.4 mL, 3.87 mmol, 1.1 eq.) dropwise. The reaction was then allowed to stir for 15 minutes, maintaining a constant temperature of reaction (-78 ± 5 °C). A solution of benzaldehyde (1.08 mL, 10.56 mmol, 3.0 eq.) in THF (50 mL) was then added dropwise, maintaining a constant temperature of reaction (-78 ± 5 °C), until the addition was complete. The reaction was then allowed to return to room temperature over two hours and then quenched by the addition of water (50 mL). The resulting mixture was extracted with dichloromethane (3 × 100 mL) and the combined organic extracts washed with a saturated solution of brine (50 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. Purification via silica gel column chromatography (dichloromethane : diethyl ether; 19 : 1) afforded 5-hydroxy(phenyl)methyl-2-methoxy-1,1,3,3-tetramethylisoindoline (9) (290 mg, 92 % yield). M.p. 92 - 94 °C. Rf = 0.40, dichloromethane : diethyl ether; 19 : 1. 1H NMR (400 MHz CDCl3): δ (ppm) = 7.42 – 7.35 (m, 4H, H arom), 7.31 – 7.28 (m, 1H, H arom), 7.21 (dd, J = 7.6, 1.6 Hz, 1H, H arom), 7.19 (d, J = 1.6 Hz, 1H, H arom), 7.06 (d, J = 7.6 Hz, 1H, H arom), 5.86 – 5.85 (m, 1H, CH), 3.79 (s, 3H, OCH3), 2.26 – 2.24 (m, 1H, OH), 1.44 (br s, 2H, 4CH2). 13C NMR (100 MHz CDCl3): δ (ppm) = 145.7, 144.9, 144.0, 143.1, 128.7, 127.7, 126.7, 126.0, 121.7, 119.8, 76.6, 67.3, 67.1, 65.7, 30.2, 30.2. HRMS (ESI) m/z: calculated for C16H16NO2 [M+H]+ 295.1567; found 295.1566. HRMS (ESI) m/z: calculated for C16H16NO2Na [M+Na]+ 317.1386; found 317.1388.

Synthesis of 5-Benzoyl-2-methoxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (11)

To a solution of 5-benzoyl-2-methoxy-1,1,3,3-tetramethylisoindoline (10) (600 mg, 1.94 mmol, 1.0 eq.) in dichloromethane (100 mL) was added m-CPBA (27 % purity) (957 mg, 4.27 mmol, 2.2 eq.) in portions. The reaction was maintained for one hour at room temperature. 2M sodium hydroxide (100 mL) was then added and the resulting mixture stirred vigorously for 15 minutes. The reaction mixture was then extracted with dichloromethane (3 × 100 mL). The combined organic extracts were then washed with water (50 mL) followed by a saturated solution of brine (50 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. Purification via silica gel column chromatography (dichloromethane : diethyl ether; 19 : 1) followed by recrystallization from methanol afforded 5-benzoyl-1,1,3,3-tetramethylisoindolin-2-yloxyl (11) as small orange needles (526 mg, 92 % yield). M.p. 149 – 150 °C. Rf = 0.35, dichloromethane : diethyl ether; 19 : 1.

General Procedure for Photolysis Studies

Photolysis studies of the diphenyl ketyl system 11 were typically performed in solution using cyclohexane as a solvent. Solutions were degassed followed by bubbling with the desired gas and placed in sealed quartz fluorescence cells. The solutions were irradiated in a Rayonet photoreactor using a 350 nm wavelength light source. The solutions were analysed typically performed in solution using cyclohexane as a solvent. Solutions were degassed followed by bubbling with the desired gas and placed in sealed quartz fluorescence cells. The solutions were irradiated in a Rayonet photoreactor using a 350 nm wavelength light source. The solutions were analysed periodically via UV-Visible spectroscopy, with aliquots taken for further analysis by LC-MS and EPR spectroscopy. Typically each solution was irradiated until the nτ absorption band at 350 nm had reached a constant minimum signal intensity.