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Singlet Oxygen Reactions of Benzannelated Isoquinolinones

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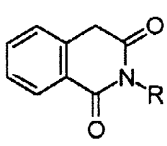
Abstract: Tetraphenylporphin (TPP) or methylene blue (MB) sensitized photooxygenation reactions of benzannelated isoquinolinones **3** and **4** took place by initial attack of singlet oxygen on the enol ether-enamine C=C double bond and proceeded *via* zwitterionic (**10**, **29**) and endoperoxidic (**11**, **28**, **30**) intermediates. The product for **3** was **5** exclusively in MeCN, and **5** and the solvent trapping products **6** in MeOH. For **4**, the products were **25** (and **26**) in MeCN, while in MeOH, solvent trapping product **31** was also obtained for **4b**. Intramolecular trapping of the zwitterionic intermediate during the singlet oxygen reaction of **4d** to form **32** was also observed.

Isoquinoline derivatives have a wide range of biological activities[1] and constitute a large group of naturally occurring alkaloids.[2] In relation to our interest in the synthesis and photochemistry of new isoquinoline derivatives of elaborate structures, we have recently reported dye sensitized photooxygenation reactions of 1,3-isoquinolinediones[3] and found that, with the enol form being the actual active species toward singlet oxygen, these reactions are very sensitive to the tautomeric equilibrium between the keto (**1**) and enol (**2**) forms of the



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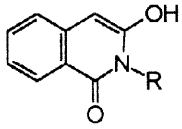

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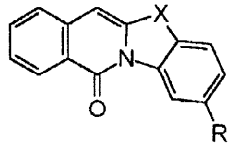
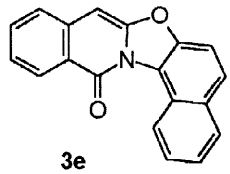
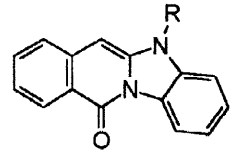


3a X = O, R = H
3b X = O, R = OCH_3
3c X = O, R = CH_3
3d X = O, R = Cl
3f X = S, R = H



3e



4a R = H
4b R = CH_3
4c R = CH_3CO
4d R = CH_2CH_2OH

substrates, and could only proceed in the presence of an added base which serves as a hydrogen bond acceptor to shift the tautomeric equilibrium to the enol side. We have also investigated the synthesis and electronic structures of several bezannelated isoquinolinone derivatives and their photochemical cycloadditions with electron deficient olefins.[4] These compounds (**3** and **4**) can be structurally viewed as masked 1,3-isoquinolinedione derivatives (*via* their enol tautomers) with enol ether-enamine structures. In contrast to simple enol ethers and enamines whose singlet oxygen reactions have been extensively investigated,[5] enol ether and enamine compounds with delicate structural features such as keto enol ether and keto enamines,[6] as

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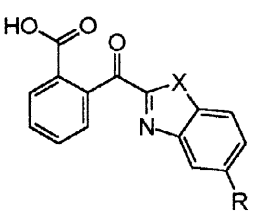
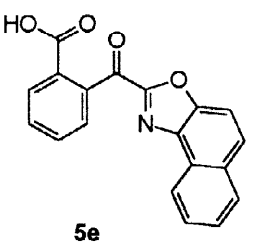
in **3** and **4**, have rarely been the subject of investigation in singlet oxygen reactions. Considering that these substrates may display different reaction modes and reactivities from those of simple enol ethers and enamines, and as a natural continuation of our investigation on the photooxygenation reactions of 1,3-isoquinolinediones, we report here the singlet oxygen reactions of compounds **3** and **4**.

Results and discussion

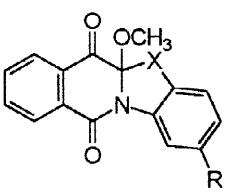
The characteristic enol ether-enamine structure of compounds **3** and **4** implies a high electron density at the C_{5a}=C_6 double bond. This has been borne out by our *ab initio* calculations of their electronic structures[4] which show that C_6 atoms are heavily negatively charged in **3**. Indeed, it was found that this C_{5a}=C_6 bond is readily attacked by singlet oxygen in photosensitized oxygenations. For example, photolysis of a benzene solution of **3a** (5×10^{-2} mol dm^{-3}) with light of wavelength longer than 400 nm under oxygen atmosphere and with tetraphenylporphin (TPP) as sensitizer (5×10^{-4} mol dm^{-3}) afforded **5a** exclusively in 99% yield. Photooxygenation of **3a** (5×10^{-2} mol dm^{-3}) in acetonitrile with methylene blue (MB, 5×10^{-4}mol dm^{-3}) as sensitizer under the irradiation with light of wavelength longer than 500 nm also gave **5a** as the sole product in 98% yield. However, when the MB sensitized photooxgenation of **3a** was conducted in methanol, a solvent trapping product (**6a**) was also obtained in 22% yield, together with **5a** (71%). MB sensitized photooxygenation reactions of **3b-3f** were subseqently investigated. In theses cases, photolyses in acetonitrile all gave the corresponding **5** as the sole product in high yield (Table 1), while reactions in methanol afforded **6** and **5** simultaneously with the exception of **3e**, where no solvent trapping product **6e** was found (Table 1). Since the structures of **5** are critically important in distinguishing the reaction mode, a crystallographic analysis for product **5c** was carried out which gave an unambiguous determination of the structures of **5** (see Fig. 1).



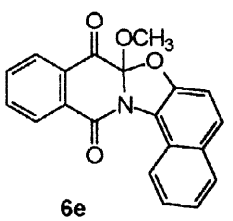
5a X = O, R = H
5b X = O, R = OCH_3
5c X = O, R = CH_3
5d X = O, R = Cl
5f X = S, R = H



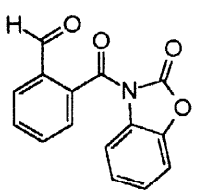
5e



6a X = O, R = H
6b X = O, R = OCH_3
6c X = O, R = CH_3
6d X = O, R = Cl
6f X = S, R = H



6e



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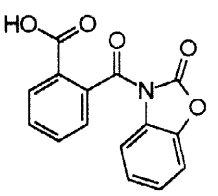

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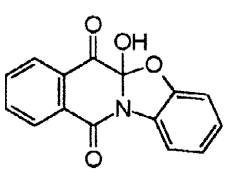

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The formation of products **5** showed that, although the enol-enamine C=C double bond in **3** is the site of initial attack of singlet oxygen, these substrates did not follow the normal reaction mode for simple enol ether and enamines without abstractable allylic hydrogens where final products are derived from the decomposition

of a dioxetane intermediate.[5] Were this reaction pathway followed for **3**, different products such as **7**, **8** and **9** would have been formed instead of **5**. Since no such products as **7**, **8** and **9** were found in these MB or TPP sensitized photooxygenation reactions either in acetonitrile, benzene or in methanol even in a trace amount, a dioxetane intermediate can be excluded from the reaction mechanism.

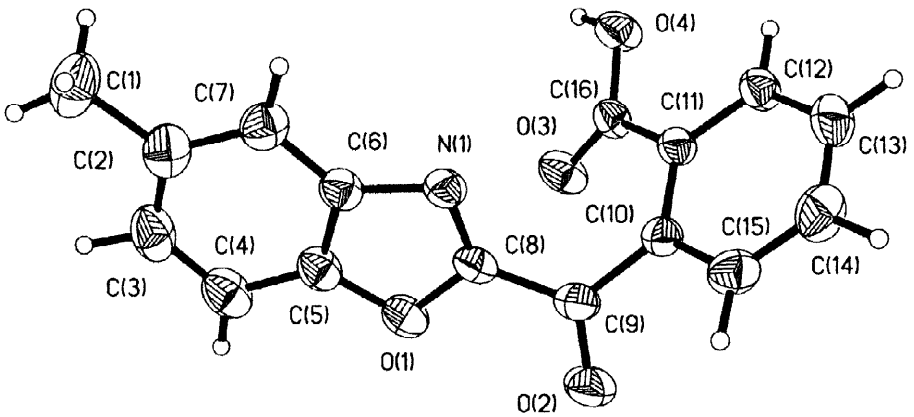


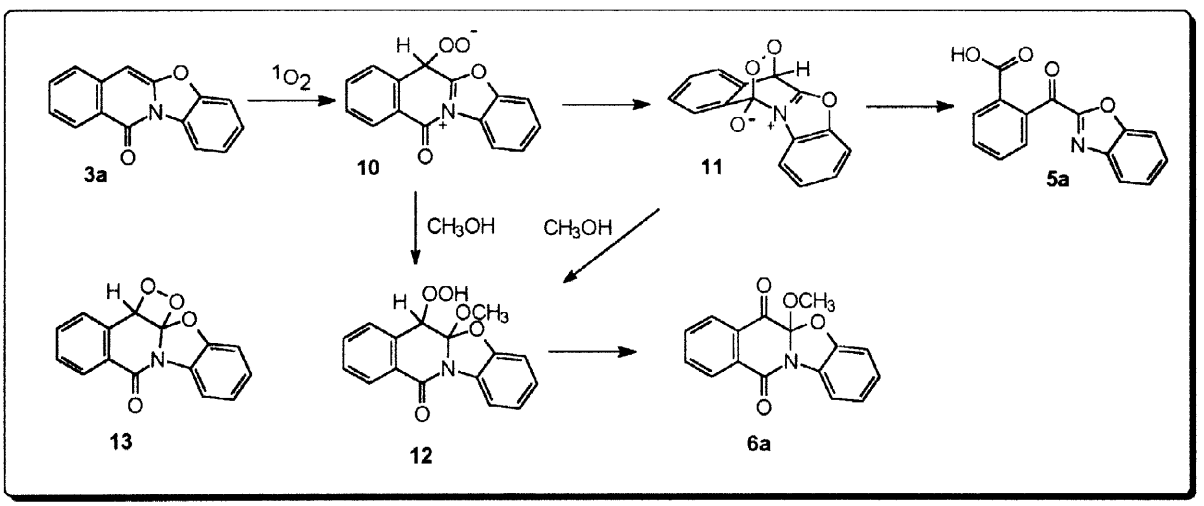
Fig. 1 ORTEP Drawing of Product **5c**

Table 1 Dye Sensitized Photooxygenation Reactions of Compounds **3** and **4**

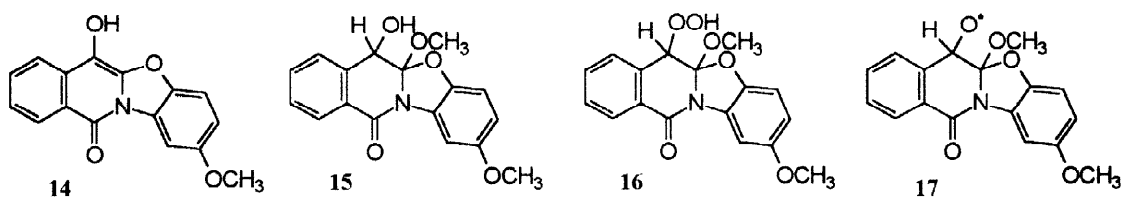
Substrate[a]	Sensitizer[b]	Solvent	Irrad. time (h)[c]	Products and yield (%)[d]
3a	TPP	C_6H_6	10	**5a** (99)
3a	MB	MeCN	10	**5a** (98)
3a	MB	MeOH	30	**5a** (71), **6a** (22)
3b	MB	MeCN	5	**5b** (98)
3b	MB	MeOH	24	**5b** (77), **6b** (15)
3c	MB	MeCN	8	**5c** (98)
3c	MB	MeOH	60	**5c** (70), **6c** (23)
3d	MB	MeCN	15	**5d** (97)
3d	MB	MeOH-MeCN (4:1 v/v)	36	**5d** (77), **6d** (13)
3e	MB	MeCN	10	**5e** (99)
3e	MB	MeOH-MeCN (4:1 v/v)	40	**5e** (95)
3f	MB	MeCN	8	**5f** (99)
3f	MB	MeOH	24	**5f** (95), **6f** (3)
4a	MB	MeCN	10	**25a** (48), **26** (50)
4a	MB	MeOH	60	**25a** (50), **26** (50)
4b	MB	MeCN	10	**25b** (86), **26** (8)
4b	MB	MeOH	12	**25b** (63), **31** (35)
4c	MB	MeCN	6	**25c** (99)
4c	MB	MeOH	80	**26** (95)
4d	MB	MeCN	10	**25d** (66), **26** (9), **32** (13)

[a] The concentration of the substrates was 5×10^{-2} mol dm^{-3} in all cases except for **3d** in MeOH-MeCN (4:1 v/v), where a concentration of 2.5×10^{-2} mol dm^{-3} was used. [b] The concentration was 5×10^{-4} mol dm^{-3}. [c] The reaction time in methanol was significantly longer than in acetonitrile due to the problem of solubility, the relative reactivities of the substrates may be roughly reflected by the reactions in acetonitrile. [d] Yield of isolated pure product based on consumed substrate.

The products **5** and **6** are therefore proposed to be formed *via* a mechanism as shown in Scheme 1. An "ene " type electrophilic attack of $^1O_2$ on C_6 of the substrates (or electron transfer from the substrates to $^1O_2$ followed by radical coupling of the radical ion pair[7]) leading to a zwitterionic intermediate **10**, in which transannular nucleophilic attack of the peroxidic anion to the *para*-carbonyl group afforded the endoperoxide **11**. Homolytic cleavage of the O-O bond and heterolytic C-N bond scission resulted in the formation of **5**. Similar intramolecular attack of a peroxidic anion to a *para*-carbonyl group in a six membered ring leading to an endoperoxide intermediate was also suggested by Matsuura *et al* in the mechanism of photooxygenations of purine derivatives[8] and in the singlet oxygen reactions of 1,3-isoquinolinedione derivatives reported by us.[3] Products **6** were derived from the nucleophilic trapping of the iminium cation in **10** or **11** by methanol. Although the formation of **6** could also be rationalized by nucleophilic attack of methanol on a dioxetane intermediate such as **13**, the absence of any cleavage products derived from the dioxetane inermediate both in acetonitrile and in methanol regards the involvement of dioxetane intermediate as unlikely to be operative in the photooxygenations.

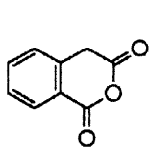


Scheme 1 Mechanism for Singlet Oxygen Reaction of **3a**



In the MB sensitized photooxygenation of **3b** in methanol, a small amount of produt **14** (2%) was also obtained, which decomposed rapidly in solution and gradually in crystalline state. No such product was found in the same reaction in acetonitrile. TLC monitoring of the photolysate right after the photolysis showed that this product was absent and was produced during work-up of the photolysate. This product is probably derived from the primary product **15** by elimination of a methanol molecule on silica gel. Control experiment showed that product **6b** could not take part in photoinduced hydrogen abstraction reactions from methanol and was stable in methanol even on prolonged irradiation with light of λ>334 nm. Therefore, the supposed primary product **15** was probably formed from the hydroperoxide intermediate **16** *via* the alkoxy radical intermediate

17. Products similar to **14** were also found as minor products during work-up of the photolysate in the reactions of **3a**, **3c** and **3d** (not **3e** and **3f**) in methanol, but we have been unable to obtain these products in pure form.



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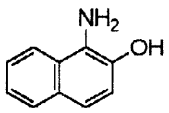

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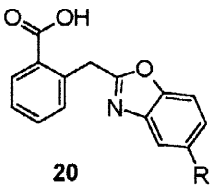

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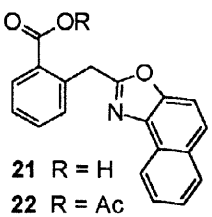
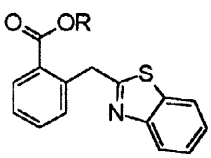
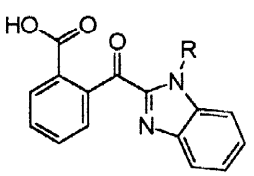


21 R = H
22 R = Ac

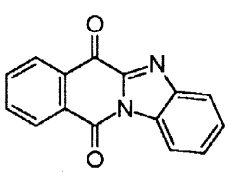


23 R = H
24 R = Ac

It is worth mentioning that in the MB sensitized photooxygenation of **3e** in methanol, solvent trapping product **6e** was not found. This showed that the naphthoxazole moiety is a better nucleofuge and has a decreased nucleophilicity compared with the benzoxazole due to the electronic effect of the naphthalene ring. As a result, nucleophilic attack of methanol on the iminium cation at C_{5a} could not compete with heterolytic cleavage of the C-N bond in **11**. The steric effect of the bulky naphthoxazole moiety on solvent attack to the iminium cation may also play some role in eliminating the solvent trapping product. The decreased nucleophilicity of the naphthoxazole moiety has previously been noted in the synthesis of **3e** by the reaction of homophthalic anhydride **18** and *o*-aminonaphthol (**19**).[4] While in the syntheses of **3a-3d**, the formation of the intermediate **20** from homophthalic anhydride **18** and the corresponding substituted *o*-aminophenols, and the subsequent cyclization of **20** by intramolecular nucleophilic attack of the benzoxazole nitrogen to the carboxy group could be achieved in one pot simply by refluxing **18** and the *o*-aminophenols in acetic acid, the intermediate **21** could not be further cyclized into **3e** in acetic acid in the same pot due to a decreased nucleophilicity of the naphthoxazole moiety. Further cyclization of **21** could only be accomplished by refluxing in acetic anhydride to transform the carboxylic acid into anhydride **22** which has a better leaving group (AcO^-) than **21** (OH^-). In the MB sensitized photooxygenation of **3f** in methanol, the much lower yield of the solvent trapping product **6f** also reflected the influence of a decreased nucleophilicity of the benzothiazole moiety compared with benzoxazole as was shown in the synthesis of **3f** from **18** and *o*-aminothiophenol where further cyclization of the intermediate **23** also needs its transformation into the anhydride **24**.



25a R = H
25b R = CH_3
25c R = CH_3CO
25d R = CH_2CH_2OH



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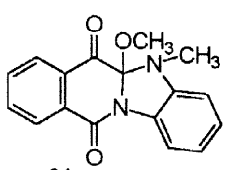

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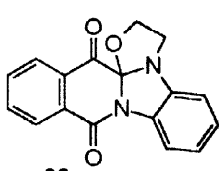

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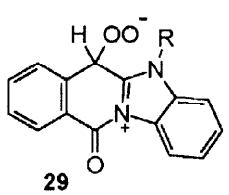

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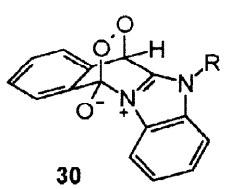

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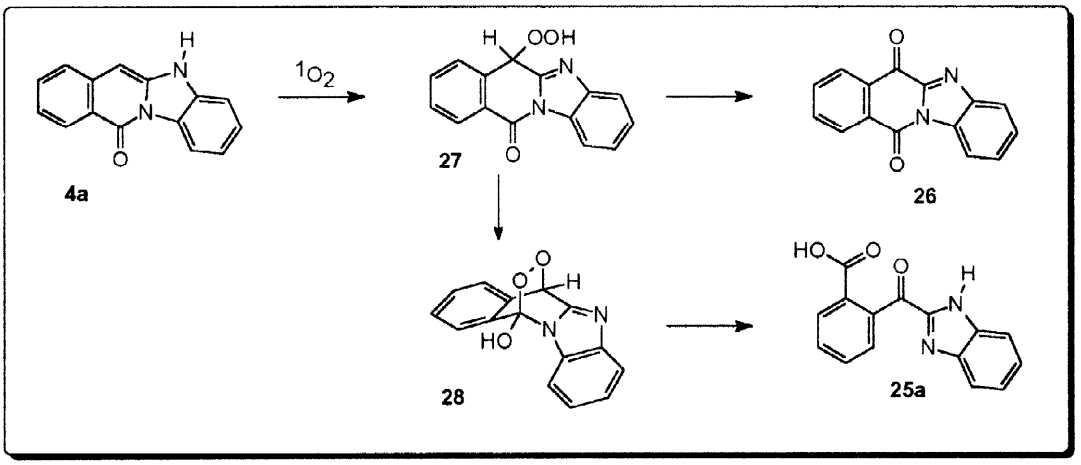
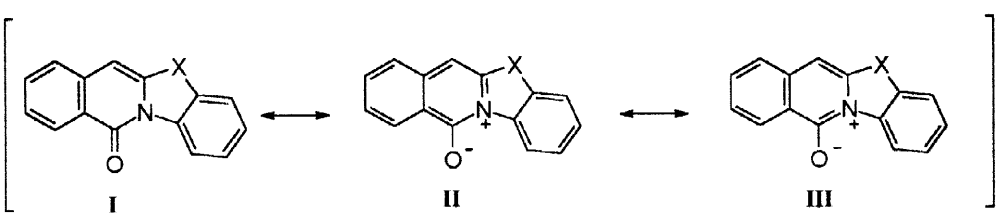
We have further investigated the MB sensitized photooxygenations of benzimidazo[1,2-b]isoquinolin-11-ones **4a-4d**. For **4a**, MB sensitized photooxygenation in acetonitrile or in methanol afforded products **25a** and **26** in comparable yields (Table 1). In this case, an "ene " attack of $^1O_2$ to C_6 leads to the hydroperoxide **27**, which on O-O bond homolysis gave **26**. Intramolecular transannular addition in **27** afforded the endoperoxide **28**, fragmentation of which gave **25a** (Scheme 2). We have also found that warming of **25a** in acetic anhydride yielded **26** almost quantitatively.

MB sensitized photooxygenation of **4b** in acetonitrile afforded products **25b** (86%) and **26** (8%). The formation of these products can be rationalized by a similar mechanism as shown in Scheme 1 with zwitterions like **29** and **30** as intermediates. The demethylation most likely took place in the zwitterionic intermediate **29** with nucleophilic assistance either intramolecularly from the peroxidic anion or intermolecularly from a trace amount of water or other nucleophiles in the solution. Similar MB sensitized photooxygenation of **4b** in methanol gave products **25b** (63%) and **31** (35%) (Table 1). In this case, **26** was not found since the demethylation could not compete with nucleophilic addition of methanol to the iminium cation in **29** or **30**.



Scheme 2 Mechanism for Singlet Oxygen Reaction of **4a**

The products obtained in MB sensitized photooxygenation of **4c** depend on the work-up procedures after the photolyses. Photolysis in methanol, for example, followed by routine chromatographic separation of the photolysate on a silica gel column afforded **26** as the sole product (Table 1). However, TLC analyses of the photolysate have shown that, there was only one product formed right after the photolysis, which was rather unstable and decomposed to give **26** during developing on silica gel. Thus, photolysis in acetonitrile, followed by evaporation of the solvent *in vacuo* at room temperature, extraction of the residue with chloroform and washing with water to remove the sensitizer yielded the primary product **25c** almost quantitatively (Table 1). The lack of solvent trapping product in this case is attributed to the high nucleofugality of the *N*-acetylbenzoxazole moiety which makes fragmentation of the endoperoxide intermediate **30** the overwhelming process over the solvent trapping reaction.



We finally successfully carried out an intramolecular trapping reaction of the zwitterionic intermediates **29** or **30** in the singlet oxygen reaction of compound **4d**. Thus, MB sensitized photooxygenation of **4d** in acetonitrile afforded the expected intramolecular trapping product **32** (13%), together with the carboxylic acid **25d** (66%) and the dealkylation product **26** (9%).

In summary, reactions of compounds **3** and **4** with singlet oxygen take place by initial attack of $^1O_2$ at the enol ether-enamine C=C bond, but follow different pathways from those of simple enol ethers and enamines. These reactions proceed exclusively *via* the zwitterionic (**10** and **29**) and endoperoxidic (**11, 28 and 30**) intermediates, bypassing the dioxetane intermediates such as **13** usually found in singlet oxygen reactions of enol ethers and enamines. The endoperoxidic intermediates **11** and **30** could also be viewed as the formal [4+2] adducts of $^1O_2$ with the resonance structures of **3** or **4** as **II** and **III**, although whether these special reactivity of compounds **3** and **4** toward $^1O_2$ reflected their dienic properties need to be further explored with other Diels-Alder dienophiles.

Experimental

Melting points were measured on a YANACO microscopic melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a JEOL PMX-60 SI spectrometer at 60 MHz or on a Bruker AC-500 spectrometer at 500 MHz with $SiMe_4$ as internal standard and $CDCl_3$ as solvent unless otherwise stated. *J* Values are given in Hz. IR spectra were taken with a Shimadzu IR 408 or a Nicolet 5DX FT-IR spectrometer in KBr pellets. Mass spectra were recorded with a VG ZAB-MS spectrometer. Elemental analyses were obtained using a Perken-Elmer-240 C analyser.

The benzannelated isoquinolinones **3** and **4** were prepared as reported elswhere.[4] Acetonitrile (CP grade) was first refluxed with phosphorus pentoxide and distilled, then refluxed with anhydrous potassium carbonate and redistilled. Benzene (AR grade) was dried with sodium and distilled before use. Other reagents were CP or AR grade and were used as received without further purification.

*General procedure for dye sensitized photooxygenation reactions of benzannelated isoquinolinones **3** and **4**.*

The reaction conditions are listed in Table 1. A solution of **3** or **4** (3 mmol) and a sensitizer (0.03 mmol) in a solvent (60 ml) was irradiated with a 500 W medium pressure mercury lamp through a cut-off light filter (aqueous sodium nitrite for λ>400 nm and aqueous potassium dichromate for λ>500 nm) at room temperature under oxygen perging. The reaction was monitored by TLC. At the end of the reaction, the solvent was removed *in vacuo* and the residue was separated by flash chromatography on a silica gel column with petroleum ether (b.p. 60-90 °C)-ethyl acetate as eluents to afford the corresponding photooxygenation products. The exceptional work-up procedures for MB sensitized photooxygenation of **4c** in acetonitrile are described in the text. The physical and spectral data for the photooxygenation products are as follows.

2-(2-Benzoxazolyl)carbonylbenzoic acid 5a. Colorless needles, m.p. 211-212 °C (from MeCN). IR: 3094, 2888, 2800, 2652, 2500, 1688, 1594, 1538, 1481, 1425, 1375, 1280, 1244, 925, 806, 744, 700, 650 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 7.50 (1H, t, *J* 7.5, ArH), 7.61 (1H, s, ArH), 7.75 (1H, d, *J* 7.5, ArH), 7.78 (1H, d, *J* 7.5, ArH), 7.83 (1H, d, *J* 7.5, ArH), 7.89-7.90 (2H, m, ArH), 8.03 (1H, d, *J* 7.5, ArH), 13.55 (1H, br, s, OH) ppm. MS (m/z, %): 267 (M^+, 7.6), 149 (51.0), 132 (21.5), 119 (100). Anal. $C_{15}H_9NO_5$. Calcd: C, 67.42; H, 3.39; N, 5.24. Found: C, 67.86; H, 3.47; N, 5.40.

2-[2-(5-Methoxybenzoxazolyl)]carbonylbenzoic acid 5b. Colorless needles, m.p. 205-206 °C (from acetone). IR: 3090, 3080, 3000, 2940, 2910, 2850, 2600, 2492, 1690, 1610, 1522, 1480, 1270, 1258, 1019, 993, 925, 822, 755, 700 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 3.80 (3H, s, CH_3), 7.0-8.1 (7H, m, ArH) ppm. MS (m/z, %): 297 (M^+, 14.6), 149 (100), 134 (31.0). Anal. $C_{16}H_{11}NO_5$. Calcd: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.65; H, 3.96; N, 4.96.

2-[2-(5-Methylbenzoxazolyl)]carbonylbenzoic acid 5c. Pale yellow prisms, m.p. 202-203 °C (from ethyl acetate). IR: 3050, 2950, 2850, 2600, 2500, 1685, 1590, 1525, 1480, 1418, 1300, 1285, 1200, 1168, 990, 970, 918, 810, 750, 700 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 2.41 (3H, s, CH_3), 7.2-8.2 (7H, m, ArH) ppm. MS (m/z, %): 281 (M^+, 8.2), 153 (22.0), 149 (47.3), 133 (100), 132 (40.0), 121 (10.5), 104 (22.9). Anal. $C_{16}H_{11}NO_4$. Calcd: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.46; H, 4.01; N, 4.98.

2-[2-(5-Chlorobenzoxazolyl)]carbonylbenzoic acid 5d. Colorless needles, m.p. 214-215 °C (from MeCN). IR: 3070, 2980, 2800, 2650, 2520, 1700, 1680, 1595, 1425, 1298, 1165, 972, 918, 819, 700 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.4-8.2 (7H, m, ArH) ppm. MS (m/z, %): 303 (M+2, 1.3), 301 (M^+, 3.9), 155 (38.2), 153 (100), 149 (90.2), 133 (21.9), 132 (34.8). Anal. $C_{15}H_8ClNO_4$. Calcd: C, 59.72; H, 2.67; N, 4.64. Found: C, 59.60; H, 2.85; N, 4.60.

2-(2-Naphth[1,2-d]oxazolyl)carbonylbenzoic acid 5e. Pale brown crystals, m.p. 213-214 °C (from ethyl acetate). IR: 3050, 3020, 2850, 2750, 2580, 2498, 2280, 1685, 1595, 1575, 1498, 1347, 1272, 1200, 1000, 912, 815, 752, 700 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 7.51 (1H, t, J 7.5, ArH), 7.74 (1H, t, J 7.5, ArH), 7.80-7.82 (2H, t, ArH), 7.87 (1H, t, J 7.5, ArH), 8.06-8.09 (2H, t, ArH), 8.16-8.18 (2H, d, ArH), 8.30 (1H, d, J 7.5, ArH), 13.50 (1H, br, s, OH) ppm. MS (m/z, %): 317 (M^+, 16.8), 283 (44.4), 265 (18.8), 169 (100), 149 (61.3), 141 (10.3), 132 (20.0). Anal. $C_{19}H_{11}NO_4$. Calcd: C, 71.91; H, 3.50; N, 4.41. Found: C, 71.79; H, 3.54; N, 4.42.

2-(2-Benzothiazolyl)carbonylbenzoic acid 5f. Pale yellow needles, m.p. 218-219 °C (from MeOH). IR: 3060, 2860, 2780, 2600, 2470, 1690, 1672, 1595, 1479, 1422, 1323, 1292, 1253, 1141, 905, 800, 790, 765, 740, 735, 680 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 7.61 (2H, s, ArH), 7.69 (1H, d, J 7.0, ArH), 7.75 (1H, t, J 7.5, ArH), 7.80 (1H, t, J 7.0, ArH), 8.04 (1H, d, J 7.0, ArH), 8.10 (1H, d, J 6.0, ArH), 8.27 (1H, d, J 6.0, ArH), 13.39 (1H, br, s, OH) ppm. MS (m/z, %): 283 (M^+, 13.4), 266 (16.5), 238 (58.0), 211 (18.1), 149 (78.2), 135 (100). Anal. $C_{15}H_9NO_3S$. Calcd: C, 63.59; H, 3.20; N, 4.94. Found: C, 63.40; H, 3.28; N, 4.82.

(±)-5a-Methoxybenzoxazolo[3,2-b]isoquinoline-6,11-dione 6a. Bright yellow needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 138-140°C. IR: 3080, 3060, 2998, 2960, 1718, 1708, 1680, 1600, 1482, 1398, 1288, 1244, 1041, 912, 748 cm^{-1}. ^1H NMR (500 MHz): 3.35 (3H, s, CH_3), 7.08-7.18 (3H, m, ArH), 7.78 (1H, t, J 7.5, ArH), 7.86 (1H, t, J 7.5, ArH), 8.00 (1H, d, J 7.5, ArH), 8.07 (1H, d, J 7.5, ArH), 8.27 (1H, d, J 7.5, ArH) ppm. MS (m/z, %): 281 (M^+, 43.8), 266 (16.6), 250 (32.1), 222 (19.7), 196 (7.0), 132 (35.5), 104 (100). Anal. $C_{16}H_{11}NO_4$. Calcd:C, 68.32; H, 3.94; N, 4.98. Found: C, 68.19; H, 4.15; N, 5.19.

(±)-2,5a-Dimethoxybenzoxazolo[3,2-b]isoquinoline-6,11-dione 6b. Golden needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 148-150 °C. IR: 3050, 3025, 2920, 2815, 1715, 1678, 1590, 1486, 1389, 1290, 1241, 1020, 912, 858, 800, 760, 718 cm^{-1}. ^1H NMR (60 MHz): 3.32 (3H, s, CH_3), 3.80 (3H, s, CH_3), 6.5-8.4 (7H, m, ArH) ppm. MS (m/z, %): 311 (M^+, 40.8), 296 (4.2), 280 (33.0), 252 (13.0), 226 (4.4), 179 (9.1), 132 (16.0), 104 (100). Anal. $C_{17}H_{13}NO_5$. Calcd: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.28; H, 4.35; N, 4.66.

(±)-5a-Methoxy-2-methylbenzoxazolo[3,2-b]isoquinoline-6,11-dione 6c. Bright yellow needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 151-153 °C. IR: 3050, 3000, 2950, 2910, 2890, 1712, 1680, 1595, 1489, 1470, 1385, 1286, 1241, 1035, 995, 910, 813, 717, 701 cm^{-1}. ^1H NMR (60 MHz): 2.37 (3H, s, CH_3), 3.30 (3H, s, OCH_3), 6.8-8.3 (7H, m, ArH) ppm. MS (m/z, %): 295 (M^+, 29.9), 280 (12.5), 264 (27.8), 236 (20.7), 210 (6.5), 163 (13.4), 132 (15.7), 104 (100). Anal. $C_{17}H_{13}NO_4$. Calcd: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.02; H, 4.43; N, 4.88.

(±)-2-Chloro-5a-methoxybenzoxazolo[3,2-b]isoquinoline-6,11-dione 6d. Pale yellow needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 184-185 °C. IR: 3100, 3050, 2945, 2900, 2830, 1720, 1684, 1593, 1470, 1382, 1288, 1231, 1040, 995, 915, 825, 698 cm^{-1}. ^1H NMR (60 MHz): 3.36 (3H, s, CH_3),

7.0-8.4 (7H, m, ArH) ppm. MS (m/z, %): 317 (M+2, 5.5), 315 (M^+, 16.2), 300 (5.6), 284 (9.9), 256 (2.4), 200 (12.9), 132 (28.5), 104 (100). Anal. $C_{16}H_{10}ClNO_4$. Calcd: C, 60.87; H, 3.19; N, 4.44. Found: C, 60.84; H, 3.33; N, 4.61.

(±)-5a-Methoxybenzothiazolo[3,2-b]isoquinoline-6,11-dione 6f. Golden needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 111-113 °C. IR: 3080, 3000, 2975, 2930, 2835, 1721, 1675, 1595, 1464, 1355, 1292, 1042, 935, 754, 712 cm^{-1}. ^1H NMR (60 MHz): 3.27 (3H, s, CH_3), 7.1-8.6 (8H, m, ArH) ppm. MS (m/z, %): 297 (M^+, 14.2), 266 (100), 238 (29.6), 209 (15.7), 163 (23.8), 104 (68.8). Anal. $C_{16}H_{11}NO_3S$. Calcd: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.41; H, 3.70; N, 4.87.

6-Hydroxy-2-methoxy-*11H*-benzoxazolo[3,2-b]isoquinolin-11-one 14. Yellow prisms, m.p. 175-177 °C (from ethyl acetate). IR: 3150, 2980, 2810, 1690, 1630, 1608, 1575, 1480, 1178, 995, 760, 682 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.72 (3H, s, CH_3), 6.75 (1H, s, ArH), 6.87-6.92 (3H, m, ArH), 7.92-7.99 (2H, m, ArH), 8.19 (1H, d, *J* 8.0, ArH), 8.24 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 281 (M^+, 100), 225 (26.8), 210 (32.6), 141 (11.7), 105 (42.8), 104 (30.4). Anal. $C_{16}H_{11}NO_4$. Calcd:C, 68.33; H, 3.94; N, 4.98. Found: C, 67.96; H, 4.08; N, 5.11.

2-(2-Benzimidazolyl)carbonylbenzoic acid 25a. Colorless needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate-acetonitrile, m.p. 276-278 °C (decomp. at 200 °C to form **26**). IR: 3360, 3300, 3040, 2850, 2720, 2600, 2420, 1689, 1669, 1595, 1442, 1315, 1294, 1271, 1233, 920, 748 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 7.26 (1H, s, ArH), 7.38 (1H, s, ArH), 7.59-7.78 (5H, m, ArH), 7.99 (1H, d, *J* 7.5, ArH), 13.17 (1H, br, s, OH), 13.52 (1H, s, NH) ppm. MS (m/z, %): 266 (M^+, 0.2), 248 (100), 220 (22.7). Anal. $C_{15}H_{10}N_2O_3$. Calcd:C, 67.67; H, 3.79; N, 10.52. Found: C, 67.67; H, 3.83; N, 10.56.

2-[2-(1-Methylbenzimidazolyl)]carbonylbenzoic acid 25b. Colorless needles, m.p. 195-196 °C (decomp.) (from MeOH). IR: 3080, 2980, 2880, 2765, 2600, 2460, 1679, 1595, 1468, 1320, 1279, 1260, 1235, 952, 803, 741, 702 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 4.17 (3H, s, CH_3), 7.30 (1H, t, *J* 7.5, ArH), 7.44 (1H, t, *J* 7.5, ArH), 7.64-7.79 (5H, m, ArH), 7.96 (1H, d, *J* 7.5, ArH), 13.24 (1H, br, s, OH) ppm. MS (m/z, %): 280 (M^+, 22.7), 265 (60.4), 253 (32.5), 243 (100), 218 (51.5), 143 (71.9), 109 (62.4). Anal. $C_{16}H_{12}N_2O_4$. Calcd: C, 68.56; H, 4.31; N, 9.99. Found: C, 68.53; H, 4.41; N, 10.02.

2-[2-(1-Acetylbenzimidazolyl)]carbonylbenzoic acid 25c. Colorless needles from petroleum ether (b.p. 60-90 °C)-acetone, m.p. 276-278 °C (decomp. at 200 °C to form **26**). IR: 3095, 2950, 2885, 2740, 2650, 1795, 1440, 1270, 1202, 1095, 979, 760 cm^{-1}. ^1H NMR (500 MHz): 2.16 (3H, s, CH_3), 7.30-7.31 (2H, t, ArH), 7.82-7.85 (3H, m, ArH), 7.79 (1H, t, *J* 7.5, ArH), 7.89 (1H, d, *J* 7.5, ArH), 8.29 (1H, d, *J* 7.5, ArH) ppm. FAB-MS (m/z, %): 309 (M+1, 1.2), 249 (3.7), 217 (31.6), 215 (14.4), 109 (33.1), 91 (100). Anal. $C_{17}H_{12}N_2O_4$. Calcd: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.19; H, 4.11; N, 9.14.

2-[2-(1-(2-Hydroxyethyl)benzimidazolyl)]carbonylbenzoic acid 25d. Pale yellow gummy solid. IR: 3390, 3050, 2950, 2600, 1670, 1598, 1480, 1460, 1279, 1138, 1080, 949, 748 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 4.0-4.8 (4H, m, CH_2CH_2), 7.0-8.0 (8H, m ArH) ppm. FAB-MS (m/z, %): 311 (M+1, 24.3), 293 (50.9), 249 (37.2), 91 (100). Anal. $C_{17}H_{14}N_2O_4$. Calcd: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.93; H, 4.54; N, 9.01.

Benzimidazo[1,2-b]isoquinoline-6,11-dione 26. Yellow plates, m.p. 277-278 °C (from THF) (lit. 267-269 °C[9]). IR: 3080, 3050, 3000, 1710, 1680, 1600, 1583, 1516, 1340, 1239, 1159, 1070, 759, 732 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.40-8.40 (8H, m, ArH) ppm. MS (m/z, %): 248 (M^+, 100), 220 (21.4), 204 (6.4), 192 (7.8), 164 (3.5), 104 (14.1). Anal. $C_{15}H_8N_2O_2$. Calcd: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.58; H, 3.29; N, 11.30.

(±)-5a-Methoxy-5-methylbenzimidazo[1,2-b]isoquinoline-6,11-dione 31. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 110-112 °C. IR: 3080, 2950, 1709, 1670, 1598, 1482, 1460, 1284, 1230, 956, 752 cm^{-1}. ^1H NMR (500 MHz): 3.57 (3H, s, CH_3), 4.26 (3H, s, CH_3), 7.30 (1H, t, *J* 7.5, ArH), 7.41 (1H, dd, *J* 7.5, 8.0, ArH), 7.50 (1H, d, *J* 8.0, ArH), 7.60 (1H, t, *J* 7.5, ArH), 7.66 (1H, d, *J* 7.5, ArH), 7.69 (1H, d, *J* 7.5, ArH), 7.79 (1H, d, *J* 8.0, ArH), 8.00 (1H, d, *J* 8.0, ArH) ppm. MS (m/z, %): 294 (M^+, 4.8), 263 (5.2), 235 (100), 163 (15.8). Anal. $C_{17}H_{14}N_2O_3$. Calcd:C, 69.38; H, 4.79; N, 9.52. Found: C, 69.12; H, 4.76; N, 9.58.

Oxazolo[3, 2-f]benzimidazo[1,2-b]isoquinoline-10,15-dione 32. Colorless needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 205-206 °C. IR: 3080, 3040, 2981, 2902, 1765, 1705, 1468, 1445, 1282, 1241, 1109, 1023, 900, 880, 763, 752 cm^{-1}. ^1H NMR (500 MHz): 4.43-4.46 (1H, m, 1/2CH_2), 4.50-4.55 (2H, m, 2×1/2CH_2), 4.82-4.88 (1H, m, 1/2CH_2), 7.34 (1H, t, *J* 7.5, ArH), 7.40 (1H, d, *J* 7.5, ArH), 7.43 (1H, d, *J* 7.5, ArH), 7.49 (1H, d, *J* 8.0, ArH), 7.68-7.76 (3H, m, ArH), 8.00 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 292 (M^+, 30.7), 248 (11.6), 220 (100). Anal. $C_{17}H_{12}N_2O_3$. Calcd: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.87; H, 4.15; N, 9.66.

Crystal Structure of 5c

$C_{16}H_{11}NO_4$, *M* = 281.26. Orthorhombic, space group Pbca with a = 12.7397(3), b = 8.6141(2), c = 25.4693(7) Å , α = β = γ = 90°, *V* = 2795.03(12) $Å^3$, z = 8, Dc = 1.337 g cm^{-3}. Absorption coefficient 0.097 mm^{-1}, F(000) = 1168. A transparent block shaped crystal of 0.52×0.22×0.12 mm was used. Data were collected on a Siemen's CCD diffractometer equipped with graphite-monochromated Mo Kα radiation in the range of θ 2.96-27.50°. The structure was solved by direct method (SHELXTL) and refined on F^2 by full-matrix least-squares method. A total of 3197 independent reflections [R (int) = 0.0870] were used in the refinement which converged with R = 0.0668 and wR = 0.1055.

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