

Stereoelectronic Effects in the Formation of 5- and 6-Membered Rings: The Role of Baldwin's Rules

C. DAVID JOHNSON

School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, U.K.

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Favored Trajectories: Baldwin's Rules

The demonstration by Dunitz and his co-workers¹ of favored trajectories for the approach of one reactant molecule toward another led to the formulation of rules governing the ease of intramolecular ring closure reactions, the so-called Baldwin's rules.^{2,3} Thus, the allowed 5-exo-trig, 6-exo-trig, and 6-endo-trig closures⁴ of Scheme I permit the desired trajectories by the nucleophile of 109° to the double bond in the plane of its p orbitals (Scheme II). The disallowed 5-endo-trig closure, however, does not permit this trajectory.

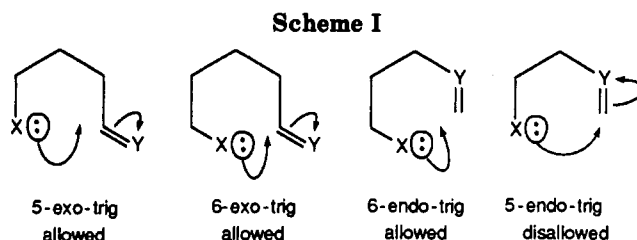
These rules do not represent a solitary island in the ocean of stereoelectronic phenomena, but fall into the mainstream of such effects. Originally designed to provide information on the feasibility of such reactions in organic synthetic routes, these rules give insights into the role of stereoelectronic effects in these reactions. This factor makes them of special interest to physical organic chemists.

As many organic chemists now recognize, there are considerable limitations on these rules. A very large number of examples are known in which they appear to break down.

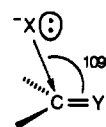
From one point of view, however, it may be contended that the rules are never disobeyed. If the favored trajectories reported by Dunitz are valid, then it must follow that Baldwin's rules are correct. This seems to be a particularly profitable approach, because the apparent collapse of the rules thus pinpoints areas of reactivity in which accepted stereoelectronic principles fail to perform as predicted. Precise mechanistic investigation, in particular, to determine the rate-limiting step of such reactions, is particularly important since we need to demonstrate that this step is indeed the one defined by Baldwin's rules. It therefore seemed to us that a detailed consideration of 5- and 6-ring closures, detailing in particular instances where Baldwin's rules appear to collapse, might give some illumination into important aspects of stereoelectronic effects.

To illustrate the stereoelectronic principles at work when the rules are in force, consider the well-known reaction³ depicted in Scheme III. This reaction follows the 5-exo-trig pathway because the nucleophile can enter the allowed trajectory of 109° in the plane of the p orbitals of the unsaturated electrophile. Such a pathway is impossible for the 5-endo-trig mode, even though in the intermolecular equivalent this would represent the preferred Michael addition. The law of

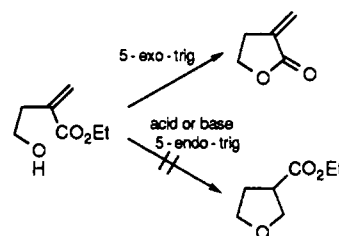
David Johnson received his B.Sc. (1957) and Ph.D. (1960) degrees from the University of London. He subsequently carried out postdoctoral work at the University of Texas at Austin. Since 1964 he has been Lecturer and then Senior Lecturer in Organic Chemistry at the University of East Anglia.



Scheme II



Scheme III



microscopic reversibility enables us to view the likelihood of the reverse reactions, when lone pairs have become bonds and bonds, lone pairs. Structure 1 shows the product of the rate-limiting step of the 5-exo-trig pathway, which is predicted to ring open readily by virtue of Deslongchamps' theory⁵ (two lone pairs antiperiplanar (app) to the cleaving bond). On the other hand, the corresponding product from 5-endo-trig closure, 2, reveals the system embarked on the second step of an Elcb reaction, which is necessarily of high energy because the orbitals embracing the negative charge are orthogonal to the breaking bond.

These arguments rely on the proviso, carefully pointed out by Baldwin,² that one is indeed looking at kinetic phenomena and that the thermodynamic stability of reactant relative to product does not influence matters. In the unimolecular breakdown of 7-oxo-6,8-

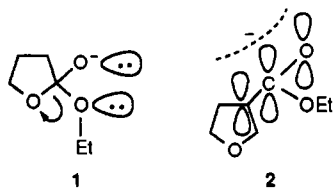
(1) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* 1983, 16, 153.

(2) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* 1976, 734. Baldwin, J. E. *Further Perspectives in Organic Chemistry*; A Ciba Foundation Symposium; Elsevier: Amsterdam, 1978; p 85.

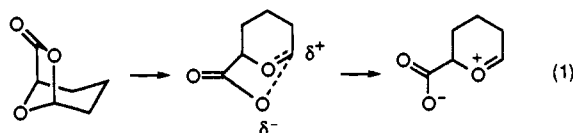
(3) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Chem. Commun.* 1976, 736.

(4) The initial number indicates the number of atoms in the skeleton of the ring formed. Exo or endo shows whether the unsaturated bond, breaking, on attack by the nucleophilic moiety, to form the ring, finishes up outside (exocyclic) or inside (endocyclic) the ring, respectively. Finally, trig and dig indicate whether the breaking unsaturated bond is a double bond (trig) or a triple bond (dig).

(5) Deslongchamps, P. *Tetrahedron* 1975, 31, 2463. Deslongchamps, P. *Heterocycles* 1977, 7, 1271 and references therein.



dioxabicyclo[3.2.1]octane,⁶ for example, the relief of ring strain leads to facile reversed 5-endo-trig reactivity (eq 1), which, despite the very strong inductive effect of the carbonyl group, is still predicted to be a kinetically unfavorable reaction.

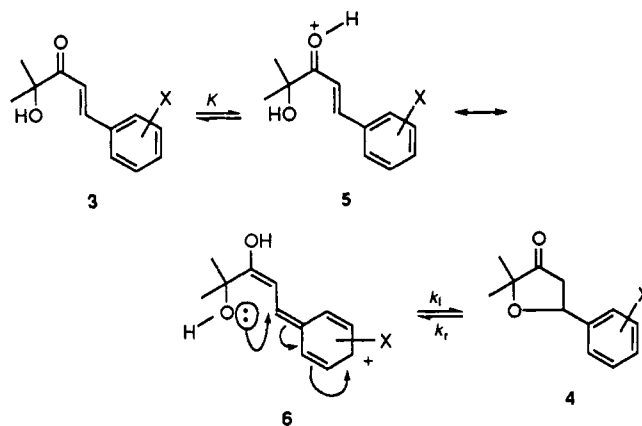


As well as correct orbital lineup, a further factor needs to be taken into account in considering the facility or otherwise of these reactions, namely, proximity effects.⁷ Since, according to Woodward,^{7a} "we all know that enforced propinquity often leads on to greater intimacy", the closer we hold reagents together, the more likely they are to react.^{7b} For efficient reactions, therefore, orbitals need to be lined up correctly, and reactants need to be held closely together. These postulates have been the basis of much recent investigation, particularly into biomimetic reactions involving molecular recognition and replication,⁸ and are seen as the factors underlying enzyme catalytic power.^{7b} Their effect is especially felt in intramolecular mode, leading to higher effective molarities,⁹ and it can be predicted that the future literature will provide increasing numbers of examples of intramolecular reactions which are without precedent in the intermolecular sense.

5-Exo-Trig Closures to CC Double Bonds: The Reversed Substituent Effect

Our investigations began with consideration of the (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol system **3**.¹⁰ Baldwin had shown¹¹ that ring closure to **4** did not occur in base (disallowed 5-endo-trig). The facile ring closure in acid was ascribed to protonation on carbonyl oxygen, which reduces the double bond character in the C2–C3 bond and allows the reaction to adopt the 5-exo-trig mode of closure (Scheme IV). The reaction cannot thus be viewed as an acid-catalyzed Michael addition. It seemed to us that, in view of this, the substituent effect

Scheme IV



of X should be the reverse of that expected for such a Michael reaction.¹⁰ Thus, rather than electron withdrawal from the double bond by X (EWG) in **5** facilitating reaction, electron donation by groups X (EDG) should stabilize the necessary canonical **6**. This reversed substituent effect was indeed observed. Trifluoroacetic acid (TFA) is a very convenient solvent in which to follow the reaction kinetics by NMR, at 35 °C. Moreover, it is a solvent in which species **3** and **4** are in equilibrium with one another, so one can be sure kinetic rather than thermodynamic factors are being considered. In this media, the ρ value is found to be -2.23 ,¹⁰ using σ^+ values which give a much better straight line than the use of σ values. This is also evidence for the involvement of structure **6** in the main reaction pathway, because here substituents X resonate directly with the positive center. For the mechanism of Scheme IV, we estimated¹⁰ that the ρ value for the preequilibrium is -5.4 (ρ_K). This gives a ρ value for the logarithmic rate constant k_f vs σ^+ of 3.2.

This may not be entirely the correct picture. A study of the reaction rates in deuterated solvent (TFA-*d*) gives a solvent kinetic isotope effect (SKIE) k_H/k_D of about 3.5.¹² This is in line with rate-limiting hydrogen transfer,¹³ not a protonation preequilibrium $\mathbf{3} \rightleftharpoons \mathbf{5}$, for which a value of less than unity is expected.¹⁴ That this is the case for TFA was verified by checking the SKIE for the Nazarov electrocyclozation reactions of compounds **7** in this medium, reacting *via* a preequilibrium protonation as shown in Scheme V. The observed value of k_H/k_D is found to be between 0.7 and 0.8, depending on X, while the ρ value from a σ^+ correlation is -0.7 .¹²

Scheme VI therefore seems to fit the experimental data better for cyclization of **3** in TFA than Scheme IV. The rates of reaction are $\sim 10\,000$ -fold less than for acid-catalyzed hydration of the correspondingly substituted styrenes,¹⁵ but the electron-withdrawing effect of the carbonyl group in the former case will drastically reduce electron availability in the double bond.

(6) Fife, T. H.; Bembi, R. *J. Org. Chem.* 1992, 57, 1295.

(7) (a) Woodward, R. B. quoted in: Sharpless, K. B. *Chem. Br.* 1986, 39. (b) For a general discussion of the importance of the proximity of the reacting centers in intramolecular reactions, see: Menger, F. M. *Acc. Chem. Res.* 1985, 18, 123; 1993, 26, 206. From another viewpoint, the best orientation in the substrate is that giving least strain on going to the transition state; see: Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* 1987, 109, 3698. Houk, K. N.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* 1990, 23, 107.

(8) See, for example: Rebek, J., Jr. *Acc. Chem. Res.* 1990, 23, 309.

(9) An effective molarity EM is the ratio of the rate constant, k , s^{-1} , for the intramolecular reaction, to the rate constant, k_2 , $M^{-1} s^{-1}$, for the corresponding intermolecular reaction.

(10) Ellis, G. W.; Johnson, C. D.; Rogers, D. N. *J. Chem. Soc., Chem. Commun.* 1982, 36. Ellis, G. W.; Johnson, C. D.; Rogers, D. N. *J. Am. Chem. Soc.* 1983, 105, 5090.

(11) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* 1977, 42, 3846.

(12) Brennan, C. M.; Hunt, I.; Jarvis, T. C.; Johnson, C. D.; McDonnell, P. D. *Can. J. Chem.* 1990, 68, 1780.

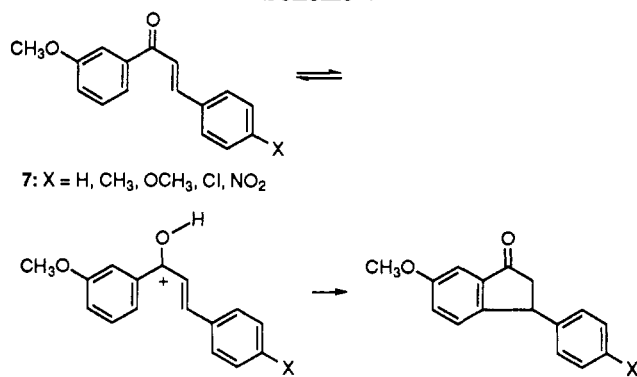
(13) Dannenberg, J. J.; Goldberg, B. J.; Barton, J. K.; Dill, K.; Weinwurzel, D. H.; Longas, M. O. *J. Am. Chem. Soc.* 1981, 103, 7764.

(14) (a) Noyce, D. S.; Jorgenson, M. J. *J. Am. Chem. Soc.* 1961, 83, 2525. (b) Noyce, D. S.; Jorgenson, M. J. *J. Am. Chem. Soc.* 1963, 85, 2420.

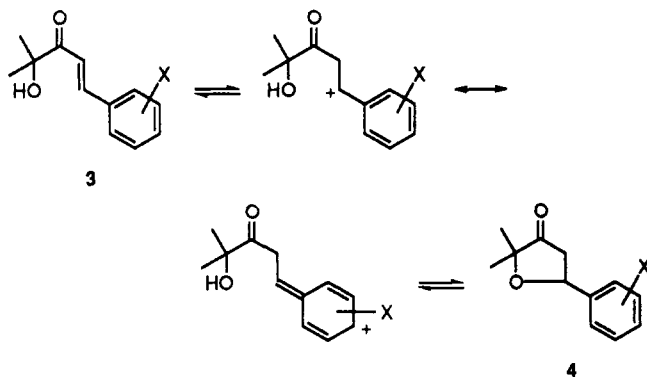
(c) Capon, B.; Kwok, F. C. *Tetrahedron* 1987, 43, 69. (d) Willi, A. V. In *Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1977; Vol. 8, p 21.

(15) Allen, A. D.; Rosenbaum, M.; Seto, N. O. L.; Tidwell, T. T. *J. Org. Chem.* 1982, 47, 4234.

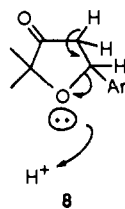
Scheme V



Scheme VI



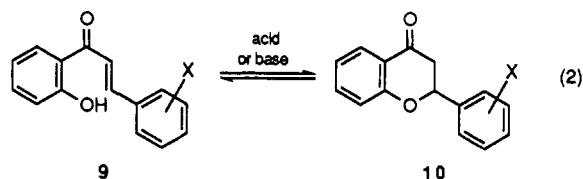
If the rate-limiting step is indeed CC double bond protonation, however, why is the ρ value not more negative, since it is -4.8^{15} for proton addition in TFA to styrenes? This may be due to significant protonation of the carbonyl group in **3** to give **5**, which now lies off the main reaction coordinate. This effect would be greatest for EDG's X, thus decelerating those members of the series more than for those where X is an EWG. But such a factor would probably be small, since the pK_a of compounds **5** would be a good deal more negative¹⁶ than the effective H_0 of TFA, about -3 .¹⁷ A possible explanation is that, due to the close proximity of the nucleophile to the protonating double bond, it attacks before that protonation is complete, while the proton is in flight. Thus the substituted phenyl ring never has to bear the extent of positive charge which it would in acid-catalyzed styrene hydration. The short lifetime of phenylethyl cations¹⁹ makes it conceivable that a suitably placed internal nucleophile will react before complete development of the positive charge. The reverse reaction shown in structure **8** is therefore not completely E1 but has a measure of E2 character.¹⁸



- (16) Gilbert, T. J.; Johnson, C. D. *J. Am. Chem. Soc.* **1974**, *96*, 5846.
 (17) Rochester, C. H. *Acidity Functions*; Academic Press: London, 1970; p 216.
 (18) (a) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818.
 (b) Capon, B.; Kwok, F. C. *Tetrahedron* **1987**, *43*, 69.
 (19) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.

5-Exo-Trig Closures to CC Double Bonds

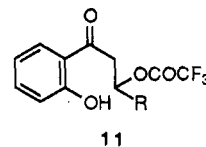
A relevant reaction, of biological importance, is the 2-hydroxychalcone 9-flavonone 10 system (eq 2). Both



X = H, *p*-OCH₃, *p*-CH₃, *p*-Cl, *p*-F, *p*-CN, *m*-OCH₃, *m*-CH₃, *m*-Cl, *m*-F

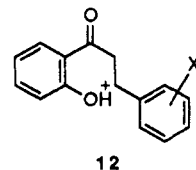
in acid and in base, the two species are in equilibrium, so again one can be sure that kinetic phenomena are being observed. Here the reaction is an allowed 6-endo-trig, but Baldwin has shown¹¹ that this mode is "not so allowed" as the 6-exo-trig. Models show that, even with a connecting chain of sp^3 -hybridized carbons between nucleophile and electrophile, the correct trajectory is only just possible. In the sp^2 -hybridized system of the hydroxychalcones **9**, with wider bond angles, together with the tendency of the conjugated system to stay in the plane, the nucleophile is held well off the desired trajectory.

One way to circumvent Baldwin's rules for trig closures would be by intermolecular nucleophilic attack by the solvent (or a component thereof) on the unsaturated system, followed by an allowed exo-tet expulsion to give the product. This route could involve intermediate **11** in the case of TFA, and such adducts have been detected by NMR for reaction mixtures in TFA where R = Me, *t*-Bu, although not when R = aryl.¹²



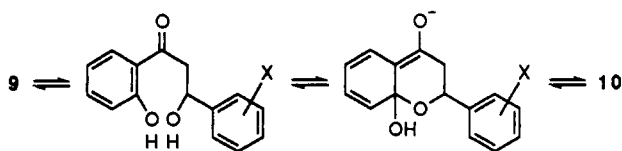
Ring closures of molecules **3** and **9**, however, are not appreciably different in 3% MeSO₃H/CDCl₃ and in TFA:¹² rate constants for the closure of **9**, X = *p*-CH₃, are 10.6×10^{-6} and 8.14×10^{-6} s⁻¹, respectively, for the two media. Since the former system contains a weaker nucleophile than the latter, it would seem probable that these adducts do not lie on the main reaction thoroughfare.

In any event, the characteristics of closure of system **9** in TFA match those of **3** very closely.^{12,20} The ρ value is -2.43 , using σ^+ values which give the best correlation, and the SKIE k_H/k_D is around 3. The conclusion must be that the rate-limiting step is again protonation of the CC double bond to give **12**, in which there is again probably a small amount of interaction between the nucleophile and the carbocation to explain the reduced negativity of the ρ value.

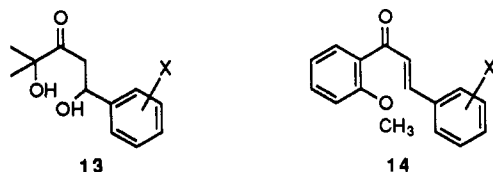


- (20) Bradley, J. P.; Jarvis, T. C.; Johnson, C. D.; McDonnell, P. D.; Weatherstone, T. A. P. *Tetrahedron Lett.* **1983**, *28*, 2851.

Scheme VII



One important difference exists, however, between the equilibrium $9 \rightleftharpoons 10$ and $3 \rightleftharpoons 4$. The former is readily set up in basic media; the latter not at all.¹¹ An attractive proposition is that the former involves intermolecular attack of nucleophile on the hydroxychalcone, followed by intramolecular nucleophilic substitution (Scheme VII). The latter step is not open to intermediate 13. An early experiment that we carried



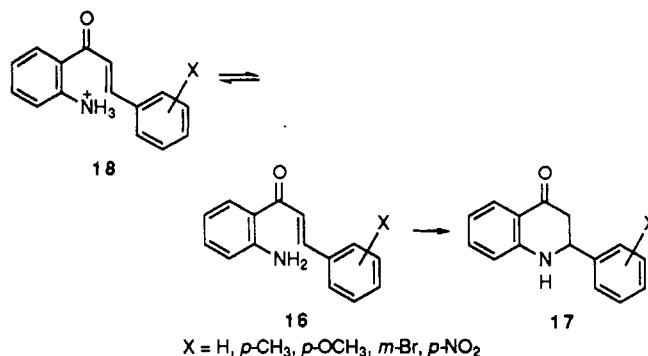
out that appeared to vindicate this was to show that **9** could not be converted to **10** in *t*-BuOK/*t*-BuOH/THF, or in sodium hydride in DMSO, or in sodium hydride in THF (all reactants carefully dried); these are strongly basic media but with no nucleophilic propensities. Doubt was thrown on this conclusion by later work which showed that the equilibrium between **9** and **10** is very much influenced by base concentration, the hydroxychalcone form being increasingly favored over flavanone in more basic media: thus $[10]/[9] = 7.7, 2.4, 0.34,$ and 0.078 in $0.00023, 0.00036, 0.0034,$ and 0.0057 M NaOEt/EtOH at 25°C . Thus on the one hand, the clear-cut definition between equilibrium and kinetic phenomena provided in both acid and basic media for the systems we have studied makes Baldwin's injunction that his rules must be applied to kinetic results easy to follow. On the other hand, it can make obtaining that data experimentally difficult.

The explanation afforded by Scheme VII is rendered further unlikely, first because calculation indicates the reaction would not be fast enough to explain the overall rate of reaction,²¹ and second because model derivative **14** does not ring close under the same conditions in base. Probably the explanation is that the 6-endo-trig reaction, while indicated to be "forbidden" by model building, particularly for system **9**, is not so disallowed as for the 5-endo-trig case, system **3**. This becomes more convincing if one accepts Menger's suggestion that one is considering reaction windows and cones of allowed trajectories rather than precise trajectories.²² A further problem with system **9** in contrast to **3** is that the conjugation between the nucleophilic site and the electrophilic site enables one to influence the other through the linking chain as well as through space. This effect is damped out in **3** by the intervening sp^3 carbon

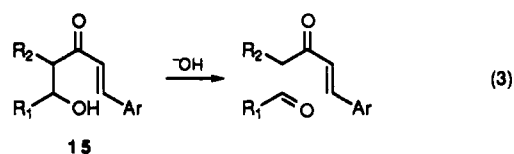
(21) Button, R. G.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. II* 1992, 1571. In this paper, it is also clearly demonstrated that, in aqueous acid, compounds **9** ring close *via* carbonyl protonation. Dr. Taylor suggests that our SKIE's of greater than unity in TFA could be explained by rate-determining enolization, but this would not explain the substituent effect (see arguments in ref 10). There seems to be no doubt of Button and Taylor's detailed mechanistic analysis, and we are reasonably certain of ours: this appears to be a case of mechanistic change induced by medium change. We thank Dr. Taylor for detailed discussions on these and other relevant issues.

(22) Menger, F. M. *Tetrahedron* 1983, 39, 1013.

Scheme VIII

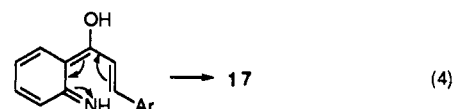


atom bearing the two methyl groups. A possible system to investigate the influence of this effect might be that shown in **15**, provided reverse Aldol reaction does not occur preferentially as shown in eq 3. This however may not be a difficulty as there is no evidence for such a reaction in the hydroxychalcones, although experimental evidence exists for the formation of Michael adducts in both acid¹² and basic media.¹¹



The O-protonated form of **9** can also yield **10** in a 6-electron electrocyclic reaction, and some of this character in the transition state may thus lower the reaction barrier for the acid-catalyzed reaction.

The aminochalcones **16** ring close to 2-aryl-1,2,3,4-tetrahydroquinolines **17** in TFA (Scheme VIII). NMR studies reveal that this reaction proceeds to completion,¹² and compounds **17** can be isolated in excellent yields. This procedure thus appears to be a very good preparative route to bicyclics **17**. Curiously enough, rates of reaction are about the same as for the hydroxychalcones **9** under the same conditions: e.g., in TFA, 35°C : $10^6 k_{\text{obs}}$ (s^{-1}) is 1.92 for **9** ($\text{X} = \text{H}$) and 25 for **16** ($\text{X} = \text{H}$), despite the fact that structure **16** represents a minority species (probably by a factor of about 10^5 , if we estimate a $\text{p}K_{\text{a}}$ for **18** of about 2, and given that the effective H_0 of TFA is -3), while majority species **18** is unreactive to ring closure. This circumstance is under investigation; an electrocyclic mechanism (eq 4) cannot be ruled out.

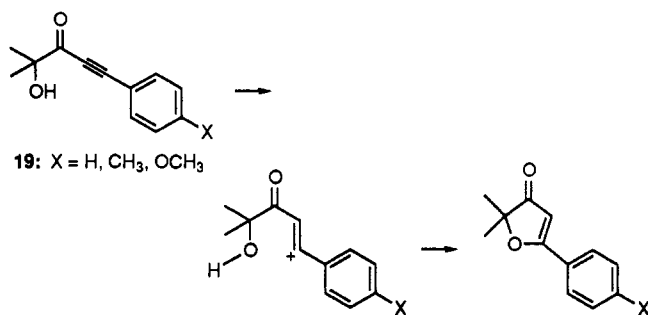


5- and 6-Exo-Dig Closures: The Importance of Proximity Effects

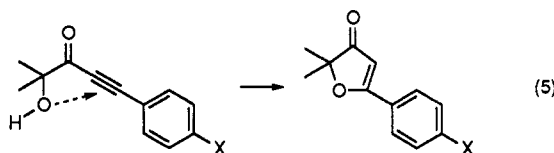
Ring closure to triple bond systems, dig ring closure,^{2,3} also reveals intriguing features. A similar mechanistic picture emerges²³ for the ring closure of the 2-hydroxy-2-methyl-5-arylpent-4-yn-3-ones **19** (Scheme IX), in TFA solution at 35°C , to that of the corresponding endo-trig closure of **3** and **9**. A ρ value of -4.0 and a SKIE of about 3 suggest rate-determining protonation

(23) Brennan, C. M.; Johnson, C. D.; McDonnell, P. D. *J. Chem. Soc., Perkin Trans. II* 1989, 957.

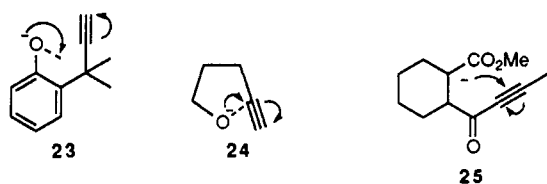
Scheme IX



of the triple bond,²⁴ but in this case the more negative ρ value suggests there is little intervention of nucleophile attack during the rate-limiting step. This is reasonable, because in the transition state for proton addition the carbon atom acquiring the positive charge will be further away from the nucleophile than in the transition states resulting from rate-determining proton addition to 3 and 9. This result discloses nothing about the preferred approach of a nucleophile to the triple bond, but ready base-catalyzed closure of system 19¹¹ reveals the allowedness of the 5-endo-dig mode (eq 5), involving acute



angle (60°) attack to the triple bond. Results^{23,25} in base (sodium methoxide/methanol) also show that, in the case of the closure of 1-(2-hydroxyphenyl)-3-arylprop-2-yn-1-ones 20, shown in Scheme X, to give flavones 21 and aurones 22, the allowedness of the 6-endo- and 5-exo-dig closures as predicted by Baldwin's rules has a high measure of experimental validity. This is in line with the observance of the allowed 5-exo-dig closures of systems 23,²⁶ 24,²⁷ and 25.²⁸ These results



flow in countercurrent to the predicted preferences for an obtuse approach to the triple bond (whether C≡C, C≡N, or ⁺N≡N)²⁹⁻³¹ as in the approach to a double bond, but of course both trajectories may be allowed,

(24) (a) Noyce, D. S.; DeBruin, K. E. *J. Am. Chem. Soc.* 1968, 20, 372. These workers gave ρ and SKIE of -4.2 and 2.0-3.9, respectively, for hydration of substituted phenylbenzoylacetylenes in H₂SO₄/H₂O. (b) Reference 13 gives 4.33 for the SKIE for rate of addition of TFA to (*E*)-but-2-ene.

(25) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* 1986, 51, 4432.

(26) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. II* 1984, 1269.

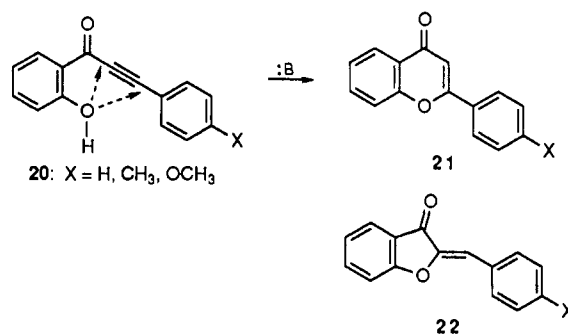
(27) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* 1981, 103, 7559.

(28) (a) Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* 1986, 27, 5451. (b) Lavallée, J.-F.; Berthiaume, G.; Deslongchamps, P. *Tetrahedron Lett.* 1986, 27, 5455. (c) See also CC bond formation by acute angle approach to the nitrilium bond: Luedtke, G.; Westling, M.; Livinghouse, T. *Tetrahedron* 1992, 48, 2209.

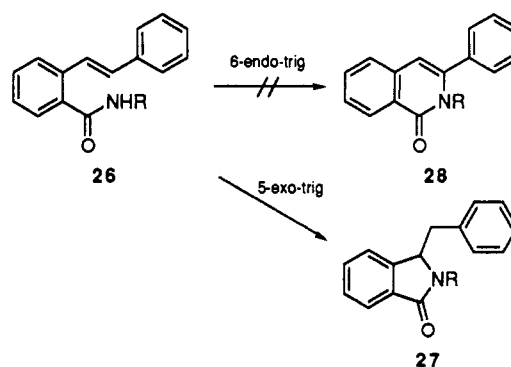
(29) Eisenstein, O.; Procter, G.; Dunitz, J. D. *Helv. Chim. Acta* 1978, 61, 2538.

(30) Wallis, J. D.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* 1984, 671.

Scheme X

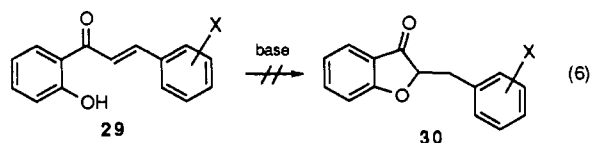


Scheme XI



or perhaps the triple bond has an exceptionally large "window".²² These reactions, proceeding *via* the intermediacy of a vinylic carbanion, reveal in their high effective molarity EM (on which only a lower limit can be set, because such reactions would be undetectable in an intermolecular sense) the power of the proximity effect. The principles of orbital overlap require that the carbonyl group cannot be involved in facilitating the reaction other than through its inductive effect. In fact, in the systems of 23 and 24 no carbonyl group is present and even the favorable influence of its inductive effect on the stability of the vinyl carbanion is eschewed in the formation of 22.

A remarkable observation (Scheme XI), vindicating the power of Baldwin's rules and proximity effects in intramolecular reactivity, is that of the ring closure of *N*-alkyl-(*E*)-stilbene-2-carboxamides 26 in basic conditions yielding benzophthalimidines 27 rather than the dihydroisocarbostyryls 28.³² This result, allied to the formation of aurone 22 as shown in Scheme X above, suggests that 2-hydroxychalcone should yield some dihydroaurone 30 in basic conditions *via* the alternative preferred conformer 29 (eq 6), but flavonone products

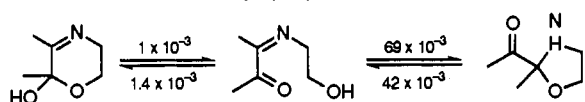


were all we could detect. This comparison may not be entirely fair, however, because formation of 28 from 26 requires disruption of aromaticity to delocalize negative

(31) (a) Perkins, M. J.; Wong, P. C.; Barrett, J.; Shalival, G. *J. Org. Chem.* 1981, 46, 2196. (b) Dykstra, C. E.; Ardvengo, A. J.; Fukunaga, F. *T. J. Am. Chem. Soc.* 1978, 100, 6007. (c) Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* 1979, 101, 1340. (d) Houk, K. N.; Strozier, R. W.; Rozeboom, M. D.; Nagaze, S. *J. Am. Chem. Soc.* 1982, 104, 323. (e) Elliot, R. J.; Richards, W. G. *J. Mol. Struct. Theochem.* 1982, 87, 247.

(32) Napolitano, E.; Fiaschi, R.; Marsili, A. *Tetrahedron Lett.* 1983, 24, 1319.

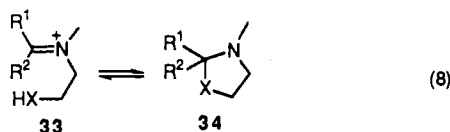
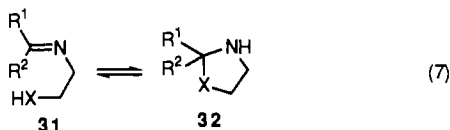
Scheme XII



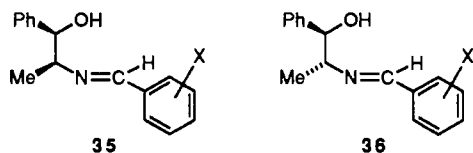
charge to a carbonyl and this would raise the energy, apparently enough to promote the 5-exo-trig alternative.

5-Endo-Trig Closures to CN Double Bonds

Considerable interest has also been shown in 5-endo-trig approaches to imino- and iminium-type double bonds, and here the formality of Baldwin's rules collapses completely.³³ Equilibria of the general form of $31 \rightleftharpoons 32$ (eq 7)^{33,34} and $33 \rightleftharpoons 34$ (eq 8)³⁴ are set up at room temperature within the time span of the NMR experiment, for a variety of different structures and different solvents. For the ring-chain tautomerism of



5,6-dihydro-2-hydroxy-2,3-dimethyl-2H-1,4-oxazine (Scheme XII),³⁵ rate constants determined by NMR are as indicated, the "disallowed" 5-endo-trig reaction being faster than the "allowed" 6-exo-trig. In another competitive situation, however, that of Scheme XIII, the only product is found to be that arising by 6-exo-trig reaction.³⁶ For the tautomerism of 1,3-oxazolidines derived from norephedrine and norpseudoephedrine, 35 and 36 , the equilibria were established relatively slowly in some cases.³⁷ No rate data have been



calculated, but, significantly, the closure of the *p*-(dimethylamino) compounds ($X = p\text{-NMe}_2$) was said to be much faster than for the nitro compounds ($X =$

(33) (a) Astudillo, M. E. A.; Chokotho, N. C. J.; Jarvis, T. C.; Johnson, C. D.; Lewis, C. C.; McDonnell, P. D. *Tetrahedron* 1985, 41, 5919.

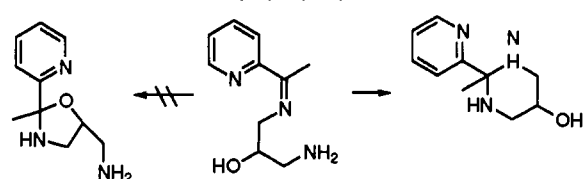
(34) Equation 7, $X = \text{O}$ or NH : (a) Paukstelis, J. V.; Hammaker, R. M. *Tetrahedron Lett.* 1968, 3557. (b) Paukstelis, J. V.; Lambing, L. L. *Tetrahedron Lett.* 1970, 299. (c) Agami, C.; Rizk, T. *Tetrahedron* 1985, 41, 537. (d) Riddell, F. G.; Arumugan, S.; Fülöp, F.; Bernath, G. *Tetrahedron* 1992, 48, 4979. Equation 7, $X = \text{S}$: (e) Fülöp, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* 1990, 46, 6545. Equation 7, $X = \text{-C-}$: (f) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* 1980, 648. (g) Goetz, F. J.; Hirsch, J. A.; Augustine, R. L. *J. Org. Chem.* 1983, 48, 2468. Equation 8, $X = \text{O}$ or NH : (h) Filer, C. N.; Granchelli, F. E.; Perri, P.; Neumeyer, J. L. *J. Org. Chem.* 1979, 44, 285. (i) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* 1979, 101, 492. (j) McClelland, R. A.; Somani, R. *J. Am. Chem. Soc.* 1981, 103, 4345. (k) Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc.* 1980, 102, 3588. (l) Lambert, J. B.; Wang, G.-t.; Huseland, D. E.; Takiff, L. C. *J. Org. Chem.* 1987, 52, 68. (m) Bunting, J. W.; Moors, R. G. *Tetrahedron Lett.* 1987, 28, 3915.

(35) Alcaide, B.; Plumet, J.; Rodriguez-Campos, I. M.; Garcia-Blanco, S.; Martinez-Carrera, S. *J. Org. Chem.* 1992, 57, 2446.

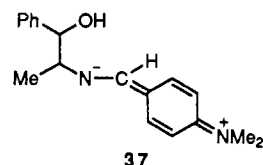
(36) Personal communication from Dr. E. L. Fenton.

(37) Fülöp, F.; Bernath, G.; Mattinen, J.; Pihlaja, K. *Tetrahedron* 1989, 45, 4317.

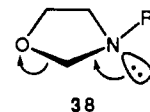
Scheme XIII



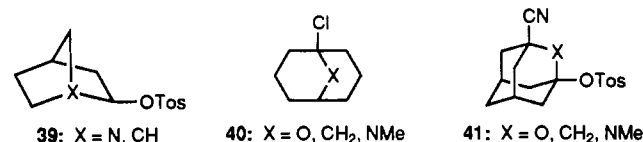
p-NO₂) even though the ring-closed species are much more favored in the latter than the former cases, as revealed by equilibrium constants. This suggests that the reaction rate is not increased by electron withdrawal by the aryl group, as expected for the intermolecular equivalent of the reaction, but indicates again the importance of the reversed substituent effect; the contribution of the canonical form 37 is still valued for facilitating reaction by an exo mode.



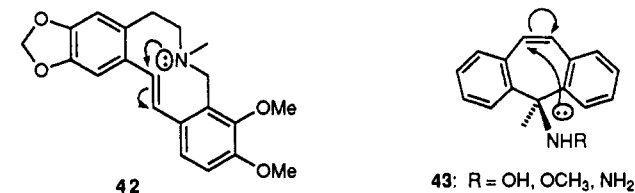
In general though, viewed, as previously recommended, from the point of view of the reverse reaction 38, it's as though the stereoelectronic requirements of



the nitrogen lone pair are less stringent than in other cases. Kirby has reviewed³⁸ examples of this type where the same conclusion may be drawn: S_N1 hydrolysis of compounds 39,³⁹ 40,⁴⁰ and 41⁴¹ shows stabilization for the N-containing transition-state carbocation species in excess of that for the carbocyclic systems and, for 40 and 41, the O-containing analogues. Moreover, unac-



tivated CC double bonds may be attacked by nitrogen nucleophiles as in 42⁴² and 43,⁴³ even though orbital-governed trajectories would appear to rule out reaction.



This model of a diffuse lone pair on nitrogen and the

(38) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983; p 125.

(39) Gassman, P. G.; Cryberg, R. L.; Shudo, K. *J. Am. Chem. Soc.* 1972, 94, 7600.

(40) Krabbenhoft, H. O.; Wiseman, J. R.; Quinn, C. B. *J. Am. Chem. Soc.* 1974, 96, 258.

(41) Meyer, W. P.; Martin, J. C. *J. Am. Chem. Soc.* 1976, 98, 1231.

(42) Kirby, A. J.; Logan, C. J. *J. Chem. Soc., Perkin Trans. II* 1978, 642.

(43) Lamanec, T. R.; Bender, D. R.; Demarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* 1988, 53, 1768.

concomitant picture of a permitted wide-angle approach of a nitrogen nucleophile to an electrophilic center is in sharp contrast to other studies. These clearly suggest that in the case of elimination reactions of hydrazonium salts⁴⁴ there is "experimental and theoretical evidence for a large stereoelectronic effect of nitrogen", due to "the localization of the lone pair on nitrogen to well-defined areas of space in contrast to oxygen".

One possible source of complication could be radical involvement in these ring closures, but we find radical scavengers have no influence on the rate of reactions shown in Scheme IV and eq 2, and ESR spectra of these two reactions and that of eq 7 give no evidence of the involvement of unpaired electron species.⁴⁵

Summary: A Fluid Situation

Lines of inquiry in physical organic chemistry opened up by consideration of Baldwin's rules thus do not lead

(44) (a) Nguyen, M. T.; Clarke, L. F.; Hegarty, A. F. *J. Org. Chem.* 1990, 55, 6177. See also: (b) Hegarty, A. F.; Mullane, M. *J. Chem. Soc., Perkin Trans. II* 1986, 995. Nevertheless, this ambiguous situation with regard to nitrogen stereoelectronic effects makes it necessary to view generalized stereoelectronic concepts based on arguments involving nitrogen with caution; see: (c) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* 1993 115, 3140.

(45) For these experiments we thank Dr. Myles R. Cheesman.

(46) Beak, P. *Acc. Chem. Res.* 1992, 25, 215.

(47) Sinnott, M. L. *Adv. Phys. Org. Chem.* 1988, 24, 113.

to well-defined conclusions. Although experiments on the tetrahedral approach to a saturated carbon of 180° suggest this angle requirement is extremely exact,⁴⁶ in general Menger's concept²² of reaction windows which in some cases may be quite wide, rather than precise trajectories seems entirely reasonable. In the limit the whole theory of stereoelectronic control may be questioned,⁴⁷ and even if one does not share the extreme view of an alternative explanation in terms of least nuclear motion,⁴⁷ the most wholehearted exponent of stereoelectronic effects must admit that they have a somewhat disconcerting "now you see it, now you don't" character. This adds to the appeal, but also to the frustration, of their investigation and makes their precise definition a matter of ongoing debate and experiment, for which each system must be treated on its own merits. Down these uncertain paths, Baldwin's rules indicate directions which in certain instances may turn out to be false. In this Account we hope to have shown, however, that a great deal may still be learned from the rules, as much in their breach as in their observance.

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