New paradigms in cycloaddition face-selectivities: remarkable effect of remote substituents in singlet oxygen addition to hexacyclo[7.5.1.0^{1,6}.0^{6,13}.0^{8,12}.0^{10,14}]pentadeca-2,4-diene system
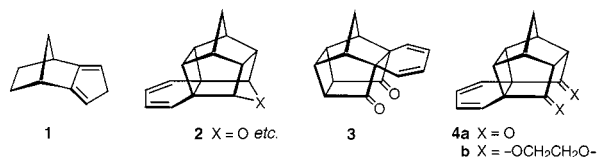
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Different modes of direct through-space interactions between remote substituents and an approaching reagent are indicated as important additional controlling factors of face selectivity in singlet oxygen cycloaddition to facially differentiated cyclohexa-1,3-dienes.

Evaluation of stereoelectronic effects that influence π-face selection and control diastereoselectivity in [4+2]-cycloadditions to cyclic dienes continues to be an area of intense scrutiny and new explorations.[1] In this context, substrates in which the 1,3-diene moiety is grafted on to a rigid polycyclic frame to eliminate conformational ambiguities are particularly advantageous, as the facial discrimination and stereoelectronic perturbations can be effected through distal modulation of functional-

ities.[2,3] In recent years, several polycyclic systems **1**–**4** embodying a cyclic 1,3-diene substructure have been devised and probed for diastereoselection employing a variety of dienophiles, but among these, **4** has been more enduring[3] because of its rigidity, ready accessibility,[4] reactivity and functional group manoeuvrability. In the hexacyclic diene **4**, facial discrimination in the cyclohexadiene moiety is manifested through the interplay of the steric effects of cyclobutyl hydrogens and the electronic interactions of the carbonyl groups. The diastereoselectivities observed in cycloadditions to several derivatives of **4** (obtained through substitutions on the diene moiety as well as modifications of the carbonyl group) have led to the identification of steric effects, filled orbital and electrostatic repulsions, the Cieplak effect and transition state geometrical distortions as the main determinants of face-selectivity.[3] We have now observed that even the simplest derivatisation can lead to a reversal in diastereoselectivity which we interpret in terms of transition state interactions, some of which have not been recognised before as contributors to face selectivity. These subtle effects, though promoted in the present case by the geometry of the hexacyclic system **4** and the relative spatial orientation of the diene unit and the remote functionality, can be operative in other substrates as well and in the absence of other dominant effects, can be the principal determinants of face selectivity; *inter alia* caution must be exercised in extrapolating stereoselectivities, even when seemingly inconsequential functional group changes are effected at distal sites.

The hexacyclic *endo,endo*-diol **5a**, its diacetate **5b** and dimethyl ether **5c** readily underwent cycloaddition with $^1O_2$ generated in the presence of Methylene Blue (500 W tungsten lamp, O$_2$, CHCl$_3$, 5–10 °C, 4–5 h) to furnish a diastereomeric mixture of endoperoxides **6a**–**c** and **7a**–**c** in 80–85% yield.[5] While the gross structures of both the 'bottom' and 'top'

addition endoperoxides **6a**–**c** and **7a**–**c**, respectively, were apparent from the spectral characteristics (^{1}H and ^{13}C NMR), their stereochemistry was unambiguously determined *via* X-ray crystal structure determination‡ of the major endoperoxides **6b** and **7c**. The diastereoselectivities observed in the $^1O_2$ additions (Scheme 1) indicated that while in the *endo,endo*-diol **5a** and diacetate **5b** 'bottom' face addition was preferred, complete reversal occurred in the case of the dimethyl ether **5c** and the 'top' addition product was exclusively obtained. The expectation from earlier studies and interpretations[3] with substrates such as **4b** was that repulsion between *endo*-directed oxygens in **5a**–**c** and the $^1O_2$ reagent should uniformly favour addition from the 'top' face. While the observed selectivity in **5c** was fully in consonance with this reasoning, the unpredicted outcome of diastereoselectivities in the case of **5a,b** suggested intervention of some additional, unrecognized interactions and these needed to be probed through transition state modelling.

The origin of the variations in face selectivities in **5a**–**c** was examined through AM1 calculations[6] on $^1O_2$ addition transition states. Saddle points with vanishing gradients and characterized by a single imaginary vibrational frequency were located for the top and bottom face addition. The possibility of conformational variation in the OR groups was considered by using different initial geometries.

For the methoxy derivative **5c**, two sets of transition structures are obtained, both favoring the top face attack by varying degrees. While the energy preference is marginal (0.2 kJ mol^{-1}) in the structures in which the methyl groups are pointed towards the diene moiety, a strong bias (10.3 kJ mol^{-1}) is predicted when the methyl groups are oriented away from the diene. In the latter, repulsive interactions involving the oxygen lone pairs towards the approaching $^1O_2$ evidently come into play [Fig. 1(*a*)]. Hence the exclusive formation of the top face adduct in **5c** is entirely consistent with electrostatic control of face selection.

For the $^1O_2$ addition to the dihydroxy derivative **5a**, a significant bottom face preference (7.9 kJ mol^{-1}) is computed, qualitatively in accord with the experimental trend. The transition structures for both the top and bottom face approach lack any symmetry (C_1) due to an intramolecular O–H···O hydrogen bond. In the bottom face attack saddle point, an additional hydrogen bonding interaction is evident. The second OH group in the structure interacts with one of the oxygen
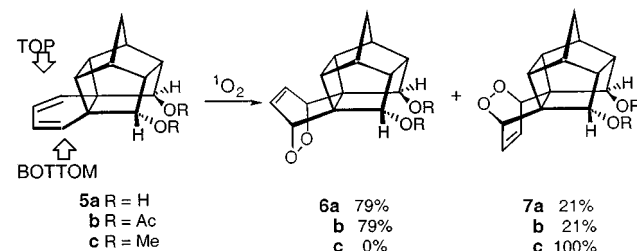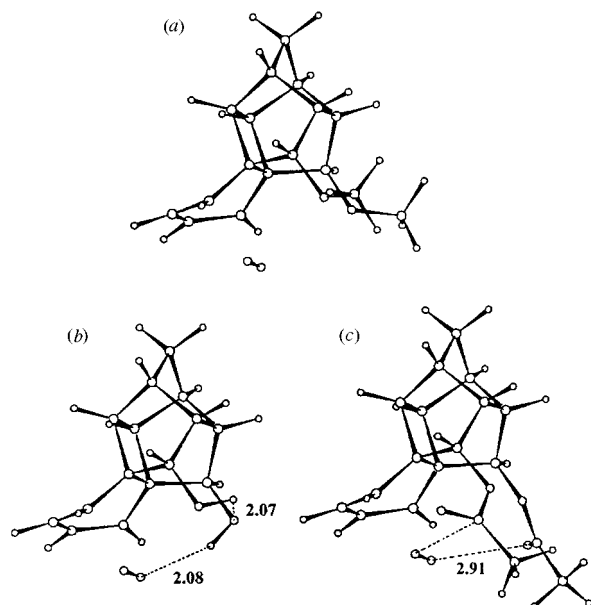

Scheme 1

Fig.1 AM1 optimised transition state structures for the bottom face addition of $^1O_2$ to (*a*) **5c**, (*b*) **5a** and (*c*) **5b**

atoms of the approaching dienophile [Fig. 1(*b*)]. The cyclic, cooperative hydrogen bonds seem to provide enough stabilization to overcome electrostatic repulsions noted in **5c**. Additional proof for the role of hydrogen bonding with the singlet oxygen was obtained by computing the energies of transition states with C_s symmetry constraints which led to conformations similar to those of the dimethoxy derivative. The face selectivity calculated in these high energy conformations is revealing. With both the OH groups pointing towards the diene, the bottom face approach of $^1O_2$ is favored by 25.6 kJ mol^{-1}. In this structure, the two OH groups form strong hydrogen bonds with either end of the dienophile. In the alternative transition structures in which the OH groups point away from the diene, an electrostatic preference for top face attack (12.6 kJ mol^{-1}) similar to that calculated for the corresponding conformation of **5c** is obtained.

Transition state energies favoring the bottom face attack for the diacetoxy derivative **5b** are also consistent with experiment. Remarkably, the computed preference (6.9 kJ mol^{-1}) is similar to that obtained in the most stable transition state structures of **5a**. While the latter allows hydrogen bonding between the substituent and $^1O_2$, the origin of the selectivity in **5b** is intriguing. The calculated transition state structure for the bottom face attack suggests a possible mode of stabilisation. The oxygen atoms of the dienophile make fairly short contacts (2.9 Å) with the carbonyl carbon atoms of the symmetrically oriented ester groups [Fig. 1(*c*)]. The O···C=O angles of 91° support the possibility of a favorable interaction between the lone pairs on $^1O_2$ with the π^* orbitals on the ester linkages. Similar long range attractive interactions have been recognised,[7] on the basis of several solid state structures, as key factors governing the nature of the reaction coordinate in nucleophilic additions to carbonyl groups. We now propose that such orbital interactions between the reagent and the remote substituent direct the approach of $^1O_2$. The attractive effects are not translated into any reaction at the substituent, but only result in the delivery of the reagent to the nearby diene face. Evidence for this model comes from calculations on a different conformation of the diester groups, with the acyl units pointing away from the diene. While the energy of the transition state for top face addition was virtually unaffected by the conformational change, in the case of the bottom face addition transition state,

the ester groups were reorientated to attain the conformation shown in Fig. 1(*c*), implying the stabilizing interactions present in this structure.

In summary, a subtle change of functionality in **5** leads to remarkable variations in the face selectivities of $^1O_2$ additions. Our results indicate that direct through-space interactions between remote substituents and the approaching reagent *via* three distinct modes, *viz.* electrostatic, hydrogen bonding and stabilizing orbital interactions, need to be considered as additional stereoelectronic factors in determining face selectivity.

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