

# Strategies for Red-Shifting Type I Photoinitiators: Internal Electric Fields versus Lewis Acids versus Increasing Conjugation\*

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Time-dependent density functional theory calculations were performed on derivatives of Irgacure 2959, a water-soluble, acetophenone-type photoinitiator, in order to assess the relative merits and drawbacks of three distinct ways of modifying its photochemistry: Lewis acid complexation, changing the amount of conjugation in the molecule, and application of an internal electric field through inclusion of a remote charged functional group. The effectiveness of each of the three methods was evaluated against the magnitude of the change in energy of the excited states. Internal electric fields were shown to provide the best method for targeting specific excited states in a controlled and rational manner. The other strategies also had significant effects but it was more difficult to independently target different transitions. Nonetheless, for the specific case of Irgacure 2959, we predict that its complexation with  $\text{Mg}^{2+}$  ions in a range of solvents will both red-shift the initiator's absorbance while improving its efficiency and it is thus a promising candidate for testing as a visible light photoinitiator.

Manuscript received: 9 June 2019.

Manuscript accepted: 12 July 2019.

Published online: 31 July 2019.

## Introduction

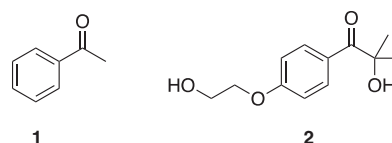
Over the past few years, much attention has focussed on harnessing electric fields – either externally or via the internal fields generated by charged functional groups – to modify chemical reactivity.<sup>[1,2]</sup> During the course of such work, it has been noted that polarizable molecules, such as resonance-stabilized radicals, show particularly large sensitivities to electric field effects.<sup>[3,4]</sup> As many excited states are highly polarizable, this raises the prospect of selectively manipulating these states with electric fields.

Recently, we used time-dependent density functional theory (TD-DFT) to investigate if electric fields offer a route for tuning the photochemical behaviour of acetophenone (**1**, Chart 1) and, by extension, other similar Type I photoinitiating compounds.<sup>[5]</sup> The study highlighted how the introduction of a non-conjugated charged functional group can either stabilize or destabilize  $n\pi^*$  and  $\pi\pi^*$  excited states. Moreover, the two types of state are affected in opposite directions depending on the sign of the charge, and there is a significant dependence of the magnitude of the electrostatic effect on ring position, thus allowing tuning of the effect. This is important if one wishes to, say, red-shift a photoinitiator without compromising its efficiency.

In the present work, we aim to assess the relative merits of using such electrostatic effects to modify photoinitiation behaviour when compared with more traditional approaches based on resonance. In particular, it is well known that extending the  $\pi$ -system of a photoactive compound will decrease the  $\pi-\pi^*$

excitation energy and hence provide a means of red-shifting excitations into the  $\pi^*$  system.<sup>[6]</sup> Moreover, aromatic systems with conjugated lone pair donors respond to pH changes, as these determine if the lone pair is available for resonance with the aromatic ring. One such example is the pH-dependent UV-vis spectrum of  $\text{F}_{420}$ .<sup>[7]</sup> A related approach is to change the extent of resonance by coordinating Lewis acids with conjugated lone pair donor and/or  $\pi$ -acceptor groups. For example, we recently showed that Lewis acids could red-shift the absorption spectra and alter the photoinitiation behaviour of the popular Type I photoinitiators methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA).<sup>[8]</sup>

To compare these different approaches, in the present work we attempt to improve the commercial Type I photoinitiator Irgacure 2959 (I2959, **2** in Chart 1). Recently, I2959 has found use in 3D bioprinting,<sup>[9–11]</sup> a process that involves the printing of biological material to form a specific tissue shape. Initially, the printable material is in the form of a 'bio-ink', a liquid-like



**Chart 1.** Chemical structures of acetophenone (**1**) and Irgacure 2959 (**2**).

\*Michelle L. Coote is the winner of the 2019 RACI Physical Division Medal.

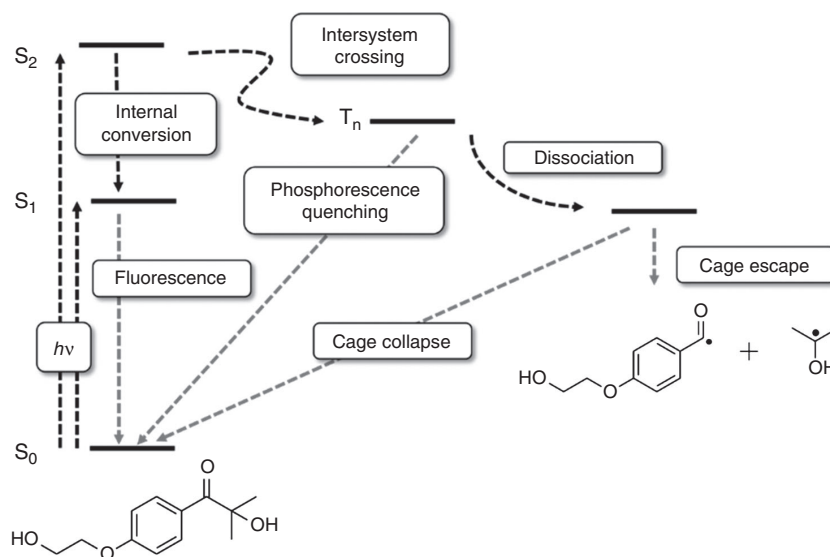


Fig. 1. Jablonski diagram describing Type I photoinitiation of acetophenone.

mixture of cellular material, monomer, and photoinitiator. At the point of printing, the ink is irradiated with UV light in order to initiate a polymerization curing reaction that hardens the ink so that a three-dimensional tissue can be additively built. UV light does, however, have a detrimental effect on the cell viability within the 3D-printed tissue, as the high-energy photons can be absorbed by the cells with damaging consequences. Moreover, I2959 exhibits a reasonably low quantum yield of photolysis, at  $\Phi = 0.29$ .<sup>[12]</sup> Although visible-light photoinitiators exist,<sup>[13–15]</sup> to date, the initiators used are not as attractive as I2959 for bioprinting applications owing to their poor solubility in water.

Summing up, I2959 exhibits several properties that make it useful in 3D-printing applications; however, these properties could be improved. In particular, the necessity for damaging UV irradiation can be altered by lowering the energies of the reactive states; the efficiency of the electronic transitions could be improved, which would result in a higher value of  $\Phi$ , and I2959's solubility in water can be increased. Herein, we investigate if, and to what extent, this can be achieved through the use of remote charged functional groups, or through other strategies including Lewis acid complexation or more direct modifications to the chromophore such as extending the  $\pi$  system.

## Theoretical Procedures

Although more accurate multireference methods are required to fully explore excited-state properties, here we are primarily interested in systematic effects on vertical excitation energies. Literature studies have shown that TD-DFT can reproduce these excitation energies for organic molecules in general<sup>[16]</sup> and acetophenone in particular.<sup>[17]</sup> Thus, as in our previous study,<sup>[5]</sup> the M06-2X density functional<sup>[18]</sup> was used for all ground- and excited-state calculations. Every species was extensively conformer-searched in order to locate the global minimum energy structure; structures were optimized with the 6-31+G(d,p) basis set, on which TD-DFT calculations were performed. Where relevant, solvent effects were considered with the SMD implicit continuum solvent model.<sup>[19]</sup> All calculations were performed with the *Gaussian 16 Revision A* electronic structure software package.<sup>[20]</sup>

## Results and Discussion

### Photochemistry of Unfunctionalized I2959

Like acetophenone, I2959 exhibits  $S_1(n\pi^*)$  and  $S_2(\pi\pi^*)$  excited states and several low-lying triplet excited states. Experimentally, I2959 exhibits  $\lambda_{\text{max}}$  at 273 nm; at these wavelengths, the predominant excited state transition will be to the  $S_2(\pi\pi^*)$  state, and the reactive triplet excited state has  $^3\pi\pi^*$  and  $^3n\pi^*$  character.<sup>[12]</sup> TD-DFT calculations suggest, however, that the  $S_1(n\pi^*)$  state at  $\sim 305$  nm has a nearby  $T_2(n\pi^*)$  at  $\sim 337$  nm and  $T_1(\pi\pi^*)$  at 348 nm. According to El Sayed selection rules,<sup>[21]</sup> the most efficient intersystem crossing (ISC) will be take place from the  $S_1(n\pi^*)$  to the  $T_1(\pi\pi^*)$  surface. Fig. 1 is a simple diagram describing Type I photoinitiation, and the different internal processes that can take place on photoexcitation. A simple approach to improving the initiation efficiency of I2959 would therefore be to reduce the  $S_1/T_1$  energy gap, resulting in a red-shift in the required wavelength of light for initiation ( $S_1$  rather than  $S_2$  is being targeted), and the different symmetries of the states would allow the efficient population of the  $T_1$  state.

### Effect of Increasing $\pi$ -Conjugation

The effect of increasing conjugation of the photoactive moiety of I2959 was investigated with the structures shown in Fig. 2. Increasing the amount of  $\pi$ -conjugation present in a molecule is the most commonly adopted method to altering photochemistry. As this is a through-bond orbital effect, rather than a through-space electric field effect, this approach ought to be the most robust to solvent effects and so gas-phase energies were studied for simplicity. To explore these effects, three ways of increasing conjugation were evaluated; by fusing either an extra phenyl ring or an antiaromatic ring system to the original I2959 phenyl moiety, or by replacing the non-equivalent H-atoms with increasingly large unsaturated alkyl chains or a benzene ring. It is noted that these structural changes would likely decrease rather than increase water solubility but they are considered here to provide a baseline as to what effects are possible with changes to  $\pi$ -conjugation.

The changes in the gas-phase energies of the  $S_1$ ,  $S_2$ , etc., states on the introduction of these functional groups relative to

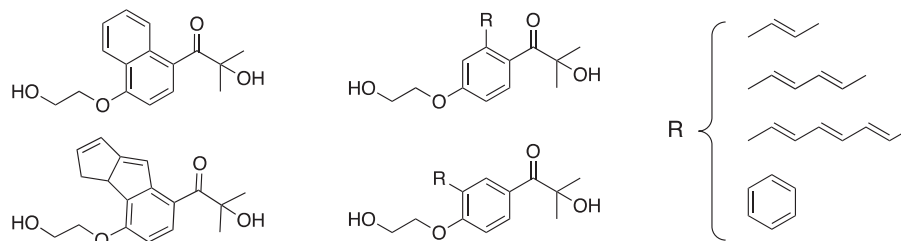


Fig. 2. Extended conjugative groups introduced into I2959.

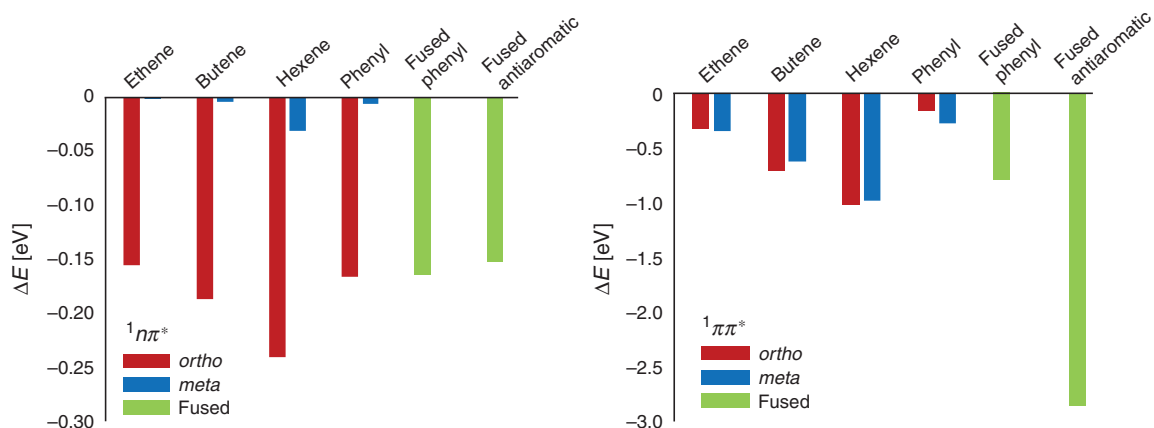


Fig. 3. Change in gas-phase vertical excitation energies of the  $1n\pi^*$  and  $1\pi\pi^*$  states on increasing the conjugation in I2959. Note that the *meta* value for the  $1n\pi^*$  transition with ethene is essentially zero.

that of I2959 are shown in Fig. 3. Owing to the presence of the phenyl ring in I2959, introducing further conjugation in the form of an extra phenyl moiety, or a long alkyl chain, is found to have only a limited effect on the energies of the  $S_1$  states; in fact, at the *meta* positions, the effects are negligible (Fig. 3). In contrast, extending the  $\pi$  system greatly lowers the energy of the  $\pi\pi^*$  transitions. This is particularly pronounced with the fused antiaromatic rings, which become aromatic in the excited state.

The net result of introducing more conjugation to I2959 is primarily to lower (red-shift) the energies for  $\pi\pi^*$  transitions, with minimal effect on the  $n\pi^*$  transitions, thus closing the gap with the  $\pi\pi^*$  states. Unfortunately, although this does red-shift the absorption of the initiator, it is unlikely to improve initiator efficiency. For instance, with the addition of butene at the *meta* position, for example, the  $S_1(n\pi^*)$  to  $S_2(\pi\pi^*)$  is reduced from 0.61 eV in I2959 to 0.15 eV. This small energy gap may allow the efficient population of the  $n\pi^*$  state via the bright  $\pi\pi^*$  state; however, the corresponding triplet excited states have also been stabilized, and are now further away in energy from the singlet states. The red-shifting of the  $1\pi\pi^*$  state is particularly profound on the addition of a fused antiaromatic unit, resulting in a 2.85 eV reduction in energy in the gas phase, and a 2.58 eV lowering in water. The  $n\pi^*$  states are stabilized to a much lower extent, and therefore whereas the absorption of I2959 in this case would be significant in the visible light region, TD-DFT calculations do not suggest this would lead to efficient photoinitiation.

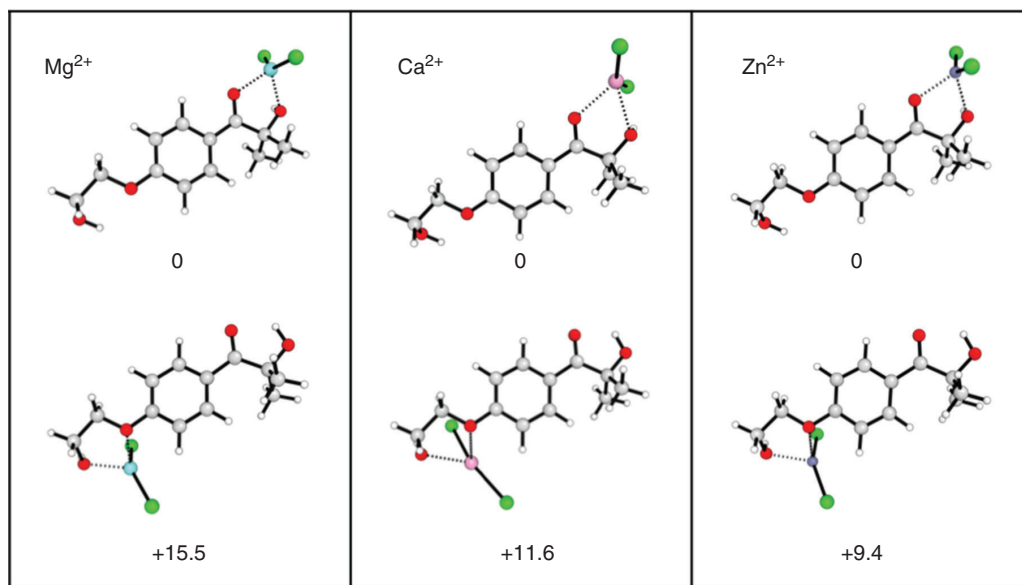
#### Effect of Lewis Acid Complexation

In order to assess the potential application of Lewis acid (LA) complexation to alter the photochemistry of I2959, three metal

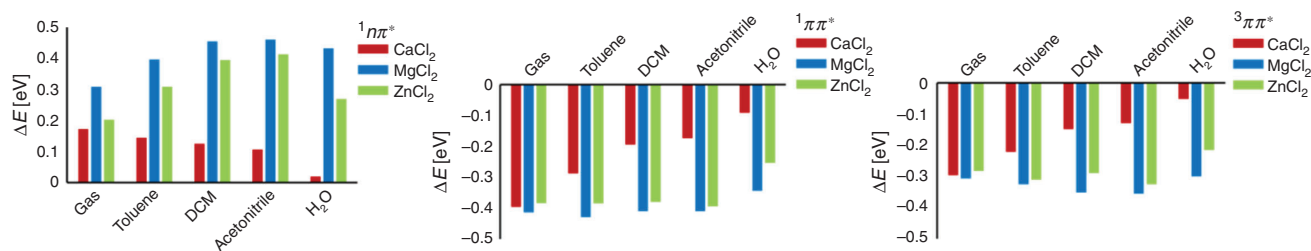
chloride species were investigated:  $ZnCl_2$ ,  $MgCl_2$ , and  $CaCl_2$ . The counterions were chosen for computational efficiency and because they had been used in our previous experimental study of the effect of LA complexation on MMMP and DMPA.<sup>[8]</sup> Depending on the conditions, other counterions could be used to enhance solubility and, particularly if non-coordinating, will have little impact on the results. It should also be added some of the reaction conditions studied (e.g. gas phase) are not practical but are included to better understand trends in the data.

There are two possible binding modes between I2959 and LA species, and each LA was modelled in both  $LA^{2+}$  and  $LACl_2$  forms in order to determine the I2959-LA complex most prevalent in different solvent environments. The thermodynamic calculations are summarized in Tables S1–S4 in the Supplementary Material, and show that for each of the LA species, the most favourable complexation position is to the acyl oxygen site (Fig. 4).

With the complexation mode of the LA with I2959 established, TD-DFT calculations were performed in order to assess the effect of their introduction on I2959 excited states. Fig. 5 shows the change in vertical excitation energy of the three excited states of interest on complexation relative to uncomplexed I2959 (Tables S10–S12, Supplementary Material). The calculations show that the  $n\pi^*$  states are destabilized and the  $\pi\pi^*$  states are stabilized by the presence of LAs. This is consistent with our previous experimental and theoretical study of the effects of zinc chloride ( $ZnCl_2$ ) and aluminium chloride ( $AlCl_3$ ) on MMMP and DMPA.<sup>[8]</sup> In the present work, we find that  $MgCl_2$  complexation has the most significant effect on the stability of the excited states of I2959. The observed splitting in stability between the  $n\pi^*$  and  $\pi\pi^*$  states arises from the



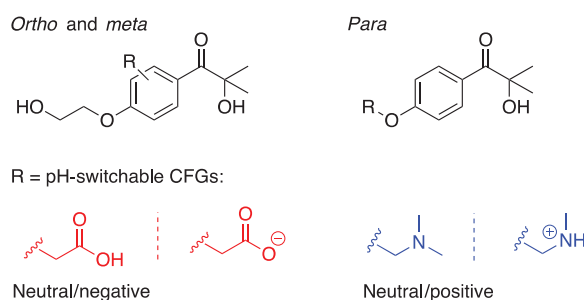
**Fig. 4.** Gas-phase Lewis acid complex structures and relative free energies ( $\text{kJ mol}^{-1}$ ) for  $\text{MgCl}_2$  (left),  $\text{CaCl}_2$  (middle), and  $\text{ZnCl}_2$  (right). In each case, the top structure is the minimum energy complex at the carbonyl and nearby alcohol, whereas the lower structure is the minimum energy complex at the ether and its nearby alcohol.



**Fig. 5.** Change in  $1n\pi^*$ ,  $1\pi\pi^*$ , and  $3\pi\pi^*$  vertical excitation energies (eV) on Lewis acid complexation.

difference in their respective Lewis basicities;<sup>[8]</sup>  $n\pi^*$  transitions involve moving an electron from the ketone oxygen  $n$ -orbitals into the  $\pi^*$ -system, resulting in a net less Lewis-basic ketone oxygen and conversely,  $\pi\pi^*$  transitions involve moving an electron from the  $\pi$ -system into  $\pi^*$ -orbitals that have some ketone delocalization, resulting in an increase in Lewis basicity at the ketone oxygen.

Compared with the remote charged functional groups (below), the complexation of LAs does not allow specific states to be selectively altered in energy based on their position or direction of charge, with complexation limited to only destabilizing the  $n\pi^*$  and vice versa for the  $\pi\pi^*$  states. As a result, their effects can be a bit hit-and-miss. For instance, in our previous study,<sup>[8]</sup> LAs red-shifted the excitation energies but caused a deterioration in initiator efficiency by prolonging triplet lifetimes. Nonetheless, the calculations presented here suggest that introduction of  $\text{MgCl}_2$  offers a promising route to increasing photoinitiation efficiency of Irgacure. On closer inspection of the excited states of the  $\text{MgCl}_2$ –I2959 complex in water, it is found the (de)stabilization of its excited states results in the ordering of the  $1n\pi^*$  and  $1\pi\pi^*$  states to swap, while the energy gap between the  $1\pi\pi^*$  and  $3n\pi^*$  states shrinks from 0.97 to 0.18 eV. If found experimentally to be accurate, this change in order of the excited states would allow the efficient population of the bright  $1\pi\pi^*$  state, followed by efficient ISC to the  $3n\pi^*$  to form radical species.



**Fig. 6.** CFG-functionalised I2959.

### Effect of Remote Charged Functional Groups

Previous work demonstrated that the attachment of non-conjugated charged functional groups (CFGs), i.e. acid and base groups that can be (de)protonated to form a charge, results in a ring-position-dependent electric field effect that can (de)stabilize  $n\pi^*$  and  $\pi\pi^*$  excited states, depending on the charge formed.<sup>[5]</sup> In I2959, the effect of attaching the carboxylic acid (CA) and tertiary amine (TA) groups at the *ortho* and *meta* positions of the phenyl ring, and replacing the alcohol group at the end of the alkyl chain as a pseudo-*para* position (Fig. 6) was investigated in solvents with increasingly large dielectric constants (Fig. 7). The *para* position was altered in a slightly

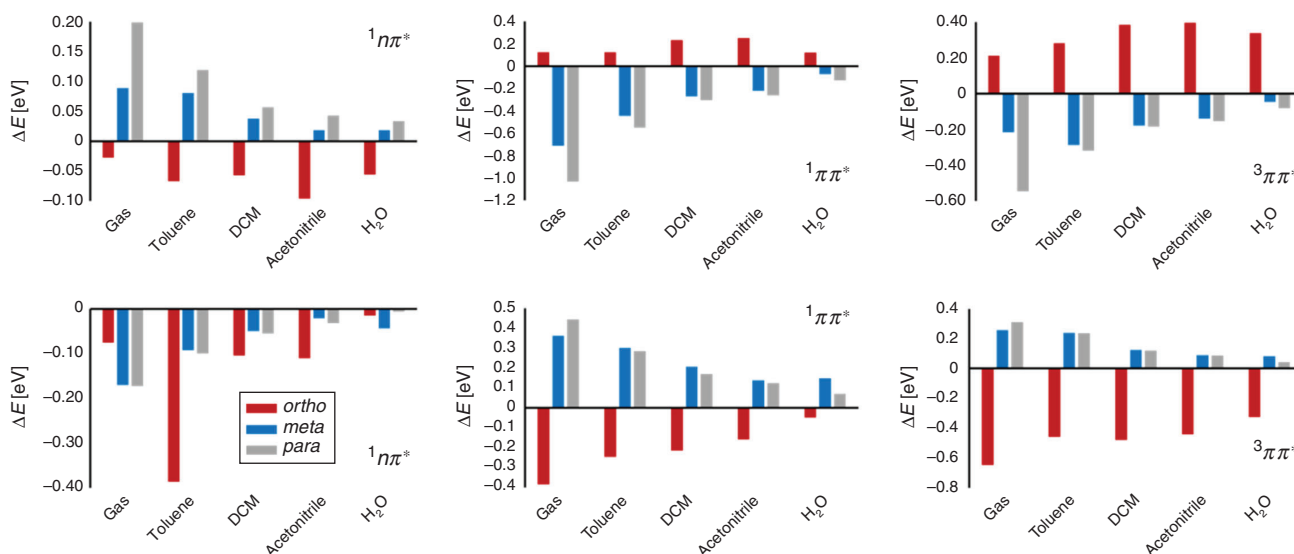


Fig. 7. Change in  $1n\pi^*$ ,  $1\pi\pi^*$ , and  $3\pi\pi^*$  vertical excitation energies (eV) on charge formation of  $\text{COO}^-$  (top row) or  $\text{NMe}_2\text{H}^+$  (bottom row).

different manner than the *ortho* and *meta* positions; in the case of the former, CFGs were introduced either by adding an acyl oxygen group to the  $-\text{CH}_2\text{OH}$  moiety or swapping the alcohol group for a tertiary amine group. For the *ortho* and *meta* positions,  $-\text{CH}_2\text{COOH}$  and  $-\text{CH}_2\text{NMe}_2$  groups were used. The difference in  $\text{pK}_a$  values of the CA and alkyl-OH groups of I2959 would be sufficient to allow selective deprotonation of the CA.

Fig. 7 includes the change in  $1n\pi^*$ ,  $1\pi\pi^*$ , and  $3\pi\pi^*$  vertical excitation energies on the formation of the charged species in the following solvent phases: gas, toluene, dichloromethane, acetonitrile, and water. Interestingly, there is a distinct *ortho/meta/para* (de)stabilization pattern different to that which has been reported previously.<sup>[5]</sup> Here, moving from the *ortho* to the *meta* positions results in a complete inversion in the effect of introducing either a positive or negative charged group. As well as this, the effect of applying a charged functional group is generally maximized at the *para* position. The reason for the observed anomalous results for the  $1n\pi^*$  state on introduction of an  $\text{NMe}_2\text{H}^+$  group is the presence of an internal hydrogen bond between it and the *n*-orbitals of the acyl moiety, which is countering the expected electrostatic destabilization of the  $n\pi^*$  excited state.

Given we wish to increase photoinitiation efficiency by lowering the  $\text{S}_1(n\pi^*)$  and raising the  $\text{T}_1(\pi\pi^*)$  states in energy, this is best achieved with a negative charge at the *ortho* position. Indeed, this results in a pH switch significant enough to make the  $1n\pi^*$  and  $3\pi\pi^*$  states degenerate in all solvents except water; even then, the resulting singlet–triplet energy gap  $\Delta E$  is reduced from  $\sim 0.5$  to  $\sim 0.1$  eV (see Supplementary Material for relevant vertical excitation energies). The convergence of these chosen excited states suggests that introducing remote charge to I2959 or, in fact, any molecule with photochemistry arising from excited states of differing symmetries is a practical and powerful method for manipulating photochemistry.

Finally, although the introduction of a positively charged group by the protonation of an amine substituent appears to be an ineffective approach to internal electric field introduction owing to spurious hydrogen-bond formation, it is important to remember that the amine group could instead be replaced with a quaternary ammonium salt. Such structures would not exhibit the unwanted internal hydrogen bond, and could be employed

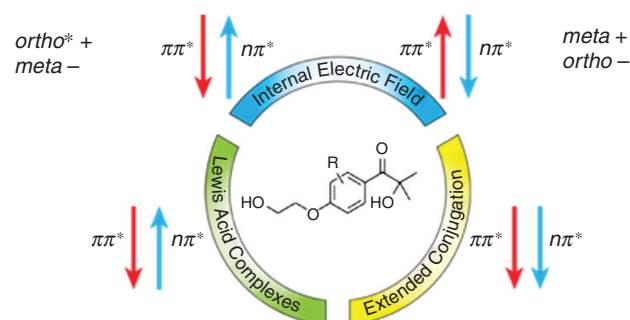


Fig. 8. Summary of calculated effects on the photochemistry of I2959 on introduction of extra functional groups. As noted in the text, the *ortho* positively charged groups stabilize the  $n\pi^*$  through a spurious hydrogen-bonding reaction that could be avoided through use of an alternative functional group to carry the positive charge.

when a low pH environment (required to form  $\text{COO}^-$ ) is inappropriate.

## Conclusions

TD-DFT calculations were performed on functionalized Irgacure I2959, a water-soluble Type I photoinitiator, in order to identify practical strategies for red-shifting its excitation energies while maintaining or improving its photoinitiation efficiency. Fig. 8 summarizes the main results and recommendations, which are also outlined below:

- Extending the  $\pi$ -system will red-shift the UV-vis spectrum, but owing to the  $\pi\pi^*$  states being stabilized and the  $n\pi^*$  being relatively unaffected, it would lead to a decline in photoinitiation efficiency.
- Including LAs to complex with the photoinitiator is a simple strategy that red-shifts  $\pi\pi^*$  transitions and blue-shifts  $n\pi^*$  transitions. The net effect on initiator efficiency varies considerably with the system but we predict that the  $\text{Mg}^{2+}$  complex of I2959 should exhibit the most significantly affected excited state energies, and therefore be a promising candidate as an efficient visible light photoinitiator.



- Including remote (non-conjugated) charged functional groups to electrostatically alter the transition energies is a very powerful strategy that can give more precise control through choice of charge and location. For I2959, best results would be achieved by inclusion of a  $\text{CH}_2\text{C}(\text{O})\text{O}^-$  group in the ortho position.

Work is under way to investigate these designs experimentally for the specific case of Irgacure I2959, but we also stress that the general findings can be applied to manipulation of other photochemical systems.

## Supplementary Material

Further computational results, including total energies and optimized geometries of all species, are available on the Journal's website.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Acknowledgements

MLC gratefully acknowledges a Georgina Sweet ARC Laureate Fellowship (FL170100041), financial support from the ARC Centre of Excellence for Electromaterials Science (CE140100012), and generous allocations of supercomputing time on the National Facility of the Australian National Computational Infrastructure.

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