Articles

Computer Assisted Mechanistic Evaluations of Organic Reactions. 26. Diastereoselective Additions: Cram's Rule

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The interactive computer program CAMEO has been refined to include Cram's rule. Incorporation of this chemistry involved modifications to the basic/nucleophilic module. Rules delineating the stereochemical outcome of the addition of a nucleophile to a carbonyl center with an adjacent chiral site have been derived and implemented. An algorithm to calculate Taft E_s values has been implemented to designate substituents on the chiral carbon as large, medium, and small. These values are dependent on the hybridization, atom type, and ring size and consider the steric contribution from atoms up to three levels away. The correct diastereoselective face is determined by vector analysis. Sample sequences are included to illustrate the scope and limitations of the treatment.

Introduction

CAMEO is an interactive computer program that, given the starting materials and reaction conditions, predicts the products of organic reactions. It uses empirical rules derived from literature precedent to guide the analyses of reactions; large databases are avoided. The program is divided into modules that, in general, are characterized by the type of intermediate involved in the reaction. The exception is the oxidative and reductive module, which encompasses several different mechanistic processes. Presently, base-catalyzed and nucleophilic,[1] acid-catalyzed and electrophilic,[2] pericyclic,[3] oxidative and reductive,[4] free radical,[5] carbenoid,[6] and transition organometallic[7] modules are implemented. In addition, a 3D module has been added to obtain facial selectivity and QSAR (log P, solubility) information.[8] A review of the program has been published.[9]

One of the most useful and versatile methods of forming a C–C bond is the addition of a nucleophile to a carbonyl group. The stereochemical outcome of these reactions is a critical issue, and models to help rationalize and predict diastereoselectivity have been proposed. One of the earliest models, Cram's rule,[10,11] deals with the addition of nucleophilic and reducing agents to acyclic carbonyl carbons with adjacent chiral centers. As presented here, criteria for the addition of organometallic reagents and carbanions to acyclic carbonyl substrates containing diastereoselective faces have been reviewed and implemented in the CAMEO program. Rules delineating the recognition of the diastereoselective faces and formation of the preferred diastereomer have been constructed from literature precedents.

This paper opens with a brief discussion of Cram's original rule and subsequent alternative representations for predicting the preferred face of attack by a nucleophile. The discussions are limited to general information necessary for understanding the empirical rules required for implementation. The third section describes the additions and refinements to the basic/nucleophilic module for the treatment of 1,2-asymmetric induction reactions. The paper closes with selected reactions that show the scope and limitations of the implementation.

Overview of Cram's Rule

The stereochemical course of 1,2-asymmetric addition reactions of aldehydes and ketones with organometallic and metal hydride reagents was first predicted by Cram and Elhafez in 1952.[10] This rule was devised for gauging the predominant product, but not for quantitative assessment. The original formulation of Cram's rule states "In noncatalytic reactions of the type shown [eq 1] that diastereomer will predominate which would be formed by the approach of the entering group from the less

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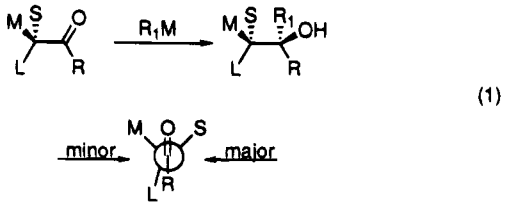

(1)

hindered side of the double bond when the rotational conformation of the C–C bond is such that the double bond is flanked by the two least hindered bulky groups attached to the asymmetric center."[10]

One and two conformer representations have been developed for Cram's rule as shown in Figure 1. In this and subsequent representations and reactions, L, M, and S indicate the large, medium and small substituent, respectively. Cram's initial statement indicates a one conformer version (**1**) from which attack on the less and more encumbered face results in the major and minor diastereomers, respectively. A later paper by Cram and Kopecky implied a two conformer representation (**2a,b**) in which, for steric reasons, the incoming nucleophile is remote from the two largest substituents.[12,13] It is assumed that the metal cation of the reagent coordinates with the carbonyl oxygen to form a bulky group which orients itself between the two smaller substituents. Hence, conformer **2a** results in the predominant diastereomer, while conformer **2b** gives the minor diastereomer due to steric interaction between the large ligand and the carbonyl oxygen.

Since Cram's rule was first proposed, several alternate representations have been suggested for the addition of a nucleophile to a chiral substrate. Karabatsos proposed a representation in which one ligand on the α carbon is eclipsed with the carbonyl C–O bond.[14] Major and minor diastereomers would arise from attack on the least hindered face, when the medium and large ligands are eclipsed with the carbonyl bond (Figure 1).

Felkin and co-workers proposed a third representation in which the bulkiest ligand is antiperiplanar to the incoming nucleophile.[15] The coordinated carbonyl oxygen is not considered to be a bulky substituent as in Cram's and Karabatsos formalisms; therefore, the dominant interaction is no longer between the carbonyl oxygen and the small and medium substituents. The primary steric interaction involves the incoming nucleophile and the achiral α-carbonyl substituent as shown in Figure 1. The major diastereomer is derived from structure **4a**.

Anh and Eisenstein reported ab initio calculations that supported the Felkin representation.[16] Hypothetical transition states for the Cram, Karabatsos, and Felkin representation for attack by a hydride ion to 2-chloro- and 2-methylpropanal were studied, and it was determined that the Felkin conformers (**4a,b**) were significantly lower in energy than the Cram or Karabatsos conformers. Anh and Eisenstein revised Felkin's formal-

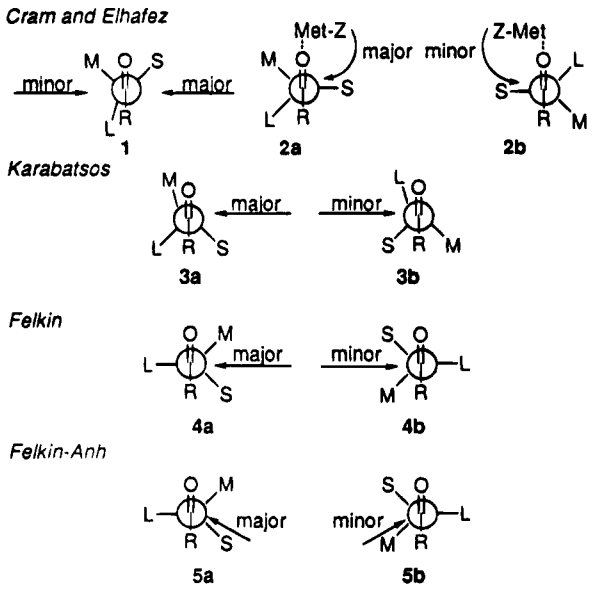

Figure 1. Representations of Cram's rule.

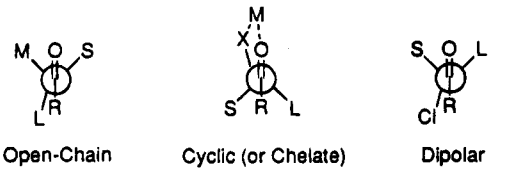

Figure 2. Three models of Cram's rule.

ism by incorporating the Bürgi–Dunitz trajectory, as shown in Figure 1. The primary steric interaction in the Felkin–Anh model is now between the incoming nucleophile and the small or medium substituent. It was also proposed, on the basis of frontier molecular orbital arguments, that the ligand with the lowest lying σ^* orbital, rather than the sterically most demanding group is perpendicular to the carbonyl plane. Recent calculations and studies by Houk,[17] Fraser,[18] and Heathcock[19] support the Felkin–Anh representation although it is still unclear which effects (electronic or steric) are dominant.[13]

Three different modes are used for the prediction of stereochemical control of asymmetric additions to chiral aldehydes and ketones (Figure 2). The open-chain and cyclic (or chelate) models have both been used extensively in rationalizing the product of Cram-type reactions. Alternatively, the dipolar model has been used infrequently and will only be discussed briefly.

Open-Chain Model. This model was originally postulated by Cram and co-workers in a series of papers studying the steric control of asymmetric induction.[10,20] The open-chain model is applied when the carbonyl center is the only polar group substituent. Although the degree of stereoselectivity varies and is generally low,

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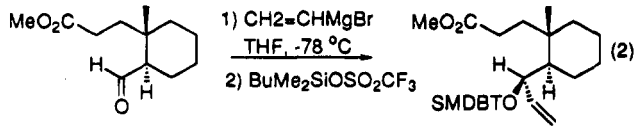
high levels have been obtained. For example, in eq 2, which yields a precursor for a taxane ring system, addition of the Grignard reagent gives a single diastereomer.[21] The quaternary center is considered to be the large group. Ohno reported high diastereofacial selectivity for the Cram product in nucleophilic additions to chiral acylsilanes.[22] Equation 3 shows the diastereomer that is favored (>100:1) upon the addition of *n*-BuLi to an α-chiral acylsilane.[22] In this reaction, the acylsilane functions as an aldehyde equivalent.



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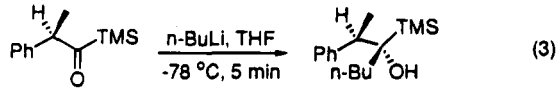
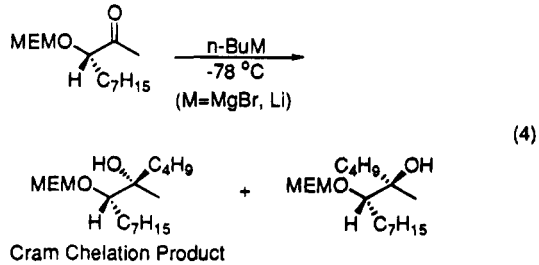


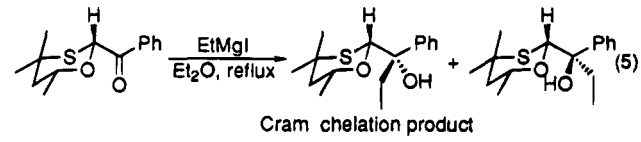
(3)

Cyclic (or Chelate) Model. If a group on the adjacent chiral center is capable of chelation, *i.e.*, if it contains an oxygen or nitrogen moiety in the α- or β-position, stereoselectivity is dictated by the cyclic model. In this model the substituent containing the oxygen or nitrogen atom is held in an approximately coplanar arrangement by simultaneous chelation with the metal counterion. The nucleophile attacks from the side with the smaller substituent. A number of studies investigating the reaction conditions of addition reactions that are rationalized using the cyclic model have been conducted.[12,23-27] Still and McDonald observed high stereoselectivity in Grignard additions to α-alkoxy ketones.[27] In eq 4,addition of *n*-butylmagnesium bromide



(4)

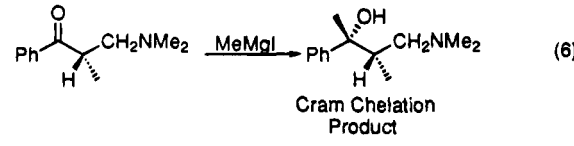
gave the Cram chelation product in ratios varying from 9:1 to >100:1, depending on the solvent. In contrast, n-butyllithium gave ratios varying from 0.7:1 to 3:1. Eliel and co-workers used Cram's chelate model to rationalize the high diastereoselectivity observed in the addition of Grignards to 2-acyl-1,3-oxathianes.[28] In eq 5 the addition of ethylmagnesium bromide to a chiral 1,3-oxathiane yielded almost exclusively the Cram chelation product. Addition of alkyllithium reagents to 1,3-oxathianes resulted in lower stereoselectivity (5:1). The addition of organometallic reagents to chiral α-amino aldehydes and



(5)

ketones has been reported to give varying selectivity by several groups.[29,30] Primary and secondary amino groups generally yield the Cram chelation product. The product arising from substrates with tertiary amino groups seems to be dependent on the size and nature of the substituents on the nitrogen. Larger groups, *e.g.*, isopropyl groups, give exclusively the anti-Cram product.

In 1968, Cram and Leitereg reported 1,3-asymmetric induction, based on Cram's rule, when the atom capable of chelation is in the β position.[31] The stereoselectivity reported in this and a subsequent study by Still and Schneider[32] was low for the addition of alkyllithium and Grignard reagents to β-alkoxy aldehydes and ketones. The use of organocuprates improved the selectivity, giving the Cram product in reactions with β-alkoxy aldehydes in diastereomeric purities ranging from 15–30:1. Greater success has been achieved with β-amino ketones. Tramontini reported exclusive formation of the Cram product in the addition of methylmagnesium iodide to the chiral β-amino ketone shown in eq 6.[33] As with α-amino groups, selectivity seems dependent on the size of the groups on the nitrogen atom. Little or no selectivity is obtained for bulky ligands (eq 7, 50:50).[34]



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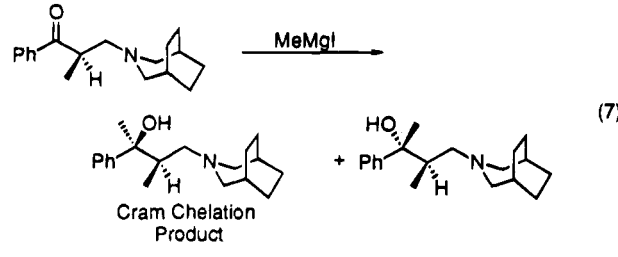

(7)

Dipolar Model. Cornforth proposed the third model of Cram's rule.[35] It appears to apply to substrates in which one of the substituents is a halogen. In this model the carbonyl group and the halogen align themselves in an antiperiplaner fashion. The nucleophile attacks from the side with the smaller substituent. This model is used infrequently.

Implementation in CAMEO

All of the changes that have been made in CAMEO to address this chemistry have been effected in the basic/

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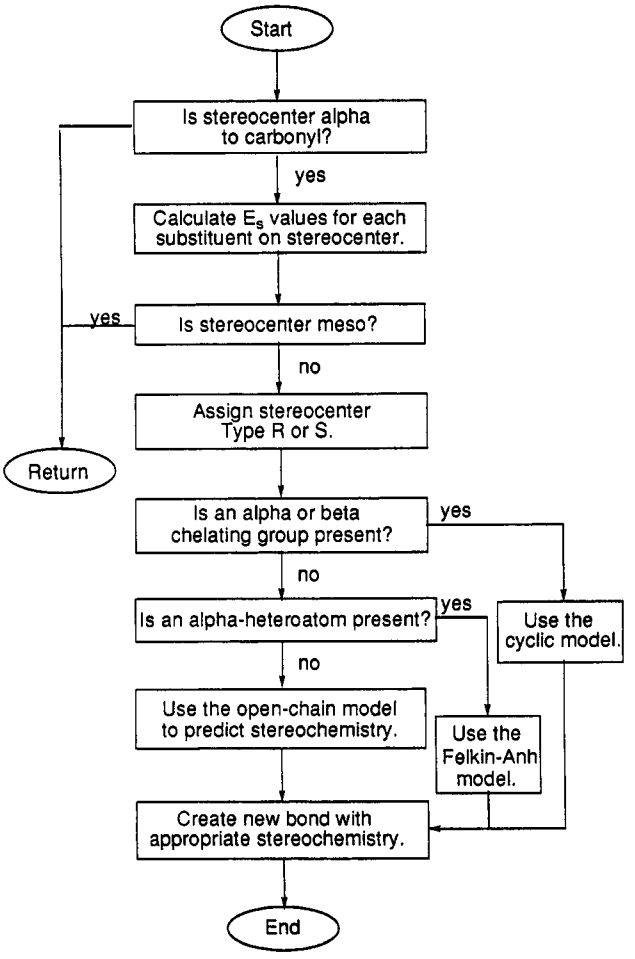

Figure 3. Flowchart of the implementation of Cram's rule.

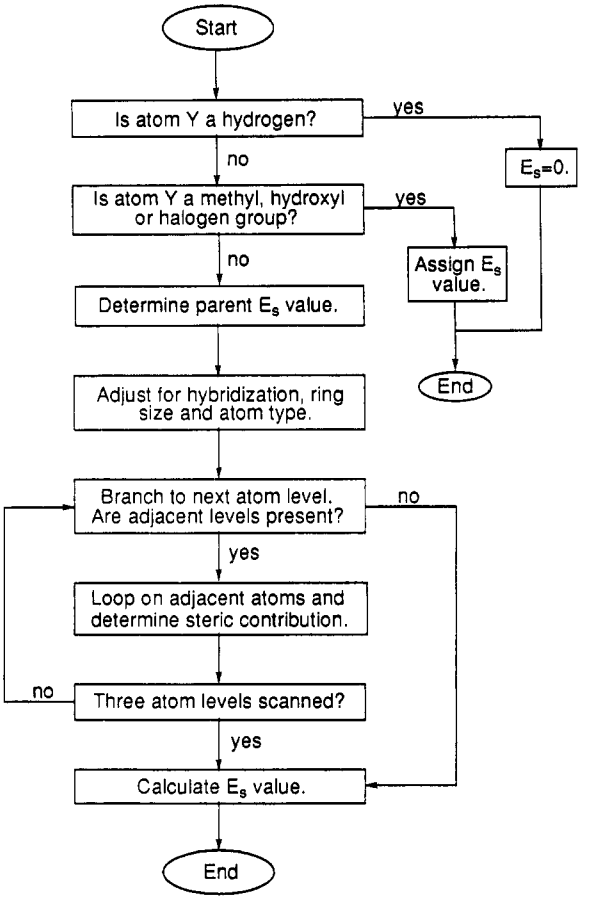

Figure 4. Flowchart of algorithm to determine E_s values.

nucleophilic module. The addition of an organometallic reagent to a carbonyl group has been implemented, and decisions regarding its feasibility have been made prior to consideration of diastereoselectivity.[36] Only specific changes needed to implement the diastereoselectivity will be discussed. The subroutine CRAM has been developed to gauge the stereoselectivity of these reactions. Figure 3 shows the general organization of this algorithm.

General Requirements. The stereochemical outcome of an addition reaction is addressed only when certain requirements have been satisfied. First, the electrophilic site under consideration must be an acyclic ketone, aldehyde, or acylsilane. Second, at least one stereocenter must be adjacent to the carbonyl group. Third, stereoselectivity is possible only when the nucleophile is a Grignard, alkyllithium, or organocuprate reagent. Reducing agents such as $LiAlH_4$ and $NaBH_4$ are handled by the oxidative/reductive module and are not considered by this module. Finally, the reaction must be intermolecular. No stereochemistry is imparted in intramolecular reactions. Once it has been determined that diastereoselectivity may be predicted, the size and nature of the substituents is examined. The two main factors that determine which diastereomer will be formed are the ranking of the substituents according to their size and the model (open-chain, cyclic, dipolar) used.

Ranking of the Substituents

The relative size of the substituents is an important factor in Cram-type reactions. In CAMEO, steric hindrance was previously calculated by considering only the number of neighbors of the atom. This method, while viable for many reactions, was limited. Ethyl and methoxy substituents were given the same steric factor since no consideration was given for atom types. A different approach to calculating the relative steric bulk of substituents was needed in order to account for atom types and ring atoms as well as hybridization. The most widely accepted steric constants based on reaction rates are Taft E_s values.[37] For acid-catalyzed hydrolysis of esters, Taft defined the steric parameter as shown in eq 8. Values range from 0 for hydrogen to −6.00 for a CPh_3 group.

$$E_s = \log\frac{k_x}{k_0} \tag{8}$$

An algorithm named ESUBS has been developed to predict Taft E_s values and is currently used in several mechanistic modules as well as in the basic/nucleophilic module. Taft E_s values can also be obtained interactively via the Sketch Menu during a CAMEO session. The values are computed in a method similar to the calculation of pK_a's.[38] A parent E_s value is given, and, in order to account for the steric contribution of nearby substituents, the program branches out three levels. The calculation of Taft E_s values is dependent on a small database. The flowchart in Figure 4 shows the organization of the

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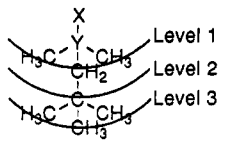
Example A

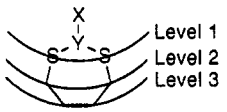


Atom Y has 4 attachments, Type III substituent	E_s^0=-2.80
Atom Y is a sp^3acyclic carbon	E_s^c=0
Level 1: 1 atom with 2 attachments	1(-.75)
2 atoms with 1 attachment	2(0)
Level 2: 1 atom with 4 attachments	1(-.15)
Level 3: 3 atoms with 1 attachment	3(0)

E_s = -2.80 + 1(-.75) + 1(-.15) = -3.70

$E_{s(experimental)}$ = -3.81

Example B



Atom Y has 3 attachments, Type II substituent	E_s^0=-1.70
Atom Y is a sp^3 7-membered ring carbon	E_s^c=.96
Level 1: 2 atoms with 2 attachments	2(-.70)
2 sulfur atoms	2(-.30)
Level 2: 2 atoms with 2 attachments	2(-.10)
Level 3: 2 atoms with 2 attachments	2(0)

E_s = -1.70 + (.96) + 2(-.70) + 2(-.30) + 2(-.10) = -2.94

$E_{s(experimental)}$ = -2.93

Figure 5. Two examples of Taft E_s calculations.

Table 1. Parent E_s^0 Values Based on the Number of Attachments to Atom Y

number of attachments on first atom of the substituent (atom Y)	Type	parent E_s^0 value
2	I	−1.30
3	II	−1.70
4	III	−2.80

ESUBS subroutine.

In eq 9, E_s^0 is the E_s value, based on the number of attachments on the first atom of the substituent. E_s^c is an empirical correction factor, derived from inspection of over 100 substituents, that is dependent on the hybridization, atom type, and whether the atom is a ring atom. The branching level index is represented by i; A_i is an empirical value dependent on the number of attachments in the branching levels, and B_i is an empirical correction factor based on the nature of the atoms in the branching levels.

$$E_s = E_s^0 - E_s^c + \sum_{i}^{\text{levels}} (A_i + B_i) \qquad (9)$$

In Figure 5, atom Y is considered to be the first atom. Parent E_s^0 can be found in Table 1. An atom with two attachments is designated as a Type I substituent and assigned the E_s value of an ethyl group (−1.30). Type II and III substituents are assigned parent values of an isopropyl and a *tert*-butyl group, respectively. A correction factor based on the hybridization, atom type, and ring size for atom Y can be found in Table 2. An E_s^c correction is taken for each applicable condition and the results are additive. If atom Y has only one non-hydrogen attachment (*e.g.*, methyl or a halogen), the experimental E_s value is assigned to the substituent. As stated above, the steric contribution of nearby substituents is accounted for by branching out three levels. In each level, adjustments are made for each group with two or more attachments (Table 3) based on the Type of substituent. Groups in the branching levels with only one attachment, such as methyl groups, are not considered in the adjustments and given a value of 0. Table 4 gives the B_i values based on the nature of the atoms in each level. Atoms in branching levels 2 and 3 in Type II, and level 3 in Type III substituents are not corrected and have been omitted from Table 4.

Table 2. E_s^c Correction Factors for Atom Y Based on Hybridization, Atom Type, and Ring Size

moiety	Type I or II	Type III
silicon	−0.50	−0.50
oxygen	0.75	0.75
sulfur	0.23	0.23
sp^2-carbon	−1.50	
sp^2-other	0.70	
sp-carbon	0.80	
three-membered ring atom	1.90	2.30
four-membered ring atom	1.90	2.30
five-membered ring atom	1.55	1.95
six-membered ring atom	1.27	1.67
seven-membered ring atom	0.96	1.36
>eight-membered ring atom	0.90	1.30

Table 3. A_i Values Based on the Number of Attachments of Atoms in Branching Levels

parent	number of attachments	level 1	A_i level 2	level 3
Type I	2	−0.30	−0.03	0
	3	−0.90	−0.10	−0.03
	4	−1.70	0	0
Type II	2	−0.70	−0.10	0
	3	−0.80	−0.30	−0.05
	4	−2.80	−0.60	−0.10
Type III	2	−0.75	−0.05	−0.01
	3	−0.80	−0.06	−0.02
	4	−2.30	−0.15	−0.05

Figure 5 shows two examples illustrating the process in which E_s values are calculated. In Example A, atom Y has four attachments; therefore, a parent E_s^0 value of −2.80 (Type III) is assigned. No E_s^c is added since atom Y is an sp^3 acyclic carbon. Branching to the first level, three atoms are considered. One of the atoms has two attachments while two atoms have one attachment. As shown in Table 3, the atom with two attachments is given a −0.75 correction factor. The two atoms with one attachment each have a zero correction factor. Branching out to the second and third level yields an additional −0.15 correction factor. The calculated E_s value is −3.70, which compares favorably with the −3.81 experimental value.[37]

In the second example, atom Y has three attachments and is assigned the parent E_s^0 value of −1.70. An E_s^c value of 0.96 is assigned from Table 2, since atom Y is a sp^3 carbon atom in a seven-membered ring. Branching to the first level, two sulfur atoms with two attachments are found. From Table 3, a correction factor of −0.70 for each atom is assigned. Furthermore, the B_i values taken from Table 4 are added to account for the sulfur atoms. Branching out to the second and third levels yields an additional −0.20 correction factor. The calculated E_s value is −2.94, which is in excellent agreement with the experimental value of −2.93.[39]

Table 4. B_i Values Based on the Nature of the Atoms in Branching Levels

moiety	Type I level 1	Type I level 2	Type I level 3	Type II level 1	Type III level 1	Type III level 2
sp^2-hybridized	0.65	0.6				
sp-hybridized			−0.11		1.55	
F	−0.18			−0.10	−0.13	
Cl	−0.18	−0.06	−0.09	−0.18(−0.56)[a]	−0.17	
Br	−0.21	−0.04		−0.47(−0.70)[a]	−0.28	
I	−0.31			−0.90	−0.40	
N^+	−1.13	1.23				
row 1 atom (excluding carbon)		−0.40				
row 2 atom		−0.60				
silicon		0.84				
oxygen				0.70	0.75	0.85
oxygen (NO_2)	−0.31					
oxygen (R_2O)				0.21[b]		
aromatic				0.15(0.25)[a]	(−0.20)[a]	
sulfur				−0.30		

[a] Values given in parentheses are used when more than one of the specified moiety is present in a branching level. [b] This value is in addition to the 0.70 correction factor taken for oxygen compounds with two attachments.

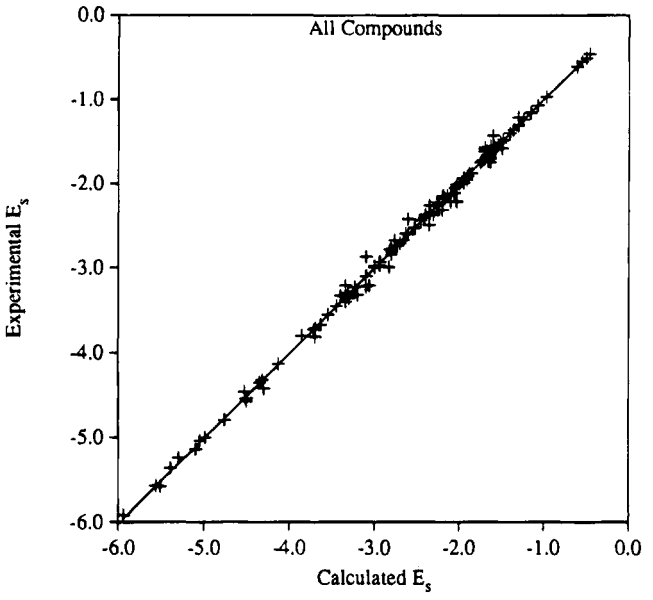


Figure 6. Experimental E_s vs calculated E_s for all compounds (n = 149, σ = 0.0783 and r = 0.9967).

Table 5. Calculated versus Experimental Taft E_s Values

functionality	number tested	σ	r
alkanes	30	0.0696	0.9980
halogens	22	0.0320	0.9979
nitrogens	10	0.0205	0.9999
sulfur/silicon	14	0.0719	0.9977
aromatic	20	0.0928	0.9966
oxygen	47	0.0912	0.9947

Predictions have been made using this method for 149 substituents with experimentally known E_s values.[40] Although the number of parameters used to calculate E_s values is large compared to our experimental database, the similarity of this method to pK_a prediction in the CAMEO program made implementation easier. Figure 6 is a plot of the experimental versus calculated Taft E_s values for all the compounds. The standard deviation is 0.0783 unit. Table 5 summarizes results for specific classes of substituents. In general, good correlation is given for alkanes as well as for substituents containing halogen, nitrogen, sulfur, or silicon. For most of these compounds, the E_s value tends to be overestimated, especially in highly branched compounds. Substituents containing aromatic units give a poorer correlation. The steric bulk of polycyclic aromatic units such as fluorenes is underestimated primarily due to the number of correction factors that are applicable to these compounds. Oxygen-containing substituents also give a lower correlation, although no trend was obvious.

Once the E_s values have been calculated, the substituents are ranked as large, medium, and small. Substituents containing α-heteroatoms not capable of chelation are designated as the large substituents, independent of the calculated E_s value. These bonds typically have lower σ^* orbitals; therefore, they are placed perpendicular to the carbonyl plane. This is only done in the absence of α-substituents capable of chelation. If the substituents are sp^3 carbons or heteroatoms capable of chelation, the ranking is accomplished simply by comparing the values. The substituent with the smallest E_s value is the largest group. The group with the largest E_s value is considered to be the small group. If two of the E_s values are identical no stereochemistry is imparted on the substrate, and the algorithm is exited.

Determination of Model. For substrates with atoms capable of chelation in the α or β position, the cyclic model is used. This is limited to oxygen and nitrogen moieties. The dipolar model is used when one of the substituents on the stereocenter is a chlorine atom. If neither of these two models is appropriate, the default is the open-chain model.

Perception of Diastereotopic Faces. In order to assign the correct stereochemistry, the diastereotopic faces of the carbonyl group must be identified and evaluated. This is dependent on the way in which the carbonyl substrate is drawn by the user. The position of the large, medium, and small substituents as well as the orientation of the carbonyl group is used to calculate the favored diastereotopic face. The clockwise order of the substituents as drawn on the screen (by sighting down a wedged or dotted bond) is determined and stored in an array.[1c] The first element is always the bond which has been wedged. The second element is the carbonyl carbon. The third and fourth elements are the other two substituents in a clockwise fashion from the second

(39) Minamida, I.; Ikeda, Y.; Uneyama, K.; Tagaki, W.; Oae, S. *Tetrahedron* **1968**, *24*, 5293.
(40) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91. Table 1 and references cited therein.

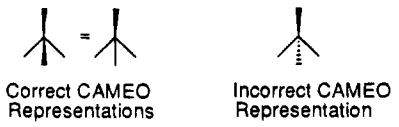


Figure 7. Representation of stereochemistry in the CAMEO program.

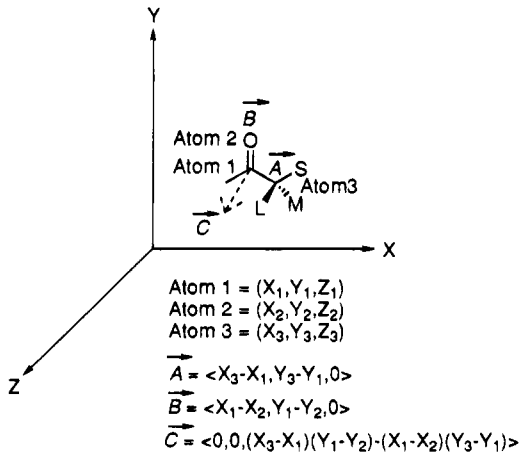


Figure 8. Chiral substrate in the XY plane of a right-handed coordinate system. Vectors $\vec{A}$ and $\vec{B}$ are placed along bonds in the substrate.

element. In the absence of a wedged bond, the dotted bond is used and the counterclockwise order is determined.

Only one stereobond is required in CAMEO to define a stereocenter (Figure 7); it is assumed that the bond opposing the stereobond has the same stereotype (wedged or dotted). Combinations in which the substituents are ordered in descending steric bulk (L/M/S, S/L/M, M/S/L) are designated as Type R substrates. If the substituents are ordered in ascending steric bulk they are considered to be Type S substrates. Note that the carbonyl carbon (the second element) is not considered in the ordering.

The diastereotopic faces of the carbonyl group are differentiated by treating the bonds in the substrate as vectors and calculating the direction of the resulting z-component. In Figure 8, the substrate lies in the XY plane of the coordinate system. The carbonyl carbon-chiral carbon bond (atom 1 to atom 3) and the carbonyl bond (atom 1 to atom 2) are treated as vectors and are labeled $\vec{A}$ and $\vec{B}$. The sign of the z-component of the resulting cross-product indicates whether movement from atom 3 to atom 2 is clockwise or counterclockwise. If the direction of the z-component is negative, then movement from atom 3 (chiral carbon) to atom 2 (carbonyl oxygen) is clockwise. A counterclockwise motion from atom 3 to atom 2 corresponds to a positive z-component.

Once the diastereotopic faces have been identified, they are used in conjunction with the ordering of the substituents to determine the stereochemistry imparted on the new bond. For the open-chain model, if the substituents are ordered in descending steric bulk (Type R) and if movement from the chiral carbon to the carbonyl oxygen is clockwise (z-component is in the negative direction) the new bond is wedged (Table 6). Attack of the nucleophile essentially comes from the front. Similarly, in a Type S substrate (acending steric bulk) with a z-component in the positive direction (movement is counterclockwise as in Figure 8), the new bond is also wedged. A dotted bond, or attack from the back, is imparted when the substituents are ordered in descending steric bulk (Type R) and movement from the chiral carbon to the carbonyl oxygen is counterclockwise. Finally, a dotted bond is designated when the direction of the z-component is negative and the substrate has been labeled as Type S.

Table 6. Stereochemistry Assigned Based on Order of the Substituents and Carbonyl Orientation for the Open-Chain Model

order of substituents[a]	direction of z-component[b]	stereochemistry
Type R	negative	wedge
	positive	dot
Type S	negative	dot
	positive	wedge

[a] Type R indicates the substituents are drawn in descending order based on steric bulk. Type S indicates the substituents are drawn in ascending order. [b] A z-component in the positive direction indicates movement from the chiral carbon to the carbonyl oxygen is counterclockwise. A z-component in the negative direction signifies a clockwise motion.

Table 7. Stereochemistry Assigned Based on the Size of the Chelating Substituent, Order of the Substituents, and Direction of the z-Component for the Cyclic Model

size of chelating substituent	order of substituents[a]	direction of z-component	stereochemistry imparted
medium	Type R	negative	wedge
		positive	dot
	Type S	negative	dot
		positive	wedge
large or small	Type R	negative	dot
		positive	wedge
	Type S	negative	wedge
		positive	dot

[a] Type R indicates the substituents are drawn in descending order based on steric bulk. Type S indicates the substituents are drawn in ascending order. [b] A z-component in the positive direction indicates movement from the chiral carbon to the carbonyl oxygen is counterclockwise. A z-component in the negative direction signifies a clockwise motion.

The predictions in Table 6 are correct only when the open-chain model is being used. For the cyclic model, if the substituent containing the atom capable of chelation is designated as the medium substituent, the same results as the open-chain model are assigned as shown in Table 7. However, opposite results of those predicted for the open-chain model are imparted if the substituent is designated the large or small group. The dipolar model, by definition, predicts the opposite results of the cyclic model. If the chloro group is designated as the medium substituent, the stereochemistry predicted is opposite of that given in Table 7. The same results as in Table 7 are given if the chloro group is the large or small substituent.

Designation of Major and Minor Products. The stereochemistry predicted by the CAMEO program is qualitative. No quantitative estimates are given regarding the stereoselectivity of the reaction. In general, the calculated favored diastereomer is deemed the major product, and only one enantiomer is shown. The enantiomer displayed is dependent on the way the user draws in the substituents. The other diastereomer is also shown; however, it is designated as a minor product. Two exceptions exist:

1. If the calculated E_s values of the large and medium groups differ by <0.05, *e.g.*, phenyl ($E_s = -3.86$) and tolyl ($E_s = -3.89$), both diastereomers are considered to be major products.

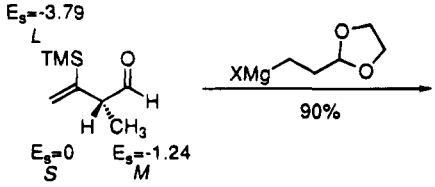
2. If the chelating atom is a tertiary nitrogen atom, the stereoselectivity may be lowered or reversed based on the size of the substituents on the nitrogen moiety. For α-amino compounds, if the cumulative E_s value is less than −3.30 (greater steric bulk), the anti-Cram product is designated as the major product. For β-amino compounds, if the cumulative E_s value is less than −3.50, both products are deemed major.

Information concerning the level of stereoselectivity is available to the user via the comment button on the tree menu.

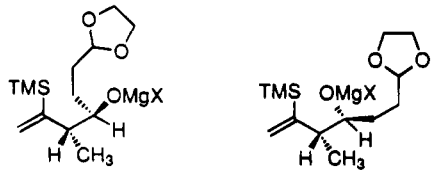
Sample Sequences

The previous section outlined the method used by the basic/nucleophilic module to predict products arising from the addition of organometallic reagents to a carbonyl compound with an adjacent chiral center. In this section, several examples are shown and discussed in detail to illustrate the program flow.

In eq 10, which yields a precursor of zincophorin, the Taft E_s values are calculated and the substituents are designated as large, medium, and small.[41] The open-chain model is used since none of the substituents is capable of chelation. The substituents are listed in ascending steric bulk; hence, it is labeled as a Type S substrate. Since motion from the chiral carbon to the carbonyl oxygen is clockwise, the direction of the calculated z-component is negative. From Table VI the new



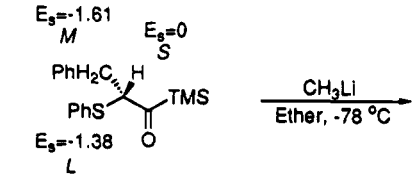
Type S
z-component, negative direction
(clockwise motion) (10)



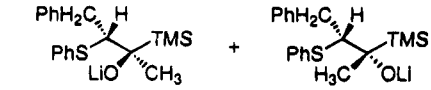
	6	7
CAMEO	Major	Minor
Experimental	100	--

bond is dotted. Although Danishefsky and coworkers identified only one product in 90% yield, the anti-Cram product is shown as a minor product.

The open-chain model is used for the substrate in eq 11.[42] Taft E_s values are calculated for each of the substituents. The sulfur substituent is designated as the large substituent based on electronic effects, regardless of the E_s values obtained. This only occurs when a sulfur atom is present and no atom capable of chelation is available. The other two substituents are labeled small and medium based on their E_s values. The substrate is labeled Type R since the substituents are in descending



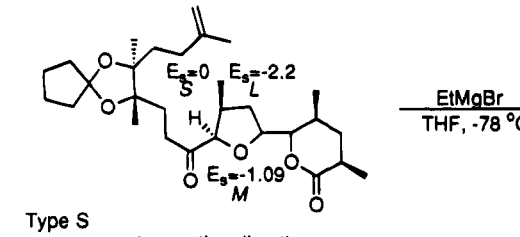
Type R
z-component, positive direction
(counterclockwise) (11)



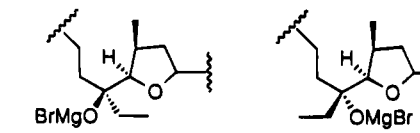
	8	9
CAMEO	Major	Minor
Experimental	97	3

order. The direction of the z-component is positive (counterclockwise motion); hence, the new bond is dotted. Experimentally the Cram:anti-Cram ratio was 97:3.

Equation 12 shows the addition of ethylmagnesium bromide to a precursor of monensin.[43] The cyclic model



Type S
z-component, negative direction
(clockwise motion)



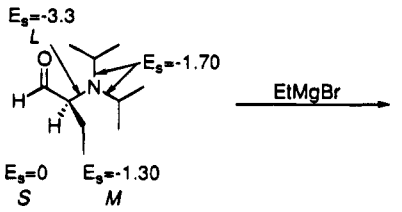
(12)

	10	11
CAMEO	Major	Minor
Experimental	100	--

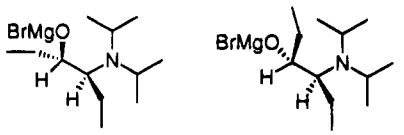
is used since an α-alkoxy group is present, and Taft E_s values are calculated. The substituents are Type S (ascending order) and the direction of the z-component is negative indictating a clockwise motion from the chiral carbon to the carbonyl oxygen. Since we are using the cyclic model, a check is made to determine if the chelating substituent is the medium group. If it is the medium-sized substituent, the stereochemistry imparted is the same as that predicted for the open-chain model (Table 7). The opposite stereochemistry is predicted if the chelating atom is the small or large substituent. In eq 12, the chelating substituent is the medium-sized group; therefore, the new bond is dotted.

A final example is shown in eq 13.[29] The Taft E_s values are calculated for this structure, and the substituents are designated as large, medium, and small. The cyclic model is used due to the presence of the α-amino group. The substituents are labeled as Type S, and movement from the chiral carbon to the carbonyl oxygen is coun-

(41) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.
(42) Reich, H. J.; Holtan, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 314.
(43) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120.



Type S
z-component, positive direction
(clockwise motion) (13)



	12	13
CAMEO	Minor	Major
Experimental	--	100

terclockwise. Since we are using the cyclic model and the chelating substituent is designated as the large group, the stereochemistry imparted can be found in Table VII. The new bond in the Cram-product is dotted. since the chelating group in the substrate is a tertiary nitrogen, the steric bulk of the substituents, excluding the chiral carbon, on the nitrogen are calculated. The two isopropyl groups give a total E_s value of −3.4. This value is less than the −3.3 cutoff discussed in the implementation; therefore, the anti-Cram product is deemed the major product. The Cram product is considered to be a minor product.

Conclusions

The treatment of stereochemistry in the basic/nucleophilic module of the computer synthesis program, CAMEO, has been refined and extended to include Cram's rule. Over 200 diastereoselective addition reactions, taken from literature precedent, were used to model Cram's rule in the CAMEO program; however, a number of reactions are better explained using the Felkin−Anh representation. In eq 11, strict adherence to labeling substituents large, medium, and small based on size would result in the experimentally minor product being designated as the major product. In the CAMEO program, the size of the substituent is generally dominant, though such electronic effects are considered when a substituent containing a heteroatom not capable of chelation is present. Implementation required the development of an algorithm to accurately predict Taft E_s values. This information coupled with consideration of the stereochemical representations of the chiral center and the diastereotopic faces of the carbonyl group allows correct prediction of the stereochemical outcome of a wide range of reactions.

Acknowledgment. Gratitude is expressed to the National Science Foundation for financial support.

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