Comments on the Electronic Structure and Reactivity of Chromones

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Ab initio calculations of ground-state wavefunctions of chromones and thiochromones have been carried out and correlated with the observed reactivity of these molecules. Quantum mechanical electrostatic potentials correctly predict nucleophilic attack to occur preferentially at C-2 and C-4 in chromones and thiochromones respectively. Frontier-orbital considerations correctly predict the site selectivity of the photochemical cycloaddition to the pyrone double bond of chromone.

A considerable difference exists between the reactivity of 4*H*-1-benzopyran-4-ones (chromones) and the corresponding thio-analogues, 4*H*-1-benzothiopyran-4-ones (thiochromones). For example, chromones are readily ring opened by aqueous base[1] involving initial nucleophilic attack at C-2, whereas this process only occurs with great difficulty with thiochromones.[2,3] Furthermore, while the preferred site of nucleophilic attack of chromones is at C-2 [1,4- (Michael) addition to the enone system], there is some evidence to suggest that on the thiochromone nucleus attack is favoured at C-4 (1,2-addition). Thus, reaction of ethyl 5-hydroxy-8-propylchromone-2-carboxylate (**Ia**) with chloroacetone and base under aprotic conditions leads to cyclopropachromones (**II**), *via* initial nucleophilic attack of Cl$\overset{-}{C}$HCOMe at C-2.[4] Under similar conditions, the corresponding thiochromone (**Ib**) gives the furothiochromone system (**III**) as the sole isolable product.

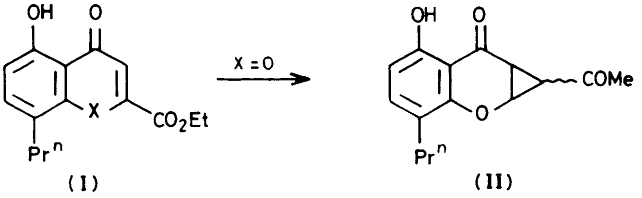
Studies of the irreversible Wessely–Moser[5] rearrangement of 5-mercaptochromone-2-carboxylic ester (**IV**) to 5-hydroxythiochromone-2-carboxylic acid (**V**) are a further demonstration of the different reactivity at C-2 of chromones and thiochromones.[3]

In this paper we describe a theoretical study of the electronic structure of chromones and thiochromones in order to interpret these reactivity data. The calculations we have carried out will also be used to discuss the photochemical cycloaddition to the pyrone double bond, where it has been found that the addition of 1,1-dimethoxyethene (DME) to 4*H*-1-benzopyran-4-one (chromone) yields only one isomer: that in which the dimethoxy-substituted carbon of DME becomes bonded to C-2.[6]

Methods and Results

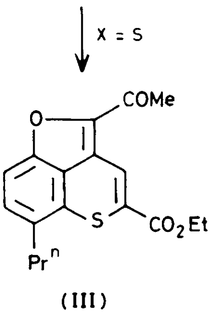
The simplest theoretical approach to the reactivity of the quite large molecules discussed herein is to attempt to correlate observed reactivities with the ground-state electronic structure of the isolated reactant molecule, *via* so-called 'static indices', which are taken to be indicative of important factors influencing the transition state. In the absence of accurate calculations of the transition state, which are certainly not feasible at the present time if *ab initio* wavefunctions are employed, we believe a study of the value of these 'static indices' to be worthwhile.

We have calculated ground-state wavefunctions for (**V**) and (**VI**) using the *ab initio* SCF-MO method, in a minimal (STO-3G) basis.[7] Owing to the lack of experimental data of the geometric structure of these two molecules, the semi-empirical MINDO/3 method was used to furnish optimal bond lengths and angles for (**VI**), which were modified for use for (**V**) by using C–S bond lengths estimated from the known structure of 2-chlorothioxanthone[8] together with the associated opening-out of the bond angles of the pyrone ring. Both molecules were assumed to be planar. The resulting electronic wavefunctions were used to calculate the formal atomic charges, *via* a Mulliken population analysis, and were also used to calculate the electrostatic potentials close to the possible sites of nucleophilic attack. Attack by a 'hard' nucleophile, such as OH^-, is generally considered to be 'charge-controlled'[9] and thus the preferential site of nucleophilic attack may be expected to correlate with atomic charges or electrostatic potentials. The relevant atomic charges for (**V**) and (**VI**) are shown in the Figure. These values do not predict the correct site of nucleophilic attack. For both molecules the carbon atom of the carboxylic acid group has the largest positive charge, but in the chromone (**VI**) C-4 bears a larger positive charge than C-2, suggesting C-4 to be more susceptible to nucleophilic attack than C-2, in disagreement with experiment. In the thiochromone (**V**) however, the atom charges correctly predict that nucleophilic attack will occur at C-4 rather than C-2. The Mulliken analysis suffers both from the lack of a unique definition of atomic charge, and from the neglect of inclusion of the Coulombic effect from neighbouring atoms. Both these deficiences may be avoided by use of the computed quantum mechanical electrostatic potential.[10] In the Figure we show values of this quantity computed 3 a.u. (1.58 Å) above the appropriate carbon atoms. This distance is somewhat

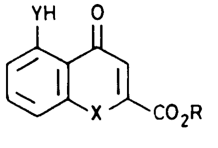


(I)
a; X = O
b; X = S

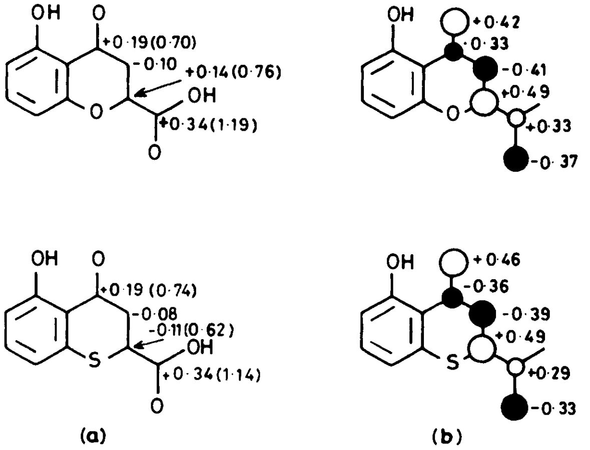
(II)



(III)



(IV) X = O, Y = S, R = Et
(V) X = S, Y = O, R = H
(VI) X = O, Y = O, R = H



(a) Mulliken atomic charges and, in parentheses, the quantum mechanical electrostatic potential (v), 3 a.u. above the molecular plane. (b) Atomic coefficients for the LUMOs of chromone and thiochromone

arbitrary, but has been chosen to be a rough estimate of the separation of the nucleophile (OH^-) from the carbon atom in the transition state. For the chromone (**VI**), the electrostatic potential now predicts C-2 to be more susceptible to nucleophilic attack than C-4, whilst for the thiochromone this order is reversed. These findings are now in agreement with the experimental reactivity data.

An alternative approach to site-specific reactivity, the frontier orbital method, will, in this case, need the atomic contributions to the lowest unoccupied orbital (LUMO).[11] These are also shown in the Figure, where it can be seen that this approach would lead to nucleophilic attack being favoured at C-2 in both (V) and (VI). However, it is generally considered that the reaction will be frontier orbital-controlled only for soft nucleophiles[12] for which experimental data are unavailable.

However, in the photochemical cycloaddition to the pyrone double bond, frontier orbital interactions are expected to exert considerable influence over the site selectivity.[13] We now discuss why DME bonds through the dimethoxy-substituted carbon atom to C-2 of chromone in such a reaction. If we assume that the site selectivity is dominated by frontier orbital effects we must consider the interaction between the ground-state HOMO of chromone (from which an electron is promoted on photoexcitation) with the HOMO of DME, and that between the corresponding LUMOs.[13] If we take the reactive excited state to be $^3(n \rightarrow \pi^*)$, then the interaction between the LUMOs will dominate, since the overlap between the HOMOs will be small in the approach to the transition state. The LUMO of DME has a higher amplitude on the dimethoxy-substituted carbon than on the other olefinic carbon, and the LUMO of chromone was found to have the largest amplitude at C-2, just as in (V) and (VI) (Figure). Hence the observed site selectivity is readily accounted for by these simple considerations. There has, however, been some discussion as to whether the reactive excited state of chromone is $n \rightarrow \pi^*$, or $\pi \rightarrow \pi^*$.[14-17] Gallivan[14] and his co-workers[18] have suggested that chromone has low-lying $^3(n \rightarrow \pi^*)$ and $^3(\pi \rightarrow \pi^*)$ states which are almost isoenergetic and may be reordered by solvents of differing polarities. Furthermore, a recent CIDEP study[17] shows that at room temperature, regardless of solvent, the chemically reactive triplet involved in the photoreduction of chromone is $^3(n \rightarrow \pi^*)$. If the reactive excited state is $^3(\pi \rightarrow \pi^*)$, HOMO interactions will also have to be considered. The positions of highest and lowest amplitude in the HOMO of DME are as expected, reversed with respect to the LUMO. Rather unusually for αβ-unsaturated ketones the two important atoms (C-2, -3) in chromone also show a similar reversal in the HOMO. Thus, the HOMO interaction favours the same site selectivity as the LUMOs, and the dominant isomer should be the same whichever of the two excited states of chromone is involved in the reaction.

Conclusions

We have here used the static index approach to understand two aspects of chromone chemistry. Within the severe approximations inherent in such a rather crude approach to reactivity we find the assumptions that the basic attack considered herein is charge-controlled, and that photochemical cycloaddition is frontier orbital-dominated, lead to an understanding of the site selectivity of these reactions.

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