Investigation of the Hydroboration–Oxidation of Hindered Cycloalkenes *via* Molecular Mechanics Calculations

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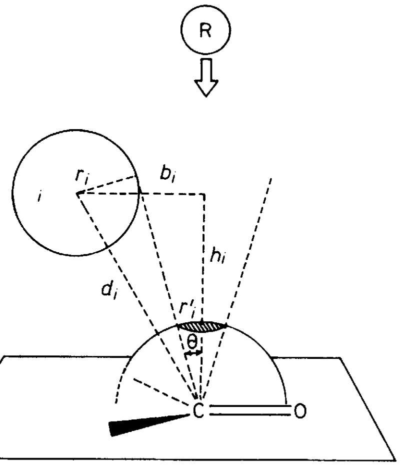
Computational procedures based on molecular mechanics calculations have been devised for investigating the outcome of multi-centre stereoselective reactions. The algorithms, one of which requires no knowledge of transition state geometry, were tested against the known product distributions arising from hydroboration–oxidation experiments on a range of sterically hindered cyclohexenes. The first algorithm performs satisfactorily provided that all possible directions of reagent approach to the reaction site are significantly hindered, whilst molecular mechanics calculations of model transition state structures provide good results whether the reaction site is crowded or not.



$$A_i = 2\pi(1 - \cos\theta_i)$$

$$\theta_i = 90 - \sin^{-1} h_i/d_i - \sin^{-1} r_i/d_i$$

$$C = \Sigma C_i = \Sigma\, 1/A_i$$

$$\left\{\begin{array}{l} C_i = 5{\cdot}32 + \exp[12(0{\cdot}25 - r'_i)] \\ r_i' = (b_i - r_i)/h_i \end{array}\right\} \quad r'_i < 0{\cdot}25 \text{ Å}$$

$$\left\{ C_i' = C_i + 65 \cos 2{\cdot}572\,\Phi \right\} \quad \Phi < 35^\circ$$

Figure 1. Illustration of the Wipke and Gund algorithm for calculating the steric congestion, *C*, at a single centre reaction site. The symbols for straightforward calculation of *C* are explained in the text. The alternative expressions in parentheses are for those cases where perpendicular reagent approach is completely precluded by a hindering atom *i*; or where the R · · · C-C-X torsion angle is <35° (*i.e.* partial eclipsing) so that transition state torsional effects are important, respectively

Stereoselectivity is a concept of great importance in the design of chemical syntheses, particularly those for large, complex naturally occurring molecules. A stereoselective reaction is one in which one of the two (or more) stereoisomeric products is produced in (great) preponderance over the other(s). Although it has long been recognised that steric hindrance by a substrate of the approach of an incoming reagent is an important factor in stereoselective transformations,[1] few attempts have been made to deal with this concept in a quantitative manner.

Most organic chemists would estimate the degree of steric congestion at reaction centres from visual inspection of a molecular model of the compound of interest. However, molecular models can be misleading, and this approach becomes particularly unreliable when there is very little steric congestion in the immediate vicinity of the reaction site, but significant hindrance arising from atoms at medium to long range (4—8 Å) from it; [2] and also when the substrate exists as a number of different conformations in the reaction mixture.

Wipke and Gund have devised an algorithm for semi-quantitative estimation of the steric congestion at reaction centres which has been successfully applied to the calculation of product ratios resulting from stereoselective nucleophilic additions to sterically hindered ketones.[3] The Wipke and Gund method generates a cone of preferred approach adjacent to each sterically hindering atom in the following manner. Consider attack on a carbonyl group by a reagent R, whose size is considered negligible,[4] as illustrated in Figure 1. If the reagent attacks the carbon atom along a line perpendicular to the plane containing the carbonyl group, its approach will be hindered by the various atoms *i* above the plane. There is good theoretical and experimental evidence which suggests that reagent approach to the carbonyl group is at an R · · · C=O angle of 100—110° rather than 90°; [5] but such niceties of detail do not in general affect the results obtained from what is after all a fairly crude algorithm.[3] The measure of each atom's ability to hinder the incoming reagent is governed by its van der Waals radius r_i, and for each hindering atom a cone of preferred approach, centred on the perpendicular to the carbonyl plane and tangent to the sphere of van der Waals radius r_i surrounding atom *i*, is defined. This cone intersects a sphere of unit radius centred on the carbon atom to generate a solid angle A_{xa}. The magnitude of this angle is equated with the accessibility $A_{xa(i)}$ of the carbon atom with respect to atom *i*. It is obvious that large solid angles are found in situations of high accessibility and conversely, a small solid angle is indicative of low accessibility. From solid geometry, equation (1) follows and θ is derived from equation (2) where $\theta_1 =$

$$A_{xa(i)} = 2\pi(1 - \cos\theta) \qquad (1)$$

$$\theta = 90 - \theta_1 - \theta_2 \qquad (2)$$

$\sin^{-1}(r_i/d_i)$ and $\theta_2 = \sin^{-1}(h_i/d_i)$ with d_i the distance of atom *i* from the centre of attack, and h_i its height above the plane of the carbonyl group. The congestion at the carbon atom is defined as the reciprocal of accessibility so that equation (3) holds. The total congestion on side *a* is generated by

$$C_{xa(i)} = 1/A_{xa(i)} \qquad (3)$$

summing the individual congestion terms for all of the atoms above the carbonyl plane [equation (4)] and that for side *b*

$$C_{xa} = \sum_{i} C_{xa(i)} \qquad (4)$$

by a similar calculation for all atoms below the plane [equation (5)]. The preferred direction of attack for the incoming

$$C_{xb} = \sum_{i} C_{xb(i)} \qquad (5)$$

reagent is that associated with the lowest value of C_x. The percentage of product resulting from reagent attack above the plane of the carbonyl group in the *j*th conformation of the substrate is given by equation (6) and similarly for attack below the plane by equation (7). If the substrate exists as a

$$p_{aj} = 100C_{xa}/(C_{xa} + C_{xb}) \qquad (6)$$

$$p_{bj} = 100C_{xb}/(C_{xa} + C_{xb}) \qquad (7)$$

mixture of *n* conformations each populated to the extent of x_j then the effective weighted-mean product percentages are given by equations (8) and (9). $P_A = p_{aj}$ if only a single con-

$$P_A = 0.01 \sum_{j=1}^{n} p_{aj}x_j \qquad (8)$$

$$P_B = 100 - P_A \qquad (9)$$

formation is populated. Despite its simplicity this algorithm has been found to be very effective when the difference in congestion between the two sides is fairly pronounced and the larger of the two calculated values is above 30.[3]

It has been suggested that these atom-centred type of calculations may be extended to include electrophilic additions to carbon–carbon double bonds by calculating the congestion on each side of the mid-point of the double bond [3] (*i.e.* the mid-point of the double bond replaces the carbonyl carbon atom for computational purposes). However, if for instance we consider hydroboration of an alkene then the reaction does not take place by reagent attachment to the mid-point of the double bond but through the cyclic transition complex shown in Figure 2.[6] The success or otherwise of the proposed bond-centred approach would appear to rest on the assumption that the double bond can be considered infinitesimally small compared with the rest of the reagent–substrate complex. This is probably too gross an approximation for general use and additions to carbon–carbon bonds are best treated in terms of the sum of two C_{sp^2} atom-centred congestions (*i.e.* a separate calculation is performed for each C_{sp^2} carbon and the pairs of values for C_{xa} and C_{xb} added together to give the final congestion values). For instance, if we take the trivial example of a hindering atom at a height of 4 Å above the C=C bond so that its van der Waals sphere, of radius say 1 Å, is tangent to the perpendicular from the centre of one of the C_{sp^2} carbon atoms then it is obvious that there will be very severe hindrance to the perpendicular approach of an electrophile. However, whilst the summed atom-centred approach yields $C_{xa} = \infty$ the alternative bond-centred approach gives a C_{xa} of only 12! The difference between these two approaches is illustrated in Figure 3.

The recent publication of the results of a series of hydroboration–oxidation experiments on the hindered 1,3,5-tri- and tetra-substituted alkylcyclohexenes (1)—(8)[7] provides reference data for testing the applicability of summed atom-centred congestion factors (SACFs) in the calculation of the outcome of stereoselective additions to hindered double bonds, since hydroboration is known to be affected by the relative steric hindrance at the two faces of the double bond [8] as illustrated in Figure 4.

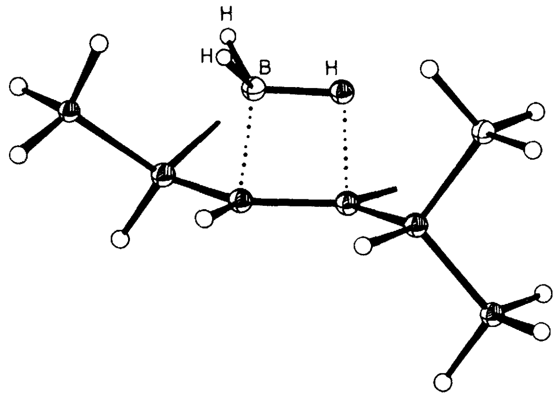


Figure 2. Transition state structure for hydroboration of an alkene

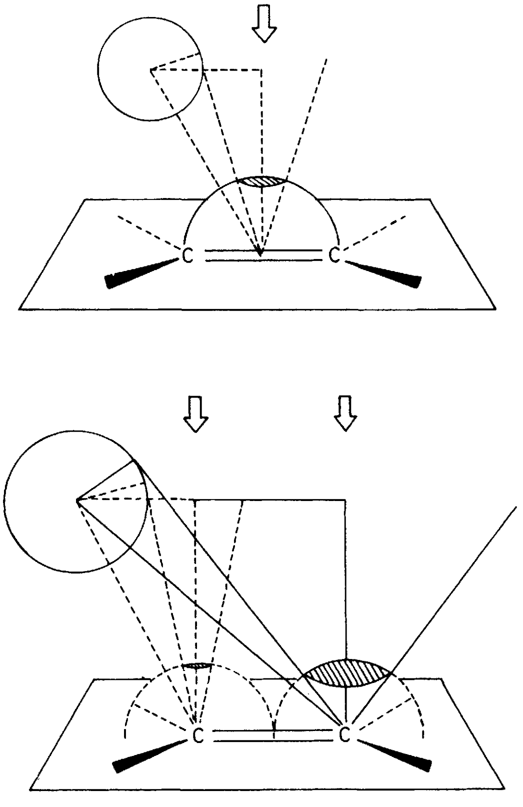


Figure 3. The bond-centred (above) and summed atom-centred (below) approaches to calculating the steric congestion above the plane of a C=C double bond

Calculations

The alkylcyclohexenes (1)—(8) can adopt one (or both) of the two possible half-chair conformations, A and B, shown in Figure 5 and so the minimum energy conformation of each molecule was calculated by the molecular mechanics method using the White–Bovill force field (WBFF)[9] and a full-matrix Newton–Raphson energy minimization procedure.[10] WBFF has been used in preference to the more recent WBFF2[11] because its overall predictive power is superior despite a significant, but extremely localized, shortcoming in predicting the ring inversion barrier of cyclohexane.

In addition to the choice between alternative half-chair conformations there is another degree of structural freedom

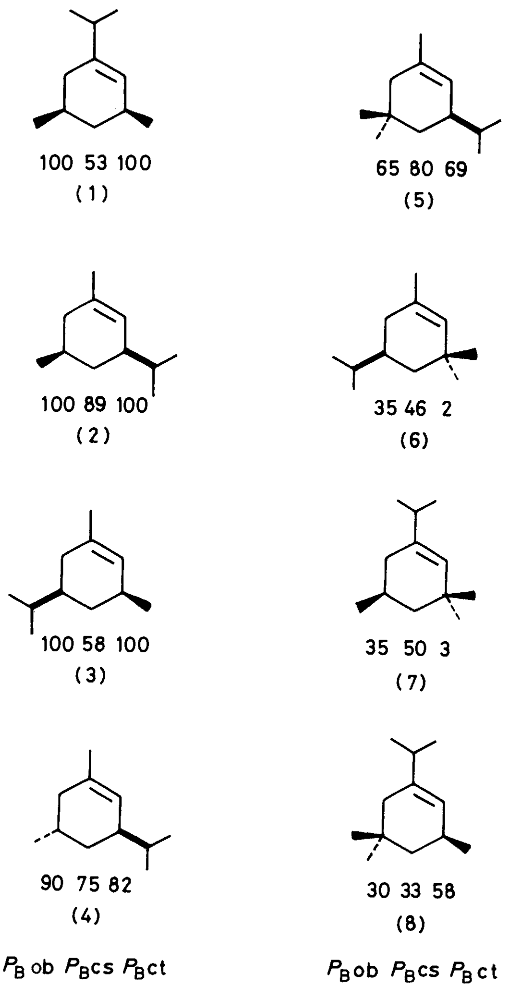


Figure 4. The alkylcyclohexenes (1)—(8) used to test the SACF and energy minimized transition state ensemble algorithms for investigating the outcome of multi-centre stereoselective reactions. The number to the left of each diagram is the observed P_B figure, $P_B$ob, the middle figure is that calculated using the SACF approach, $P_B$cs, and the rightmost figure is derived from the energy minimized transition state ensembles, $P_B$ct

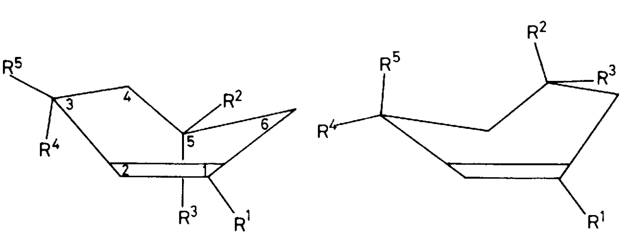


Figure 5. The two alternative half-chair forms of the alkylcyclohexenes (1)—(8) showing the substituent numbering used in the text. A is on the left and B on the right

which will influence the outcome of the SACF calculations, and this is the population of the various non-equivalent rotameric states of the isopropyl group in each molecule. Accordingly, molecular mechanics calculations were performed on models of the minimum energy half-chair conformations with the isopropyl group in each of its three preferred orientations.

The algorithm used for the SACF calculations was exactly as described in the introduction without any correction terms for non-perpendicular reagent approach or transition state torsional effects. The van der Waals radii used in the SACF calculations were the same as those used by Wipke and Gund.[3]

Results and Discussion

The salient results of the molecular mechanics calculation are shown in the Table and indicate that olefins (1)—(3) and (5)—(8) prefer half-chair conformation A to the extent of between 1.3 and 2.5 kcal mol^{-1} whilst conformations A and B are separated by only 0.2 kcal mol^{-1} for olefin (4). In subsequent calculations (1)—(3) and (5)—(8) are regarded as having conformation A exclusively and (4) having a mixture of A and B as proposed by Gordon and Robinson[7] (*n.b.* a difference of 1.3 kcal mol^{-1} in E_s corresponds to 90% of the preferred conformation in an equilibrium mixture at room temperature). It is also obvious from the Table that each of the staggered rotameric states of the isopropyl group around the ring-tertiary carbon atom bond is appreciably populated in all of the olefin conformations under consideration, and the percentage of each rotamer present at equilibrium, x_j, was calculated on the basis of Boltzmann weighted steric energies, E_s. The calculated percentage of product resulting from reagent attack below the plane of the double bond for each of the three populated forms of olefins (1)—(3) and (5)—(8) together with the six forms of olefin (4) are again shown in the Table as the various p_{bj}. The weighted mean values, P_B, for each olefin were calculated by means of equation (9) and are compared with the experimental values in Figure 4.

The value of P_B is within ±15% of the observed value for olefins (2) and (4)—(8) with the major product correctly predicted in all cases. The hypothesis that the high stereoselectivity shown by (1)—(3) is due to R^5 (Figure 5) hindering attack from the upper face of the double bond is only partly supported by these calculations in that the pseudo-equatorial 3-isopropyl group in (2) strongly hinders attack from above the double bond whereas the 3-methyl group in (1) and (3) has little effect on the calculated stereoselectivity. Torsional effects in the reagent–substrate complex can be important[3] but in the case of (1) and (3) would favour the reverse stereoselectivity to that observed. It is also difficult to invoke ' product development control ', whereby the more thermodynamically stable product is preferentially formed, rather that ' steric approach control '[12] for the reactions involving (1)—(3) as the major products from hydroboration of (6)—(8) are the least preferred on a thermodynamic basis and there appears to be no obvious fundamental difference between the two sets of reactants which would account for mechanistic variations.

The excellent calculated results for (2) and (4)—(8) appear to indicate that the distribution of products resulting from the hydroboration reactions under discussion is largely a consequence of the steric congestion or otherwise of the different ' sides ' of the double bonds. The reasons for the poor calculated results with (1) and (3) would appear to lie with the congestion algorithm itself. However, to be completely objective the congestion value differences between the two faces of the double bonds in the cycloalkenes concerned is not large, 7 for (1) and 5 for (3), and the larger of the two values is less than 30 in both cases, which puts these particular calculations outwith the range of applicability for the algorithm as originally specified. Electronic effects, which could be important, are neglected by this simple algorithm.

Although the SACF approach is adequate as it stands and has the merit of simplicity, the discrepancies mentioned above prompted investigation of alternative procedures for calculating the steric congestion at the reaction sites in (1) and

Results of molecular mechanics and SACF calculations on hindered alkylcyclohexenes (1)—(8). E_{sj} denotes the steric energy (kcal mol^{-1}) of the alkylcyclohexene with the isopropyl group in each of its j rotameric states. x_j denotes the percentage population of the alkylcyclohexene containing the jth rotamer in the equilibrium mixture, and p_{bj} represents the percentage of product resulting from reagent attack below the plane (Figure 5) of the double bond of the alkylcyclohexene for the isopropyl group in its jth rotameric state

	Compound																							
	(1)			(2)			(3)			(4)			(5)			(6)			(7)			(8)		
	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}	E_{sj}	x_j	p_{bj}
Conformation A																								
$j = 1$	4.09	45	46	4.30	57	95	5.36	37	55	4.95	31	91	5.35	56	93	6.02	38	58	4.81	43	57	5.17	42	28
$j = 2$	4.36	29	66	4.74	28	93	5.37	36	58	5.40	15	91	5.79	28	83	6.12	32	41	5.05	29	40	5.30	34	32
$j = 3$	4.42	26	49	5.15	15	61	5.54	27	60	5.73	9	32	6.12	16	30	6.19	30	38	5.06	28	52	5.51	24	45
Conformation B																								
$j = 1$	6.00			6.78			7.19			5.19	21	3	7.26			7.70			6.49			6.46		
$j = 2$										5.36	16	94												
$j = 3$										5.78	8	75												

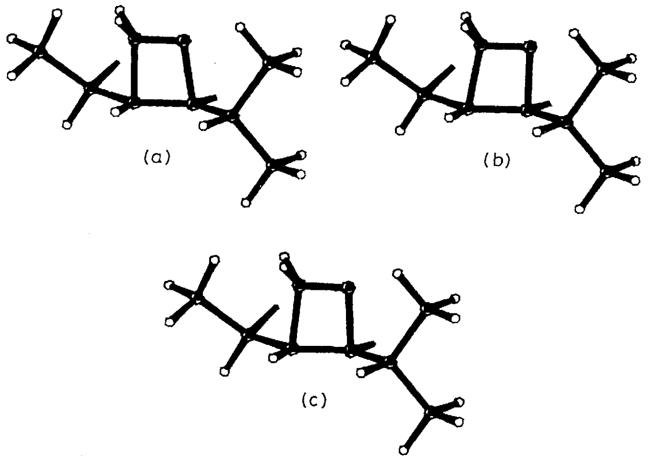


Figure 6. (a), (b), and (c) show the three possible alternative placements of the B–H bond relative to the >C=C< moiety in the transition state model for alkene hydroboration

(3). Neglect of reagent size is the most obvious deficiency in the previously described algorithm and so a strategy similar to Müller and Perlberger's scheme for nucleophilic attack of a ketone was adopted.[4] A B–H (in fact C–H as the force field is not parameterized for boron) fragment was introduced into the molecular mechanics derived model of (1) at a distance of 1.5 Å both above and, in a separate calculation, below the plane of the double bond. The boron atom was placed directly above or below the least substituted C_{sp^2} carbon atom[6] with the B–H vector parallel to the C=C vector as shown in Figure 6(a). The steric energies of these two arrangements were calculated without any concomitant optimization of the molecular geometries. The model in which the B–H fragment lay above the plane of the double bond was 15.9 kcal mol^{-1} higher in steric energy than the corresponding version with B–H below the double bond and, furthermore, *ca.* 95% of this difference is accounted for by repulsive non-bonded interactions between the above-the-plane boron atom and the 3-methyl group! This approach correctly predicted 100% attack from below the plane of (1) and so it was applied to olefin (8) to test its applicability where significant amounts of product were produced by reagent attack from both sides of the double bond. In this case the model with B–H below the double bond was preferred to the extent of 3.8 kcal mol^{-1}, or a predicted proportion of product resulting from attack below the >C=C< plane of 100% compared with 30% observed. Clearly this model is inadequate, and so in order to gauge the effect of B–H placement on the above calculations they were repeated as per Figures 6(b) and (c) with the hydrogen atom directly above or below the most substituted C_{sp^2} carbon atom and also with the B–H centroid directly above or below the >C=C< centroid respectively. The differences in steric energy E_s (above) $-E_s$ (below) in these two cases were -2.4 and 0.2 kcal mol^{-1} for (8) whilst the figure of 15.9 kcal mol^{-1} for (1) did not change by a significant amount. The B–H $\cdots$ >C=C< separation was altered to 1.75 then 2.0 Å and the preceding calculations repeated in an unsuccessful attempt to further improve the energy difference for the two configurations of (8). The optimum placement for the B–H fragment is therefore with its centroid 1.5 Å above or below the double bond.

The simple transition state model discussed above is successful with (1) and (3) but markedly worse than the SACF algorithm for the remaining olefins (2) and (4)—(8) in that it predicts the wrong products (4) and (8).

The remaining possibility available for refining the transition state model is to perform an energy minimization of the whole ensemble whilst keeping the B–H fragment fixed first above and then below the double bond, but otherwise allowing complete relaxation. A series of calculations of this type were performed on olefins (1)—(8) with B–H 1.5, 1.75, and 2.0 Å above and then below the plane of the double bond. As before, optimum results were obtained with a distance of 1.5 Å. P_B values were calculated from Boltzmann weighted steric energies. The results of these (1.5 Å) calculations are shown in Figure 4. It is immediately obvious that the overall agreement between calculation and experiment is superior to that, also shown in Figure 4, for the SACF approach, although the incorrect major product is predicted for (8). It is also interesting to note that ring conformation B was preferred by the transition state ensembles for (6) and (7) whilst the olefins themselves prefer conformation A.

Provided that something is known about the nature of the transition state then energy minimization calculations on complete transition state models, representing reagent attack from both above and below the substrate, are obviously both the fastest (as energy minimization calculations have to be performed before the SACF approach can be applied to the equilibrium structure) and most accurate computational procedure for predicting the outcome of stereoselective reactions.

Conclusions.—It has been shown that, in the absence of any knowledge of transition state geometry, the SACF method allows calculation of the outcome of multi-centre stereoselective reactions with reasonable accuracy for moderate effort, given the availability of interactive computing facilities, especially if graphics are available.

If some knowledge of transition state geometry is available then the faster and more reliable procedure of performing molecular mechanics calculations on alternative transition state models, and deriving the product distribution from Boltzmann statistics, is to be preferred.

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