conductivity detector was used. The areas of the peaks obtained with the flame ionization detector, however, was corrected for the carbon number of the product (area × 1/number of carbons). Several mixtures were analyzed with both detection systems and the results were the same within ±5%.

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References and Notes

(1) Department of Chemistry, University of Minnesota, Minneapolis, MN 55455.
(2) (a) H. Suhr in "Techniques and Applications of Plasma Chemistry", J. R. Hollahan and A. T. Bell, Ed., Wiley, New York, N.Y., 1974. Chapter 2; (b) A. T. Bell, *ibid.*, Chapter 1, and references therein.
(3) R. H. Huddlestone and S. L. Leanord, Ed., "Plasma Diagnostic Techniques", Academic Press, New York, N.Y., 1965, p 4.
(4) B. D. Blaustein and Y. C. Fu in "Techniques of Chemistry", Vol. I, part IIB, A. Weisberger and B. W. Rosesiter, Ed., Wiley, New York, N.Y., 1971, Chapter 11.
(5) M. Venngopalan in "Reactions under Plasma Conditions", Vol. I, M. Venngopalan, Ed., Wiley-Interscience, New York, N.Y., 1971, Chapter 1.
(6) Butadiene can be formed if a solid catalyst is present; H. Suhr, private communication.
(7) D. H. Stedman and D. W. Setser, *Prog. React. Kinet.*, **6**, 193 (1971).
(8) The 2-butene radical anion is a fourth possible intermediate for unimolecular isomerization. Its chemistry has not been characterized, and it must remain a formally viable alternative.
(9) L. W. Sieck, S. K. Searles, and P. Ausloos, *J. Am. Chem. Soc.*, **91**, 7627 (1969); S. G. Lias and P. Ausloos, *ibid.*, **92**, 1840 (1970); S. G. Lias and P. Ausloos, *J. Res. Natl. Bur. Stand., Sect. A*, **75**, 589 (1971).
(10) J. M. S. Henis, *J. Chem. Phys.*, **52**, 281 (1970); *ibid.*, **52**, 292 (1970); S. J. Wisniewski, R. P. Clow, and J. H. Futrell, *J. Phys. Chem.*, **74**, 2234 (1970).
(11) (a) J. P. Chesick, *J. Chem. Phys.*, **45**, 3934 (1966); (b) G. J. Collin and P. M. Perrin, *Can. J. Chem.*, **50**, 2823 (1972).
(12) (a) P. Kebarle and M. Arrahami, *J. Chem. Phys.*, **38**, 700 (1963); (b) R. J. Cvetanovic, H. E. Gunning, and E. W. R. Steacie, *J. Chem. Phys.*, **14**, 501 (1946).
(13) H. Suhr and U. Schucker, *Synthesis*, 431 (1972).
(14) L. L. Miller and J. G. Huntington, *Tetrahedron Lett.*, 1181 (1975), and unpublished results.
(15) (a) Z. B. Alfaseri, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **5**, 991 (1973); (b) D. Masson, C. Richard, and R. Martin, *ibid.*, **8**, 37 (1976).
(16) Experiments in these laboratories suggest that butadiene is not more reactive under these conditions than 2-butene. Hence we consider it unlikely that it is consumed more rapidly.
(17) J. H. Kim and E. P. Thornton, *J. Am. Chem. Soc.*, **97**, 1866 (1975).
(18) It is important to realize that the selection rules for low-energy electrons may be quite different than for photons, and a different set of excited states can be reached. Indeed, photolysis at 10 eV gives different products than those at 200 nm. It should also be noted that comparisons of plasma reactions with low-pressure, 70-eV mass spectral reactions are not readily compared with plasma reactions since the energy content of the ions may be quite different.

Simulation and Evaluation of Chemical Synthesis. Congestion: a Conformation-Dependent Function of Steric Environment at a Reaction Center. Application with Torsional Terms to Stereoselectivity of Nucleophilic Additions to Ketones[1a]

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Abstract: An empirical, conformation-dependent function, related to congestion at a reaction center, is derived. Based upon calculating the surface area of cones of access defined by each hindering atom, the congestions calculated from three-dimensional models of 52 ketones were correlated with stereoselectivity of steric approach controlled nucleophilic addition reactions. For hydride reductions which were not steric approach controlled, addition of an empirical transition state again afforded good correlation correction with experimental stereoselectivity. It is proposed that the present function permits "factoring out" the steric effect for ketone addition reactions, and that it may also be useful in evaluating different conformations. An example of the latter is illustrated with 2-methylcyclopentanone. The mechanism of nucleophilic attack on ketones is discussed. The concept of a torsional effect is strongly supported by our results.

The most challenging problems for the synthetic organic chemist are generally those which involve stereoselective transformations. A large number of empirical rules have been formulated to aid the chemist in this regard.[2] Unfortunately such rules are often very specific with respect to the class of compounds to which they apply; furthermore, they are not always well grounded mechanistically. Orbital symmetry rules[3] have elegantly rationalized many selective transformations, but application to large polyfunctionalized molecules of synthetic interest is not always straightforward in the absence of detailed molecular orbital calculations.

While the synthetic chemist can usually look at a Dreiding model of a compound and predict which side of a reactive center is more "sterically hindered" to attack by a reagent, there has been no simple method of quantifying the chemist's perception. We have addressed the task of formulating the organic chemist's stereochemical rules in forms amenable for computer analysis of synthesis.[4,5]

Many stereochemical properties of molecules are independent of conformation (e.g., cis-trans relationships in rings), and may be perceived symbolically and manipulated algebraically.[6] Other conformation-dependent stereochemical relationships, e.g., axial-equatorial, group proximity, least hindered side, require, in general, evaluation of a three-dimensional molecular model. The models utilized in this paper were built by computer from two-dimensional structural diagrams with stereochemistry designated using the SYMIN module,[5-7] an interactive Westheimer type molecular mechanics[8] program.

Steric Control of Reactions. While steric hindrance is well

accepted as an important effect in controlling stereoselectivity for a number of reactions,[2] the concept is applied by chemists in a rather intuitive manner. Our goal was to discover a function which afforded a quantitative description of the steric environment about a reaction center, and then to calibrate that function by correlating it with experimentally observed stereoselectivity for reaction at that center. As a model reaction, we chose nucleophilic attack on carbonyl carbon.[9] Since we will later comment on the mechanism of such reactions, we briefly review this somewhat controversial area.

Nucleophilic Addition to Ketones.[9] The importance of steric factors in the stereoselectivity of nucleophilic attack on acyclic ketones was recognized very early by Cram's rules:[10] if it is assumed that that rotamer predominates in which, of three attachments to an adjacent asymmetric center, the two smallest flank the carbonyl carbon, then the diastereomer formed by reagent attack on the side of the smallest group predominates. Cram's rules are quite successful empirically, but Karabatsos pointed out that conformers in which the carbonyl group is eclipsed are more stable, and that the Cram rules could be rederived on the basis of different preferred rotamers.[11] Felkin suggested that, due to torsional strain in the transition state, an all-staggered conformation is more likely. This viewpoint also gives rise to an equivalent of Cram's rules.[12]

Steric control of additions to cyclic, *hindered* ketones has also been well established since rationalized by Dauben in terms of "steric approach control" of direction of attack.[13] On the other hand, additions to unhindered cyclic ketones seemed not to be governed by steric effects. Dauben proposed that, in such cases, "product development control" prevailed, i.e., the more thermodynamically stable product was preferentially formed.

This last proposal has been the subject of some controversy.[9] It has seemed strange to many workers that additions to acyclic and hindered cyclic ketones should have a transition state resembling starting materials, while additions to unhindered cyclic ketones have transition states resembling products. Furthermore, it was found that the major product may predominate by *greater* than its equilibrium concentration.[14] Alternate explanations have been advanced for the cyclic, unhindered ketone additions. For instance, Kamernitzky[15] proposed that dipolar effects could account for observed stereoselectivites, but while this is undoubtedly true for polar groups,[16] it is less clearly true for simple alkyl substitutents. Richer[17] proposed that for cyclohexanones, the axial α-hydrogens hinder equatorial attack of small nucleophiles more strongly than axial β-hydrogens hinder axial attack (Figure 1). While this ground-state proposal failed to stand up to experiment, Marshall[18] converted it to a transition-state argument as follows. For a nucleophile approaching a cyclohexanone carbonyl carbon from the two possible perpendicular directions (Figure 1), the β-hydrogens are closer to the perpendicular (and therefore more interfering) for distances of reagent above 1.6 Å from the reaction center. At 1.6 Å the α- and β-hydrogens are equally interfering, while below 1.6 Å the α-hydrogens are more interfering.[19] It was suggested that for hydride attack there was a short carbonyl-hydride distance in the transition state and α-hydrogens were more interfering. For attack by large nucleophiles (e.g., Grignard reagents), an early transition state with a longer C-H developing bond length, and therefore more hindrance by β-hydrogens, was proposed to account for the observed reversal of stereoselectivity.[18] This hypothesis has been criticized by Ashby.[9b] Chérest and Felkin suggested[20] that additions to cyclohexanones proceed via reactant-like transition states, in which axial attack is dominated by steric effects (from the axial β-hydrogens) while equatorial attack is hindered by torsional interactions between the developing C-nucleophile bond and the axial β-hydrogens. The relatively mild hindrance caused by axial substituents α to the carbonyl carbon is attributed to the relative insensitivity of torsional strain to steric size.[20] Similarly, Pasto and Gontarz[21] emphasized the separability of steric effects into "remote steric effects" and "torsional angle effects"; the latter primarily affect the transition-state energy.

It is reasonable that bulkier reagents would place more steric demand on a reaction center, and Ashby[22] noticed that, for nucleophilic addition to 4-*tert*-butylcyclohexanone, the proportion of axial product varied with the A value[23] of the reagent.

If the *tert*-butyl value is dropped, the data collected by Ashby[22] give an excellent linear correlation of percent axial alcohol vs. both A value and Taft E_s constant[24] of the reagent (Table I).[25] Similar variation of product ratio with reagent size has been observed for 3-cholestanone.[26] These observations suggest that interference of the axial β-hydrogens with axial attack is the predominant steric effect in cyclohexanones, and that attacking hydride is subject to the same effects as other nucleophiles.

The torsional strain proposal has been advocated in several recent studies,[14,27] but questions still remain.[9] In particular, the idea that the transition state for borohydride reduction of ketones is reactant-like has been questioned. Eliel[14b] has summarized the evidence for substantial sp^3 hybridization at the carbonyl carbon in the transition state: namely, a large cyclohexanone/cyclopentanone rate ratio, a large Hammett ρ value for the reaction, and the borodeuteride isotope effect.[28a] Geneste[28b] has shown that the position of the transition state along the reaction coordinate varies with the nucleophile, and that the transition state for borohydride attack is product-like. Ashby[9b] has recently advocated an additional "compression effect", a different type of torsional effect which apparently was originally proposed[29] and later rejected[30] by Klein.

In summary, although our model stereoselective reaction has been studied in great detail, many questions remain about all the factors affecting stereoselectivity. A mathematical model accounting for all effects would be complex indeed. But we might expect that ketones which exhibit substantial congestion would correlate with a function which measures steric congestion. Relatively uncongested ketones may not correlate because of possible dominance by other effects. However, in the latter cases we may still be able to assess the steric environmental effects, since bulky nucleophiles appear to make more steric demand upon the ketone.[31] In particular, catalytic reduction in acid solution appears to be governed strongly by steric effects,[32] while reduction in neutral solvents usually gives the more stable alcohol. Dissolving metal reductions may also be sterically controlled,[32] although epimerization of the products can occur.

Methods

Congestion Function Derivation. According to Velluz,[2b,c] the stereochemistry of the product obtained by asymmetric attack at a trigonal carbon atom is determined largely by four factors: perpendicularity of attack, accessibility of the reaction center, relative transition-state energies, and equilibration of products. For the present we ignore the last two effects, and attempt to develop a function which assesses the consequences of the perpendicularity and accessibility criteria. Later we will examine torsional transition-state effects of the incoming reagent.

Clearly steric hindrance in a reaction is a function of the substrate molecule, the reagent (solvated), and the structure of the transition state. First, consider the substrate molecule. Let us use the term *steric congestion* to refer to the steric environment of the isolated substrate in its ground state, and

Table I. Nucleophilic Addition Reactions to 4-*tert*-Butylcyclohexanone

No.	Nucleophile, RM R	Nucleophile, RM M	% axial alcohol[a]	*A* value[a]	E_S[b]	Calcd % axial alcohol Eq 1[c]	Calcd % axial alcohol Eq 2[d]
1	H	$LiAlH_3$	8	0	1.24	7	9
2	H	$LiAl(O\text{-}t\text{-}Bu)_3$	10	0	1.24	7	9
3	CN	H	10	0.17		13	
4	C≡CH	H	11	0.18		13	
5	CH_2=$CHCH_2$	MgBr	48				
6	Me	MgBr	60	1.70	0	65	62
7	Et	MgBr	69	1.75	−0.07	66	65
8	*n*-Pr	MgBr	74		−0.36		77
9	*i*-Pr	MgBr	82	2.15	−0.47	80	82
10	*t*-Bu	MgCl	100	(>4.2)[e]	(−1.54)[e]		(127)

[a] Reference 22. [b] Reference 24. [c] % axial = 6.730 + 34.099*A*; $n = 7$, $r^2 = 0.992$. [d] % axial = 61.636 − 42.289E_S; $n = 6$, $r^2 = 0.994$. [e] Excluded from the correlation.

Table II. van der Waals Atomic Radii Used in Congestion Calculation[a]

Atom type	Radius, Å	Atom type	Radius, Å
H	1.2	C	1.7
N	1.55	C (unsaturated)	1.8[b]
O	1.52	C (methyl)	2.2[c]

[a] Unless otherwise noted, values are from A. Bondi, *J. Phys. Chem.*, 68, 441 (1964). [b] Half-thickness of benzene ring: L. Pauling, "The Nature of the Chemical Bond", 3rd ed, Cornell University Press, Ithaca, N.Y., 1960, p 260. [c] This value for a symmetrical spinning top methyl group gave better results than the value of 2.0 Å recommended by Pauling (footnote *b*) but is less than the maximum value of 2.23 Å along the C–H axis (M. Charton, *Progr. Phys. Org. Chem.*, 8, 247 (1971)).

reserve the term *steric hindrance* to refer to steric environment with respect to the approach of a specific reacting partner.

Thus, we define *steric congestion* at a reaction center as a *property of the substrate molecule in its ground state, independent of reaction partners and transition-state structure.* It seems clear that a function which measures steric congestion must take account of the number, type, and location of hindering atoms on each side of the reactive locus. We have defined such a function in the specific context of our model system, nucleophilic attack on a ketone,[9] as illustrated in Figure 2; however, this general model should also be applicable to other types of reaction.[33] Let us assume that a nucleophile *R* of negligibly small radius preferentially approaches the carbon, *x*, along a line perpendicular to the plane of the carbonyl group.[34] For each hindering atom, *i*, we may define a cone of preferred approach, centered on the perpendicular and tangent to the sphere of van der Waals radius r_i surrounding atom *i*. Intersection of this cone with a sphere of unit radius centered on *x* defines a spherical cross section of preferred approach. We equate this solid angle[35] with $A_{xa}(i)$, the *accessibility* of *x* on side *a* with respect to *i* (Figure 2). Thus, each atom *i* allows a certain accessibility to atom *x*. Angle θ is easily derived from r_i, d_i (the distance from *x* to *i*), and h_i (the height of *i* above the plane).

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

We further define $C_{xa}(i)$, the congestion at *x* on side *a* caused by *i*, as the reciprocal of the accessibility; then the total congestion for each side is the sum of the contributions from each atom on that side.

$$C_{xa} = \sum_i C_{xa}(i) = \sum_i (1/A_{xa}(i)) \quad (2)$$

As accessibility approaches zero, i.e., when atom *i* starts to overlap the perpendicular pathway, congestion from eq 2 becomes infinite. Experimentally, however, the observation of products resulting from such attack indicates congestion does not become infinite, but instead nonperpendicular approaches apparently become significant. In such cases, *C* is set to the congestion from eq 1 at the arbitrary changeover point (θ = 14°, r' = 0.25 Å) and a corrective displacement term is added:

$$C_{xa}(i) = 5.32 + \exp[12(0.25 - r')] \quad (3)$$

when $r' < 0.25$ Å and where $r' = (b_i - r_i)/h_i$.

While the displacement term is strictly empirical in nature, it may be envisioned as reflecting the nonbonded repulsive interaction of incoming reagent and hindering atom. Nonbonded repulsive energy is often represented as an exponential function of distance.[36]

van der Waals radii used are collected in Table II. Hydrogens are considered explicitly except for methyl groups, which are treated as symmetrical, spinning tops.

Torsion Corrected Congestion Derivation. As will be discussed later, the calculated congestions correlate well with stereoselectivity of ketone additions by large nucleophiles, or in highly congested substrates, i.e., additions which are dominated by steric effects. But for addition of small nucleophiles reverse stereospecificity is observed. We attempted to find an empirical correction function which would allow correlation with these latter cases. we first tried a function based on Marshall's concept of axial α-hydrogens hindering only large reagents.[18] However, all such correction functions we tried, which varied with the distance of the hindering atom centers from a line drawn perpendicular to the carbonyl carbon atom (distance = $b_i - r_i$, Figure 2), varied wildly with small changes in geometry of the model and, when parameterized for one system, failed to give good results for other systems.

An empirical correction function based on Chérest and Felkin's proposal of torsional transition state effects[20] was more successful. We calculated the dihedral angle between hindering β atoms and a line drawn through the carbonyl carbon perpendicular to the plane of the carbonyl group (Figure 3), and designed a function[37] which gave a congestion correction of 65 when the incoming reagent was completely eclipsed (ϕ = 0), and 0 when ϕ was 35° or greater:

$$C_i = 65\cos(2.572\phi) \text{ for } \phi < 35° \quad (4)$$

As a simplification, the function was made independent of atom type.[20] The resulting torsional "correction" was added to the normal congestion (eq 2 and 3) for a hindering β atom, giving a "torsion-corrected congestion" which correlated remarkably well with product stereoselectivity for attack by small nucleophiles, as discussed below.

Results

The ketones studied are collected in Figure 4, with the less congested face[38] of each ketone indicated by an arrow. For each face of these ketones, calculated congestions (*C*) and torsion-corrected congestions (*TCC*) are given in Table III,

Table III. Congestions and Torsion-Corrected Congestions for Some Selected Ketones

No.	Ketone	Congestion[c] Overt[a]	Congestion[c] Covert[b]	Torsion correction Overt[a]	Torsion correction Covert[b]	Congestion ratio C_{overt}/C_{covert}, %	TCC ratio,[c] overt/covert, %	Obsd ratio for nucleophilic attack (covert/overt) Large[d]	Obsd ratio for nucleophilic attack (covert/overt) Small[e]	Nucleophile	Ref.
					A. Bridged-Ring Ketones						
1	Norbornanone-2	7.4	30.3	8.7 (H, H)[f]	41.5 (C)[f]		15:85		8:92, 10:90	$LiAlH_4$	*g, h*
									14:86	$NaBH_4$	*i*
						20:80		0:100		CH_3MgI	*j, k*
2	Norbornenone	6.6	23.8		43.3 (C)		9:91		9:91	$LiAlH_4$	*g*
									5:95	$NaBH_4$	*i*
						22:78			~10:90	CH_3MgI	*l*
3	1-Methylnorbornan-2-one	9.5	23.4	8.3 (H)	45.5 (C)	29:71	20:80		15:85	$NaBH_4$	*i*
4	α-Santenone	10.1	24.2	8.7 (H)	46.3 (C)	29:71	21:79		10:90[m]	$LiAlH_4$	*n, o*
5	Apocamphor	32.4	574.8	45.0 (C; H)	6.0 (H)	5:95	12:88		10:90	$LiAlH_4$	*h*
									22:78	$NaBH_4$	*h*
6	Camphor	24.4	454.7	47.7 (C)	12.1 (H)	5:95	13:87		8:92	$LiAlH_4$	*p*
									14:86	$NaBH_4$	*i*
								0.2:99.8		LDMB	
7	Fenchone	45.6	99.4	51.2 (C)	57.6 (C)		41:59		10:90[m]	$LiAlH_4$	*n*
						31:68		5:95		CH_3MgI	*k*
8	7-Methylene-2-norbornanone	13.9	31.4	17.4 (C)	44.7 (C)	31:69	29:71		6:94	$LiAlH_4$	*g*
9	7-Methylenenorbornen-2-one	16.3	26.6	9.6 (H)	31.9 (C, H)	38:72	31:69		11:89	$LiAlH_4$	*g*
10	7-Isocamphanone	30.9	72.3	3.8 (C)	3.2 (C)	30:70	31:69		93% ovt	$LiAlH_4$	*q*
11	Camph-2-en-7-one	31.4	207.5	0	0	13:87	13:87		81% ovt	$NaBH_4$	*q*
12	Norbornen-7-one	29.3	37.4	0	4.3 (C)	44:56	41:59		85:15	$NaBH_4$	*i*
13	Tricyclo[2.2.2.$0^{3,5}$]-octan-2-one	6.4	45.6	0	58.8 (C)	12:88	6:94		9:91	$LiAlH_4$	*p*
14	Isopinocamphone	5.6	200.9	79.2 (H, H)	0	3:97	30:70		11:89	$LiAlH_4$	*p*
15	2-Protoadamantanone	6.6	1747.9	0	102.8 (C, C)	0:100	0:100		0:100	$LiAlH_4$	*r*
16	2-Isoprotoadamantanone	8.3	12472.0	65.0 (H)	51.6 (C)	0:100	1:99		9:91	$LiAlH_4$	*r*
17	2-Isotwistanone	5.6	43.2	14.7 (H)	64.9 (C)	11:88	16:84		0:100	$LiAlH_4$	*r*
18	9-Protoadamantanone	12.1	50.5	0	94.5 (C, C)	19:81	8:92		>50% ovt[m]	$LiAlH_4$	*r*
19	7-Protoadamantanone	20.1	41.7	2.2 (C)	48.7 (C)	32:68	20:80		>50% ovt[m]	$LiAlH_4$	*r*
20	4-Twistanone	15.5	61.8	59.0 (H)	32.0 (C)	20:80	44:56		0:100	$LiAlH_4$	*r*
21	Chrysanthenone	51.7	261.9	0	125.3 (C, C)	16:84	12:88		62% cvt[s]	$LiAlH_4$	*t*
22	Bicyclo[4.2.1]nona-2,4,7-trien-9-one	4.9	356.0	0	129.1 (C, C)		1:99		0:100	$NaBH_4$	*u, v*
						1:99		0:100		PhLi	*u*
23	Bicyclo[4.2.0]oct-4-en-2-one	3.3	23.4	94.8 (H, H)	0	12:88	81:19		8:92	$NaBH_4$	*w*
24	Bicyclo[3.2.1]oct-6-en-3-one	3.6	37.9	130.0 (H, H)	0	9:91	80:22		(95:5[x])	(Na/EtOH)	*r*
25	Cyclopentadiene–tropone adduct	112.8	207.4	114.7 (C, C)	0	35:65	52:48		0:100	$LiAlH_4$[y]	*z*
26	Codeinone	5.1	75.9	4.1 (H)	33.6 (O)	6:94	8:92		>65% ovt[m]	$NaBH_4$	*aa*
27	Trichodermin precursor	17.1	195.5	0	96.8 (C, O)	8:92	5:95		0:100	$CH_2{=}SMe_2$	*bb*

					B. Steroidal Ketones					
28	1-Cholestanone	22.5	69.2	0	81.9 (H, C)		13:87		65:35	$LiAlH_4$ *cc*
						25:75		0:100		$H_2/Pt/H^+$ *cc, dd*
29	2-Cholestanone	3.2	153.2	87.1 (H, H)	0		37:63		41:59	$LiAlH_4$ *cc*
						2:98		0:100		$H_2/Pt/H^+$ *cc, ee*
30	3-Cholestanone	3.4	20.9	87.5 (H, H)	0		81:19		90:10	$LiAlH_4$ *cc*
								56:44		CH_3MgI *ff*
						14:86		25:75		$H_2/Pt/H^+$ *cc, gg*
31	4-Cholestanone	3.8	488.3	82.0 (H, H)	0		15:85		7%:90%	$LiAlH_4$ *cc*
						1:99		0:100		$H_2/Pt/H^+$ *cc, hh*
32	6-Cholestanone	1.1	386.4	71.5 (H, H)	0		16:84		6:94	$LiAlH_4$ *cc, ii*
						1:99		0:100		$H_2/Pt/H^+$ *cc, ii*
33	7-Cholestanone	6.4	28.1	91.3 (H, H)	0		78:22		55:45	$LiAlH_4$ *cc*
									73:27	$NaBH_4$ *cc*
						18:82		40:60		$H_2/Pt/H^+$ *cc, jj*
34	11-Cholestanone	6.6	346.9	59.0 (H, H)	6.0 (C)		16:84		0:100	$LiAlH_4$ *cc*
						2:98		0:100		$H_2/Pt/H^+$ *cc, kk*
35	12-Cholestanone	24.5	56.8	0	93.1 (H, C)		14:86		25:75	$LiAlH_4$ *cc, ll*
						30:70		0:100		$H_2/Pt/H^+$ *cc, mm*
36	3-Coprostanone	5.6	15.3	98.7 (H, H)	0		87:13		95:5	$LiAlH_4$ *nn*
						27:73		5:95		$H_2/Pt/H^+$ *gg*
37	*trans*-10-Methyl-2-decalone	3.3	19.8	93.0 (H, H)	0	14:86	83:17		85:15	$NaBH_4$ *oo*
38	*trans*-9-Methyl-2-decalone	3.0	499.1	93.1 (H, H)	0	1:99	16:84		41:59	$NaBH_4$ *oo*
					C. Cyclopentanones					
39a	2-Methylcyclopentanone (env)	3.6	17.2	51.6 (H, H)	10.3 (H, H)		67:33		79:21	$LiAlH_4$ *p*
						17:83		6.94		Pin_2BH^{pp} *qq*
								35:65		$H_2/Pt/H^+$ *rr*
39b	(Intermediate)	3.6	23.6	38.5	20.2	13:87	49:55			
39c	(Almost half-chair)	3.6	32.1	26.4	30.0	10:90	36:63			
					D. Cyclohexanones					
40	Cyclohexanone	3.2	12.1	109.1 (H, H)	0	21:79	90:10		80:20[ss]	$NaBH_4$ *ss*
41	4-*tert*-Butylcyclohexanone	3.0	17.8	99.5 (H, H)	0		85:15		90:10	$LiAlH_4$ *tt*
						14:86		40:60		CH_3MgBr *uu*
								0:100		*t*-BuMgCl *ff*
								20:80		$H_2/Pt/H^+$ *vv*
								6:94		$LDMB^{bbb}$ *ccc*
42	2,2-Dimethyl-4-*tert*-butylcyclohexanone	14.5	88.6	0	125.3 (H, C)	14:86	6:94		6:94	$LiAlH_4$ *tt*
									8:92	$LiAlH(O\text{-}t\text{-}Bu)_3$ *ww*
43	*cis,cis*-3,5-Dimethylcyclohexanone	3.3	10.8	117.9 (H, H)	0	23:77	92:8		83:17	$LiAlH_4$ *tt*
									89:11	$LiAlH(O\text{-}t\text{-}Bu)_3$ *ww*
44	3,3,5-Trimethylcyclohexanone	2.7	52.6	30.2 (H, H)	31.2 (C, C)		28:72		40:60	$LiAlH_4$ *tt*
						5.95		1:99		$LiPbpH^{xx}$ *yy*
45	2-Methylcyclohexanone	3.1	17.3	97.0 (H, H)	0		85:15		76:24	$LiAlH_4$ *p*
						15:85		3:97		$LiPbpH^{q,x}$ *yy*
46	2,5,5-Trimethylcyclohexanone	3.0	938.5	91.3 (H, H)	0	0:100	9:91		29:71	$NaBH_4^{zz}$ *aaa*
47	3-Methylcyclohexanone	3.0	15.7	92.8 (H, H)	0	16:84	86:14		87:13	$NaBH_4^{zz}$ *aaa*
								1:99		$LDMB^{bbb}$ *ccc*

Table III (*continued*)

No.	Ketone	Congestion[c] Overt[a]	Congestion[c] Covert[b]	Torsion correction Overt[a]	Torsion correction Covert[b]	Congestion ratio C_{covert}/C_{covert}, %	TCC ratio,[c] overt/covert, %	Obsd ratio for nucleophilic attack (covert/overt) Large[d]	Obsd ratio for nucleophilic attack (covert/overt) Small[e]	Nucleophile	Ref.
48	*cis*-3,4-Dimethylcyclohexanone	2.9	678.2	81.6 (H, H)	0	0:100	11:89		13:87	$NaBH_4$[zz]	*aaa*
49	*trans*-3,4-Dimethylcyclohexanone	3.0	17.7	96.6 (H, H)	0	14:86	85:15		88:12	$NaBH_4$[zz]	*aaa*
50	3-*tert*-Butylcyclohexanone	3.7	13.0	112.4 (H, H)	0	22:78	90:10		83:17	$NaBH_4$[zz]	*aaa*
51	3,5-Di-*tert*-butylcyclohexanone	4.3	12.5	121.7 (H, H)	0	25:75	91:9		81:19	$NaBH_4$[zz]	*aaa*
52	4-Methylcyclohexanone	2.9	16.9	87.4 (H, H)	0	15:85	84:16		89:11	$NaBH_4$[zz]	*aaa*
									83:17	$LiAlH(O\text{-}t\text{-}Bu)_3$	*ddd*
								6:94		LDMB[bbb]	*ccc*

[a] Overt (least congested) side of ketone. [b] Covert (most congested) side of ketone. [c] Torsion corrected congestion ratio. [d] Reagent having large effective steric bulk controlled reaction (large nucleophile). [e] Effective bulk is small (small nucleophile). [f] Eclipsing atom types. [g] C. H. DePuy and P. R. Story, *J. Am. Chem. Soc.*, **82**, 627 (1960). [h] R. Howe, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, 87, 379 (1965). [i] H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966). [j] N. J. Towonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fenn., Ser. A2*, 64 (1955). [k] J. Korvala, Ph.D. Thesis, University of Juväskylä, Finland, 1972. [l] Unpublished results of M. Lajunen, quoted in ref *k*. [m] Minimum ratio; actual stereoselectivity is probably higher. [n] S. Beckmann and R. Mezger, *Chem. Ber.*, 89, 2738 (1956). [o] Reference 31a. [p] H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, 87, 5620 (1965). [q] E. E. van Tamelen and C. I. Judd, *J. Am. Chem. Soc.*, 80, 6305 (1958). [r] L. A. Spurlock and K. P. Clark, *J. Am. Chem. Soc.*, 94, 5349 (1972). [s] Stereochemistry of alcohol product assigned on basis of assumed less hindered attack from the olefinic side (footnote *t*). [t] J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960). [u] J. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Schechter, *J. Am. Chem. Soc.*, 94, 5366 (1972). [v] M. Sakai, R. F. Childs, and S. Winstein, *J. Org. Chem.*, 37, 2517 (1972). [w] L. A. Pacquette, O. Cox, M. Oku, R. P. Henzel, and J. A. Schwartz, *Tetrahedron Lett.*, 3295 (1973). [x] Thermodynamically controlled conditions. [y] No reaction with $NaBH_4$ or Na/EtOH. [z] S. Ito, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Jpn.*, 39, 1351 (1966). [aa] M. Gates, *J. Am. Chem. Soc.*, 75, 4340 (1953). [bb] E. W. Colvin, S. Malchenko, R. A. Raphael, and J. S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1989 (1973). [cc] Reference 13b. [dd] P. Streibel and Ch. Tamm, *Helv. Chim. Acta*, 37, 1094 (1954). [ee] L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 27, 524 (1944). [ff] Reference 26. [gg] L. Ruzicka, H. Brüngger, E. Eichenberger, and J. Meyer, *Helv. Chim. Acta*, 17, 1407 (1934). [hh] R. Tschesche and A. Hagedorn, *Ber.*, 68, 2247 (1935). [ii] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952). [jj] W. G. Dauben, D. F. Dickel, O. Jeger, and V. Prelog, *Helv. Chim. Acta*, 36, 325 (1953). [kk] S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, 18, 1166 (1953). [ll] R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Windler, *J. Am. Chem. Soc.*, 76, 4013 (1954). [mm] A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 26, 586 (1943). [nn] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950). [oo] Reference 18. [pp] Lithium diisopinylborane. [qq] H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, 83, 3166 (1961). [rr] W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Justus Liebigs Ann. Chem.*, 616, 46 (1958). [ss] Extrapolated from the Hammett correlations of ref 16b. [tt] Reference 14b. [uu] H. O. House and W. L. Respess, *J. Org. Chem.*, 30, 301 (1965). [vv] E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, 79, 5992 (1957). [ww] Reference 14a. [xx] Lithium perhydro-9b-boraphenalylhydride. [yy] H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, 92, 709 (1970). [zz] Extrapolated to 0% reaction. [aaa] Reference 27c. [bbb] Lithium dimesitylborohydride bis(dimethoxyethane). [ccc] J. Hooz, S. Akiyama, F. J. Cedar, M. J. Bennett, and R. M. Tuggle, *J. Am. Chem. Soc.*, 96, 274 (1974). [ddd] Reference 17.

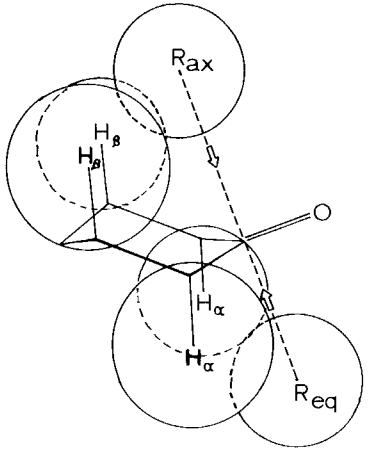


Figure 1. (Left) Hindrance of axial attack on cyclohexanone by β-hydrogens and of equatorial attack by α-hydrogens (Marshall's analysis).[18]

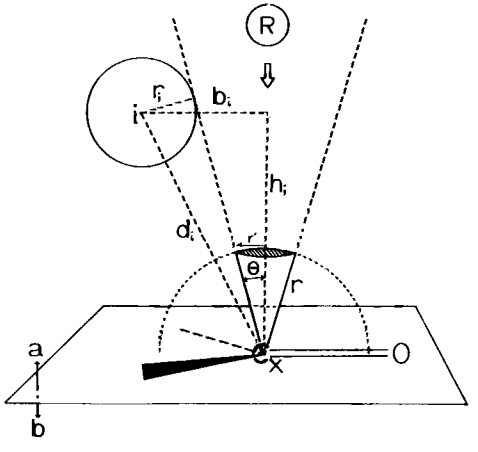


Figure 2. (Right) Cone of preferred approach of reagent *R* to carbon *x* defined by hindering atom *i*. The *accessibility* of *x* on side *a* with respect to *i* is defined by this solid angle and is numerically equal to the area on a unit sphere cut by this cone (shaded area).

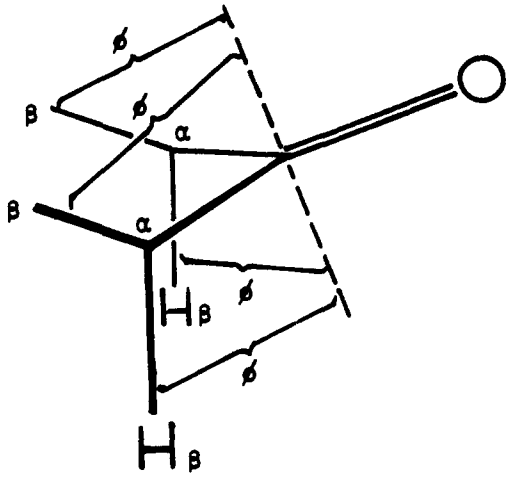


Figure 3. Definition of dihedral angles (ϕ) from incoming reagent R to substituents for torsion correction term.

along with percent ratios and experimental product ratios. We have listed experimental product ratios according to the effective steric size of the nucleophile: small (predominantly additions of $LiAlH_4$ or $NaBH_4$) or large (reagents which are highly sensitive to steric environment, e.g., $H_2/Pt/H^+$ [32]). In fact $LiAlH_4$ and $NaBH_4$ are not strictly interchangeable since $LiAlH_4$ reacts faster and often leads to slightly different product ratios, but for the purposes here can be classified together.

Despite the simplicity of the congestion function, we do observe semiquantitative correlation between the congestion ratios (C) and experimentally observed product ratios from additions involving *large* nucleophiles. We also observe good correlation, independent of nucleophile size, for additions in which one side of the ketone is highly congested, e.g., 11-cholestanone (**34**), camphor (**6**), and 2-protoadamantanone (**15**). When steric demands are high, our congestion function correlates well with experiment. The overall steric effect might be expressed in the following form: steric hindrance = (substrate C) (reagent bulk) + (transition-state effects). Thus, substrate steric congestion allows prediction of stereoselectivity when substrate C, or reagent bulk, or both are large.

However, when substrate congestion and reagent bulk are both small then C fails to correlate with experiment and steric effects appear not to predominate. For unhindered cyclopentanones, cyclohexanones, and steroids in Table III, the torsion corrected congestion (*TCC*) correlates with the experimental additions of small nucleophiles better than does congestion (C) alone.

For systems where the experimental ratios were reasonably well established, the observed percent endo (for polycyclics) or percent equatorial (for monocyclics and steroids) nucleophile attack was compared with that calculated from C and *TCC* ratios (Table IV). For cases with substantial congestion ($C \geq 25$) on at least one side of the ketone (first 19 compounds of Table IV), C alone accounted for 92% of the variance in the observed $LiAlH_4$ product ratios. Where data for bulkier nucleophiles are available, they in general correlate even better with C than does hydride reduction. Furthermore, *TCC* accounted for 83% of the product variance in hydride reduction of 38 ketones of widely different types, *including* the highly congested compounds which correlated with ground-state congestion. When the four worst correlated cases (compounds **7, 20, 33,** and **38**) are dropped, the remaining 34 ketones show an almost one-to-one correlation of observed and calculated ratios, and account for 92% of the variance (% obsd = 0.908 + 0.980% calcd; $n = 34$; $r^2 = 0.924$). Considering that the data were obtained in many different laboratories under different

Table IV. Correlation of Observed and Calculated Product Ratios for Hydride Addition to Various Hindered Ketones

No.	Compd no.[a]	Direction of attack	Congestion-calcd % attack	Torsion-corrected congestion calcd % attack	Obsd % attack[b]	Calcd % attack Eq 1[c]	Calcd % attack Eq 2[d]
1	1	Endo	20	15	10	15	15
2	2	Endo	22	9	9	17	9
3	3	Endo	29	20	15	24	19
4	4	Endo	29	21	10	24	20
5	5	Endo	95	88	90	88	82
6	6	Endo	95	87	92	88	81
7	7	Endo	31	41	10	26	39
8	13	Endo	12	6	9	7	6
9	14	Endo	3	11	30	−2	11
10	15	Endo	0	0	0	−5	1
11	16	Endo	0	1	9	−5	2
12	17	Endo	11	16	0	6	16
13	20	Endo	20	44	0	15	41
14	22	Endo	1	1	0[e]	−4	2
15	31	Equat	99	85	92	92	79
16	32	Equat	99	84	94	92	78
17	34	Equat	98	84	100	91	78
18	35	Equat	30	14	25	25	14
19	42	Equat	14	6	6	9	6
20	29	Equat	98	63	59		59
21	30	Equat	86	19	10		18
22	33	Equat	82	22	45		21
23	36	Equat	73	13	4		13
24	37	Equat	86	17	15[e]		16
25	38	Equat	99	84	59[e]		78
26	39	Equat	83	33	21		31
27	40	Equat	79	10	20[e]		10
28	41	Equat	86	15	10		15
29	43	Equat	77	8	17		8
30	44	Equat	95	72	60		67
31	45	Equat	85	15	24		15
32	46	Equat	100	91	71[e]		85
33	47	Equat	84	14	13[e]		14
34	48	Equat	100	89	87[e]		83
35	49	Equat	86	15	12[e]		15
36	50	Equat	78	10	17[e]		10
37	51	Equat	75	9	19[e]		9
38	52	Equat	85	16	17		16

[a] See Figure 5. [b] $LiAlH_4$ reagent unless specified otherwise. [c] (For 1–19) % obsd = −4.78 + 0.997% calcd (congestion; $n = 19$, $r^2 = 0.919$). [d] (For 1–38) % obsd = 0.85 + 0.920% calcd (torsion-corrected congestion; $n = 38$, $r^2 = 0.831$). [e] $NaBH_4$.

experimental conditions (temperature, solvent, reaction times, stoichiometry, heterogeneity, side reactions, workup, even reagents differed) and with different isolation methods, the correlation must be considered highly satisfactory. In fact, the variance in the experimentally reported ratios, especially for some of the steroidal ketones,[31b] is at least as high as that in the regression equations.

A referee pointed out that because molecules occupy vibrational states which differ from one another, when one is dealing with small energy differences, we should not expect a continuous function to perfectly represent what we might think of as essentially discontinuous quantities. Thus perhaps the agreement is as good as we can reasonably expect.

Discussion

For hydride reduction of 38 ketones without other functionality for which good experimental ratios were found (**18** and **19** were excluded), 15 were correlated within 5% by *TCC*, 11 were correlated within 10%, two (**4, 44**) within 15%, four (**14, 17, 34, 46**) within 20%, three (**10, 33, 38**) within 25%, two (**7, 20**) within 45% with the correct major product predicted, and one (**28**) was wrongly predicted.

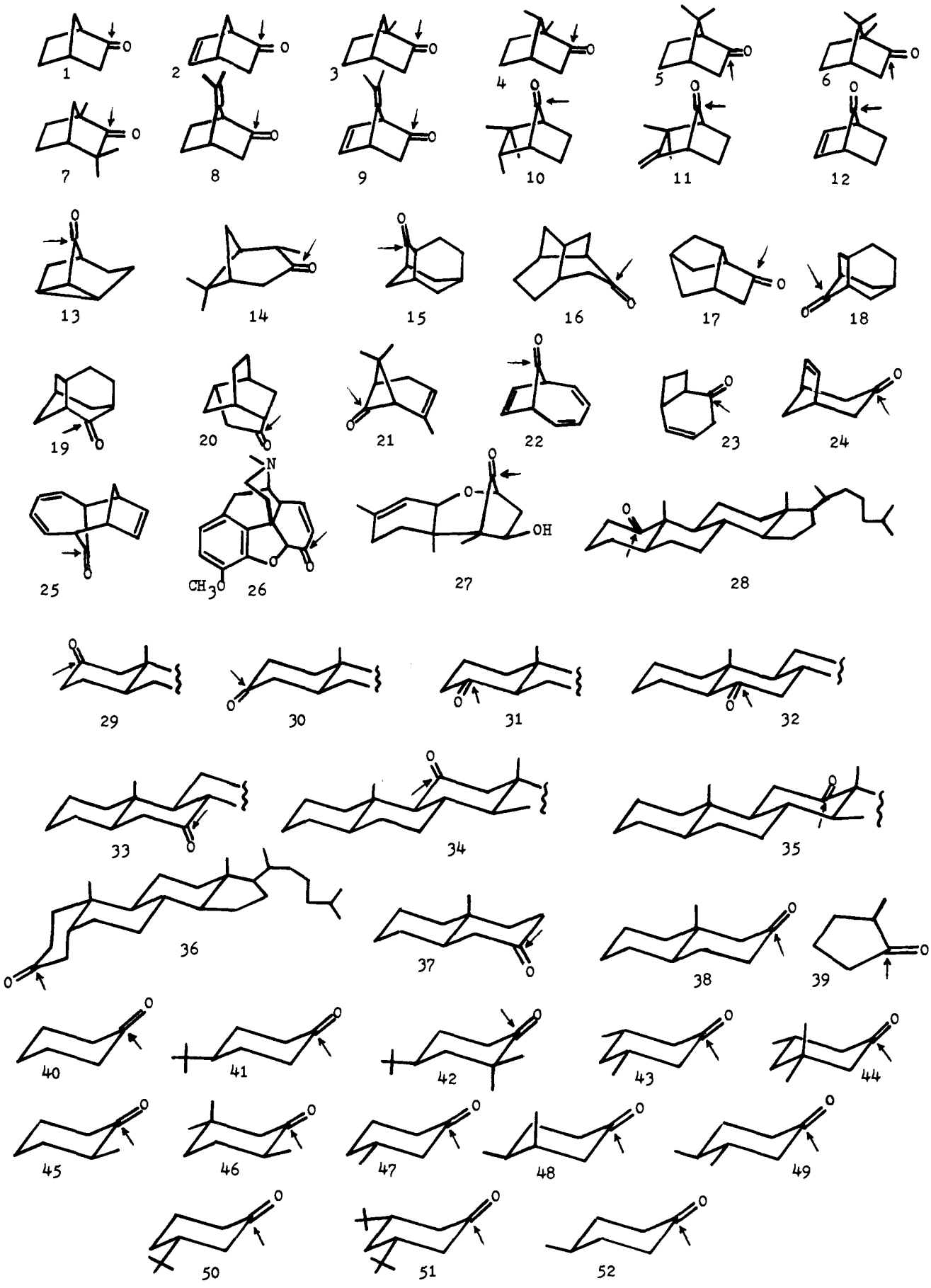


Figure 4. Ketones investigated. Arrow points to the overt face of each ketone. Diagrams are the normal top views; the lower edge is closest to the viewer.

Looking more closely at those structures which deviate by more than 15% from *TCC*-predicted stereoselectivity, isopinocamphone (**14**) is highly congested on one side and observed selectivity correlates better with *C* than with *TCC*; torsion correction appears to be overemphasized here. 2-Isotwistanone (**17**) is slightly better correlated by *C* than by *TCC*; we see no obvious reason for the greater than expected stereospecificity. 11-Cholestanone (**34**) has extremely high congestion on one side and correlates perfectly with *C* but less well with *TCC*; torsion effects appear to be swamped here by congestion. The reduction of 2,5,5-trimethylcyclohexanone (**46**) is less specific than the high congestion on the axial side would predict; a twist-boat transition state[39] may be involved. 7-Isocamphanone (**10**) is strongly congested on both sides, neither *C* nor *TCC* ratios appear adequate to explain the observed specificity. 7-Cholestanone (**33**) exhibits less stereoselectivity with $LiAlH_4$ than we would expect, but with $NaBH_4$ there is good agreement. *trans*-9-Methyl-2-decalone (**38**) is remarkably congested on the axial side; lower specificity than predicted (from *C* or *TCC* ratios) may be due to poor modeling of the ground state, or to a twist-boat transition state.[39] Fenchone (**7**) is highly hindered on both sides; torsion effects seem to be swamped and the congestion ratio is also inadequate to describe the observed specificity. 4-Twistanone (**20**) is fairly congested on both sides, and torsion effects do not appear to be expressed. Finally, 1-cholestanone exhibits a specificity on catalytic hydrogenation consistent with that predicted by the *C* ratio; while the *TCC* ratio predicts stereospecificity in the same direction, the other stereomer actually predominates on $LiAlH_4$ reduction, owing perhaps to preferential reaction from a less congested twist-boat conformation.[39]

Of 12 *olefinic ketones* for which correlations were attempted, *C* was generally as good as or better than *TCC* in explaining reaction specificity. The one exception was norbornenone (**2**), which correlated better with *TCC* (exactly) than with *C* (specificity underpredicted by 13%). On the other hand, **8, 9, 11, 22, 26,** and **27** correlated as well with *C* as with *TCC*, and **23** was nicely correlated by *C* but wrongly predicted by *TCC*. Compound **25,** which is strongly hindered on both sides, was also correctly predicted by *C* but wrongly by *TCC*. Reduction of **24** was reported using Na/EtOH, conditions which may allow equilibration and predominance of the observed most stable product; the less stable alcohol is predicted by the *C* ratio to be favored under steric control conditions. Norbornen-7-one (**12**) is interesting, in that both *C* and *TCC* ratios suggest that attack from the side of the double bond should be slightly more hindered, while attack from that side is experimentally strongly favored. Based on our results, this appears not to be a steric or torsional effect, but may be due to a chelating effect of the double bond. Apparently, predominating isomer can vary with experimental conditions.[9b] Finally, chrysanthenone (**21**) is predicted by both *C* and *TCC* ratios to strongly prefer attack on the side of the four-membered ring (exo), while stereospecific formation of the other isomer in 62% yield is the reported result.[40] However, since the stereochemistry of the alcohol was assigned[40] by examining models and assuming that endo attack was less hindered, further proof of configuration may be in order.[41] On the basis of congestion the assignment of stereochemistry should be reversed, unless interactions involving the double bond prevail. We briefly examined some olefinic steroidal ketones[42] and found them to be relatively unhindered from either side; attack did not generally correlate with congestion and other than ground-state steric effects appear to predominate. Further studies in this area are in progress.

Cyclopentanones and Cyclohexanones. An intuitive analysis of 2-methylcyclopentanone (**39**) might lead one to expect on the basis of the steric bulk of the methyl group that preferred attack by hydride would be trans to the methyl. With large

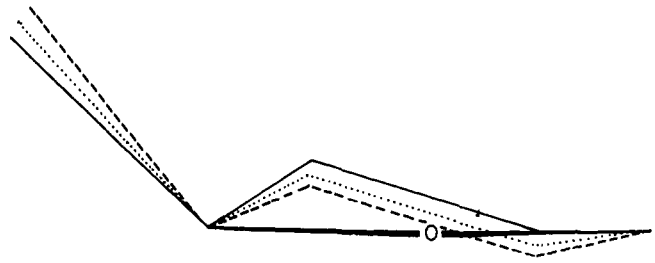


Figure 5. (a) Envelope, (b) intermediate, and (c) almost half-chair conformations of 2-methylcyclohexanone (**39**) are solid, dotted, and dashed, respectively.

reagents, $H_2/Pt/H^+$ or lithium diisopinylborane, the major product is in fact the cis alcohol (see Table III). However, lithium aluminum hydride reduction produces primarily the trans alcohol (cis/trans, 21:79).[43] Consider three possible conformations of **39**: an envelope **39a,** an almost half-chair **39c,** and an intermediate conformation, **39b** (Figure 5). Note that in going from the envelope to the half-chair, the methyl becomes more axial, increasing congestion (*C*) on that side (17 → 32), while the tertiary α-hydrogen becomes less axial, decreasing the torsional term on the *overt* side (52 → 26). Similar changes occur on the other side of the carbonyl. All three conformations favor trans (*overt*) attack of *large* reagents (*C* ratio, selectivity increases in half-chair), but only one conformation, the envelope **39a,** favors cis attack by *small* reagents (*TCC* ratio). Previous analysis of 2-methylcyclopentanone assumed the half-chair conformation,[9b,44] for which the torsional terms for approach from either side of the carbonyl plane must be about equal (the torsional term for methyl should be approximately the same as for hydrogen[20]). But if the torsion terms are equal, then congestion should dominate and trans attack should also prevail for small reagents. Since this is not observed, our ground-state model of congestion suggests that 2-methylcyclopentanone is reacting through an envelope conformation **39a**.

According to the Curtin-Hammett principle, when conformations are in rapid equilibrium, it is the transition state, not the ground state, which determines the rate of reaction. Basically, we are using the ground-state geometry as an approximation of the transition-state geometry. Congestion and torsional terms are calculated from the ground-state geometry as an approximation of the terms that may exist in the transition state. Thus, this analysis is not a violation of the Curtin-Hammett principle.

Cyclohexanones have been the classic examples of "unhindered" ketones. The intrinsic difference in steric environment on either side of the carbonyl in cyclohexanone is pointed out by *C* ratios in Table III. The axial β-hydrogens do in fact contribute more to congestion than do the axial α-hydrogens. As expected, torsional terms for the α-axial hydrogens are larger in cyclohexanones than cyclopentanones, and control direction of addition of small reagents.

In summary, congestion and/or torsion corrected congestion ratios offer satisfactory explanations of preferred direction of nucleophilic addition to a wide variety of bridged and steroidal ketones, cyclopentanones, and cyclohexanones. While such correlations are not without exceptions, they offer a useful semiquantitative guide to reaction stereoselectivity and may also be used to suggest conformations consistent with experimental product ratios. For alicyclic ketones, the ratios offer the possibility of quantitative assessment of reaction stereoselectivity.

Congestion vs. Reaction Rates. The reaction of nucleophile with a ketone is a complex process, dependent on many effects besides the ground-state steric environment which is probed by congestion. Consequently, it is not surprising that the partial rate factors for ketone reductions do not correlate as well with

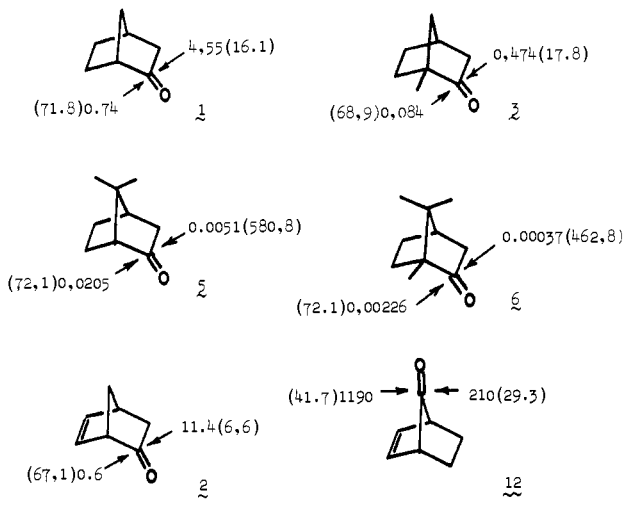
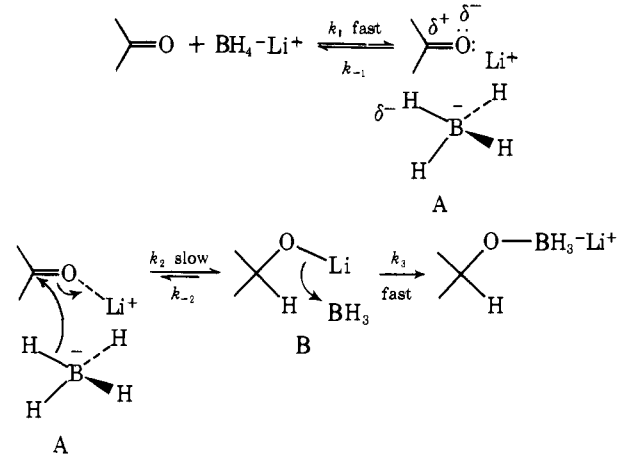


Figure 6. Partial rate factors for $NaBH_4$-*i*-PrOH reduction[45] and (in parentheses) torsion corrected congestion (this work) for some bicyclic ketones.

Scheme I



congestion (*C*), or torsion corrected congestion (*TCC*), as do the less sensitive rate ratios. Figure 6 gives partial rate factors for some rigid ketones (measured by Brown and Muzzio[45]) and corresponding torsion-corrected congestions in parentheses; the expected inverse relationship is not found. For example, in comparing **3** to **1** and **6** to **5**, we see that an α-methyl group in the 1 position causes a tenfold decrease in rate of reduction of the 2-ketone, but does not increase *TCC* because the methyl group is essentially in the plane of the carbonyl and in our treatment the torsional term (eq 4) for the methyl is the same as for the 1-hydrogen it replaced.[20] Brown argued that the inductive effect of the methyl was too small to explain this rate difference.[45] Thus, the 1-methyl must increase crowding in the transition states leading to exo and endo products equally, an effect not adequately measured by our ground-state congestion function.

A more obvious effect of transition-state crowding is illustrated by comparing the rates for endo attack on norbornanone (**1**) and apocamphor (**5**). As predicted,[45] the 7,7-dimethyl group in **5** forces the carbonyl group into the endo hydrogens, slightly increasing congestion on the endo side, but the 35-fold decrease in rate is clearly a result of the interference between the geminal methyls and the complexed oxygen atom in the transition state. This effect can be anticipated from the high congestion (581) on the exo side. Thus, the rate of attack on the overt side is a function not only of the overt congestion, but also of the covert congestion.

Mechanism of Nucleophilic Ketone Additions. We now consider congestion in relation to the mechanism of the model reaction. Uelzmann[46] proposed a mechanism for ketone reductions illustrated in Scheme I for $NaBH_4$.

This mechanism and a similar mechanism for Grignard additions to ketones appear to be in agreement with most of the experimental results,[9b] and may allow resolution of some of the differences of opinion regarding interpretation of those results. The evidence supporting this mechanism is as follows.

(1) Initial Complexation. The rate of $NaBH_4$ reduction of ketones is first order in each reactant,[28b,47] consistent with—but not requiring[9b]—prior coordination of reagents before the slow step. The observed kinetic order for B_2H_6 reduction of ketones[48] (1 in ketone, 3/2 in diborane) is also consistent with complexation before reduction:

$$B_2H_6 \overset{\text{fast}}{\rightleftharpoons} 2BH_3$$

$$\text{ketone} + BH_3 \overset{\text{fast}}{\rightleftharpoons} \text{ketone}\cdot BH_3$$

$$\text{ketone}\cdot BH_3 + B_2H_6 \xrightarrow{\text{slow}} \text{products}$$

Dauben, Noyce, and coworkers,[15] in their original postulation of steric approach control and product development control, suggested that prior complexation of hydride and ketone occurred before hydride transfer. Similarly, complexation before ketone addition has been invoked to explain the stereoselectivity of Grignard additions.[24,27b] Finally, Uelzmann[46] pointed out that prior coordination is necessary to explain the variation of hydride reactivity with changes in the cation, and the failure of $NaBH_4$ in ethylene glycol dimethyl ether to reduce ketones (complexation of the sodium cation by the ether apparently reduces the strength of the ketone-$NaBH_4$ complex). Ashby et al. have very recently confirmed that initial complexation occurs.[49]

(2) Hydride Transfer Step. Addition of borohydride to the carbonyl carbon appears to be the rate-determining step on the basis of a high Hammett ρ value for these reactions and other evidence.[14b] Correlation of product ratios with torsional effects of the incoming nucleophile (this work) also requires that hydride attack occur during the slow step, both for $NaBH_4$ and $LiAlH_4$. Similarly, nucleophilic attack appears to be kinetically controlling in additions of Grignard reagents.[21,27b] Better correlation with cones of accessibility with respect to the carbon of the carbonyl rather than to the oxygen also suggests that addition of hydride to carbon is the slow step.

The metal displacement step (k_3) should be fast.[46] The resulting $ROBH_3^-Li^+$ reacts further to reduce another mole of ketone by a similar series of steps.

(3) Violation of Hammond Postulate. It has been suggested that, since ketone reductions by hydride are highly exothermic processes (ΔH = 125-130 kcal/mol),[14b] the transition state should resemble the starting materials according to the Hammond postulate.[50] It has also been pointed out,[31b] however, that it is inconsistent with the postulate to maintain that sterically hindered ketones have reactant-like transition states for reduction, while the unhindered ketones are product-like.

We suggest that the Hammond postulate may not apply here. The exothermicity of the reaction is actually over four stepwise replacements of hydrogen on boron, so each step is less exothermic (less than 45 kcal). Furthermore, the actual heat of reduction must be even less, since some heat should be evolved upon initial complexation of the hydride and ketone (step k_1). Since the reactions have appreciable activation energies (7-13 kcal/mol)[15,51] which may not be totally overcome by the high heat of reaction, the reactions may fall in the intermediate area where it is not obvious (according to the Hammond postulate) that the transition state resembles either reactants or products.[52]

(4) Entropy Effects. If the transition states for these reactions

do not resemble starting materials, of what relevance is ground-state congestion? It is possible to associate our derived congestion function, C, with a reaction entropy of activation.[53] We may then propose that, when congestion on one side of a ketone is high, borohydride is more likely to be on the other side when hydride attack is begun. The possibility of entropic control of ketone reductions was recognized by Kamernitsky and Akhrem in 1962.[15] Recently, Lewis and coworkers[54] found that photochemical α-hydrogen abstraction by alkyl phenyl ketones is controlled primarily by conformational entropy effects. However, while entropy effects did not appear to be important in a study of ketone reduction by borohydride,[51] they were important in reduction by organoaluminum compounds.[55]

(5) Activation Energy Effects. Congestion may also affect the activation energy for step k_2 (Scheme I) by hindering hydride approach, an effect working in the same direction as the entropic effect, and perhaps impossible in practice to completely separate from the latter effect. It seems that increasing congestion must also displace the transition state toward starting materials; thus, in the extreme case of a reactive center surrounded by distant bulky groups such that the energy needed by the reagent to pass by these groups is rate determining, the transition state may have no bond making character at all.

Torsional effects involving the developing C-H bond may be felt during the slow step and, as we have seen, may prevail when the congestion effect is not too large. An element of product development control may also occur during k_2 in that, as the carbonyl carbon tends toward tetragonality in the transition state (leading to B), the presence of congestion on the side of the ketone opposite the nucleophile can both reduce k_2 and increase k_{-2}. Furthermore, the well-established effects of polar substituents[15-17] most likely act by stabilizing or destabilizing A and/or B. Finally, we note that changes in mechanism change the stereoselectivity of nucleophilic ketone addition somewhat,[9b,22,27b,d,e] and this can be accounted for in the above mechanism by entropic variations for tight (four-center greater steric congestion control) or loose (six-center or linear) transition states, and by reduced torsional effects in the latter.

(6) Electronic Effects. A different interpretation of the stereochemistry of cyclohexanone reductions was proposed by Klein, involving a distortion of the electron density on each side of the carbonyl π cloud due to interactions with the C-C$_\beta$ σ bonds.[30,56] Klein proposes that the electronic effect will prevail only "when additional steric or polar interactions are absent".[30] This apparently special qualitative explanation for cyclohexanones ignores the effect of the axial α substituents or hydrogens, which are crucial appendages according to the torsion effect argument which we advocate. It is not clear how complexation of the carbonyl would affect the π-electron distribution arguments or how this interpretation extends to nonchair conformations. This concept has also been criticized by Ashby and Laemmle.[9b]

Other Applications of Congestion. We suggest that as a conformation-dependent property of the local environment of any reactive center in a molecule, congestion has broad utility as a method of estimating steric effects. In addition to the work reported here, congestion has also been used to study steric effects in electrophilic additions to double bonds,[33] and in the Simulation and Evaluation of Chemical Synthesis program[5] (SECS) to assess the stereoselectivity of synthetic transforms during computer-assisted synthetic planning.

Congestion allows comparison of steric environments in different conformers of the same molecule, or in different related molecules. Thus, Geneste[28b] used adamantanone as a model for 4-*tert*-butylcyclohexanone (**41**) in comparing rates of nucleophilic addition, but the model is not exact, since congestion in the rigid adamantanone (27.4) is higher than in the flatter **41** (17.8). We believe congestion may prove applicable to other reactions such as cycloadditions,[57] ionization,[58] and the correlation of biological activity with steric effects.[59]

Limitations of Method. In addition to the limitations mentioned regarding rates, we wish to point out additional problems which may be areas for future development of the function. The calculation of congestion takes each atom independently of all others, so that atoms which are hidden from the incoming reagent may still be assigned a congestion contribution.[60] While such contributions have been negligible in the models studied, it could be a significant source of error in some structures. Avoidance of this pitfall essentially involves solving the well-known hidden surface problem.[61] A more sophisticated function, which calculates the integrated hemispherical area about a ketone which is not eclipsed by other atoms in the molecule, has been found to give similar results.[62]

The torsional correction function might also be improved by using different parameters for eclipsed C-C and C-H bonds. A more complex function, which contains the absolute magnitude of congestion on each side plus the ratio, may correlate observed stereoselectivity better than the simple ratio.

Our function estimates the steric environment from a static model of the ground state, and ignores orbital, Coulombic, and solvent effects, reagent size, etc., which affect transition-state energy. Finally, stereoselectivity predictions are limited by the accuracy of the model of the ground state. While the function varies smoothly and continuously with conformation, the congestion ratio will depend strongly upon the exact molecular conformation and, where more than one conformation may react, as in flexible molecules, calculation of congestion of just one conformation may have no predictive utility.[63]

Conclusion

Empirical functions have been developed which quantify the steric congestion and torsion effects at a reaction center, and which correctly predict preferred direction of attack for a large variety of cyclohexanones, cyclopentanones, and steroidal and polycyclic ketones. Our results strongly support the view that the effect of α-axial hydrogens in ketone reductions is torsional in nature. The concept of varying transition-state nucleophile approach distance was tested but could not be converted to a predictively useful function. Apparently congestion and torsion contributions are always present, but for strongly congested reactants and/or bulky reagents, simple steric effects prevail.

These functions also appear useful for "factoring out" steric and torsional effects, in order to assess such other factors as dipole interactions, change in mechanism, and reaction through a distorted conformation. Thus, we concluded that 2-methylcyclopentanone is probably reduced through the envelope rather than chair conformation, and that 2,5,5-trimethylcyclohexanone (among others) may react through a twist-boat conformation.

Finally, the results were interpreted in favor of a mechanism for ketone reduction involving prior complexation with reagent and rate-determining transfer of nucleophile. It was concluded that steric congestion can be manifested in both entropy and activation energy contributions.

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References and Notes

(1) (a) A portion of this work was presented as a communication: W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **96,** 299 (1974); (b) present address: Board of Studies in Chemistry, University of California, Santa Cruz, Calif. 95064; (c) National Institutes of Health Special Postdoctoral Research Fellow, 1971–1973.

(2) Reviews: (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971; (b) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4,** 181 (1965); (c) L. Velluz, J. Valls, and J. Mathiey, *ibid.*, **6,** 778 (1967); (d) J. W. Scott and D. Valentine, Jr., *Science*, **184,** 943 (1974).

(3) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.

(4) (a) E. J. Corey and W. T. Wipke, *Science*, **166,** 178 (1969); (b) E. J. Corey, W. T. Wipke, R. D. Cramer III, and W. J. Howe, *J. Am. Chem. Soc.*, **94,** 421 (1972), and following papers.

(5) Simulation and Evaluation of Chemical Synthesis (SECS) program: W. T. Wipke, "Computer Representation and Manipulation of Chemical Information", Wiley, New York, N.Y., 1974, pp 147–174, and references therein.

(6) W. T. Wipke and T. M. Dyott, *J. Am. Chem. Soc.*, **96,** 4825 (1974).

(7) SYnthesis MINimization program: W. T. Wipke, P. Gund, T. M. Dyott, and J. G. Verbalis, manuscript in preparation.

(8) Reviews: J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19,** 531 (1968); E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95,** 8005 (1973).

(9) Reviews: (a) Reference 2a, Chapter 3; (b) E. C. Ashby and J. T. Laemmle, *Chem Rev.*, **75,** 521 (1975); (c) S.-I. Yamada and K. Koga, in "Selective Organic Transformations", Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1970, p 1; (d) E. Goller, *J. Chem. Educ.*, **51,** 183 (1974).

(10) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74,** 5828 (1952).

(11) G. J. Karabatsos, *J. Am. Chem. Soc.*, **89,** 1367 (1967); see also the review by D. R. Boyd and M. A. McKervey, *Q. Rev. Chem. Soc.*, **22,** 95 (1968).

(12) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2201 (1968).

(13) (a) W. G. Dauben, G. J. Fonkin, and D. S. Noyce, *J. Am. Chem. Soc.*, **78,** 2579 (1956); (b) W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli, *ibid.*, **78,** 3752 (1956).

(14) (a) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968); (b) E. L. Eliel and Y. Senda, *Tetrahedron*, **26,** 2411 (1970); see also ref 2a, p 126; (c) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79,** 5992 (1957).

(15) A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18,** 705 (1962).

(16) (a) A. Calvet and J. Levisalles, *Tetrahedron Lett.*, 2157 (1972); (b) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **84,** 2833 (1962); (c) see, however, D. N. Kirk, *Tetrahedron Lett.*, 1727 (1969).

(17) J. C. Richer, *J. Org. Chem.*, **30,** 324 (1965).

(18) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30,** 2748 (1965).

(19) Marshall's measurements were made from a Dreiding model of ethylcyclohexylidene–cyanoacetate using a ruler. We have verified his distances by computer calculation, using the improved cyclohexanone coordinates of E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, p 454.

(20) M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968). For a related but different interpretation, see D. H. Wertz and N. L. Allinger, *Tetrahedron*, **30,** 1579 (1974).

(21) D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93,** 6909 (1971).

(22) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37,** 1918 (1972).

(23) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, pp 44, 333.

(24) R. W. Taft, in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 598.

(25) However, correlation of A value with E_s is not general: C. D. Johnson, "The Hammett Equation", Cambridge University Press, New York, N.Y., 1973, p 77.

(26) G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. C*, 1106 (1968).

(27) (a) J.-M. Cense, *Tetrahedron Lett.*, 2153 (1972); (b) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34,** 3566 (1969); (c) R. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92,** 6894 (1970); (d) M. Chérest, H. Felkin, and C. Frajerman, *Tetrahedron Lett.*, 379 (1971); (e) M. Chérest and H. Felkin, *ibid.*, 383 (1971).

(28) (a) D. C. Wigfield and D. J. Phelps, *Chem. Commun.*, 1152 (1970); (b) P. Geneste, G. Lamaty, and J.-P. Roque, *Tetrahedron Lett.*, 5007 (1970); (c) P. Geneste, G. Lamaty, C. Moreau, and J.-P. Roque, *ibid.*, 5011 (1970).

(29) J. Klein and D. Lichtenberg, *J. Org. Chem.*, **35,** 2654 (1970).

(30) J. Klein, *Tetrahedron Lett.*, 4307 (1973).

(31) (a) Review: A. H. Hajos, "Komplexe Hydride und ihre Anwendung in der Organischen Chemie", VEB Deutsch, Verlag der Wiss., West Berlin, 1966; (b) review: D. M. S. Wheeler and M. M. Wheeler, *Org. React. Steroid Chem.*, **1,** 61 (1972).

(32) J. H. Brewster, *J. Am. Chem. Soc.*, **76,** 6361 (1954).

(33) The function defined here may be properly termed *atom centered congestion. Bond centered congestion* will be discussed in a later paper covering other reaction types, e.g., electrophilic addition to olefins.

(34) Cf. H. B. Burgi, J. D. Dunitz, and E. Shefter, *J. Am. Chem. Soc.*, **95,** 5065 (1973); H. B. Burgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, **30,** 1563 (1974); and H. B. Bürgi, *Angew. Chem., Int. Ed. Engl.*, **14,** 460 (1975).

(35) The dimensionless unit of solid angle is the steradian, that solid angle which encloses a surface on the sphere equivalent to the square of the radius.

(36) J. O. Herschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids" Wiley, New York, N.Y., 1954, p 31.

(37) Torsional strain is usually represented as a cosine function of dihedral angle.[8]

(38) There appears to be no accepted nomenclature for designating steric environment at a reaction center—accessible, crowded, congested, hindered, and sterically hindered have been used. We propose that the faces of an sp^2 reaction center be termed *overt* (open, open to view) for the less congested side. By congestion we mean simple ground-state congestion (no torsional corrections), as estimated from models or, more accurately, as calculated from eq 2 and 3. Note that assignments of the overt and covert faces depends on conformation.

(39) S. R. Landor and J. P. Regan, *J. Chem. Soc. C*, 1159 [1967).

(40) Table III, footnote *t*.

(41) The "thickness" of the double bond must be kept in mind when examining Dreiding models of unsaturated molecules.

(42) See, e.g., N. C. Cohen, *Tetrahedron*, **27,** 789 (1971).

(43) Table III, footnote *p*.

(44) Reference 2a, p 118.

(45) Table III, footnote *i*.

(46) H. Uelzmann, *J. Org. Chem.*, **25,** 671 (1960).

(47) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84,** 373 (1962).

(48) J. Klein and E. Dunkelblum, *Tetrahedron*, **23,** 205 (1967).

(49) E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **97,** 3158 (1975).

(50) G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955).

(51) D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **98,** 543 (1974).

(52) D. Farcasiu, *J. Chem. Educ.*, **52,** 76 (1975).

(53) From the derivation of C, it may be considered to be a measure of the proportion of possible approach trajectories which may be fruitful. This is related to the preexponential term (A of the Arrhenius equation) according to collision theory, which in turn is related to the entropy of activation by Eyring's transition state theory. See: S. W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill, New York, N.Y., 1960, p 278; J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, p 57.

(54) F. D. Lewis, R. W. Johnson, and D. R. Kory, *J. Am. Chem. Soc.*, **95,** 6470 (1973).

(55) G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Am. Chem. Soc.*, **97,** 4009 (1975).

(56) J. Klein, *Tetrahedron*, **30,** 3349 (1974).

(57) (a) W. T. Brady and A. D. Patel, *J. Org. Chem.*, **38,** 4106 (1973); (b) J. C. Dalton, D. M. Pond, and N. J. Turro, *J. Am. Chem. Soc.*, **92,** 2173 (1970).

(58) (a) H. C. Brown, "Boranes in Chemistry", Cornell Press, Ithaca, N.Y., 1973, p 181; (b) E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **96,** 263 (1974).

(59) C. Hansch, *J. Med. Chem.*, **13,** 964 (1970).

(60) It may be argued that such atoms do have an indirect, "buttressing" effect that hinders the nearer atoms from moving out of the way of the incoming reagent.

(61) I. E. Sutherland, *Sci. Am.*, **222,** 56 (1970).

(62) W. T. Wipke and A. Zelicoff, manuscript in preparation.

(63) Recent evidence for steric approach control and against product development control has been reported: E. C. Ashby and S. A. Noding, *J. Am. Chem. Soc.*, **98,** 2010 (1976). Our concepts of accessibility and congestion have also proven useful in rationalizing preferred alkylation of one of two chemically equivalent tertiary nitrogen atoms in the tumor-inhibitory alkaloid tetradrine, and for suggesting that its solution conformation is similar to its crystal conformation: C. J. Gilmore, R. F. Bryan, and S. M. Kupchan, *J. Am. Chem. Soc.*, **98,** 1947 (1976).