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STEREOELECTRONIC EFFECTS IN RING CLOSURE REACTIONS

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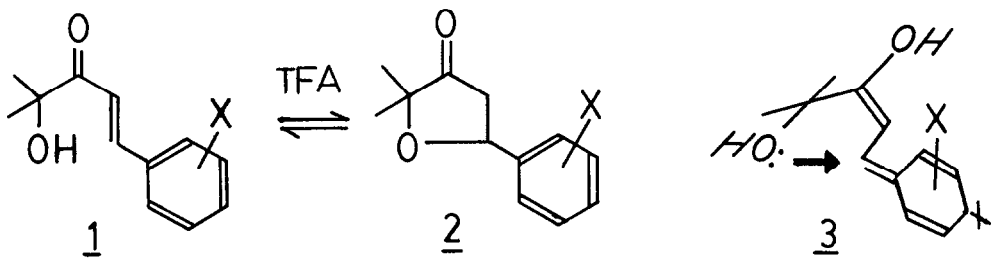
The mechanistic criterion of reversed substituent effects in reactions, formally classified as 5-endo-trig and 6-endo-trig, is examined.

Pronounced accelerative effects of electron donation by substituents X (ρ^+ = -2.2) have previously been demonstrated in the ring closure induced by trifluoroacetic acid, shown in Scheme 1, in contrast to the deceleration observed for an intermolecular Michael addition.[1] This supports the suggestion,[2] that reaction proceeds via a 5-exo-trig route involving structure 3.



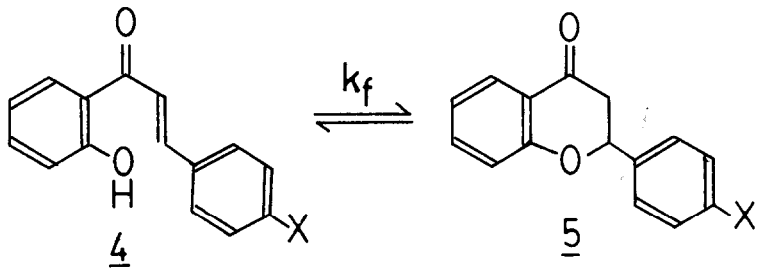
1 2 3

Scheme 1

According to Baldwin's rules, 6-endo-trig closures are allowed,[3] although "not so allowed" as 6-exo-trig.[4] Models reveal that in the former case, an influence comes into play not specifically dealt with in the rules, namely the character of the connecting chain between the two reacting centres. If it is of mobile sp^3 hybridised carbon atoms, the necessary trajectory is obtainable. For an sp^2 hybridised connecting system, however, with the larger bond angle of 120°, the nucleophile appears well off line for correct alignment to the electrophilic double bond, and this will be augmented by the tendency of a conjugated system to stay in plane.

A suitable system to examine this effect experimentally appeared to be

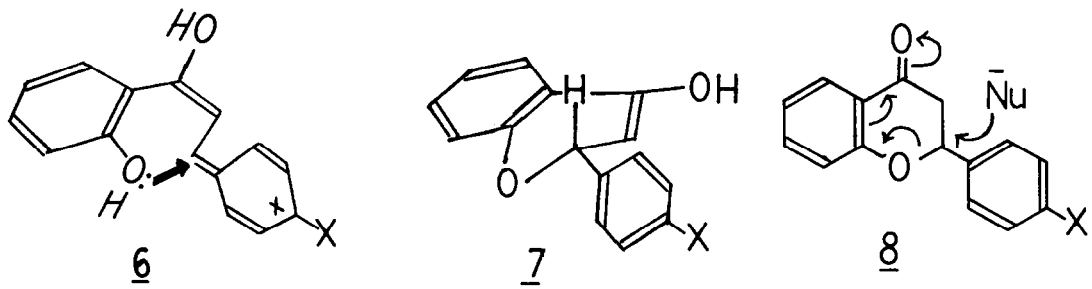
the hydroxychalcone-flavanone system (Scheme 2), a key step in the biosynthesis of flavanoids in higher plants. k_f was measured in TFA, by



4 5

Scheme 2

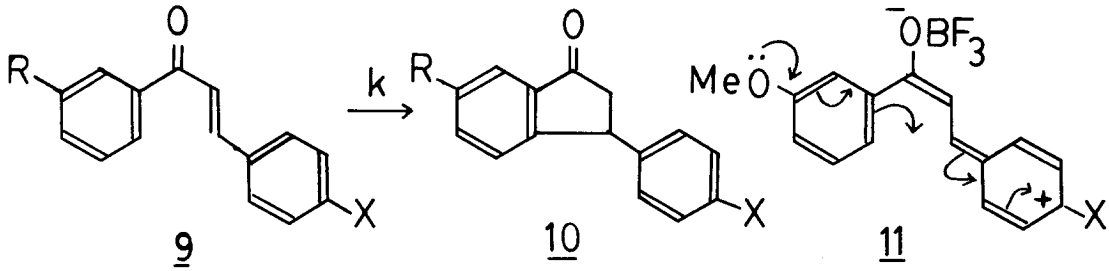
following the rate of growth of the ABX system of 5, in the proton NMR pattern, relative to the total methyl peak (the methyl peaks overlap for 4 and 5 for both compounds). This leads to values of 201 x 10^{-6} and 3.6 x 10^{-6} s^{-1} at 35°C for X=OMe and Me respectively, a reversed substituent effect even larger than that found for Scheme 1.[1,5] This indicates that the 6-endo-trig mode is indeed a high energy pathway in this case, and the reaction adopts the alternative 6-exo-trig route via structure 6. Considering the reverse reaction of Scheme 2, a model of (7) shows the p-orbitals of the enol system to be almost orthogonal to the cleaving C-O bond.[6]



6 7 8

The mechanism for base catalysed hydroxychalcone-flavanone interconversion thus becomes of some interest. The reaction proceeds readily (though strongly pH dependent),[8] in contrast to that of Scheme 1, which does not occur in base. It may be of significance that 5, in contrast to 2, may be susceptible to reaction as shown in 8.

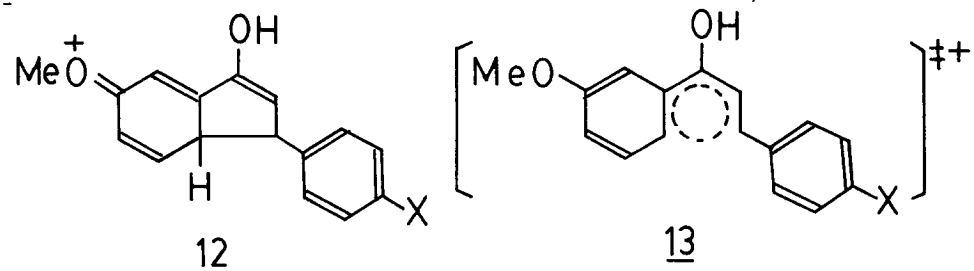
A 5-exo-trig route via an intermediate analogous to that of 3 and 6, namely 11, has been proposed[9] for the intramolecular Friedel-Crafts type aromatic electrophilic substitution, Scheme 3, in boron trifluoride etherate.



9 10 11

Scheme 3

The reaction proceeds smoothly to completion in TFA at 35°C when R = OMe. When R = H, no reaction occurs at this temperature; presumably in this case the potential intermediate lacks the stabilisation of the methoxy group shown in 12. However, unlike the reactions of Schemes 1 and 2, the influence on



12 13

rate[10] of increasing electron donation of X is much smaller (X = Me, H, Cl, $k = 6.5, 4.9, 3.7 \times 10^{-6}$ s^{-1} respectively) of which a large part can be explained by the increased concentration of reactive protonated form sponsored by electron donor groups X. This leads us to propose that the alternative suggestion,[9] that the rate limiting step of the reaction is an electrocyclic rearrangement of Nazarov type, may be the correct one, involving transition state 13. In such a case, the rate would be little affected by the nature of X, and there are a number of precedents[11] which show that such reactions may indeed involve the double bond of an aromatic ring. This would also explain the facile acid-catalysed ring closure of 1-(3-methoxyphenyl)-4,4-dimethylpent-2-en-1-one.[9]

The examples, which we have described above, and which we are investigating further, may thus provide some indication of how the occurence or non-occurence of the reversed substituent effect can afford mechanistic information in ring closure reactions.

References and Notes

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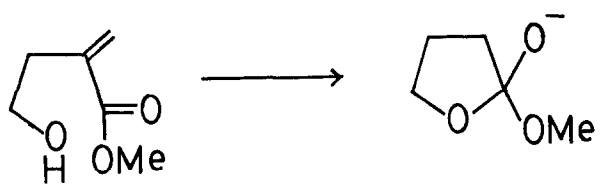
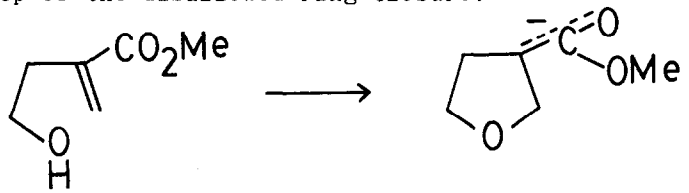
2. J.E. Baldwin, R.C. Thomas, L.I. Kruse, and L. Silberman, J. Org. Chem., 1977, 42, 3846.
3. J.E. Baldwin, J. Chem. Soc., Chem. Commun., 1976, 734.
4. J.E. Baldwin, J. Chem. Soc., Chem. Commun., 1977, 77; E. Napolitano, R. Fiaschi, and A. Marsili, Tetrahedron Lett., 1983, 24, 1319.
5. k_f (OMe)/k_f (Me) for Scheme 2 is 60 implying a ρ^+ value of -3.7; for Scheme 1 the corresponding ratio is 18. The equilibrium in Scheme 2 lies at least 5 to 1 in favour of the flavanone for both compounds. The rates of ring closure of 4, X=H, Cl fit approximately this correlation, but accurate kinetics are harder to obtain because of lack of a methyl peak in the NMR spectra. We are investigating the possibility of use of internal standards, or alternative techniques involving HPLC or UV. In these reactions, phenolic OH does not form trifluoroacetate as alcoholic OH does.
6. It is frequently an illuminating way of looking at stereochemical consequences of Baldwin's rules, to consider the reverse ring opening reaction. This shows their relevance to general stereochemical principles. For example, if we consider reversal of the rate determining allowed ring closure:



it can be seen that cleavage of the ring C-O bond is promoted by two anti-periplanar lone pairs on each external O atom.[7] However, the reverse step of the disallowed ring closure:



involves an ElcB reaction in which the orbitals enclosing the negative charge are orthogonal to the C-O bond which has to be cleaved.
7. P. Deslongchamps, Tetrahedron, 1975, 31, 2463; C.L. Perrin and G.M.L. Arrhenius, J. Am.Chem.Soc., 1982, 104, 2839.
8. K.B. Old and L. Main, J. Chem. Soc. Perkin Trans. II, 1982, 1309; P.G. Taylor, private communication.
9. W.S. Murphy and S. Wattanasin, J. Chem. Soc. Perkin I, 1980, 1555.
10. Again followed by proton NMR. Compound 9, X=OMe, appears to ring close with a rate constant of ca. 7 x 10^{-6} s^{-1}, but accurate kinetics are difficult to obtain because the methyl peaks of both reactant and product overlap in the proton NMR.
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