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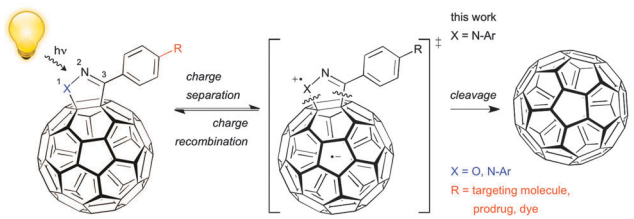
Modification of fulleropyrazolines modulates their cleavage by light†

Reida N. Rutte, Thomas B. Parsons and Benjamin G. Davis*

The extraordinary electrochemistry and the tunability of their energy levels allows the use of fulleropyrazolines in photovoltaics and charge-transfer systems. Here we show that substitution in position 1 tunes photolytic stability; electron-donating groups facilitate 1,3-dipolar cycloreversion to fullerene. This discovery has implications not only for photovoltaic stability but also highlights a potential strategy for photo-controlled fullerene release systems ('photo-caged'/'photo-activated' fullerene).

The unique electronic properties of fulleropyrazolines have enabled their use in photovoltaics.[1] Their photoactivity arises from the ability of fulleropyrazolines to undergo photonic excitement, charge separation and stabilisation, and then subsequent recombination (Scheme 1).[2] The effect of altering the C-3 pyrazoline substituent has been investigated both experimentally[1a,2c] and computationally.[2d] Modification of fulleropyrazolines at C-3 is essential for the energy transfer required in photovoltaic applications.[3] Substituents on the *N*-phenyl group (*N*-1) increase electronic interaction with the fullerene moiety and have been found to be essential for the charge transfer process.[4] However, to the best of our knowledge, the stability of fulleropyrazolines towards light has not been previously investigated.

The fundamental properties of photovoltaic substrates are the excitation energy and the lifetime of charge separated species.



Scheme 1 Fulleroheterocycles can charge separate upon photoirradiation. Substituents have potential to tune reactivity & stability and to deliver cargo.

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: Ben.Davis@chem.ox.ac.uk

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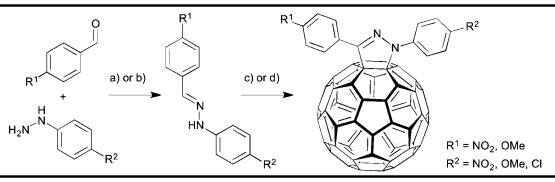
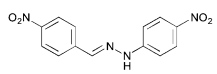
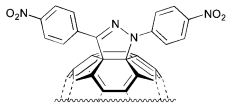
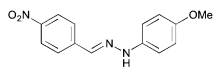
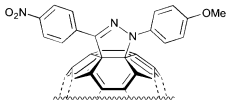
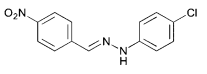
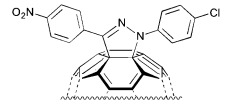
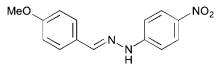
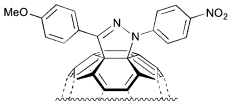
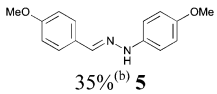
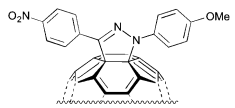
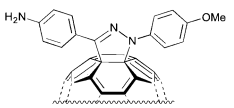
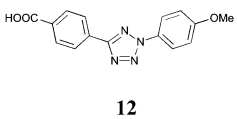
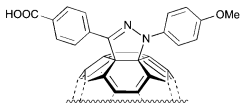
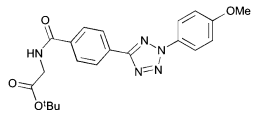
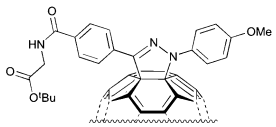
The lifetime of these substrates, especially fulleropyrazolines, may be tuned by incorporation of groups that can participate in charge transfer and stabilise or destabilise the radical cation formed upon excitation and charge separation.[2a,5] Intermediates of this type have the potential to disproportionate, as reported recently during the photocleavage of *para*-dimethylaminophenyl fulleroisoxazoline.[6] Yet, it is notable that despite the wide range of cycloaddition-type reactions which have been utilised in functionalization of fullerenes, the only reports of photoinduced cycloreversion (de-functionalization) are limited to the [3+2]-isoxazoline systems and the inefficient [2+2] reaction.[7] Limitations of these reactions are the uncontrollable equilibrium state of the photocycloaddition/-reversion as well as their lack of functionality.

Unlike isoxazolines, pyrazolines possess a second nitrogen atom (*N*-1) enabling further functionalization. This intriguing substrate class inspired us to combine dual functionalization and photocleavage in modified fulleropyrazolines (Scheme 1) for photoinduced cycloreversion as a technologically-useful delivery system for drugs,[8] dyes,[9] or targeting moieties.[10] A representative range of 1,3-disubstituted fulleropyrazolines was prepared from the appropriate aryl hydrazones, which in turn were readily accessed by condensation of the corresponding 4-substituted-benzaldehydes & phenylhydrazines (Table 1).[5b] Treatment of aryl hydrazones **1–4** with *N*-bromosuccinimide and triethylamine generated the nitrile imine *in situ*[4a,11] which in the presence of C_{60} fullerene gave the [3+2] fulleropyrazoline cycloadducts **6–9** in 15–51% yield. In all cases the pyrazoline was formed at the dipolarophilic 6,6-bond (ESI†).[12] Hydrazone **5** and fulleropyrazoline **10** were found to be very unstable in solution and could not be synthesised by this approach; instead basic milling[13] was used to generate **5** which was then halogenated with (diacetoxyiodo)benzene[4d] to give **10**. The labile amino derivative **11** was accessed by reduction of **7** using tin.[4c] To introduce a putative carboxylate handle for further modification the benzoic acid derivative **13** was also accessed by photolytic generation of the 1,3-dipole from tetrazole **12**.[14]

We found that the modified fullerenes were soluble in a number of solvents. 1,3-Dipolar cycloreversion of fulleropyrazolines would, in principle, release pristine fullerene. Initial investigations into the

Table 1 Synthesis of hydrazones and fulleropyrazolines



Precursor	Fulleropyrazoline
 13% **1**	 15% **6**
 83% **2**	 40% **7**
 92% **3**	 51% **8**
 23% **4**	 24% **9**
 35%[(b)] **5**	 1%[(d)] **10**
 **7**	 6% **11**
 **12**	 39% **13**
 **14**	 25% **15**

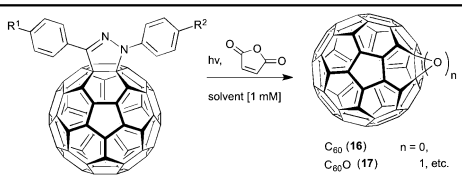
Reagents & conditions: (a) aldehyde, hydrazine, AcOH, EtOH, 78 °C;[5b] (b) aldehyde, hydrazine, NaOH, silica, 40 min;[13] (c) hydrazone, NBS, $CHCl_3$, r.t., 30 min; then C_{60}, NEt_3, toluene, microwave;[5a,12] (d) hydrazone, C_{60}, (diacetoxyiodo)benzene, toluene, 40 °C, 3.5 h;[4d] (e) Sn–HCl(aq), $CHCl_3$, reflux, 6 h, 6%;[4c] (f) tetrazole, C_{60}, toluene, Hg-lamp.[14]

photocleavage reaction were conducted in degassed toluene with an excess of maleic anhydride. Based on previous reversible cleavage reactions[6,15] we initially included this trapping alkene in the reaction mixture to prevent re-addition of the released 1,3-dipole with free C_{60}. Photocleavage reactions were monitored by t.l.c., HPLC, NMR, and mass spectrometry. Where possible, the photocleavage products were isolated and fully characterised (see ESI†). Various light sources of different λ_{max} were investigated. Medium-pressure mercury, handheld U.V. (λ = 365 nm),‡ Rayonet (λ = 350 nm), filtered medium-pressure mercury (λ = 313 nm),[16] and commercial halogen lamps all gave cycloreversion products with comparable efficiency (60–75% conversion after 1.5 hours). For ease of practicality all subsequent experiments used the Hg lamp.

Fulleropyrazolines which possessed a *para*-methoxyphenyl substituents on *N*-1 (**7**, **10**, **11**, and **13**) underwent photo-induced cycloreversion to produce C_{60} and $C_{60}O$ whereas those carrying a *para*-nitro group (**6** and **9**) were unreactive under the same conditions (Table 2).§ We speculated that the strong positive mesomeric effect of the methoxy group[17] stabilises the development of the ensuing radical cation during the transition state of the 1,3-dipolar cycloreversion (Scheme 2). This was confirmed by fulleropyrazoline **8** that bears a less +M *para*-chloro substituent, which was cleaved, but far more slowly than the methoxy analogue. The importance of the substituent at *N*-1 confirmed a key role of this atomic centre, perhaps through the lone pair of the sp^3 nitrogen, in charge transfer processes.[4d]

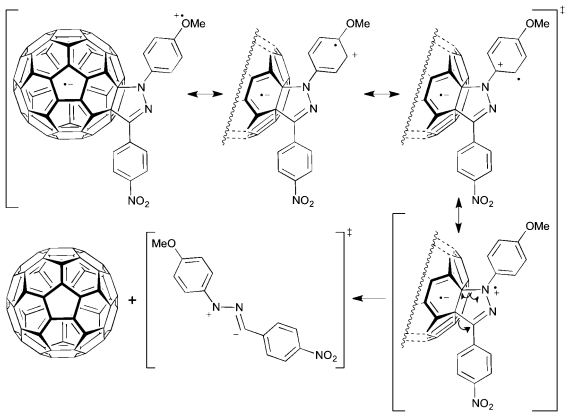
Notably, photocleavage of fulleropyrazolines gave not just pristine C_{60} **16** but a mixture of monooxidised $C_{60}O$ **17** with

Table 2 Photocleavage of fulleropyrazolines



R^1	R^2	Fulleropyrazoline	Result
NO_2	NO_2	**6**	No reaction
NO_2	OMe	**7**	Cleavage
NO_2	Cl	**8**	Cleavage
OMe	NO_2	**9**	No reaction
OMe	OMe	**10**	Cleavage
NH_2	OMe	**11**	Cleavage
COOH	OMe	**13**	Cleavage
$CONH_2$–Gly–OBu^t	OMe	**15**	Cleavage

Reagents & conditions: toluene or chloroform [1 mM], 20 eq. maleic anhydride, medium pressure mercury lamp, 4 min–12 h.



Scheme 2 Possible mechanism of fulleropyrazoline photocleavage.

traces of $C_{60}O_n$ in varying ratios. The proportions of C_{60} and $C_{60}O$ obtained did not show any simple correlation with reaction conditions (solvent, trapping alkene, degassed or anhydrous solvent, irradiation wavelength).† Irradiation of pristine C_{60} gave oxidation to $C_{60}O$ as previously reported.[18] Oxidation of C_{60} occurred only at a 6,6-bond, an observation which is in accordance with previous reports.[19] Surprisingly, the use of non-degassed solvent shortened the reaction time to around one quarter, but only marginally increased the ratio of $C_{60}O/C_{60}$. These results together suggested that $C_{60}O$ resulted from the *in situ* generation of singlet oxygen and subsequent reaction with the photo-released C_{60} and not as a direct result of photo-cleavage.

To test the necessity and role of dipolarophile traps, various other alkenes were investigated as additives in the photocycloreversion of fulleropyrazoline **7** (Table S2, ESI†). The rate of the photocleavage could be improved in the presence of 3,3-dimethylallylbromide or *para*-chlorostyrene. Pleasingly the cycloreversion also proceeded efficiently without alkene (Table S2, entry 8, ESI†), thus confirming the utility of this process even in the absence of a trapping partner.

The reaction rate for photocleavage showed clear solvent effects; it was enhanced in more polar solvents such as chloroform and benzonitrile and further enhanced in mixed aqueous–organic solvent systems. This supports suggested formation of a charge-separated diradical species (Scheme 2). Notably in the presence of base (pyridine as solvent, DABCO as additive) the photocleavage does not occur, presumably because the putative pyrazoline radical cation is quenched under these conditions.[20] In this mechanism, under photoirradiation fulleropyrazolines form a charge separated diradical species.[2c,3,5b,6,21] The positive charge that is formed can be stabilised particularly effectively by the *N*-1 methoxy group, which promotes bond cleavage to release free C_{60}. The breakdown products are discussed further in the ESI.†

Finally to test utility in future applications, the reaction was tested in various mixed aqueous solvent systems (see ESI†); pleasingly, it proceeded efficiently in all and with rates enhanced by the presence of water. This could vitally enable the use of fulleropyrazolines under conditions suitable for biologically-relevant photo-controlled substrates when *e.g.* used in putative drug-delivery systems or for '1,3-dipole delivery' to olefin-containing biomolecules. The proof-of-principle for such a system was demonstrated by the construction of the amino-acid-carrying fulleropyrazoline **15** and subsequent successful 'photo-release' under aqueous conditions (see ESI†).

In conclusion we have shown that the reactivity of fulleropyrazolines may be tuned to enable highly efficient photocleavage. The reaction proceeds in various solvent systems and without the need for additional trapping agents to remove 1,3-dipolar species generated *in situ*. An electron donating substituent on *N*-1 of the pyrazoline is sufficient to enable the reaction to proceed; various substituents are tolerated at C-3. This synthetic flexibility and the aqueous compatibility could enable the use of C_{60} fullerenes as carriers for prodrugs or other photocontrolled elements.

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Notes and references

‡ Handheld lamp at λ = 254 nm gave 22% conversion after 3.5 hours.
§ This cleavage process was induced by exposure to light from a medium pressure mercury lamp and did not occur when **7**, **10**, **11**, and **13** were subjected to heat. Cycloreversion of fulleropyrazolines was previously reported to occur only in the presence of $Cu(OTf)_2$.[15]

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