# Singlet Oxygen Additions to Hexacyclo[10.2.1.0$^{2,11}$.0$^{4,9}$.0$^{4,14}$.0$^{9,13}$]pentadeca-5,7-dien-3,10-diones. A Remarkable Substituent Effect on π-Face Selectivity Induced by Transition State Geometric Distortions

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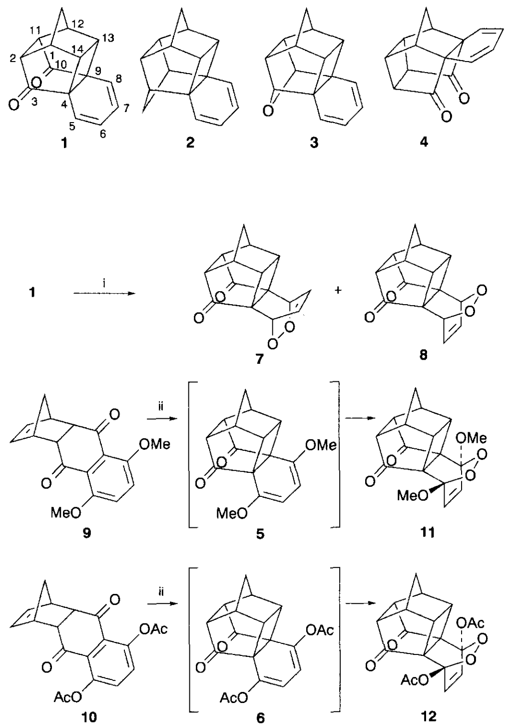
Face selectivity in singlet oxygen addition to a rigid polycyclic diene is reversed by sterically neutral 1,4-substitution, an effect attributed to lone pair repulsions induced by out-of-plane bending at the transition state.

Evaluation of factors that control stereoselectivity in cycloadditions to substrates embodying facially differentiated 1,3-diene moieties continues to attract considerable theoretical and experimental scrutiny.[1] Diene moieties embedded in rigid polycyclic frames are particularly useful probes, as facial discrimination due to subtle steric and electronic perturbations can be finetuned without conformational uncertainties. Recent results on structurally related caged polycyclic cyclohexa-1,3-dienes **1–4** have revealed the role of steric, filled-orbital and electrostatic interactions.[2] We now report the face selectivity of singlet oxygen addition of **1** and its dramatic reversal in the derivatives **5** and **6** bearing 1,4-substitution on the diene moiety, which we attribute to geometrical distortions in the transition state on the basis of MO calculations.

Photooxygenation of the readily available hexacyclic diene **1**[3] in the presence of methylene blue sensitizer led smoothly to the formation of endoperoxides **7** and **8** in 78 : 22 ratio (Scheme 1).† While the stereostructures of **7** and **8** were indicated through careful analyses of their $^1$H and $^{13}$C NMR data, unambiguous proof was secured through an X-ray crystal structure determination of the minor diastereoisomer **8** (Fig. 1).‡ As this structure corresponds to oxygen addition from the cyclobutane face, the major product **7** must be derived through addition from the carbonyl face.

The 1,4-disubstituted hexacyclic dienes **5** and **6** proved to be elusive and defied isolation and characterisation. However, when their tricyclic precursors **9** and **10** were subjected to photooxygenation in the presence of methylene blue, a single crystalline endoperoxide was obtained in each case through intramolecular [2 + 2] photocycloaddition and concomitant singlet oxygen addition (Scheme 1). The two endoperoxides **11** and **12** obtained from **9** and **10** *via* **5** and **6**, respectively, were shown to be formed through addition from the cyclobutane face on the basis of their $^1$H and $^{13}$C NMR data;† the pronounced deshielding of the cyclobutane protons owing to the trans-annular peroxo bridge was particularly informative. The stereochemical assignments were further confirmed through the X-ray crystal structure determination of the diepoxide **13** (Fig. 2),‡ formed through the facile quantitative rearrangement of the labile endoperoxide **12**. Thus, photooxygenation of **9** and **10**, proceeding through the hexacyclic dienes **5** and **6**, respectively, occurs exclusively from the cyclobutane face and represents a reversal in the face selectivity as compared to the parent compound **1**.



Scheme 1 *Reagents and conditions*: i, 500 W tungsten lamp, methylene blue, O$_2$, CHCl$_3$, 10–15 °C, 6 h, 88%; ii, 400 W Hanovia Hg lamp, methylene blue, EtOAc, 10–15 °C, 15–120 min, 60% for **11**, 30% for **12**

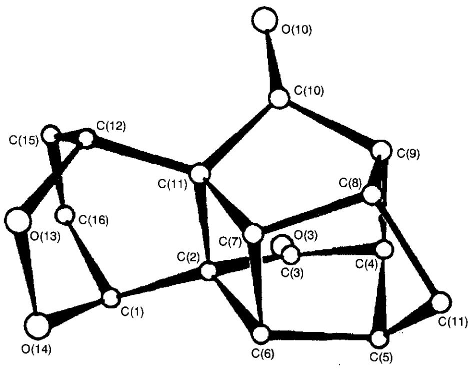


**Fig. 1**

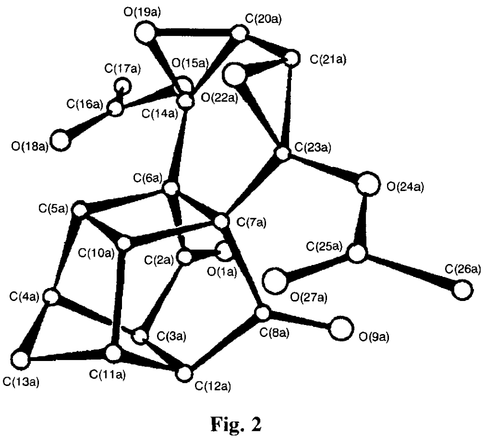


**Fig. 2**

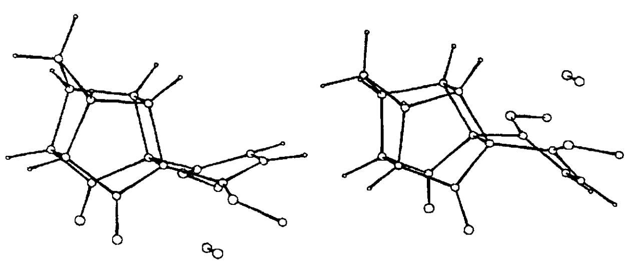
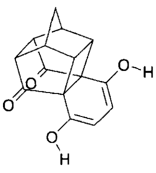
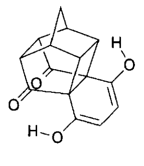


**Fig. 3** Optimised geometries of synchronous-constrained transition states for singlet oxygen addition to **5**. Carbonyl (cyclobutane) face addition is shown on the left (right). The hydrogen atoms on the –OMe substituents are omitted for clarity.



**14a**



**14b**

The influence of substituents on the π-face selectivity is remarkable, since the groups are expected to remain in the π-plane in the reactant and in the sterically neutral bridgehead positions in the product. Hence the unexpected observation was probed through MNDO calculations.[4] The optimised synchronised-constrained ($C_s$) transition states§ for singlet oxygen addition to **1** reveal that addition to the carbonyl face is preferred by 4.2 kJ mol$^{-1}$, consistent with the experimental trend. The reversal of face selectivity in the dimethoxy derivative **5** is also reproduced by MNDO calculations. The corresponding transition state energetics correspond to a preference for cyclobutane face addition by 5.4 kJ mol$^{-1}$.

The computed geometries of these structures (Fig. 3) reveal a possible reason for the reversal. The diene is twisted at the 1,4-positions such that the substituents move *towards* the dienophile. Thus, the O–C(1)–C(4) angle is 169°. This feature has been noted in previous calculations on Diels–Alder transition states for a variety of substrates and has been suggested to be a requirement for maximising frontier orbital interactions.[1d,5] For carbonyl face addition of oxygen to **5**, the methoxy lone pairs are brought closer to the carbonyl oxygen atoms at the transition state. The consequent repulsion would lead to relative destabilization of the corresponding transition state.¶ The same effect should account for the face selectivity in the diacetoxy derivative **10**.

The above interpretation was further confirmed by calculations on the corresponding dihydroxy derivative **14**. In **14a**, with the hydroxy lone pairs oriented in the same direction as in the transition state involving **5**, cyclobutane face addition is again favoured, by 4.6 kJ mol$^{-1}$. An alternative conformation **14b** is conceivable, with the hydroxy hydrogens pointing towards the cage, which is not energetically accessible for **5** and **6**. In this conformation, addition to the carbonyl face no longer suffers increased lone pair repulsion. The corresponding transition state is favoured over cyclobutane face addition by 2.5 kJ mol$^{-1}$. These results confirm the presence of interactions between the 1,4-substituents and the dione in the carbonyl face addition transition state.

It may be emphasised that the critical geometric distortion which subtly controls face selectivity in these systems is not present either in the reactant or the product, but is specific to the transition state. The interpretation provides an interesting complement to earlier suggestions of face selectivity being influenced by out-of-plane bending at the 2,3-positions of the diene.[1d,5]

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## Footnotes

† All compounds were characterized on the basis of their spectral data and elemental analyses. *Selected spectral data* for **7**: mp 243 °C; $\delta_H$ (200 MHz, $CDCl_3$; *J*/Hz) 6.84–6.83 (m, 2H), 4.96–4.92 (m, 2H), 2.94 (m, 2H), 2.86 (s, 2H), 2.73 (s, 2H), 2.03 (1/2 ABq, 1H, *J* 12), 1.82 (1/2 ABq, 1H, *J* 12); $\delta_C$ (50.0 MHz, $CDCl_3$) 208.1, 131.4, 69.5, 55.4, 48.0, 43.6, 40.6, 40.4. For **8**: mp 220 °C (decomp.); $\delta_H$ (200 MHz, $CDCl_3$) 6.79–6.78 (m, 2H), 4.72–4.68 (m, 2H), 3.45 (br s, 2H), 3.08–3.07 (m, 2H), 2.72–2.71 (d, 2H), 2.10 (s, 2H); $\delta_C$ (50.0 MHz, $CDCl_3$) 208.4, 131.6, 70.9, 55.3, 44.3, 42.0, 39.2. For **11**: mp 204 °C; $\delta_H$ (200 MHz, $CDCl_3$) 6.78 (s, 2H), 3.52–3.51 (s, 8H), 3.06 (br s, 2H), 2.75 (br s, 2H), 2.1 (s, 2H); $\delta_C$ (50.0 MHz, $CDCl_3$) 206.3, 132.2, 100.6, 60.1, 56.1, 53.8, 43.7, 41.7, 38.5. For **12**: mp 179–180 °C; $\delta_H$ (200 MHz, $CDCl_3$) 6.79 (s, 2H), 3.55 (br s, 2H), 3.13 (br s, 2H), 2.78 (br s, 2H), 2.12 (s, 8H); $\delta_C$ (50.0 MHz, $CDCl_3$) 205.7, 167.1, 132.4, 98.2, 59.4, 55.9, 44.1, 41.2, 39.5, 21.3.

‡ *Crystal data* for **8**: $C_{15}H_{12}O_4$, $M_r$ = 256.26; monoclinic, $P2_1/n$, $a$ = 8.710(1), $b$ = 6.390(3), $c$ = 20.58(1) Å, $\beta$ = 97.99(3)°, $V$ = 1134.3(8) Å$^3$, $Z$ = 4, $D_c$ = 1.501 g cm$^{-3}$, $F(000)$ = 536.0, $T$ = 295 K, Mo-K$\alpha$ ($\lambda$ = 0.7107 Å). Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer in $\omega/2\theta$ scan mode on a crystal (0.45 × 0.20 × 0.15 mm). A total of 2876 measured ($0 < \theta < 27°$), out of which 2464 unique and 1008 observed, $|F_o| > 5.0\sigma(|F_o|)$. Convergence at $R$ = 0.076. For **13**: $C_{19}H_{16}O_8$, $M_r$ = 372.33; triclinic, $P1$, $a$ = 10.105(6), $b$ = 14.327(2), $c$ = 23.382(2) Å, $\alpha$ = 81.06(2), $\beta$ = 86.03(2), $\gamma$ = 89.17(3)°, $V$ = 3336(2) Å$^3$, $Z$ = 8, $D_c$ = 1.483 g cm$^{-3}$, $T$ = 295 K, $F(000)$ = 1552, Mo-K$\alpha$ ($\lambda$ = 0.7107 Å). Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using a transparent crystal (0.2 × 0.15 × 0.15 mm) in $\omega/2\theta$ scan mode. A total of 8852 reflections ($0 < \theta < 20°$) of which 8160 unique and 3844 [$|F_o| > 5.0\sigma(|F_o|)$] observed. Convergence at $R$ = 0.052. Both structures were solved by direct methods[6a] and full-matrix least-squares refinements[6b] with the non-H atoms anisotropic and H-atoms isotropic. Atomic coordinates, bond lengths and angles, and thermal parameters for both structures have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ First-order saddle points at the MNDO level for cycloadditions tend to be highly asynchronous. However, synchronous-constrained structures (with vanishing gradients and a hessian of 2) are quite similar to true transition state geometries obtained at *ab initio* levels.[5]

¶ The distance between the substituent oxygen and carbonyl oxygen is shorter for the carbonyl face addition (3.00 *vs.* 3.27 Å for the cyclobutane face addition structure). Correspondingly, MMX calculations on **5** constrained at the alternative transition state geometries reveal increased electrostatic repulsion (by 3.0 kJ mol$^{-1}$) for the carbonyl face addition.

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