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PHOTOELECTRON SPECTRA OF CYCLIC AROMATIC ETHERS

THE QUESTION OF THE MILLS-NIXON EFFECT

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Abstract—UV photoelectron spectra (UPS) of the cyclic aromatic ethers (**1**; R = H, n = 1, 2) are compared with each other and with those of non-cyclic ethers. The spectrum of the chroman (**1**; R = H, n = 2) is clearly distinguishable from those of all the other ethers. The differences in the spectra have been interpreted in terms of differing conjugative effects of oxygen and of "hyperconjugative" effects of methylene with the aromatic ring. These conclusions are supported by MO calculations. The bearing of these differing conjugative effects on reactivity of cyclic aromatic ethers is discussed and the conclusion reached that the orientational preferences customarily explained by the "Mills-Nixon effect" do not depend upon variation of bond lengths or bond angles in the aromatic ring but upon cross-conjugation effects in "Wheland" transition states.

The 6-hydroxychroman nucleus (**1**, R = OH, n = 2) shows a remarkable regiospecificity towards oxidation and electrophilic substitution that has not been explained despite numerous studies. Acyclic phenols related to 6-hydroxychroman brominate mostly at the β-position (**1**) as do phenols with other ring sizes (**1**; R = OH, n = 1, 3, 4) yet 6-hydroxychroman itself is attacked mainly at the α-position.[1,2] Similar, but less pronounced, regiospecificity is found in the carbocyclic phenols (**2**; n = 0, 1, 3, 4) in which β-substitution is the rule in contrast to the α-substitution observed in the 6-membered carbocyclic phenol (**2**; n = 2). Parallel phenomena are found in the nitrogen heterocyclics (**3**) in which β-substitution is again the rule except for the compound (**3**; n = 2). Relative rates of detritiation from the α- and β-positions of labelled ethers (**4**; **1**; R = OMe, n = 1; **1**; R = OMe, n = 2) again demonstrate the anomaly of the chroman. The ratio of rates of detritiation[3] at the α- and β-positions of ether (**4**) is 1 : 23·1 and for ether (**1**; R = OMe, n = 1) it is 1 : 16·7, yet for the chroman (**1**; R = OMe, n = 2) the ratio is 1 : 0·34.

Many other examples of unusual changes in reactivity with change in ring size exist. For example, in α-tocopherol (**5**; $R^1 = R^2 = R^3$ = Me), the α-Me group is readily oxidised but not the others. In δ-tocopherol (**5**; $R^1 = R^2$ = H, R^3 = Me), oxidative coupling occurs at the α- but not the β-position. In other compounds of the tocopherol series, oxidative coupling occurs at the α-position instead of attack at a β-Me and, most surprisingly, an α-Me group is attacked in preference to β-coupling.[4] The variety of reagents showing similar regiospecificity includes alkaline ferricyanide,[4,5] benzoyl peroxide,[6] silver salts,[7] iron(III) salts,[8] quinones,[9] and irradiation by UV[10] or γ-rays.[11] Little has been done with respect to other heterocyclic ring sizes on the point of oxidative attack, but the one derivative of compound **1**; (R = OH, n = 1) that has been studied reacted at the β-position again suggesting a reversal of orientation with change of ring size.[12] In carbocyclic phenols there is a similar but less marked regiospecificity in brominations.[13]

It has been customary to discuss such orientations in terms of the "Mills-Nixon effect", a concept that has never been defined clearly.[2,12,14] The ring fused to the phenolic nucleus has been considered to affect either the bond angles at the positions of ring fusion or the bond length between the atoms forming the ring junction, and so the stabilities of the transition states for electrophilic substitution.

To investigate possible electronic differences between compounds such as **1**(n = 1 or 2) we have examined the UPS of a number of aromatic ethers and carried out molecular orbital calculations using CNDO/2 and simple Hückel theory.

RESULTS

Ionization potentials for the outer orbitals of a number of ethers are listed in Table 1. The spectra of the 5-(**1**; R = H, n = 1) and 6-membered ring compound **1** (R = H; n = 2) are contrasted in Fig. 1. Symmetry arguments show that the lone-pair electrons on oxygen in a compound like anisole can interact with the outer and inner orbitals (π_3 and π_1) of the benzene ring.[15] Since the orbital energy (*ca.* 9·4 eV) of lone-pair electrons in acyclic and alicyclic ethers is close to that of the π_3 level (9·24 eV) and about 2 eV different from the π_1 level, most of the interaction can be expected between the lone-pair and π_3 orbitals; the interaction will give four new pi-type orbitals of which π'_4 and π'_2 will represent the new orbitals formed from the oxygen lone-pairs and the π_3-orbital of benzene. These qualitative considerations are supported by CNDO/2 m.o. calculations and allow assignment of the orbitals shown in Table 1. Thus, in anisole and 1,4-dimethoxybenzene the $\pi'_4 - \pi'_1$ orbitals are as listed in Table 1 and are the same as reported by others.[16] Assuming free rotation in anisole, there is a plane of symmetry through the plane of the benzene ring and the attached oxygen so that only one "lone-pair" π-type orbital (11·02 eV) would be expected although oxygen has two lone-pairs. Similarly, in 2-methylanisole, this symmetry plane still exists and, apart from movement of the $\pi'_4 - \pi'_1$ orbitals through "hyperconjugation" with the Me group, the spectrum of this compound is very similar to that of anisole. Again, in the 5-membered ring compound **1** (R = H; n = 1), the same situation exists if the somewhat buckled 5-membered ring inverts rapidly; the spectrum of this compound is very similar to that of 2-methylanisole, except that vibrational structure can be discerned in the more rigid bicyclic system. The π-orbital at 9·09 eV in the 5-membered ring compound shows vibrational bands separated by 1020 cm^{-1} which we tentatively ascribe to aromatic

Table 1. Vertical ionization potentials for outer orbitals in esters

Ether	I.P. (eV)[a]
Diethyl ether	9.73 (9.41; n).
Tetrahydrofuran	9.77 (9.38; n)
Tetrahydropyran	9.49 (9.16; n)
2-Methylanisole	8.20 (7.90; π), 8.90 (8.80, π), 10.90 (10.70, n), 11.34 (π)
2,3-Dihydrobenzofuran (I; R = H; n = 1)	8.22 (8.02; π), 9.09 (9.03; π),[b] 10.81 (10.51; n), 11.46 (π)
Chroman (I; R = H; n = 2)	8.13 (7.93; π), 8.82 (8.77; π),[b] 10.27 (n),[b] 10.63 (n),[b] 11.50 (π)
Anisole[c]	8.42 (π), 9.23 (π), 11.02 (n)
1,4-Dimethyoxybenzene[c]	7.90 (π), 9.25 (π), 10.25 (n).

[a] Adiabatic ionization potential and assignment of band-type (π, n) are shown in brackets. Assignment as n-type means the orbital is an extended pi-system with some concentration of electron density on oxygen.

[b] Fine structure observed - see text.

[c] These values have been reported previously[16] and are included here for completeness.

ring-breathing;[17] similarly the band at 10·81 eV shows vibrational structure of energy, 1050 cm^{-1}.

There are no quasi-equatorial or -axial groupings on a 5-membered ring because so little energy is needed for ring inversion but the energy required for ring inversion in the 6-membered ring is much greater so that axial and equatorial forms are found. In the 6-membered ring ether (1; R = H, n = 2), the simple plane of symmetry through the benzene ring and carbocyclic ring no longer exists if the rate of inversion of the 6-membered ether-carbocyclic ring is slow. If no plane of symmetry exists, two "lone-pair" π-type orbitals would be expected. The UP spectrum of the ether (1; R = H, n = 2) has two bands at 10·27 and 10·63 eV having vibrational structure respectively at 2170 and 2500 cm^{-1} (Fig. 1). The lower ionization potentials of these bands compared with those in anisole and the other aromatic ethers suggests that the oxygen "lone-pair" electrons are less strongly bonded (less conjugated) with the aromatic π-system.

The UPS of all the above ethers were compared with the eigenvalues obtained from CNDO/2 calculations using either known geometries[18] or estimated geometries based on known ones and assuming Koopmans' theorem.[19] For the outer four π-levels it was found that, $\text{I.P.} = 0{\cdot}603\,E + 0{\cdot}920\,\text{eV}$; $\rho = 0{\cdot}975$; mean square deviation $\pm 0{\cdot}253$; E = eigenvalue. It is well known that CNDO/2, parameterized originally to predict dipole moments, tends to mix the ordering of π- and σ orbitals, possibly because the p-orbital exponents in the basis sets are too large.[20] The good correlation observed between ionization potentials and eigenvalues was useful for confirming the assignments of the two bands at 10·27, 10·63 eV in the 6-membered ring ether to oxygen "lone-pair" π-type orbitals.

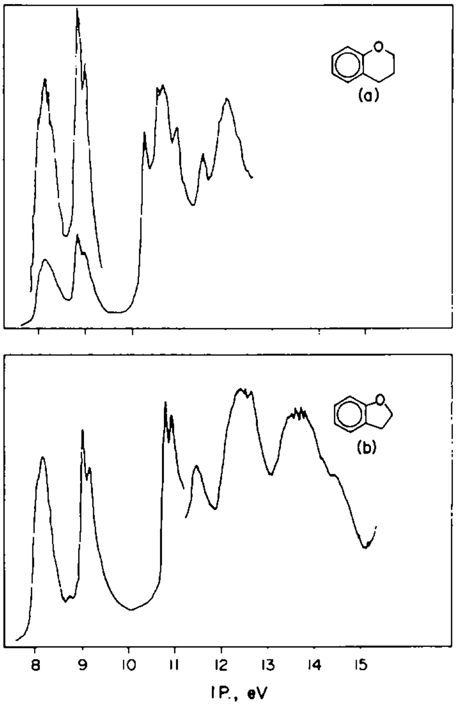


Fig. 1. UP spectra of (a) chroman (1; R = H, n = 2) and (b) ether (1; R = H, n = 1). The detail on the tops of the bands centred at 12·5 and 13·5 eV in (b) is instrumental noise.

Although the oxygen lone-pair electrons are less strongly bound into the aromatic π-system in the 6-membered ring ether, the ionization potentials of the outer π-orbitals are little different from those of 2-methylanisole or the 5-membered ring ether (1; R = H; n = 1). This suggests that the decrease in the conjugation with oxygen is made up by increased conjugation to the methylene group directly attached to the aromatic ring (1; R = H). There is actually a small decrease (8·22–8·13 eV; Table 1) in the ionization potential of the outer π-orbital in going from the 5-membered ring ether (1; R = H; n = 1) to the 6-membered ring one (1; R = H; n = 2) even though the oxygen "lone-pair" π-orbital decreases from 10·81 to 10·27, 10·63 eV in the two compounds.

DISCUSSION

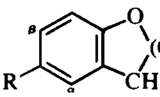
Invoking a "Mills-Nixon effect" to explain orientation control of reactivity in these systems has generally meant assuming that the ring fused to the aromatic system affects either the bond angles at the common link or the bond length of the link itself and, through these features, the stabilities of the various possible transition states for substitution. In a recent example, the quinone (**6**) when treated with acid was converted into the quinone methide (**8**) rather than (**7**); this selectivity was thought to reflect a better accommodation of bond angles at the ring junction of the methide (**8**) compared with (**7**).[21] The former methide also corresponds to the initial oxidation product of α-tocopherol with N-bromosuccinimide.[22]

Other workers have commented that effects upon bond lengths or bond angles must be too small to account for the orientation results. Early molecular orbital calculations designed to test the Mills-Nixon hypothesis failed to detect any differences in bond angles or lengths capable of explaining the phenomena.[23] Our own CNDO/2 calculations support this earlier work, changes in bond lengths and angles of up to 10% from those normally accepted for these systems[18] having little effect.

In an attempt to find an explanation of the reversal in the site of reaction, bearing in mind the UPS results, we first sought some other aspect of structure which could single out the chroman nucleus. The reduced conjugation to oxygen and increased "hyperconjugation" to the benzylic methylene observed in the UPS of the 6-membered ring ether (**1**; R = H; n = 2) suggested a possible explanation. Dreiding molecular models show that in the chroman system a C–H bond on the benzylic methylene group can be maintained perpendicular to the plane of the benzene ring without ring strain, i.e. this C–H bond is held in the best position for maximum hyperconjugation in accord with the UPS results discussed above. In marked contrast, no other ring size under consideration can achieve a corresponding orientation without incurring much ring strain; and it follows that, towards electron-demanding reagents, chroman derivatives should behave in a special way.

Next we considered why these changes in conjugation to oxygen and methylene lead to a reversal of reactivity at the α- and β-positions. The reactivity may be concerned with an "early" transition state when electron density at the α- and β-positions of the ethers would influence orientation, but although CNDO/2 appears to be good for predicting charge densities in a molecule (good dipole moments), in our calculations we found no reversal of electron densities at the α- and β-positions in going from the 5- to the 6-membered ring ether. On the other hand, a "late" transition state suggests that the energies required to reach a "Wheland" type transition state from the ground-state would be important in determining orientation. Qualitatively, this means that valence bond structures (**9**, **10**) need to be considered in (as in this example) protonation. Structures (**9**, **10**) are cross-conjugated and it is not easy to see what the effect of changing conjugation would be on the energies either of the "transition states" or of the ground-state molecules they started from. As CNDO/2 is not a good method for total energy properties of molecules[20] we have used the simple Hückel m.o. treatment which has already been used successfully to discuss "Wheland" type transition states.[24a]

For the Hückel calculations, the model compound (**11**) was considered and the energy of the π-system was calculated with the following parameters (i) the C–O^1 overlap integral was maintained constant (k = 1 in the usual Hückel m.o. description),[24b] (ii) the C–O^2 overlap integral was varied between k = 0·5 and k = 1·0 in steps of 0·1, (iii) the C–Me link was treated as a pseudo hetero-atom[24b] with k = 0·5–1·0 for each value of k(C–O^2) used in (ii), and (iv) the Coulomb integrals for O^1, O^2, and Me were varied from h = 0 to h = 2. Then, these parameters were used to calculate the energies of the π-systems (**12**, **13**) resulting from substitution at the α- and β-positions in **11**. From these energies, the energy increments $\Delta E_\pi(\alpha)$ and $\Delta E_\pi(\beta)$ required to pass from the ground-state of the model (**11**) to the "Wheland" type transition states (**12**, **13**) were obtained, these increments being a theoretical measure of the rates of reaction at the α- and β-positions in **11**. The results of these calculations are illustrated in Fig. 2 for variations in k(C–O^2) and k(C–Me) with h = 0; similar results were obtained for other values of h. All of them predict the following. The energy $\Delta E_\pi(\alpha)$ varies with k(C–Me) (k_2 in Fig. 2) but the changes in $\Delta E_\pi(\alpha)$ for different k(C–O^2) are small (compare graphs B, C, D in which k(C–O^2) = 0·9, 0·7, 0·5 respectively). Contrariwise, the energy, $\Delta E_\pi(\beta)$, changes



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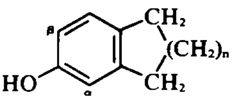

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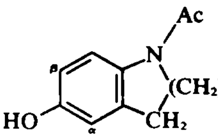

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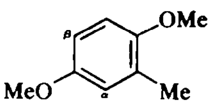

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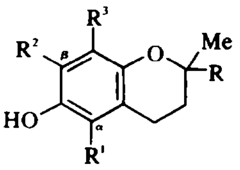
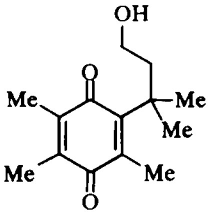


5: R = 4,8,12-trimethyltridecyl



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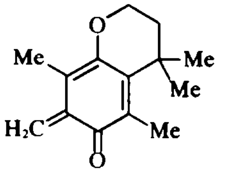

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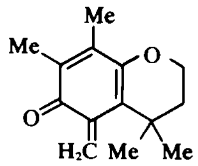

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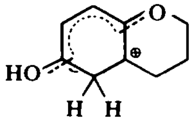

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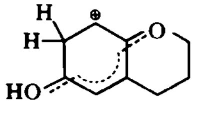

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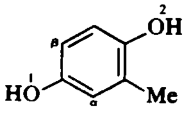

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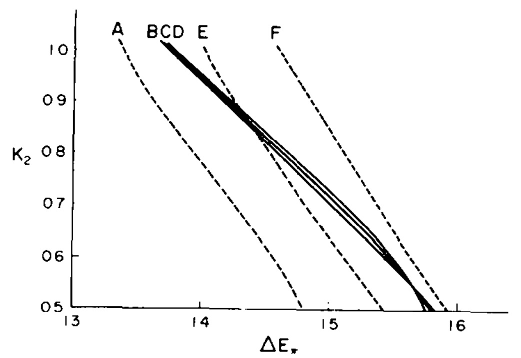


Fig. 2. Variation of $\Delta E_\pi(\alpha)$ and $\Delta E_\pi(\beta)$ with changes in the overlap integrals $k(C\text{–}O^2)$ and $k(C\text{–}Me)$ for all $h = 0$.

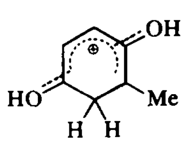
considerably as $k(C\text{–}O^2)$ is varied (compare graphs A, E, F in which $k(C\text{–}O^2) = 0{\cdot}9, 0{\cdot}7, 0{\cdot}5$ respectively). At approximately $k(C\text{–}Me) = 0{\cdot}9$ and $k(C\text{–}O^2) = 0{\cdot}5\text{–}0{\cdot}9$, the graphs cross, i.e. the calculations predict a cross-over in orientation of reactivity as the conjugative effect to oxygen decreases and the hyperconjugative effect to Me increases. Further, the calculations suggest that the rates of reaction at the α-position for different conjugative effects (as in different ethers) will not vary nearly so markedly as rates of reaction at the β-position (graphs B, C, D compared with A, E, F). Experimentally, the rates of detritiation[3] at the α-position are 2·1, 0·3 and 7·3 ($k \times 10^6$ sec^{-1}) respectively for the ethers **5**, **1** (R = OMe, n = 1) and **1** (R = OMe, n = 2) but for the β-position these rates are 48·6, 5·0, 2·5 ($k \times 10^6$ sec^{-1}).

The cross-over in reactivity at the α- and β-positions of the aromatic ethers when the ring attached to the aromatic system is 6-membered can therefore be ascribed to simple changes in conjugative effect, i.e. the decreased conjugation with the ring ether oxygen combined with the increased conjugation to the benzylic methylene group that occurs only with the 6-membered ring ethers.

These conclusions are supported by other observations. The O atoms in the quinol nucleus appear to act in opposition; they are placed so that whichever activates the π-system by releasing electrons into it, the other deactivates the σ/π-system by inductive or field effects. For example, although the rate of detritiation of labelled tetralin is increased about a thousand-fold by introduction of the OMe group, the quinol derivative (**1**; R = OMe, n = 2) is only about as reactive as tetralin itself.[3] The difficulty of brominating an acyclic quinol as opposed to other phenolic nuclei has been noted previously.[25] Ring size has not been observed as having any directive influence in the resorcinol series where the O atoms act in concert, despite the many examples studied in connection with the synthesis of naturally occurring compounds.[26]

A correspondence between the nitrogen series (**3**) and the oxygen series (**1**) is to be expected. The bromination of the salt (**14**) is particularly interesting since electronic diagrams like (**9–13**) are not possible and β-substitution might be expected even with the 6-membered ring compound. In fact β-substitution has been observed although the result was marred by extensive oxidation.[27] Purely carbocyclic phenols (**2**) can be accommodated by the above hypothesis provided both benzylic methylene groups hyperconjugate, although selectivity would be less as has been observed, and in fact the UPS of carbocyclic benzenes do show the effects of hyperconjugation.[28] At the other extreme, the limited results available for ring systems (**15**; n = 1, 2) with two oxygen atoms and no benzylic methylene group[29] also conform to the present views.

Finally, the connection with oxidation of tocopherols requires exposition. There is general agreement that quinone methides are the important intermediates, or perhaps transition states, as for example the cases shown (**16, 17**); the charge-separated forms must be of particular importance for such molecules because they have full aromatic stabilization. The structure (**16**) is an analogue of the "Wheland" transition state **9** as is **17** of **10** and similar stability arguments apply, i.e. oxidative coupling at the α-Me group occurs. Oxidative coupling in the absence of Me groups still occurs at the α-position since transition states like **9**, **10** are then directly applicable.



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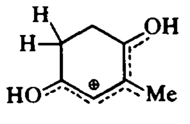

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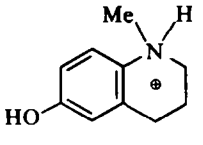

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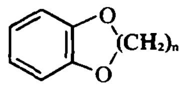

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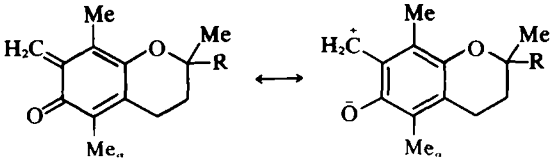
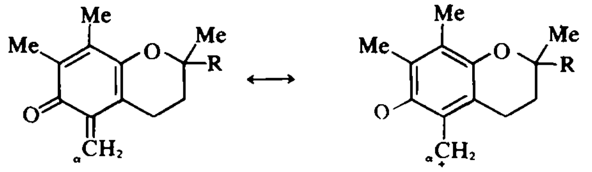


16: R = 4,8,12-trimethyltridecyl



17: R = 4,8,12-trimethyltridecyl

From UPS results and MO calculations, we therefore conclude that the orientation phenomenon known as the "Mills-Nixon effect" is primarily a consequence of cross-conjugation upon ring sterochemistry and not of bond-fixation or angle strain.

EXPERIMENTAL

All compounds are known and were redistilled before use. Spectra were measured on a Perkin-Elmer PS-16 photoelectron spectrometer using 21·21 eV incident photon irradiation (He I). Spectra were calibrated against both argon and xenon.

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