

COMMUNICATION

Modification of Fulleropyrazolines Modulates Their Cleavage by Light

Cite this: DOI: 10.1039/x0xx00000x

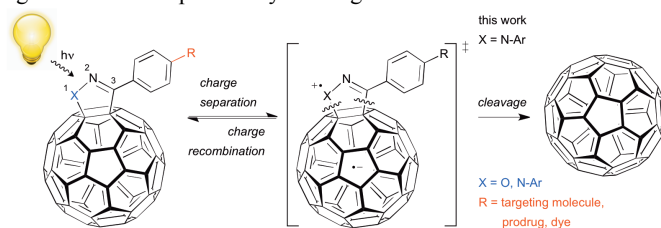
Reida N. Rutte,^a Thomas B. Parsons^a and Benjamin G. Davis^{a*}Received 00th May 2014,
Accepted 00th ?? 2014

DOI: 10.1039/x0xx00000x

www.rsc.org/

The extraordinary electrochemistry and the tunability of their energy levels allows the use of fulleropyrazolines in photovoltaics. Here we show that substitution in position 1 tunes photolytic stability; electron-donating groups facilitate 1,3-dipolar cycloreversion to pristine fullerene. This discovery has implications not only for photovoltaic stability but also highlights a potential strategy for photo-controlled fullerene release (a ‘photo-caged’ 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) showed stronger electronic interaction with the fullerene moiety and were 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.



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

The fundamental properties of photovoltaic substrates are the excitation energy and the lifetime of charge separated species. 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 fullerisoxazoline.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-2) 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 nitric imine *in situ*^{4a, 11} which in the presence of C₆₀ 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†.¹² Hydrazone **5** and fulleropyrazoline **10** were found to be very unstable in solution and could not be synthesised by this approach; instead basic milling¹³ 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, future 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 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 C₆₀. 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. ($\lambda = 365$ nm),[¶] Rayonet ($\lambda = 350$ nm), filtered medium-pressure mercury ($\lambda = 313$ 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.

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

Reagents & conditions: a) aldehyde, hydrazine, AcOH, EtOH, 78°C;^{5b} b) aldehyde, hydrazine, NaOH, silica, 40 min;¹³ c) hydrazone, NBS, CHCl₃, r.t., 30 min; then C₆₀, NEt₃, toluene, microwave;^{5a, 12} d) hydrazone, C₆₀, (diacetoxyiodo)benzene, toluene, 40°C, 3.5 h;^{4d} e) Sn/HCl(aq), CHCl₃, reflux, 6 h, 6%;^{4c} f) tetrazole **12**, C₆₀, toluene, Hg-lamp, 3.5 h, 39% (95% b.r. C₆₀)¹⁴

Fulleropyrazolines which possessed a *para*-methoxyphenyl substituents on N-1 (**7**, **10**, **11**, and **13**) underwent photo-induced cycloreversion to produce C₆₀ and C₆₀O whereas those carrying a *para*-nitro group (**6** and **9**) were unreactive under the same conditions.⁸ We speculated that the strong positive mesomeric effect of the methoxy group¹⁷ 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 sp³ nitrogen, in charge transfer processes.^{4d}

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

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

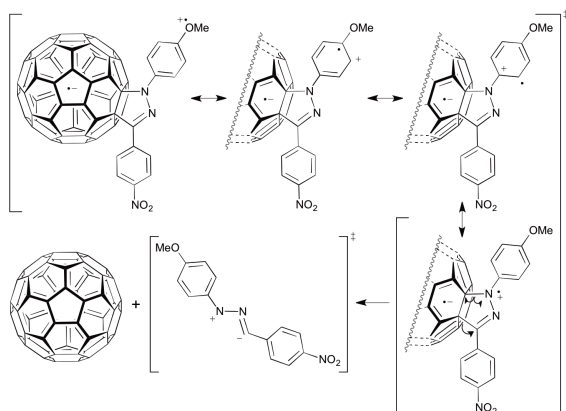
Notably, photocleavage of fulleropyrazolines gave not just pristine C₆₀ **14** but a mixture of monooxidised C₆₀O **15** with traces of C₆₀O_n in varying ratios. The proportions of C₆₀ and C₆₀O obtained did not show any simple correlation with reaction conditions (solvent, trapping alkene, degassed or anhydrous solvent, irradiation wavelength)†. Irradiation of pristine C₆₀ gave oxidation to C₆₀O as previously reported.¹⁸ Oxidation of C₆₀ 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 C₆₀O/C₆₀. These results together suggested that C₆₀O resulted from the *in situ* generation of singlet oxygen and subsequent reaction with the photo-released C₆₀ and not as a direct result of photo-cleavage. Notably, the addition of 10 equivalents of DABCO to quench any singlet oxygen²⁰ suppressed the photocleavage reaction completely.

To test the necessity and role of dipolarophile traps, various other alkenes were investigated as additives in the photocycloreversion of fulleropyrazoline **7** (Table S1). 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 S1, Entry 8), thus confirming the utility of this process even in the absence of a trapping partner.

The reaction rate for photocleavage also showed clear solvent effects; it was enhanced when the solvent was changed to chloroform. This was consistent with the 'heavy atom effect' of

halogens that can lead to enhanced $S_1 \rightarrow T_1$ intersystem crossing by induced spin-orbit coupling;²¹ its observed promotion of the photocycloreversion here is consistent with the mechanism proposed in Scheme 2. In this mechanism, under photoirradiation fulleropyrazolines form a charge separated diradical species.^{2c, 3, 5b, 6, 22} 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} .

Finally to test utility in future applications, the reaction was tested in mixed aqueous solvent systems; pleasingly, it proceeded efficiently in systems such as toluene/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. This will be reported in due course.



Scheme 2 Possible mechanism of fulleropyrazoline photocleavage.

In conclusion we have shown that the reactivity of fulleropyrazolines may be tuned to enable highly efficient photocleavage. The reaction proceeds efficiently 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.

Notes and references

We thank the EU FP7/2007-2013/ (REA grant n° 290023) for funding and Dr S. van Berkel for tetrazole **12**.

^a University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK. Email: Ben.Davis@chem.ox.ac.uk

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

§ 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

¶ handheld lamp at $\lambda = 365$ nm gave 22% conversion after 3.5 hours.

- 1 (a) J. L. Delgado, N. Martín, P. de la Cruz and F. Langa, *Chem. Soc. Rev.*, 2011, **40**, 5232; (b) F. Langa and F. Oswald, *Targets in Heterocyclic Systems*, 2004, **8**, 120.

- 2 (a) D. M. Guldi and M. Prato, *Acc. Chem. Res.*, 2000, **33**, 695; (b) F. Langa, P. de la Cruz, E. Espildora, A. de la Hoz, J. L. Bourdelande, L. Sanchez and N. Martin, *J. Org. Chem.*, 2001, **66**, 5033; (c) A. Gouloumis, F. Oswald, M. E. El-Khouly, F. Langa, Y. Araki and O. Ito, *Eur. J. Org. Chem.*, 2006, **2006**, 2344; (d) J. J. Oviedo, M. E. El-Khouly, P. de la Cruz, L. Pérez, J. Garín, J. Orduna, Y. Araki, F. Langa and O. Ito, *New J. Chem.*, 2006, **30**, 93.
- 3 F. Langa and F. Oswald, *C. R. Chim.*, 2006, **9**, 1058.
- 4 (a) Y. Matsubara, H. Tada, S. Nagase and Z.-i. Yoshida, *J. Org. Chem.*, 1995, **60**, 5372; (b) F. Langa, P. de la Cruz, J. L. Delgado, E. Espildora, M. J. Gómez-Escalonilla and A. de la Hoz, *J. Mat. Chem.*, 2002, **12**, 2130; (c) J. L. Delgado, P. de la Cruz, V. López-Arza and F. Langa, *Tetrahedron Lett.*, 2004, **45**, 1651; (d) B. Lu, J. Zhang, J. Li, J. Yao, M. Wang, Y. Zou and S. Zhu, *Tetrahedron*, 2012, **68**, 8924.
- 5(a) J. L. Delgado, P. de la Cruz, V. López-Arza, F. Langa, D. B. Kimball, M. M. Haley, Y. Araki and O. Ito, *J. Org. Chem.*, 2004, **69**, 2661; (b) J. L. Delgado, P. de la Cruz, V. López-Arza, F. Langa, Z. Gan, Y. Araki and O. Ito, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1500.
- 6 F. Hörmann, W. Donaubaue, F. Hampel and A. Hirsch, *Chem. Eur. J.*, 2012, **18**, 3329.
- 7 (a) X. Zhang, A. Fan and C. S. Foote, *J. Org. Chem.*, 1996, **61**, 5456; (b) G. Vassilikogiannakis and M. Orfanopoulos, *J. Am. Chem. Soc.*, 1997, **119**, 7394; (c) *Tetrahedron Lett.*, 1997, **38**, 4323; (d) *J. Org. Chem.*, 1999, **64**, 3392.
- 8 (a) T. Da Ros and M. Prato, *Chem Commun*, 1999, 663; (b) H.-C. Wu, X. Chang, L. Liu, F. Zhao and Y. Zhao, *J. Mat. Chem.*, 2010, **20**, 1036.
- 9 E.M. Sletten and C.R. Bertozzi, *Angew Chem, Int Ed*, 2009, **48**, 6974.
- 10 S. Aoki, N. Matsuo, K. Hanaya, Y. Yamada and Y. Kageyama, *Bioorg. Med. Chem.*, 2009, **17**, 3405.
- 11 R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403.
- 12 P. de la Cruz, A. Diaz-Ortiz, J. J. Garcia, M. J. Gomez-Escalonilla, A. de la Hoz and F. Langa, *Tetrahedron Lett.*, 1999, **40**, 1587.
- 13 A. R. Hajipour, I. Mohammadpoor-Baltork and M. Bigdeli, *J. Chem. Res.*, 1999, 570.
- 14 C. Rodriguez-Emmenegger, C. M. Preuss, B. Yameen, O. Pop-Georgievski, M. Bachmann, J. O. Mueller, M. Bruns, A. S. Goldmann, M. Bastmeyer and C. Barner-Kowollik, *Advanced Materials*, 2013, **25**, 6123.
- 15 J. L. Delgado, F. Oswald, F. Cardinali, F. Langa and N. Martin, *J. Org. Chem.*, 2008, **73**, 3184.
- 16 M. Kasha, *J. Opt. Soc. Am.*, 1948, **38**, 929.
- 17 L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 96.
- 18 K. M. Creegan, J. L. Robbins, W. K. Robbins, J. M. Millar, R. D. Sherwood, P. J. Tindall, D. M. Cox, A. B. Smith III, J. P. McCauley, D. R. Jones and R. T. Gallagher, *J. Am. Chem. Soc.*, 1992, **114**, 1103.
- 19 R. G. Bulgakov, Z. S. Kinzyabaeva, L. M. Khalilov and V. M. Yanybin, *Russ. J. Org. Chem.*, 2011, **46**, 1776.
- 20 D. M. Guldi, R. E. Huie, P. Neta, H. Hungerbühler and K.-D. Asmus, *Chem. Phys. Lett.*, 1994, **223**, 511.
- 21 (a) W. Hartmann and H.-G. Heine, *Angew. Chem., Int. Ed.*, 1971, **10**, 272; (b) A. K. Chandra, N. J. Turro, A. L. Lyons and P. Stone, *J. Am. Chem. Soc.*, 1978, **100**, 4964.
- 22 N. Armaroli, G. Accorsi, J.-P. Gisselbrecht, M. Gross, V. Krasnikov, D. Tsamouras, G. Hadzioannou, M. J. Gómez-Escalonilla, F. Langa, J.-F. Eckert and J.-F. Nierengarten, *J. Mat. Chem.*, 2002, **12**, 2077.