Rules for Ring Closure

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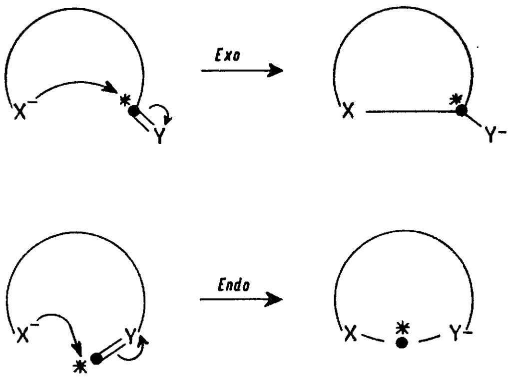
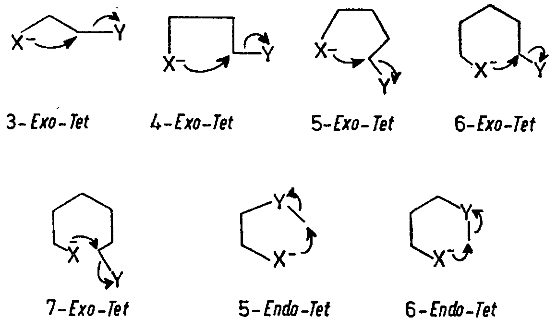
Summary Three rules which have been found useful, on an empirical basis, to predict the *relative facility* of ring forming reactions are presented; the physical bases of such rules are described.

RING-FORMING reactions are important and common processes in organic chemistry. I now adumbrate a set of simple rules which I have found useful in predicting the relative facility of different ring closures. I believe these will be useful to organic chemists, especially in planning syntheses. Also these rules indicate certain experiments which may be helpful to define more precisely their limits. The rules are of a stereochemical nature and it is likely that unambiguous cases of all the possibilities I will discuss are as yet unknown.



SCHEME 1



SCHEME 2: Tetrahedral

I will describe a ring-forming process with the prefix *Exo*, when the breaking bond is exocyclic to the *smallest so formed ring* and *Endo* correspondingly, as in Scheme 1.

Further, I shall use a numerical prefix to describe the ring size, being the number of atoms constituting the skeleton of the cycle, and finally, the suffixes *Tet*, *Trig*, and *Dig*, to indicate the geometry of the carbon atom undergoing the ring-closure reaction (asterisk, Scheme 1). The suffixes refer to tetrahedral, trigonal, and digonal carbon atoms respectively. The various possibilities are shown in Schemes 2—4.

The Rules are as follows:—

Rule 1: *Tetrahedral Systems*: Scheme 2.

(a) 3 to 7-*Exo-Tet* are all favoured[1] processes with many literature precedents;[2]

(b) 5 to 6-*Endo-Tet* are disfavoured.[3]

Rule 2: *Trigonal Systems*: Scheme 3.

(a) 3 to 7-*Exo-Trig* are all favoured processes with many literature precedents;[4]

(b) 3 to 5-*Endo-Trig* are disfavoured;[5] 6 to 7-*Endo-Trig* are favoured.

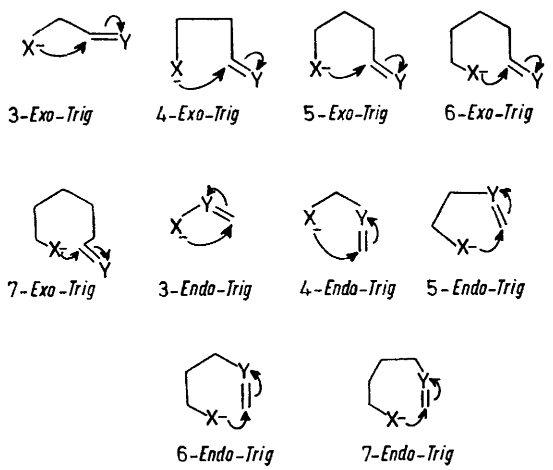
Rule 3: *Digonal Systems*: Scheme 4.

(a) 3 to 4-*Exo-Dig* are disfavoured processes; 5 to 7-*Exo-Dig* are favoured;[6]

(b) 3 to 7-*Endo-Dig* are favoured.[7]

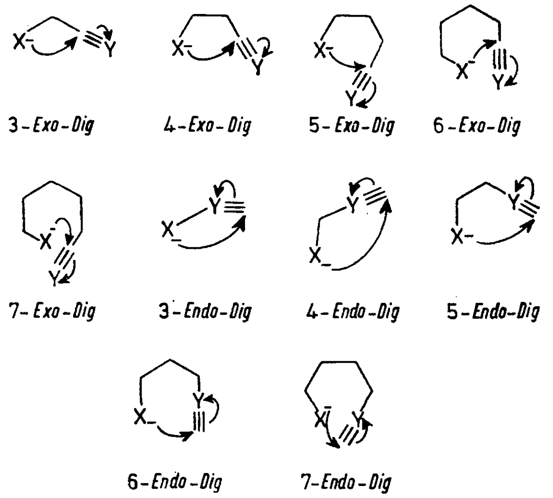
As a consequence of the larger atomic radii and bond distances in atoms of the second Periodic row the geometric restraints on disfavoured ring closures may be bypassed.[5] Therefore a condition to the application of these rules is that X *must be a first row element* (Scheme 1—4).

The physical bases of the rules lie in the stereochemical requirements of the transition states for the various tetrahedral, trigonal, and digonal ring closure processes. Since the linking chain restricts the relative motion of the terminal groups X and Y (Scheme 1) then the nature and length of this chain, and hence the ring size, will determine whether X and Y can attain the required transition-state geometry and hence the facility, or otherwise, of ring closure. For closures to a carbon atom (asterisk, Scheme 1) the favoured paths to the transition states are represented



SCHEME 3: Trigonal

by Figures 1—3. Thus (**1**) → (**2**) represents the classical and well established Walden inversion of the S_N2 reaction. The trigonal situation, (**3**) → (**4**), is supported by recent work of Dunitz and Bürgi[8] on additions to the carbonyl group. The digonal case, (**5**) → (**6**), is supported by the general predominance of *Endo*-ring closures in digonal



SCHEME 4: Digonal

systems[9] as well as by some recent *X*-ray work.[10] In each case, Figures 1—3, the subtended angle α between the three interacting atoms is maintained during the reaction pathway, becoming the angle between these atoms in the product.[11]

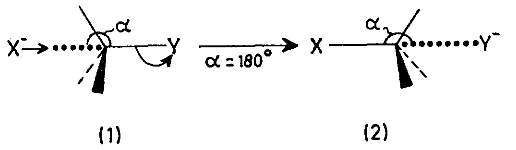


FIGURE 1: *Tet.*

Thus the *favoured* ring closures are those in which the length and nature of the linking chain enables the terminal atoms to achieve the required trajectories, Figures 1—3, to form the final ring bond.[12] The *disfavoured* cases in fact require severe distortion of bond angles and distances to achieve such trajectories, consequently alternative reaction pathways, if available, will dominate and the desired ring closure will be difficult.

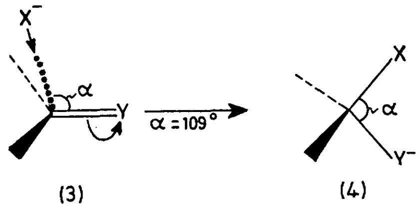


FIGURE 2: *Trig.*

Although this treatment has discussed nucleophilic closures (X^- in Scheme 1), it also applies to homolytic and cationic processes. Thus the radical (**7**) closes only by the 3-*Exo-Trig* and not the 4-*Endo-Trig* mode. Similarly (**8**) yields preferentially the cyclopentylmethyl radical by a 5-*Exo-Trig* closure rather than the 6-*Endo-Trig* path. In

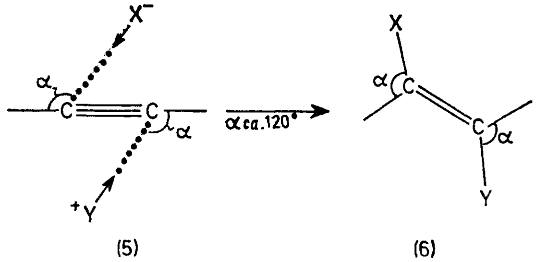
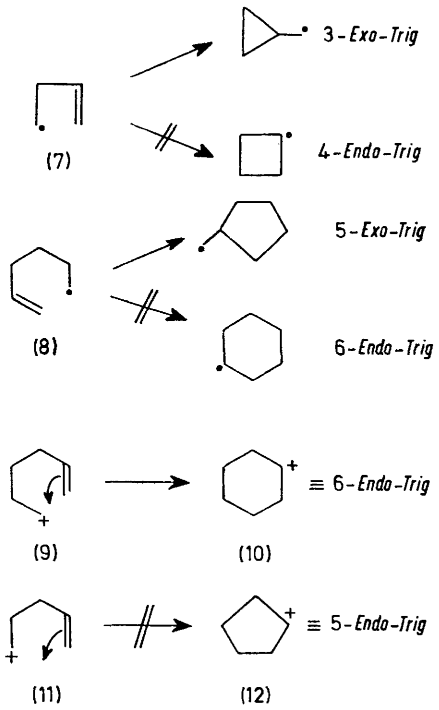
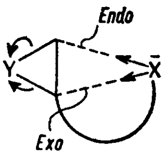


FIGURE 3: *Dig.*



both cases the thermodynamically less stable product is formed.[13] For cationic closures the equivalent of the 6-*Endo-Trig* reaction is well known, *i.e.*, (**9**) → (**10**), whereas the 5-*Endo-Trig* case, (**11**) → (**12**), is, for simple cations, not known.[14]



(**13**)

The rules for opening three-membered rings to form cyclic structures (**13**), seem to lie between those for tetrahedral and trigonal systems, generally preferring *Exo*-modes.[15]

It is hoped that these ideas will be useful to synthetic chemists in both planning syntheses and analysis of unsuccessful constructs.

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[1] The words *favoured* and *disfavoured* in these Rules were chosen to imply a facility or otherwise of ring closure. Any generalization about a reaction pathway is necessarily limited by reaction conditions, *e.g.*, at very high temperatures or under photochemical activation sufficient vibrational energy may be available to achieve otherwise sterically inaccessible conformations. For this reason a *disfavoured* ring closure is not an impossible reaction, merely a process which may not compete effectively with alternative *favoured* ring closures or other reaction pathways.

[2] A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1968, 66.

[3] L. Tenud, S. Faroog, J. Seible, and A. Eschenmoser, *Helv. Chim. Acta.*, 1970, **53**, 2059. Although 5-*Endo-Tet* and 6-*Endo-Tet* are not formally ring closures, they were included for completeness. They may be so regarded in systems in which the breaking *endo* bond is part of an existing ring structure, leading to a ring expansion.

[4] The literature is replete with examples of **3** to 7-*Exo-Trig* reactions; *e.g.*, all lactonisations of ω-hydroxy acids or esters are of this type, as are the formation of lactams from ω-amino acids and their derivatives and also the Dieckmann cyclisation of diesters.

[5] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, following communication.

[6] Some examples of *Exo*-digonal closures are as follows: (a) 5-*Exo-Dig*: S. A. Kandil and R. E. Dessy, *J. Amer. Chem. Soc.*, 1966, **88**, 3027; (b) 6-*Exo-Dig*: R. E. Dillard and N. R. Easton, *J. Org. Chem.*, 1966, **31**, 122.

[7] Examples of *Endo*-digonal closures: (a) 4-*Endo-Dig*: G. L. Hekkert and W. Drenth, *Rec. Trav. Chim.*, 1961, **80**, 1285; (b) 5-*Endo-Dig*: ref. 6(a); (c) 6-*Endo-Dig*: A. T. Bottini, F. P. Carson, and E. F. Bottner, *J. Org. Chem.*, 1965, **30**, 2988; (d) 7-*Endo-Dig*: ref. 6(b). I have not found examples of 3-*Endo-Dig* and 7-*Exo-Dig* closures.

[8] H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.

[9] Tetrahedral and trigonal ring closures generally proceed by the *Exo*-modes, whereas the digonal closures are generally of the *Endo*-type. Furthermore, the digonal trajectory, Figure **3**, α *ca.* 120°, affords explanation for the electrocyclic reactions of triple bonds which previously seemed to present geometric difficulties, *e.g.*, the Cope reaction of hex-1-en-5-yne.

[10] (a) G. Wegner, *Polymer Letters*, 1971, **9**, 133; (b) R. H. Baughman, *J. Appl. Phys.*, 1972, **43**, 4362.

[11] This angular relationship is to be expected in interactions of p-type orbitals to maximise orbital overlap.

[12] The favoured paths, Figures 1—**3**, imply inversions at the reacting carbon atom, as has been stated. For this reason, these Rules may not apply to concerted electrocyclic processes in which geometric changes other than inversions are often observed. I thank Professor R. B. Woodward for pointing this out to me.

[13] (a) A. L. J. Beckwith, 'Essays in Free Radical Chemistry,' *Chem. Soc. Special Publ. No.* 24, 1970, 239; (b) M. Julia, *Pure Appl. Chem.*, 1967, **15**, 167.

[14] (a) W. S. Johnson, *Angew. Chem.*, 1976, **88**, 33; (b) W. D. Closson and S. A. Roman, *Tetrahedron Letters*, 1966, 6015. The closure of acylium ions from γ,δ-unsaturated acids to cyclopentenones, formally a 5-*Endo-Trig* process, is well known, *cf.*, P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, 1972, **94**, 1014 and also M. F. Semmelhack, J. S. Foos, and S. Katz, *ibid.*, 1973, **95**, 7325; however, this may result from the special stereoelectronic properties of the approach of cations to olefins.

[15] (a) G. Stork and J. F. Cohen, *J. Amer. Chem. Soc.*, 1974, **96**, 5270; (b) *cf.* ref. **3**.