Approach Vector Analysis: A Stereochemical Approach to Reactivity

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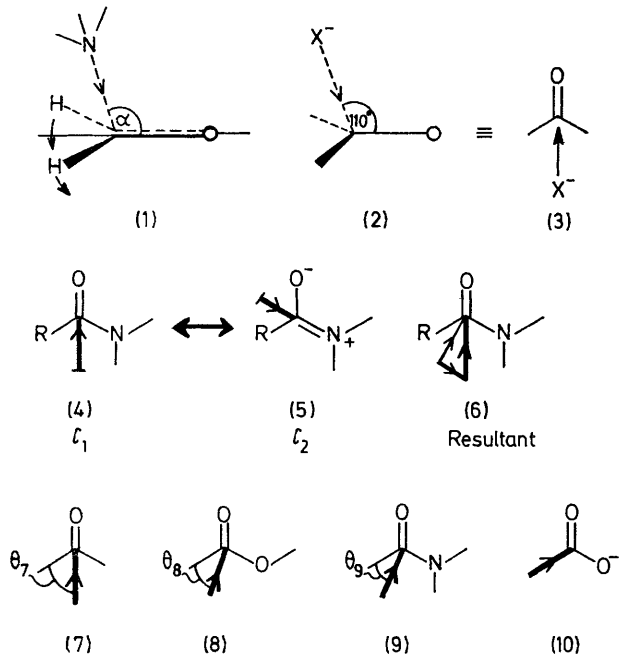
Summary A method of approximating preferred nucleophilic approach geometries to unsaturated functions, based on classical Lewis resonance structures, is described; the application of this *approach vector analysis method* to the stereochemistry of enone reductions is explained.

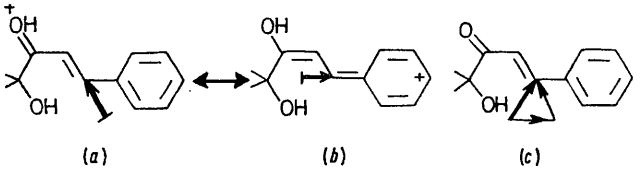
RECENTLY evidence has been obtained, both experimental[1,2] and theoretical,[3] which indicates that nucleophilic attack on the carbonyl group proceeds with stringent stereochemical restraints. Thus, for example, in the reaction of ammonia and formaldehyde, at a separation of nitrogen and carbon atoms of 1·99 Å, the angle α (N · · C · · O) was found experimentally to be 107 $\pm$ 5°,[4] as in (**1**), the nitrogen atom being in a plane containing the C–O bond and orthogonal to the molecular plane. We have used an approximation of this result, as (**2**), and its projection (**3**) based on inversions in the bent or banana bond model of unsaturation[5] to draw up a set of rules or guidelines for the closure of rings,[6] and have provided some experimental evidence for support of this method.[7]



SCHEME 1. $[\theta_7 > \theta_8 > \theta_9; \theta_{10} = 0]$

I now extend this scheme to other types of unsaturated function, to reveal a simple method of assessing the stereochemical restraints in an approximate fashion and also to provide some initial evidence for the utility of this approach.

The method may be exemplified by the general amide function, whose electronic structure is described by the resonance structures (**4**) and (**5**) with weightings C_1 and C_2 ($C_1 > C_2$). By treating structure (**4**) as a ketone, as (**3**), I assign an approach direction shown in projection as (**4**) with weight C_1. Similarly I treat the immonium structure (**5**) with an approach direction, weight C_2, also shown in projection (**5**). Now using a simple vector summation I derive a resultant approach direction or *approach vector* as in (**6**). This analysis indicates that the approach vector for nucleophilic attack on an amide function is shifted from the symmetric disposition as in a ketone (**3**) to a position in space closer to the residue R. In this approximate treatment, the angle subtended to the plane of the amide by the resultant approach vector is taken to be *ca.* 110° as in the ketone (**2**). A list of approximate approach vectors for different common functionalities in projection is shown in Scheme 1, in order of decreasing angle θ, the projected angle of the approach vector to the carbon–carbon bond bearing the substituent.[8]



SCHEME 2

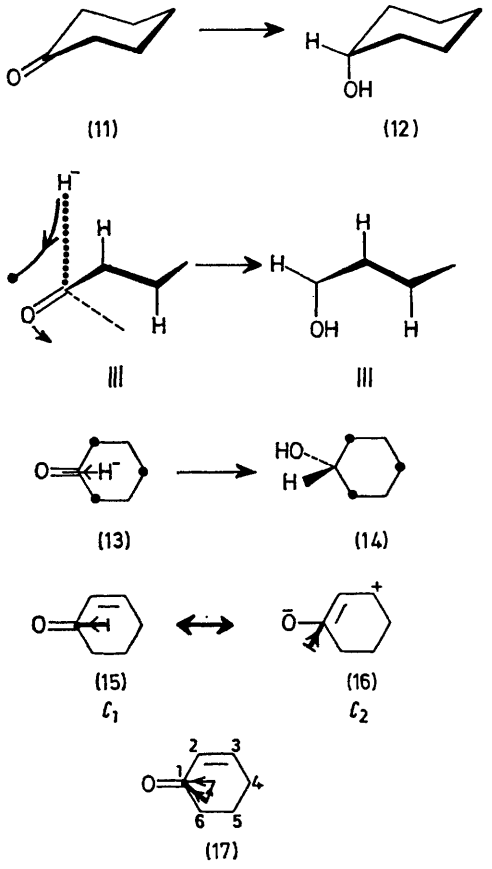
How is this approach vector analysis useful to the organic chemist? It is useful as a refinement to the ideas regarding closure of rings.[7] Herein the approach vector of a protonated β-phenyl enone, the result of combinations of two structures *a* and *b*, enabled closure to the furanone to occur in acid, a reaction which did not occur in base, *cf.* Scheme 2. I will now show how it is useful for example in correlating the stereochemistry of reduction of cyclic enones.

TABLE

Compound	6q-ax[a]	5q-ax[a]	OH Configuration P[b]	OH Configuration F[b]
(**18**)	β-Me	α-H	1β	1β (> 70) [1α (65)]
(**19**)	α-H	β-H	4α	4α (> 95) [4β (> 85)]
(**20**)	α-H	β-H	6α	6α (> 90) [6β (> 90)]
(**21**)	β-H	α-H	3β	3β (70—80) [3β (91)]
(**22**)	β-H	α-H	3β	3β (70—90) [3β (91)]
(**23**)	β-H	α-H	7β	7β (70—75) [7α (55)]
(**24**)	α-H	β-Me	6β	6β (100) [6β (99)]
(**25**)	α-H	β-Me	11β	11β (100) [11β (100)]
(**26**)	α-H	β-H	6α	6α (90) [6β (100)]
(**27**)	β-H	α-H	β	β (100)
(**28**)	α-H	β-H	α	α (82)
(**29**)	β-H	α-H	β	β (95)
(**30**)	β-Me	α-H	β	β (70)
(**31**)	β-Me	α-H	β	β (main)
(**32**)	β-CH_2	α-H	β	β (80)
(**33**)	α-(OPh)	—	α	α (83)

[a] 6q-ax and 5q-ax refer to the configuration (α or β) of quasi-axial substituents at C-6 and C-5 in formula (**17**). [b] P = predicted, F = found (%). The configuration (%) of the reduction product of the corresponding saturated ketone is given in square brackets, where known.

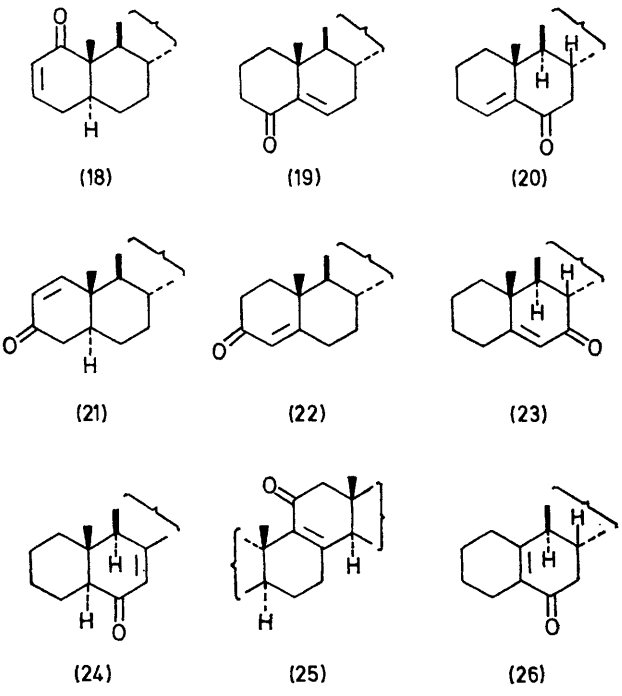
In the reduction of a ketone to a secondary alcohol we shall assume the same motion as in the nucleophilic addition in (**1**), with hydride replacing ammonia. As the hydride approaches closely to the carbonyl carbon atom the substituent groups move down below the initial molecular plane as this atom becomes tetrahedral. For clarity it is best to refer all motion to a plane described by the carbonyl carbon atom and its two substituents. Then, for reduction of a cyclohexanone, as (**11**), to an axial alcohol (**12**), the trajectory of the hydride is shown in both plan and projection as (**13**) and (**14**), respectively[9] (dashed line for alternative axial attack). It is evident how axial substituents at both α and β positions, with respect to the ketonic function, could impede the motion of nucleophiles on these trajectories.



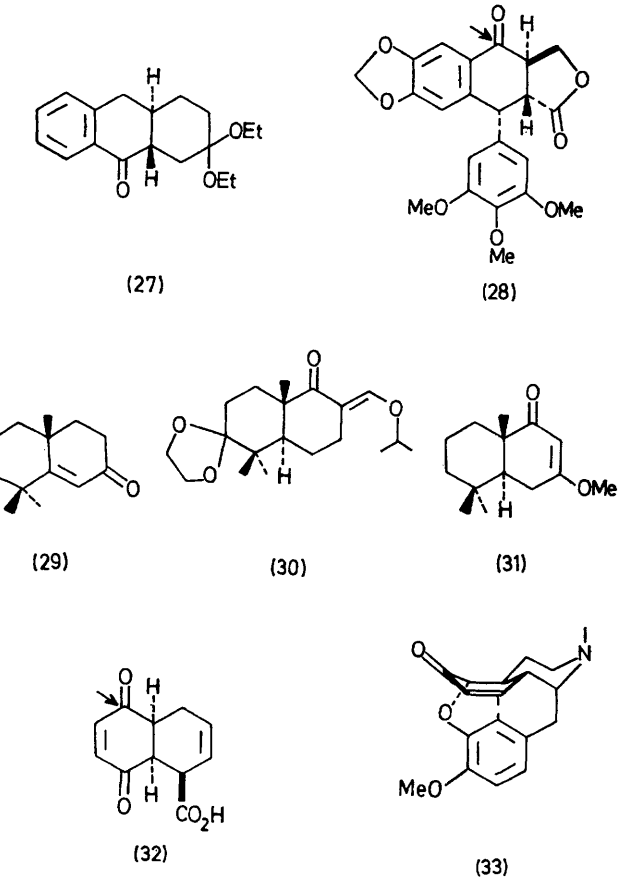
The corresponding resultant approach vector for a conjugated cyclohexenone is derived, as before, by summation of vectors for the two structures (**15**) and (**16**), weights C_1 and C_2, as in (**17**). This projection (**17**) shows that approach of a nucleophile to an enone carbonyl should be very sensitive to quasi-axial substituents at C(6) and C(5). This indeed is so. In an analysis of 16 cases of cyclohexenone reductions this approach vector analysis method leads to excellent agreement with experiment, in that quasi-axial substituents at C(6) and C(5) (**17**) appear totally to control the stereochemistry of reduction, whereas those at C(4) have very little effect. The weightings of substituents[10] in their relative effects are:

6 quasi-axial Me > 6 quasi-axial H > 5 quasi-axial H
and
5 quasi-axial Me > 6 quasi-axial H.

The resultant predictions and observed results for compounds (**18**)—(**33**) are shown in the Table.[11] Particularly striking are examples (**18**), (**19**), (**20**), and (**26**) where the introduction of the double bond essentially completely reverses the stereochemistry of reduction. Also in accord with this approach vector analysis is the observation, cases (**21**), (**22**), and (**23**), where the large axial substituent (methyl) lies symmetrically with respect to the ketone



[C-4 in nomenclature of (**17**)] the stereochemistry of reduction is essentially unchanged on introduction of the double bond.



I believe that this excellent correspondence of predicted and found stereochemical results supports the approach vector idea and demonstrates its utility in organic chemistry.

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[1] H. B. Burgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.
[2] H. B. Burgi, *Angew. Chem. Internat. Edn*, 1974, **14**, 460.
[3] H. B. Burgi, J. M. Lehn, and G. Wipff, *J. Amer. Chem. Soc.*, 1974, **96**, 1956.
[4] H. B. Burgi, J. D. Dunitz, and E. Shefte, *J. Amer. Chem. Soc.*, 1973, **95**, 5065.
[5] L. Pauling, 'The Nature of the Chemical Bond,' 3rd edn., Cornell University Press, New York, 1960, p. 136.
[6] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.
[7] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, preceding communication.
[8] It must be emphasized that of course this is a very approximate treatment. However, it has the advantage of being easily understood and utilised by organic chemists familiar with the Lewis resonance structures. Functionality other than that in Scheme 1 can be treated similarly, provided a reasonable guess can be made to the weights of the two extreme Lewis structures. In Scheme 1 the weighting of the second structure, C_2, increases to the right becoming equal to C_1 in the carboxylate (**10**).
[9] Note, the hydride trajectory terminates at the nuclear position of the hydrogen atom on the secondary alcohol product.
[10] This weighting is based simply on the size of the substituents and their proximity to the hydride trajectory.
[11] An excellent review of the experimental results of enone reductions is that of E. Toromanoff in 'Topics in Stereochemistry,' Vol. 2, ed. N. L. Allinger and E. L. Eliel, Interscience, New York, p. 157. The stereochemical results of carbanion addition to unsaturated ketones can also be rationalized by this approach vector method.