Reversal of Electronic Effects between Inter- and Intra-molecular Michael Addition Reactions

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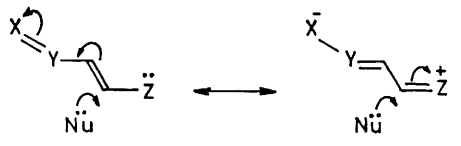
Measurement of the rates of cyclisation of (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol and its *p*-methoxy-derivative in trifluoroacetic acid, together with the rates of the reverse reaction, indicates an influence of stereoelectronic origin which is not present in intermolecular Michael additions.

Concepts of stereoelectronic factors in shaping reaction pathways are of current interest.[1] The idea of directed attack by orbital steering has led to the postulation of rules governing ring closure reactions.[2] We report an example of how such effects lead to the reversal of electronic influences on reaction routes, and may provide a method for their *quantitative* evaluation.

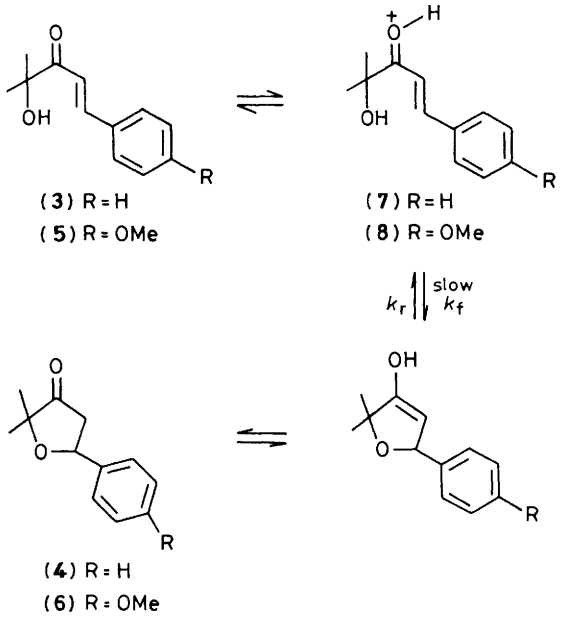
In intermolecular Michael addition reactions (Scheme 1), a resonance donor group Z in (**1**) produces a decelerative effect, because, although it introduces an alternative reactive canonical (**2**), overall nucleophilic attack cannot be accelerated by *donation* of electrons to a nucleophilic site.[3]

5-*endo*-*trig* ring closure of (**3**), an intramolecular Michael addition, is predicted to be disfavoured, and indeed base-catalysed ring closure does not occur.[4] However, the reaction proceeds in acidic media through the alternative, favoured, 5-*exo*-*trig* pathway *via* the protonated form (**7**) involving canonical (**9**).[4] An alternative way of looking at it is that the effect of the -OMe group is to reduce the barrier to rotation about the C–4, C–5 bond, and thus facilitate attack of the nucleophile on the p-orbital at C-5.[5] This suggests that, in contrast with the intermolecular reaction (Scheme 1), the intramolecular reaction (Scheme 2) should be sponsored by *release* of electrons to the site of nucleophilic attack.

To test this proposal, we synthesised compounds (**5**) and (**6**) and observed the changes in their ^{1}H n.m.r. spectra (trifluoroacetic acid, 35 °C, recorded on a Perkin Elmer 60 MHz R12 instrument). The initial spectra are as follows: (**5**): δ 8.09 (d, *J* 16 Hz, 1 vinyl H), 7.42 (m, 4 arom. H and 1 vinyl H),



Scheme 1



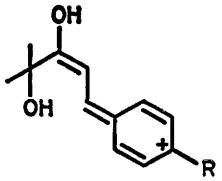
Scheme 2

3·97 (s, 3 H, OCH_3), 1·70 (s, 6 H, CH_3); (**6**): δ 7.36 (dd, *J* 9 Hz, 4 arom. H), 5.57 (dd, X of ABX, J_{AX} 9 Hz, J_{BX} 9 Hz, 1 methine H), 3.97 (s, 3 H, OCH_3), 3.06 (complex, 2 H, AB of ABX), 1.58 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3). The final spectra are identical, and consist solely of the initial peaks of (**5**) and (**6**).

Integration of the methyl peaks at suitable time intervals yielded the following values:† $k_f(OMe) = 2.6 \times 10^{-4}\ s^{-1}$, $k_r(OMe) = 1.3 \times 10^{-4}\ s^{-1}$, $K = 2.0$. A similar experiment with (**3**) and (**4**) gave $k_f(H) = 4.3 \times 10^{-6}\ s^{-1}$ and $K = 3.52$; an accurate value for $k_r(H)$ was unobtainable because of preponderance of ring compound at equilibrium, but k_r may be calculated as $1{\cdot}2 \times 10^{-6}\ s^{-1}$. The accelerating effect of the -OMe group, which for ring closure is 60 [$k_f(OMe)/k_f(H)$] and for ring opening is 108 [$k_r(OMe)/k_r(H)$], provides evidence for the reversed electronic effect expected if orbital steering is influential in such cyclisations.

This conclusion assumes that the reactive protonated carbonyl compounds (**7**) and (**8**) are majority species in CF_3CO_2H, or if a minority species their concentrations are comparable. The shifts of the methyl proton signals downfield on changing solvent from $CDCl_3$ to CF_3CO_2H are similar for (**3**) and (**5**), suggesting that the extent of protonation is about the same. Moreover, the reversed effect is even more marked for the ring opening reactions which from the law of microscopic reversibility proceed *via* a common transition state in the same rate determining step; here the basicity of carbonyl compounds (**4**) and (**6**) must be almost identical. Indeed, the influence of the orbital steering effect should be most pronounced in the reverse reaction because the stability of ring compounds (**4**) and (**6**) will be very similar, little affected by the substitution of the aryl ring, whereas, on the other hand, the open chain methoxy-compound (**5**) is more stabilised by resonance than the unsubstituted compound (**3**).

† Rate constants were obtained from linear first order plots; J. A. Hirsch, 'Concepts in Theoretical Organic Chemistry,' Allyn and Bacon, 1974, pp. 116—117. The n.m.r. patterns of the equilibrium mixture of (**5**) and (**6**) show that secondary reactions occur, but some time after equilibrium is established. They probably include intermolecular reaction between the -OH of one molecule and the activated double bond of a second, and also reaction of the OH of (**3**) and (**5**) with CF_3CO_2H, since n.m.r. spectroscopy shows formation of CF_3CO_2Et when ethanol is dissolved in CF_3CO_2H. Secondary reactions also occur within the equilibrium mixture of (**3**) and (**4**).



(**9**)

The validity of our deductions also demands that the rate determining step is the attack of nucleophile on the double bond (or its reversal) *via* canonical (**9**), rather than keto–enol tautomerism.[3] In support of this, the attack of water on protonated phenalenone by acid-catalysed Michael-type addition is the rate determining step in the hydrogen-exchange of phenalenone.[6] Although Bell considered that the acid catalysed addition of water to mesityl oxide involves a rate determining keto–enol tautomerism,[7] in general the C-protonation of vinyl ethers, and therefore presumably of enols, is a very rapid process.[8]

Received, 18th September 1981; Com. 1110

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