A Steric Model for the Prediction of Stereoselectivity at Carbonyl Carbons in Cyclic Compounds

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A fast computerized model for the prediction of the stereochemical outcome of reactions at carbonyl carbons in cyclic compounds has been developed. The purpose of the model is a very fast prediction that can be used interactively in programs for synthesis design. For the model, 234 substrates and 8 reagents have been used to correlate 395 reactions found in the literature. The model emanates from the ground state geometry of the substrate, and the space available for the incoming reagent is explored for two hypothetical transition states. This model is consistent with a steric approach and strongly supports the concept of a torsional effect. The mean quotient between the calculated and measured selectivity is 2.18 using a geometrical mean. This value is well within what can be expected for such a model.

INTRODUCTION

The outcome of reactions at sp^2-centers in general and at carbonyl carbons in particular has been of general interest to the organic chemist for a long time. The possibility to change the stereochemical result of a reaction only by a small change in either reagent or substrate or by changing the reaction conditions has been intriguing and set out a need for prediction of the outcome of these reactions. This is done in order to limit the number of necessary experiments to perform. The first rules outlined were for acyclic substrates, *i.e.* Cram's rule.[1] Later other rules for both acyclic and cyclic substrates have been outlined.[2] The applications of these rules have in most cases been limited to special classes of substrates and reagents. Pure *ab initio* methods can only give the answers for very small substrates and reagents. Combinations of *ab initio* and molecular mechanics methods have been successful for a variety of cases[3] but are still too slow to be used interactively. Our goal was to create a model accurate enough to be useful for synthesis planning and fast enough to be used in an interactive program, *e.g.*, LHASA.[4] We have here designed a model that calculates the selectivity with reasonable accuracy and speed. The model determines the steric accessibility for the two faces of the π bond of a ketone and requires a precalculated geometry. A selectivity calculation usually takes less than 1 s, although the total time, including obtaining a good geometry, may be significantly longer. The results presented in this paper all concern reactions of cyclic compounds, but the model is not restricted to those compounds. Cyclic substrates were selected simply on the basis of the accessibility of numerous reliable experimental results in the literature and a desire to limit the number of reasonable conformations. For a similar treatment see Wipke and Gund.[5] A method where the steric requirement is built up as a potential has been developed recently.[6]

METHOD OF CALCULATION

Substrates. For each substrate, a few ground state geometries have been calculated by molecular mechanics (MMP2-84)[7] or by semi-empirical methods (AM1).[8] For the 234 substrates a total of 341 geometries has been used in the calculations. An additional set of 23 substrates with 43 geometries which all can hold a heteroatom in an equatorial β position and thereby direct the reagents by electrostatic interaction have been included. This set has not been used in the optimization of the parameters. Several hundred geometries (all local minima) have been rejected due to high steric energies. We have discarded all conformations with an energy of more than 2 kcal/mol above the lowest lying geometry. The search for candidate conformations has by no means been extensive, and there are certainly other conformations that we have overlooked which might be important. Our methods of generating the geometries are not the only possible ones. X-ray data or any method of generating reasonable geometries can be used. The accuracy of the calculated selectivity is thus dependent on the geometries used, but is somewhat compensated for by using more than one geometry for each substrate.

Reagents. The eight reagents have all been treated as spheres. This is of course not true, but for the reagents chosen and for the purpose of our predictions, this approximation is not unreasonable. Furthermore, the methyl reagents may in most cases be seen as models for all corresponding primary reagents. In only a few cases would such a view be inconsistent, *i.e.*, when there are stronger geometrical limitations in all directions a bit further out from the reaction center than in its immediate vicinity. The reason for choosing the alumina reagent $LiAl(OMe)_3H$ instead of the apparently bulkier $LiAl(O\text{-}t\text{-}Bu)_3H$ is that the former often gives higher selectivities. This unexpected result was explained by the decomposition of $LiAl(O\text{-}t\text{-}Bu)_3H$ prior to reaction[9] but seems to originate from the fact that $LiAl(OMe)_3H$ associates much better with the solvent (usually THF) than $LiAl(O\text{-}t\text{-}Bu)_3H$. $LiAlH_4$ occupies an intermediate position.[10] This means that, in solution, the apparent bulkiness of $LiAl(OMe)_3H$ is larger than that of $LiAl(O\text{-}t\text{-}Bu)_3H$. In many cases, even $LiAlH_4$ appears to be of the same size as $LiAl(O\text{-}t\text{-}Bu)_3H$. In the modeling of the size of the reagents, we have not tried to take this extra bulkiness into account other than that it is to some extent taken care of in the parametrization of the reagents.

The reagents with radius, incoming attack angle, and two characteristic distances are given in Table I. The first distance is the length between the center of the reagent to the attacking

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Table I. Reagents with Some Parameters (All Distances in angstroms)

reagent	radius	attacking angle	distance between center of reagent and attacking atom	covalent radius of attacking atom
BH_3	2.10	85	1.24	0.33
$LiAlH_4$	2.38	105	1.63	0.33
$NaBH_4$	2.10	95	1.24	0.33
$LiAl(OMe)_3H$	2.91	95	1.63	0.33
MeLi	2.10	95	0	0.77
MeMgX	2.10	105	0	0.77
PhLi	2.90	95	0.80	0.76
PhMgX	2.90	105	0.80	0.76

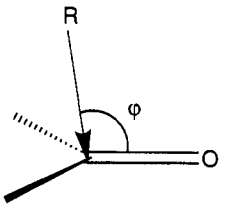


Figure 1. Definition of the attacking angle.

atom, and the second is the covalent radius of the attacking atom.

The attacking angle is defined according to Figure 1. The value of the attacking angle is selected to give a hint about the electronegativity of the reagent and was briefly optimized for each reagent (to within 5 degrees).

The Model. Two tentative TS points are calculated for each conformation, one at each side of the carbonyl group, at a distance of 1.25 times the bonding distance of the bond being formed, in the direction given by the attacking angle. The value 1.25 was arbitrarily chosen at the outlining of this project. Calculations by Houk *et al.*[3b] indicate that this value should be considerably larger, in some instances even above 2.0. We have also performed some of our calculations with larger values of this factor (1.50 and 1.75) for the reagent $LiAlH_4$ but found no significant differences for the three distances. We thus decided to keep our original value 1.25. It can be noted that, in calculations of the attack of H^- at formaldehyde in the gas phase, no reaction barrier is observed, and also when small nucleophiles are used, the only source for the reaction barrier is the desolvatization of the nucleophile. Although these calculations differ from the actual conditions, they indicate that the value of the distance might not be critical for a number of reagents. The values selected for the attacking angle have some justification in *ab initio* calculations done by Houk *et al.*[3] Others are selected to give an indication of the electronegativity of the reagent. Reagents that are electrophilic should have attack angles less than 90 degrees so that they can interact with the filled π-orbitals of the carbonyl group while nucleophilic reagents correspondingly have larger angles so that they can interact with empty π^*-orbitals.

The effects of steric interactions are calculated as follows:

(1) For each TS the distances to all atoms, excluding the four atoms comprising the carbonyl group, are calculated. For those atoms that are within van der Waals (vdW) contact of the reagent, the contributions to the total infringement are calculated according to a weighting procedure (eq 1). The

$$I_i = \sum_j 2^{-j}(d_j - r_j - r_{\text{reagent}}) \qquad (1)$$

ordering of the atoms j is performed so that the difference $(d_j - r_j - r_{reagent})$ increases with j. In eq 1, d_j is the distance from atom j to the reagent on side i and r_j and $r_{reagent}$ are the vdW radii of atom j and the reagent, respectively. An atom is added only to the list for the side where it has the largest steric influence, except if the difference between the distances to the two TS points is less than 0.1 Å when the atom is added to both lists. The reason for such a weighting procedure is that if one atom infringes the reagent to a very large extent, this atom should make a larger contribution to the overall infringement than a number of further away laying atoms that combined have the same spatial overlap with the reagent. The vdW radii used are those of Bondi[11] for sp^3 centers. For sp^2 and sp centers, somewhat larger values than those of Bondi were chosen; see Table II. Using larger values for unsaturated atoms is based on the fact that Bondi's values are spherical means, but the electron clouds are somewhat distorted so they reach further out perpendicular to the bonds and are a little bit less expanded in the directions of the bonds. There is no need to treat these atoms in an asymmetric manner because in the direction of a bond there is always another atom that will dominate the overlap of the vdW radii if that should be the point that lies nearest to the TS point. Methyl groups are treated as superatoms with a radius of 2.2 Å in order to avoid the necessity of considering different rotational conformers of the methyl group.

(2) The selectivity between the two sides of the carbonyl group is calculated to be proportional to the difference of the exponential of the summed up infringement, I_i, eq 2. The

$$C_i = k_1 \exp(-k_2 I_i) \qquad (2)$$

parameters k_1 and k_2, which are different for each reagent, are given in Table III. This implies that the selectivity corresponds to an energy difference proportional to the

Table II. vdW Radii Used Differing from Those of Bondi (Bondi's Values within Parentheses)

atom	sp^2	sp
C	1.92 (1.77)	1.95 (1.80)
O	1.65 (1.50)	
N	1.70 (1.55)	1.75 (1.60)

Table III. Constants Used for Calculating the Congestion for the Reagents Used[a]

reagent	k_1	k_2	k_3
BH_3	0.13	0.98	7.8
$LiAlH_4$	$1.8*10^{-7}$	4.3	5.1
$NaBH_4$	0.067	1.3	8.7
$LiAl(OMe)_3H$	$7.3*10^{-4}$	2.4	16.6
MeLi	$8.5*10^{-4}$	3.0	3.8
MeMgX	$3.7*10^{-5}$	3.7	3.6
PhLi	$1.6*10^{-4}$	2.4	1.6
PhMgX	$3.0*10^{-4}$	2.3	5.2

[a] The constants k_1, k_2, and k_3 are derived by fitting calculated data to experimental data.

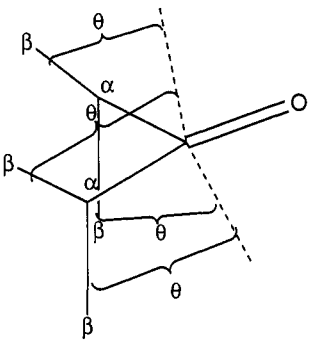


Figure 2. Definition of dihedral angles (θ) from incoming reagent R to substituents which are used for the torsion correction term. Chart I

Table IV. Calculated Results with Experimental Results within Parentheses[a]

substrate[b]	conformations	BH_3	$LiAlH_4$	$NaBH_4$	$LiAl(OMe)_3H$	MeLi	MeMgI	PhLi	PhMgI
1 trans	1	4.05 (1.44)[c]	3.5 (3.0)[c]						
2 trans	2	2.21 (3.0)[c]	4.2 (3.8)[c]		7.5 (1.28)[c]	0.48 (0.43)[e]	1.83 (1.22)[e]	1.06 (0.053)[e]	2.4 (0.0101)[e]
3 cis	2						0.92 (1.50)[e]		0.87 (1.38)[e]
4 cis	1						0.85 (1.17)[e]		
5 cis	1						2.9 (12.5)[e]		4.3 (12.5)[e]
6 trans	2		3.1 (10.8)[f]		6.8 (3.3)[f]	0.94 (2.0)[f]			
7* cis	1		1.71 (4.0)[g]	4.4 (4.0)[g]					
8* cis	1		3.5 (1.33)[g]						
9 trans	1	2.21 (2.8)[a]	4.3 (3.2)[d]	5.8 (2.7)[q]	0.45 (0.45)[c]	0.21 (0.19)[t]	0.27 (0.14)[e]	0.21 (0.136)[e]	0.099 (0.099)[e]
10 trans	3	1.05 (1.04)[e]	4.4 (2.0)[e]				0.37 (0.19)[e]		
11 trans	3	0.72 (0.45)[e]	3.2 (1.70)[e]						
12 cis	1	1.22 (3.3)[e]	1.90 (1.38)[k]		13.2 (1.78)[k]				
13 trans	1		9.8 (23)[f]		12.2 (4.0)[f]	4.0 (3.4)[f]			
14 trans	1		9.8 (19.0)[l]		10.5 (4.0)[o]	3.4 (3.4)[o]			
15 trans	1		4.1 (4.9)[o]		0.21 (0.47)[o]	0.179 (0.19)[o]	0.23 (0.20)[e]		
16 trans	1		2.8 (1.13)[k]						
17 cis	1			4.1 (2.4)[d]					
18 trans	1		10.7 (19.0)[f]		15.2 (15.7)[f]	5.7 (24)[f]	6.0 (4.0)[e]		
19 cis	1	3.35 (3.3)[l]	5.6 (5.7)[l]	6.9 (6.7)[d]		0.26 (0.52)[t]		0.23 (1.27)[e]	0.122 (0.69)[e]
20 cis	1	3.87 (2.7)[l]	6.0 (4.6)[l]	6.8 (4.9)[d]		0.22 (0.27)[t]			
21 cis	1			6.8 (7.3)[d]					
22 cis	1			7.0 (4.3)[d]					
23 cis	1		5.4 (4.9)[d]	6.8 (4.0)[s]					
24 trans	1	1.94 (1.94)[r]	34 (4.0)[f]	2.9 (2.45)[d]	100 (24)[f]	100 (100)[e]	100 (100)[e]		100 (100)[e]
25 cis	1			7.5 (6.7)[d]					
26 trans	1	3.46 (3.8)[l]	5.8 (4.9)[l]	7.1 (8.1)[d]				0.25 (0.88)[e]	0.14 (0.85)[e]
27 trans	1	3.41 (4.6)[l]	5.6 (9.0)[d]	7.0 (6.1)[q]	1.95 (1.56)[f]	0.26 (0.54)[e]	0.47 (0.67)[e]	0.22 (0.72)[e]	0.115 (1.04)[e]
28* trans	3			2.3 (5.7)[g]			0.49 (0.053)[g]		
29* trans	3		3.7 (8.1)[q]	1.02 (8.1)[g]			0.30 (0.053)[g]		
30* trans	2			0.29 (8.1)[g]			0.065 (0.053)[g]		
31* trans	2			0.37 (5.7)[g]			0.074 (0.176)[g]		
32* trans	3		3.4 (4.0)[g]	0.64 (4.0)[g]			0.103 (0.053)[g]		
33* trans	2			0.61 (60)[g]					
34* trans	4			3.6 (60)[g]					
35* trans	2			2.2 (60)[g]					
36* trans	2			4.5 (60)[g]					
37 cis	1							4.8 (60)[g]	9.5 (60)[g]
38 cis	1							4.9 (2.2)[g]	
39 trans	1		3.1 (24)[g]	5.0 (2.7)[g]				0.23 (0.020)[g]	
40 trans	1			11.5 (11.5)[g]		2.3 (1.33)[u]		0.27 (0.25)[g]	
40a trans	1			12.7 (9.0)[v]					
40b trans	1			15.8 (99)[v]					
41 trans	1			5.1 (49)[g]					
41a trans	1			5.5 (49)[v]					
42a cis	2			13.5 (12.5)[g]					
43 trans	2			6.8 (5.2)[g]		0.29 (0.22)[u]		0.27 (0.33)[u]	
43a trans	2			7.1 (9.0)[w]					
43b trans	1			9.2 (24)[g]					
44 trans	2			6.4 (49)[g]		0.24 (0.18)[u]		0.24 (0.23)[u]	
44a trans	2			6.8 (32)[v]					
44b trans	1			9.0 (99)[v]					
45 cis	2			3.1 (3.2)[v]		100 (19)[u]			
45a cis	2			2.8 (4.4)[v]					
45b cis	1			0.52 (3.7)[v]					
46 trans	5			6.6 (19)[g]					
46a trans	5			7.0 (32)[g]					
47a trans	1			6.6 (49)[g]					
48 trans	2			5.6 (5.7)[v]		0.20 (0.25)[u]			
48a trans	2			6.2 (11.5)[v]					
48b trans	1			7.9 (49)[v]					
49 trans	1			6.6 (9.0)[w]		0.40 (0.190)[u]		0.26 (0.27)[u]	
49a trans	1			6.9 (15.7)[w]					
50 trans	1					0.15 (4.0)[u]		0.17 (0.67)[u]	
50a cis	1			6.1 (13.3)[w]					
51 trans	1			5.5 (3.4)[al]		5.9 (15.7)[u]			
51a trans	2			5.9 (5.7)[al]					
51b trans	1			7.8 (13.3)[al]					
52 trans	1			5.2 (3.55)[al]		5.6 (8.1)[u]			
52a trans	1			5.7 (5.7)[al]					
53 trans	1			4.3 (3.0)[w]					
54 trans	1			5.5 (3.0)[al]					
54a trans	1			5.7 (4.6)[al]					
55 cis	2					1.94 (1.94)[u]		3.0 (0.89)[u]	
56 cis	1			2.1 (2.6)[w]		71 (24)[u]		49 (49)[u]	
57 cis	1					64 (49)[u]		39 (16)[u]	
57a cis	1			1.02 (9.0)[w]					
58a cis	2			1.55 (11.5)[w]					
59a trans	1			6.4 (11.5)[v]					
60a trans	1			6.9 (15.7)[v]					
61a trans	1			5.9 (4.0)[al]					
62 cis	2							2.66 (90)[q]	3.6 (1.00)[g]
63 cis	1							2.45 (9.0)[q]	

Table IV (Continued)

substrate[b]	conformations	BH_3	$LiAlH_4$	$NaBH_4$	$LiAl(OMe)_3H$	MeLi	MeMgI	PhLi	PhMgI
64 trans	1			7.9 (2.0)[am]					
64a trans	1			6.7 (4.3)[am]					
64b trans	1			0.23 (2.3)[am]					
65 trans	2			7.5 (9.0)[an]					
65a trans	2			6.8 (49)[an]					
65b trans	1			0.45 (5.7)[an]					
66 trans	5			7.1 (2.85)[an]					
66a trans	5			6.3 (19)[an]					
66b trans	5			0.34 (1.04)[an]					
67 trans	4			7.4 (2.7)[an]					
67a trans	4			6.2 (11.5)[an]					
67b cis	4			3.1 (1.5)[an]					
68 trans	1			7.5 (2.6)[an]					
68a trans	1			6.3 (11.5)[an]					
68b cis	1			4.4 (1.70)[an]					
69 trans	2			14.4 (100)[ao]					
69a trans	1			13.2 (100)[ao]					
69b trans	1			6.6 (2.33)[ao]					
70 trans	1			6.3 (5.7)[ap]					
70a trans	1			5.3 (6.1)[ap]					
70b cis	1			3.3 (1.1)[ap]					
71a trans	2			7.2 (7.3)[am]					
72a trans	2			5.2 (9.0)[aq]					
73a trans	2			5.6 (7.3)[aq]					
74a trans	1			4.8 (10.0)[ar]					
75a trans	2			2.9 (8.5)[as]					
76a trans	3			2.8 (5.2)[at]					
77a trans	1			2.5 (3.3)[at]					
78a trans	1			14.6 (100)[au]					
78b trans	2			13.4 (49)[au]					
79a trans	2			3.5 (1.5)[av]					
80a trans	2			6.1 (24)[av]					
81a trans	1			14.1 (100)[av]					
82 trans	1		5.6 (24)[n]				0.53 (1.08)[n]		
83 trans	2		8.4 (15.7)[n]				5.9 (100)[n]		
84 cis	1		7.8 (5.7)[n]				13.3 (13.3)[n]		
85 cis	1	3.09 (2.8)[l]	6.3 (2.7)[l]						
86 cis	6	1.28 (4.6)[l]	5.0 (2.7)[l]						
87† cis	1		1.00 (0.27)[be]	1.39 (1.78)[be]	2.1 (1.13)[be]				
88† cis	2		0.41 (1.86)[be]	0.30 (1.27)[b,e]	0.31 (1.17)[be]				
89 trans	1						3.8 (2.0)[g]		4.9 (4.9)[g]
90 trans	3			4.6 (3.16)[x]					
91* trans	1			18.5 (99)[az]					
92 cis	1			15.0 (8.0)[ax]					
93† trans	1		1.28 (2.33)[af]	2.0 (2.33)[ag]					
94† trans	3		1.24 (2.85)[af]	2.0 (1.63)[ag]					
95† cis	3		1.01 (1.13)[af]	2.1 (3.0)[ag]					
96† cis	1		1.18 (1.22)[af]	2.7 (6.14)[ag]					
97† trans	3		0.088 (1.5)[af]						
98† trans	1		1.00 (2.33a0[af]						
99† cis	1		10.1 (2.03)[af]						
100† trans	3		0.21 (1.63)[af]						
101* cis	2		5.0 (0.89)[g]	7.7 (19.0)[g]					
102 cis	2			2.5 (11.5)[d]					
103 trans	1		8.9 (15.7)[ak]	10.8 (15.7)[ak]			0.81 (1.22)[ak]		
104 cis	1			6.0 (9.0)[g]					
105 cis	1			6.5 (4.6)[g]					
106 trans	1		7.3 (9.0)[ak]	8.1 (9.0)[ak]			0.63 (0.88)[ak]		
107 trans	1		5.8 (20)[aa]						
108 trans	1		4.0 (4.0)[ak]	5.5 (3.5)[ak]			0.24 (0.11)[ak]		
109 cis	1						1.50 (1.50)[g]		0.41 (0.41)[g]
110 trans	1			5.8 (4.3)[g]					
111 trans	3		3.7 (20)[ay]						
112 cis	1			0.159 (1.13)[g]					
113 trans	2			6.7 (3.5)[ba]					
114 trans	2			6.8 (2.7)[g]					
115 trans	1		5.6 (5.7)[ak]	7.0 (7.3)[ak]			0.49 (0.47)[al]		
116 cis	1			9.4 (5.7)[d]					
117 trans	1			1.45 (1.44)[d]					
118 cis	1		6.5 (5.2)[f]	7.3 (5.2)[f]					
119 cis	1		6.6 (13.3)[f]	7.1 (13.3)[f]					
120 trans	1							9.1 (43)[g]	
121 cis	1		9.1 (75)[ac]						
122 cis	1		1.86 (1.86)[d]						
123 trans	1		52 (1.44)[d]						
124 cis	1		8.3 (9.0)[d]				1.48 (1.27)[d]		
125 cis	1		59 (12.9)[d]						
126 cis	1		100 (15.7)[d]						
127 trans	1		4.3 (1.22)[d]	6.0 (2.7)[d]					
128 cis	1		72 (100)[d]						
129 trans	1		3.4 (3.0)[d]						
130* cis	1			7.3 (84)[aw]					

Table IV (Continued)

substrate[b]	conformations	BH_3	$LiAlH_4$	$NaBH_4$	$LiAl(OMe)_3H$	MeLi	MeMgI	PhLi	PhMgI
131 cis	1			3.4 (5.8)[av]					
132 trans	1		21 (1.38)[y]	0.24 (4.6)[y]					
133 cis	1			5.4 (13.5)[y]					
134* trans	1			8.1 (1.4)[av]					
135 cis	1			3.2 (1.9)[y]					
136 cis	1		6.6 (19.0)[d]						
137 cis	1			1.90 (2.85)[y]					
138 trans	2		0.46 (1.28)[xz]						
139* cis	1			2.4 (91)[z]					
140* cis	2			33 (91)[z]					
141 trans	1		100 (100)[aj]						
142 cis	1		100 (92)[aj]						
143 endo	1			7.4 (5.7)[d]		10.7 (3.4)[e]	12.1 (24)[e]	6.5 (0.39)[e]	15.7 (2.8)[e]
144 endo	1		100 (93)[d]						
145 endo	1			11.7 (4.3)[d]					
146 endo	1	6.04 (49)[l]	9.3 (11.5)[d]	12.2 (6.1)[d]	41 (49)[k]	19.7 (100)[r]	16.7 (100)[d]	11.2 (100)[e]	27 (100)[e]
147 endo	1		10.0 (12.7)[f]	12.8 (5.7)[d]	44 (24)[f]	22 (49)[f]			
148 endo	1		10.5 (9.0)[d]		48 (50)[bd]				
149 exo	1	0.17 (1.08)[l]	7.0 (12.5)[d]	0.119 (6.2)[d]	50 (99)[l]	100 (100)[d]	100 (100)[e]		64 (100)[e]
150* endo	3		0.38 (4.0)[g]						
151* exo	1		5.9 (1.22)[g]						
152 endo	1		9.6 (9.0)[d]		50 (32)[k]		24.7 (19.0)[d]		
153 exo	1		2.56 (9.0)[d]	0.112 (3.6)[d]	29 (50)[bd]				
154 endo	1							5.1 (11.6)[g]	
155 endo	1				49 (50)[bd]				
156 endo	1				100 (500)[bd]				
157 endo	1				41 (50)[bd]				
158 endo	1				100 (50)[bd]				
159 endo	1				100 (50)[bd]				
160 endo	1				50 (50)[bd]				
161 endo	1				95 (50)[bd]				
162 endo	1				100 (50)[bd]				
163 endo	1				100 (50)[bd]				
164 exo	1				23 (50)[bd]				
165 exo	1		100 (62)[d]						
166 endo	1		7.6 (10.1)[d]	9.0 (19.0)[d]			16.4 (9.0)[d]		
167 exo	2		4.5 (9.0)[g]						
168 endo	1		9.2 (15.7)[d]						
169 endo	1		7.4 (8.1)[d]						
170* endo	3		1.17 (19.0)[g]						
171* endo	1		0.045 (3.0)[g]						
172 endo	1		100 (8.1)[k]		100 (40)[k]				
173 trans	1				2.3 (2.3)[bc]				
174 cis	1		3.4 (1.0)[ae]						
175 trans	2		1.14 (2.12)[ae]						
176 trans	3		2.7 (2.6)[ae]						
177 cis	1		23 (5.7)[ae]						
178 cis	2		13.5 (19)[ae]						
179 endo	1		53 (32)[g]						
180 endo	1			21 (10.1)[g]		30 (100)[g]	31 (100)[g]		
181 exo	1			5.5 (1.63)[g]		5.2 (2.0)[g]	4.3 (2.0)[g]	2.3 (2.2)[g]	2.7 (2.2)[g]
182 endo	1			57 (19.0)[g]		100 (100)[g]	100 (100)[g]	100 (100)[g]	100 (100)[g]
183* endo	1		1.92 (19.0)[g]						
184* endo	1		2.1 (2.2)[g]						
185[†] exo	1		4.7 (2.33)[ak]		2.0 (4.9)[bc]				
186 exo	2			2.1 (3.0)[g]					
187 endo	1		51 (100)[d]					100 (100)[d]	
188 endo	1								45 (30)[g]
189 endo	1		11.2 (10.1)[k]		49 (49)[k]				
190[†] endo	1		100 (100)[d]						
191 endo	1		7.9 (100)[d]						
192 cis	1		2.2 (1.0)[ah]						
193 trans	3		0.99 (1.27)[ah]	1.10 (1.38)[ah]					
194 trans	1			1.64 (2.12)[ah]		1.79 (2.3)[ah]			1.70 (2.6)[al]
195 trans	1			1.59 (2.03)[ah]					
196 trans	1		1.49 (1.44)[ah]						
197 cis	3			1.08 (1.33)[ah]					
198 trans	1			1.46 (1.44)[ah]		1.37 (2.6)[ah]			
199 trans	1			1.44 (1.78)[bb]					
200 endo	1		100 (10.1)[d]						
201 endo	1		100 (100)[d]						
202 endo	1		16.9 (50)[d]						
203 endo	1		100 (50)[d]						
204 endo	1		30 (100)[d]						
205 endo	1					100 (76)[x]			
206 cis	1		0.39 (2.33)[af]						
207 exo	2					46 (65)[g]			
208 exo	2					48 (65)[g]	70 (40)[g]		
209 exo	2					68 (65)[g]			
210 exo	2					36 (65)[g]			
211 exo	1		17.8 (60)[g]					19 (75)[g]	51 (75)[q]
212 trans	1		1.06 (1.33)[ad]			0.53 (1.56)[ad]			

Table IV (Continued)

substrate[b]	conformations	BH_3	$LiAlH_4$	$NaBH_4$	$LiAl(OMe)_3H$	MeLi	MeMgI	PhLi	PhMgI
213 cis	1		2.3 (1.86)[ae]						
214 trans	3		0.68 (1.04)[ae]						
215 trans	3		2.1 (4.0)[ae]						
216 cis	1		26 (3.35)[ae]						
217 cis	2		37 (100)[ae]						
218 cis	1		1.06 (1.22)[ae]						
219 cis	3		2.6 (1.0)[ae]						
220 trans	1		1.66 (2.03)[ad]			0.32 (2.03)[ad]			
221 trans	1		1.36 (2.03)[ad]			2.4 (2.12)[ab]			
222 endo	1		100 (99)[ab]			100 (75)[ab]			100 (84)[ab]
223 cis	1			6.8 (4.6)[d]					

[a] The side for the dominating product according to the experiment is also given; cis–trans refers to the nearest substituent. If different isomers dominate for different reagents for some substrates, the order of importance for the reagents are in decreasing order $NaBH_4$, $LiAlH_4$, BH_3, $LiAl(OMe)_3H$, MeLi, MeMgX, PhLi, and PhMgX. [b] An asterisk indicates that the compound was not included in the optimization; the † symbol indicates that AM1 geometries have been used. [c] Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. [d] Reference 5. [e] Reference 2e. [f] Rei, M.-H. *J. Org. Chem.* **1983**, *48*, 5386. [g] Reference 12. [h] Mukherjee, D.; Wu, Y.-D.; Franczek, F. R.; Houk, K. N. *J. Am. Chem Soc.* **1988**, *110*, 3328. [i] Reference 3b. [j] Reference 2f. [k] Reference 9. [l] Brown, H. C.; Varma, V. *J. Org. Chem.* **1974**, *39*, 1631. [m] Ayres, D. C.; Sawdaye, R. *J. Chem. Soc. B* **1967**, 581. [n] Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* **1978**, *111*, 3442. [o] Fang, J.-M.; Sun, S.-H.; Rei, M.-H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 747. [p] Aycard, J. P.; LaFrance, R.; Boyer, B. *Can. J. Chem.* **1979**, *57*, 2823. [q] Kim, S.; Lee, S. J.; Kang, H. *J. Synth. Commun.* **1982**, *12*, 723. [r] Klein, J.; Dunkelblum, E. *Tetrahedron* **1967**, *23*, 205. [s] Reference 2h. [t] Rei, M.-H. *J. Org. Chem.* **1979**, *44*, 2760. [u] Mistryukov, E. A.; Smirnova, G. N.; Aronova, N. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1382. [v] Katvalyan, G. T.; Mistryukov, A. E. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 1809. [w] Mistryukov, E. A.; Katvalyan, G. T.; Smirnova, G. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1131. [x] Coates, R. M.; Shrenik, K. S.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198. [y] Jacquesy, J. C.; Jacquesy, R.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1967**, 1649. [z] Levisalles, J.; Teutsch, G. *Bull. Soc. Chim. Fr.* **1971**, 263. [aa] Metha, G.; Kapoor, S. K. *Tetrahedron Lett.* **1973**, 497. [ab] Metha, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543. [ac] Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1969**, 299. [ad] Li, H.; Metha, G.; Padma, S.; leNoble, W. J. *J. Org. Chem.* **1991**, *56*, 2006. [ae] Varech, D.; Brienne, M.-J.; Jacques, J. *J. Chem. Res. (M)* **1979**, 3622. [af] Brienne, M.-J.; Varech, D.; Jacques, J. *Tetrahedron Lett.* **1974**, 1233. [ag] Caro, B.; Jaouen, G. *Tetrahedron Lett.* **1974**, 1229. [ah] Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; leNoble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. [ai] Lin, M.-H.; Silver, J. E.; leNoble, W. J. *J. Org. Chem.* **1988**, *53*, 5115. [aj] Paquette, L. A.; Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841. [ak] Reference 2g. [al] Mistryukov, E. A.; Katvalyan, G. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1378. [am] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 220. [an] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 1335. [ao] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1585. [ap] Katvalyan, G. T.; Semenova, N. A.; Mistryokov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 1806. [aq] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1829. [ar] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 576. [as] Katvalyan, G. T.; Mistyrukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 2352. [at] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2328. [au] Katvalyan, G. T.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2324. [av] Katvalyan, G. T.; Mistryukov, E. A.; Shaskov, A. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 867. [aw] Levisalles, J.; Rudler-Chauvin, M. *Bull. Soc. Chim. Fr.* **1969**, 3947. [ax] Metha, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875. [ay] Metha, G.; Singh, B. P. *Tetrahedron Lett.* **1975**, 4495. [az] Plamendon, L.; Wuest, J. D. *J. Org. Chem.* **1991**, *56*, 2076. [ba] Tyllick, C.; El-Zohry, M. F.; Li, M.; Roberts, R. M. *J. Org. Chem.* **1991**, *56*, 2939. [bb] Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229. [bc] Malek, J. *Org. React. (N.Y.)* **1985**, *34*, 1. [bd] Stothers, J. B.; Tan, C. T.; Teo, K. C. *Can. J. Chem.* **1976**, *54*, 1211. [be] Banthorpe, D. V.; Davies, H. ff. *S. J. Chem. Soc. B* **1968**, 1356.

infringement, which is an attractive view to hold. We have also tried several other functions that all have been less successful.

(3) If only the steric congestion is taken into account, the results for substrates with small steric congestion or when small reagents are used are a bit disappointing. An empirical correction function based on Chérest and Felkin's proposal of torsional transition state effects,[2c] which also has been used by Wipke and Gund,[5] has proved to significantly improve the results. The cause for this torsional effect has been debated. Chérest and Felkin's original idea was that it was a four-electron destabilizing interaction between the vicinal covalent bond and the bonding orbital of the incipient bond.[2c] Anh considered it to be a two-electron stabilizing interaction with the adjacent antibonding orbitals.[2g] Cieplak postulated that it would be a two-electron stabilizing interaction of the vicinal occupied orbitals with the antibonding orbital of the incipient bond that would be the dominating contribution.[2h] We are not in a position to argue about the reason for this effect, but we have found it necessary to include it in this study. By using the torsional correction term, we can correctly predict the side of attack on several systems (*e.g.* 5-haloadamantan-2-one and 3-alkylbicyclo[2.2.2]cycloocten-2-one) which are impossible using only sterical terms. We calculate the dihedral angle between the hindering groups on the α-atoms and a line drawn through both the TS point and the carbonyl carbon (Figure 2). We have used the same kind of function as Wipke and Gund, eq 3, but with a parameter for each reagent (see Table III). Wipke and Gund proposed that there should be a different parameter for each kind of β-atoms, but they never realized this idea.

$$C_{\theta i} = k_3 \cos(90\theta/35) \qquad \text{for} \quad \theta < 35 \tag{3}$$

(4) The total congestion for each side is then calculated according to eq 4.

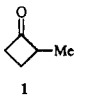
$$C_{i\text{tot}} = C_i + C_{\theta i} \tag{4}$$

(5) The selectivity, S, expressed as the ratio between the major and the minor products, is calculated as the difference between the lowest total congestion for the allowed conformations for the two sides (eq 5). C_j is the congestion calculated for the opposite face of the carbonyl from C_i.

$$S = 1 + \left|\min_{\text{conf}} C_{i,\text{tot.}} - \min_{\text{conf}} C_{j,\text{tot.}}\right| \tag{5}$$

Evaluation. We have minimized the geometrical mean deviation between our calculated selectivity and the values reported in the literature. We feel that it is important not to use standard root mean square (rms) methods in cases like this, because such a method would overemphasize the importance of data points that lay widely off the main stream and try to adjust the parameters to those few points. It could be any of a number of reasons why a single data point may lie far away from the others. Reaction conditions (solvent, temperature, or pH) could be far from the ones normally used, which might not be clearly stated in either the primary or secondary source an investigation like this must rely on. It would be a different matter if all the experiments were surely

Chart I



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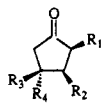
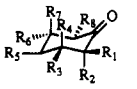
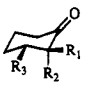


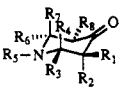
2 R_1 = Me
3 R_2 = Me
4 R_2 = *t*-Bu
5 R_2 = R_3 = Me
6 R_1 = R_3 = R_4 = Me
7 R_1 = NMe_2 *
8 R_1 = N-piperidyl *



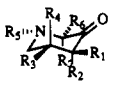
9 R_1 = Me
10 R_1 = Et
11 R_1 = *i*-Pr
12 R_1 = *t*-Bu
13 R_1 = R_2 = R_5 = Me
14 R_1 = R_2 = Me, R_5 = *t*-Bu
15 R_1 = Me, R_5 = *t*-Bu
16 R_1 = R_4 = Me, R_5 = *t*-Bu
17 R_1 = R_6 = R_7 = Me
18 R_2 = Me, R_5 = *t*-Bu
19 R_3 = Me
20 R_3 = *t*-Bu
21 R_3 = R_5 = Me
22 R_3 = R_6 = *t*-Bu
23 R_3 = R_6 = Me
24 R_3 = R_4 = R_6 = Me
25 R_4 = R_5 = Me
26 R_5 = Me
27 R_5 = *t*-Bu



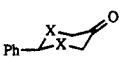
28 R_1 = NMe_2 *
29 R_1 = NPr_2 *
30 R_1 = N-piperidyl *
31 R_1 = N-morpholino *
32 R_1 = NMe *c*-C_6H_{11} *
33 R_1 = NH_2, R_2 = Ph *
34 R_1 = NMe_2, R_2 = Ph *
35 R_1 = NEt_2, R_2 = Ph *
36 R_1 = N*i*-Pr_2, R_2 = Ph *
37 R_3 = NMe_2
38 R_3 = N-piperidyl
39 R_1 = CH_2NMe_2



40 R_1 = R_2 = R_5 = R_8 = Me
41 R_1 = R_3 = Me, R_5 = *i*-Pr
42 R_1 = R_4 = Me, R_5 = Et
43 R_1 = R_5 = Me
44 R_1 = R_5 = R_6 = Me
45 R_1 = R_5 = R_6 = R_7 = Me
46 R_1 = Me, R_5 = Et
47 R_1 = R_6 = Me, R_5 = *i*-Pr
48 R_1 = R_3 = R_5 = Me
49 R_1 = Me, R_5 = *t*-Bu
50 R_1 = R_6 = Me, R_5 = *t*-Bu
51 R_1 = R_5 = R_8 = Me
52 R_1 = R_8 = Me, R_5 = *t*-Bu
53 R_1 = R_3 = Me, R_5 = *t*-Bu
54 R_1 = R_8 = Me, R_5 = *i*-Pr
55 R_3 = R_5 = Me
56 R_1 = R_7 = Me, R_5 = *t*-Bu
57 R_1 = R_4 = Me, R_5 = *t*-Bu
58 R_1 = R_4 = R_5 = Me
59 R_1 = R_3 = Me
60 R_1 = R_6 = Me
61 R_1 = R_8 = Me
a indicates N quarternized with H,
b indicates N quarternized with Me

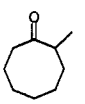


62 R_5 = Bn, R_1 = Me
63 R_5 = $PhCH_2CH_2$, R_1 = Me
64 R_3 = R_5 = *t*-Bu
65 R_3 = R_5 = Me
66 R_3 = Me, R_5 = Et
67 R_3 = Me, R_5 = *i*-Pr
68 R_3 = Me, R_5 = *t*-Bu
69 R_3 = R_7 = Me, R_5 = *t*-Bu
70 R_1 = Me, R_5 = *t*-Bu
71 R_3 = *t*-Bu, R_5 = Me
72 R_3 = R_6 = R_5 = Me
73 R_3 = *t*-Bu, R_5 = R_6 = Me
74 R_1 = R_3 = Me, R_5 = *t*-Bu
75 R_1 = *i*-Pr, R_3 = Me, R_5 = *t*-Bu
76 R_1 = *i*-Pr, R_5 = *t*-Bu
77 R_1 = R_5 = *t*-Bu
78 R_1 = R_6 = R_7 = Me
79 R_3 = R_5 = Me, R_6 = *i*-Pr
80 R_4 = R_5 = Me, R_6 = *i*-Pr
81 R_3 = *t*-Bu R_5 = R_7 = Me
a indicates N quarternized with H,
b indicates N quarternized with Me

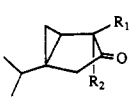


82 X = CH_2
83 X = O
84 X = S

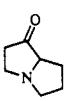
85



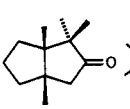
86



87 R_1 = Me †
88 R_2 = Me †



89



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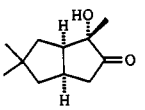
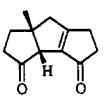
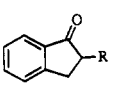


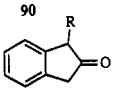
91*



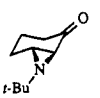
92



93 R = Me †
94 R = Et †
95 R = *i*-Pr †
96 R = *t*-Bu †
97 R = Ph †



98 R = Me †
99 R = *t*-Bu †
100 R = Ph †



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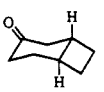

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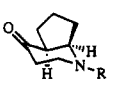
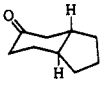


104 R = H
105 R = Me



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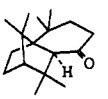

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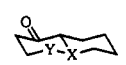
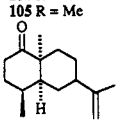


108 X = Y = CH
109 X = N, Y = CH
110 X = CH, Y = NCOPh



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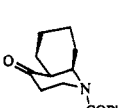

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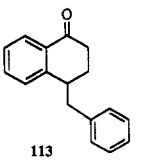

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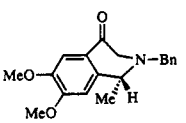

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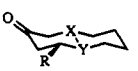
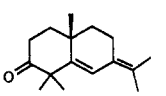


115 X = Y = CH
116 X = CMe, Y = CH
117 X = CH, Y = CMe
118 X = N, Y = CH
119 X = CH, Y = N
120 X = Y = CH, R = NMe_2



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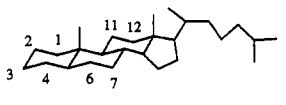
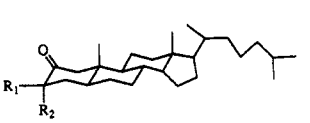
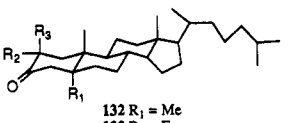


carbonyl function at carbon #

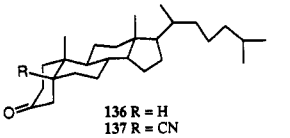
122 1	126 6
123 2	127 7
124 3	128 11
125 4	129 12



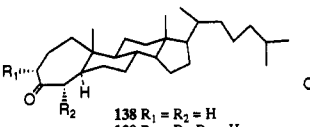
130 R_1 = F *
131 R_2 = F



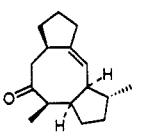
132 R_1 = Me
133 R_3 = F
134 R_2 = F *
135 R_1 = CN



136 R = H
137 R = CN



138 R_1 = R_2 = H
139 R_1 = Br, R_2 = H
140 R_1 = H, R_2 = Br



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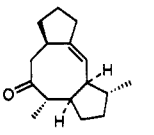

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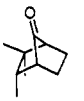

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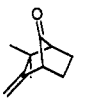

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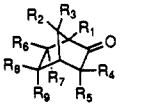

146
147 R_1 = Me
148 R_1 = R_2 = Me
149 R_1 = R_2 = R_3 = Me
150 R_1 = R_2 = R_3 = Me, R_5 = NH_2 *
151 R_1 = R_2 = R_3 = Me, R_5 = NMe_2 *
152 R_1 = R_4 = R_5 = Me
153 R_2 = R_3 = Me
154 R_4 = CH_2NMe_2
155 R_6 = Me
156 R_7 = Me
157 R_8 = Me
158 R_9 = Me
159 R_6 = R_7 = Me
160 R_6 = R_8 = Me
161 R_6 = R_9 = Me
162 R_7 = R_8 = Me
163 R_7 = R_9 = Me
164 R_6 = R_3 = Me

165

166

167

168 X-X = CH_2CH_2
169 X-X = CHCH

170 R = NH_2 *
171 R = NMe_2 *

172 R_1 = Me
173 R_2 = Me

174 R = Me
175 R = Et
176 R = *i*-Pr
177 R = *t*-Bu
178 R = Ph

179

180 n = 1
181 n = 2
182 n = 3

183 R = N-piperidyl *
184 R = N-morpholino *

185 †

186

187

188

189

190 †

191

192 R = *t*-Bu
193 R = Ph
194 R = F
195 R = Cl
196 R = Br
197 R = OH
198 R = CF_3
199 R = I

200

201

202

203

204

205

206

207 R_1 = Me
208 R_1 = Me, R_2 = MeO
209 R_1 = Et
210 R_1 = Et, R_2 = MeO

211

212

213 R = Me
214 R = Et
215 R = *i*-Pr
216 R = *t*-Bu
217 R = Ph

218 R = Me
219 R = Et

220

221

222

223

Table V. Distribution of the Ratio between Experimental and Calculated Selectivities for Each Reagent Summarized

ratio	BH_3	$LiAlH_4$	$NaBH_4$	$LiAl(OMe)_3H$	MeLi	MeMgX	PhLi	PhMgX	total
1–2	10	55	78	21	26	22	9	12	233
2–3	2	16	23	6	8	3	3	1	62
3–5	1	14	12	3	3	2	7	2	44
5–10	2	8	16	2	3	1	2	5	39
10–20	0	4	2	0	0	1	4	0	11
20–40	0	1	1	0	1	0	1	0	4
40	0	0	1	0	0	0	0	1	2
total	15	98	133	32	41	29	26	21	395
mean	1.81	2.22	2.23	1.88	1.86	1.77	3.27	2.71	2.18

performed under invariable conditions and if the substrates had some kind of absolute intrinsic reactivity, but even then merely a little inconsistency in nature's behavior would urge for the use of a non-rms method. A geometrical method on the other hand, overemphasizes the values that are in good accordance with the model, but that is easier to accept. Our approach has been to provide a method that could aid the synthetic organic chemist. To be useful in synthesis planning it is more important to correctly predict ratios in the range 3–10 than to be able to distinguish a 20:1 ratio from a 100:1 ratio. This is also the reason why we are presenting our results as ratios rather than diastereomeric excesses (de) since de would overemphasize ratios close to 1:1, which are not very important to a synthetic chemist.

RESULTS

In Table IV the results for the calculated reactions along with the experimental results are given (structures are given in Chart I). Most of the experimental data are taken from either Wipke and Gund[5b] or a review on amino alcohols by Tramontini.[12] When more than one experimental result has been found for a reaction, we have chosen a value near the higher end of the spectrum. Results, both experimental and calculated, which indicate a selectivity higher than 100 are adjusted to 100. If experimental results were given as a yield for one isomer and nothing is stated about the other isomer, the yield of the minor isomer is assumed to be 1%, except for in a few instances, where the minor isomer is taken to be the rest of the reaction mixture. For the Grignard reagents, the iodide and bromide have been used, and when both have been available, the iodine reagent has been chosen.

The results have been summarized in Table V, where the quotient between the calculated and the experimental value is given.

For the 32 reactions not included in the parameter optimization the geometrical mean is 6.3; *i.e.* for substrates where a heteroatom can direct the reagent to the side on which to attack on by electrostatic interactions, our model is not sufficient.

We would like to point out a few results to show the power and generality of our method.

For some of the substrates, *e.g.* the substituted cyclohexanones (**9–27**), the reagents have different preferred sides of attack (values in Table IV being both above and below 1.0). This variation is usually correctly predicted by our model.

For the 2-alkyl substituted indanones, **93–96**, the correct assignments were made for all eight reactions investigated with a slight underestimation of the face difference in a few cases. The three substrates **103**, **106** and **115** all show similar trends for the three reagents $LiAlH_4$, $NaBH_4$, and MeLi, which are well described by the calculations. Note also that MeLi shows a much lower selectivity.

For the 3-substituted [2.2.2]bicyclooctan-2-ones **134–138**, the correct side is predicted in all cases, two cis, two trans, and one ambiguous. For the bicyclic compounds **180–182** the enlargement of one of the rings dramatically changes the stereochemical outcome. The trends are well described for all five reagents for which we have data available. For the 5-substituted 2-adamantones **192–199** the correct side was assigned in all but one case (0.99 calculated, 1.27 found). Even the cis preference for the 5-hydroxy compound was correctly assigned. Some of the first published results for these substrates have been revised.[13]

The more complex polycyclic compounds **187–191**, **200–205**, **207–210**, and **222** are all correctly predicted to give high selectivities. Some of these predictions are off by a factor of 10, but in these cases this only means that 10:1 is predicted and 100:1 is found, or vice versa. With such high selectivities it is not as important to obtain very good predictions, the reactions are nevertheless synthetically useful.

DISCUSSION

We have developed a model for the fast prediction of the stereochemical outcome of reactions at carbonyl carbons in cyclic compounds. There is no principal reason why the model could not be expanded to include acyclic substrates, although there is often a rather large number of conformations of the substrate that must be taken into account. Also, other kinds of sp^2 centers should be possible to treat in the same manner, especially since we already have included both electrophilic and nucleophilic reagents. Here, the problem of regioselectivity arises and one has to include some kind of an electronic distribution calculation on the substrate. There are several ways to do this; most of them are much too slow to be considered here, but we have not yet addressed this problem in great detail.

There are a few data points in the results that are disappointing, six points where the ratio in Table V is above 20. For the substrates that can direct the reagent by electrostatic interactions, *i.e.*, the examples marked with an asterisk in Table IV, 5 of 30 have a ratio above 20. In these cases the selectivities are attributed to specific deliverances of the reagent by the equatorial heteroatom. To be able to correctly take electrostatic interactions into account, a method to calculate the electron distribution for the substrate has to be incorporated.[14] The difference in selectivity for **50** for MeLi and PhLi cannot be found by our method. Cholestan-2-one, **123**, reduction with $LiAlH_4$ is predicted to show a high selectivity, which is not found experimentally. In examples from the norbornanone series **146–164**, 2 of 38 are not satisfactorily. The steric influence of the methyl group at R_3 (endo-7) is not taken into account for the reduction with $NaBH_4$, although it is for done for the other reagents. In some cases, we cannot predict the rather unexpected experimental results. Substrate **143** reacts with MeLi, MeMgI, and PhMgI to give mostly the *anti* alcohol, but with PhLi one

gets primarily the *syn* alcohol. The very high selectivity of **2** with PhMgI, which is not seen with other reagents, is also hard to explain.

How does this model compare to others? Pure *ab initio* methods are today infeasible for all but the most simple substrate–reagent couples. The model that is most similar to ours is the one by Wipke and Gund.[5] That model gave a mean quotient of 3.23 for 66 reactions, compared to ours, 2.18 for 395 reactions. The combination of *ab initio* methods with molecular mechanics by Houk *et al.*[3,17] gives results that are somewhat better but is too slow to be used in an interactive application, which is our ultimate goal. The newly created model by Orsini and Sello[6] is attractive but still too slow for our purpose.

EXPERIMENTAL SECTION

All calculations have been performed on HP workstations, either a HP 9000/340 or a HP 9000/350 SRX, running HP-UX. Manipulations of the structures have been done by using a molecular graphics package written by one of us (T.O.). An all new program code has been written in standard C. The program used for calculating the selectivities consists of less than 1000 lines of code. Typical response times for a calculated structure are 0.6 s on the 340 and 0.3 s on the 350, respectively.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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

(2) (a) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. (b) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (c) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (d) Klein, J. *Tetrahedron Lett.* **1973**, 4307; *Tetrahedron* **1974**, *30*, 3349. (e) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. (f) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (g) Anh, N. T. *Topics in Curr. Chem.* **1980**, *88*, 145. (h) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (i) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc* **1982**, *104*, 7162.

(3) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(4) (a) Corey, E. J. *Q. Rev.* **1971**, *25*, 455. (b) Corey, E. J.; Long, A. K.; Rubenstein, S. D. *Science* **1985**, *228*, 408.

(5) (a) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1974**, *96*, 299. (b) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107.

(6) Orsini, F.; Sello, G *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 451.

(7) This method is very similar to MM2–85, which was the next official release. Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581.

(8) Ampac: Austin Method 1 Package; QCPE Program No. 527.

(9) Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620.

(10) Ashby, E. C.; Sevenair, J. P.; Dobbs, F. R. *J. Org. Chem.* **1971**, *36*, 197.

(11) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(12) Tramontini, M. *Synthesis* **1982**, 605.

(13) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, 4391. See also references *af* and *az* in Table IV.

(14) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219. Gasteiger, J.; Saller, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 687.

(15) Mukherjee, D.; Wu, Y.-D.; Franczek, F. R; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328.