

Geometric Requirements for Reactivity: The Simulation of Access to Reaction Centers and the Influence of Atomic Deformation on It

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Steric effects on reactivity are considered to be a combination of the strength of the interaction between reactant atoms and the repulsion among noninteracting atoms. A method for calculating the influence of atomic deformation on the magnitude of atomic interactions is described. A model for simulating the approach of two interacting molecules is discussed. The idea of accessibility to a reaction center is quantified through the analysis of a series of successive steps along the reaction path. The choice of the preferred direction of approach is made from an analysis of the sphere of potential surrounding the most reactive atom. The application of the model to the addition reaction of methyllithium, *tert*-butyllithium, and neopentyllithium to some ketones is reported, and the results are discussed.

INTRODUCTION

Molecular reactivity is a fundamental field in organic chemistry. Its control and management is one of the main objectives in every laboratory, and its modeling has become a most important target for theoreticians.

All the theoretical models simulate a reaction by representing the interacting molecules as objects equipped with sets of variables that change their values depending on the perturbations introduced by the surroundings. In other words the electronic states of the molecules are changing because of the molecular interactions.

Experimentally, the electronic states of the reactant molecules can furnish the basis for a reaction, but the three-dimensional geometric behavior of the molecules during the interaction often determines the real possibility of getting something out of the pot.

Throughout the long tale of chemical reactivity the presence of the phantom "steric hindrance" has caused the "successful" elucidation of the most obscure experimental results; however, the term was very seldom translated into something that chemists could calculate and clearly understand.

Our literature search¹⁻³ brought to light only two methods which appear to quantify geometric requirements for reactions: (1) one comprises all the systems based on linear regression analysis of kinetic data;² (2) the other concerns an analysis of the space around the reaction center that determines the hindrance of the nearest substituents represented by their van der Waals radii and corrects the results by using a torsional term derived by molecular mechanics.³

The reliability of the first method is based upon well-known experimental statistical validation; the results are always very good for specific classes of reactions and substances but as soon as an equation is applied to a different situation the results become unreliable due to the reaction or the reactants. Wipke's approach is completely different and its validity is proved only a posteriori by comparison with experimental results. The ratio between "convert and over"⁴ faces quantifies even the ratio of the product stereoisomers. The approach has been applied to a particular class of substances (cyclic ketones) in nucleophilic additions to the double bond.

Our approach to the problem is quite different. The model is based on the following assumptions:

- (1) Molecular conformations are derived from molecular mechanics⁵ calculations and are assumed rigid.
- (2) Molecular interaction, at long distances, is represented by a modified potential interaction in a particular space area.
- (3) Molecules approach rigidly, and the only allowed movements are translations along the two axes per-

pendicular to the movement direction.

- (4) Each collision is solved only through these translations.
- (5) The interaction produces a reaction as soon as the molecules are nearer than a threshold distance (where molecular deformation begins to control the interaction).

The values of some variables direct the evolution of the system; they are

- (1) the potential energy of interaction
- (2) the energy used to avoid collisions
- (3) the minimum distance of approach (i.e., the threshold distance).

The model is applied to the addition reaction of lithium derivatives to carbonyls with increasing steric congestion around the reaction centers.

THE MODEL

The model is based on three successive phases.

(1) The conformations of the molecules are calculated through the use of a molecular mechanics program. Some atomic characteristics (e.g., charges, polarizabilities) are evaluated by using a program of ours;⁶ this phase will not be described.

(2) Four interacting atoms (two for each molecule) are chosen as the most reactive among all the atoms, i.e., those giving the greatest minimum distance of interaction with a unit charge of opposite sign. These are coupled to give two pairs, each composed of two atoms (one for each molecule) with opposite charges. A potential sphere is built around each atom of the most reactive pair, the radius being the relative calculated distance. A mapping procedure on the spheres gives the spots of maximum negative and positive potentials. The molecules are oriented so that the opposite spots face each other; an interaction axis is defined as the axis perpendicular to the segments connecting the opposite spots in each molecule and lies in the plane defined by the two reacting atoms and the four spots. Along this axis, one of the molecules is then translated "out of" the second. This phase gives the starting situation for the interaction, the molecules being correctly oriented.

(3) An infinite cylinder is built oriented along the interaction axis with a base radius equal to the minimum interaction distance of the most reactive pair of atoms (see Figure 1). At fixed distances (0.3 or 0.5 Å) along the cylinder the potential is calculated and the moving molecules oriented so as to maximize the interaction. One of the molecules is then translated toward the other which is kept stationary. After each translation a check is made to verify the possibility of

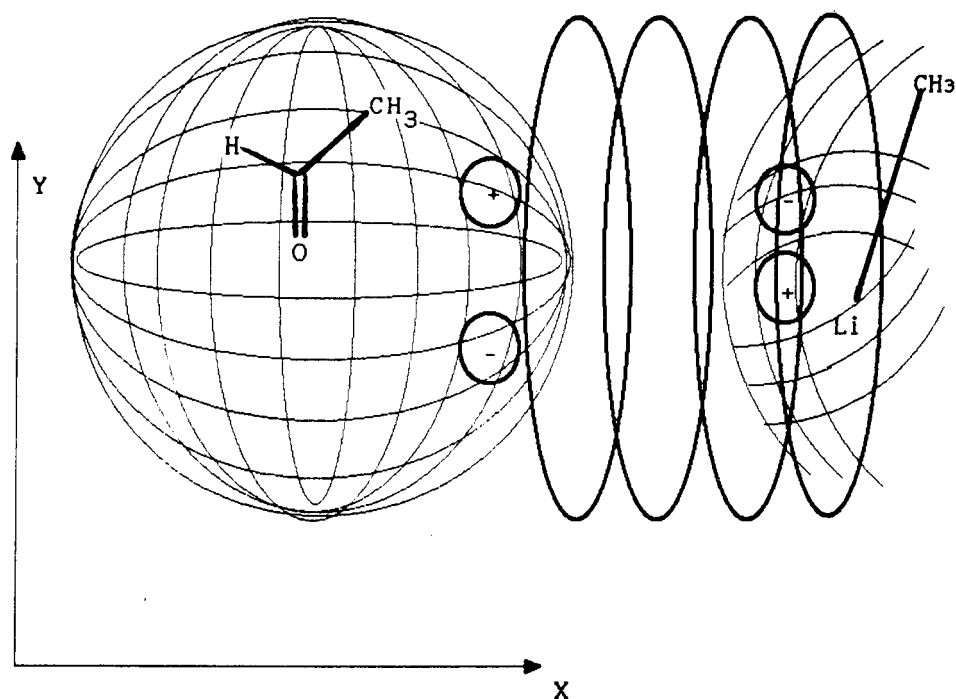


Figure 1. Simulated approach of CH_3Li to CH_3CHO . The interaction axis (X axis) lies in the plane (XY plane) defined by the two interacting atoms (O and Li) and by the two pairs of spots of maximum negative and positive potential, each on each molecule (small circles) and it is perpendicular to the segments joining each spot pair.

collisions, and small movements are done to eliminate the collision state. As soon as the two molecules reach the minimum interacting distance of the less reactive pair, the reaction is considered as beginning.

Minimum Interaction Distance Calculation. The calculation of the minimum distance of interaction is the first step required by the model. It represents a general concept: given two molecules in their ground state, each of their atoms has a potential tendency to interact with each atom of the other molecule; the distance where this interaction is strong enough to be considered is exactly the quantity that must be calculated. The interaction energy threshold has been fixed equal to 0.1 au (i.e., 30–35 kcal/mol), that is near three times the energy of a coordinative hydrogen bond and one-half of the weakest bond dissociation energies.

The interaction energy between an atom and its partner is equal to the electrostatic potential energy of the specified atom. A correction concerning the influence of atomic polarizability on potential energy has been introduced into the calculation of this energy.

In this perspective a new variable has been introduced: atomic electric deformability. It is calculated with

$$D_{\text{rel}} = D/D_{\text{ref}} = (\alpha - \alpha_{\text{min}})/\exp(1/R - r_{\text{cov}}) \quad (1)$$

where D_{rel} is the atomic deformability relative to a reference atom (neutral carbon), D is the absolute atomic deformability, D_{ref} is the deformability of the reference atom, α is the atomic polarizability, α_{min} is the atomic polarizability of H^+ , R is the distance where the deformability is calculated, and r_{cov} is the atomic covalent radius. Atomic polarizabilities are calculated by using a method already described.^{6d}

In this system the α of H^+ is equal to 0.12699, the α of C is equal to 1.11867, and therefore the D of carbon at infinite distance is equal to 0.99168 (i.e., approximately 1); this has been chosen as the reference deformability.

The interaction energy becomes

$$E = Q_1 Q_2 / R(D_{\text{rel}} + 1) \quad (2)$$

where Q_1 is equal to 1 and the deformability of an isolated charge is assumed to be meaningless.

This equation combined with eq 1 gives the following results: (1) the energy equals the standard electrostatic energy for a distance equal to r_{cov} where the deformability is equal to 0; (2) at any other distance the energy depends on the deformability; (3) at a distance shorter than r_{cov} both equations lose their meanings.

Considering two atoms A and B , eq 2 becomes

$$E = Q_A Q_B / R(D_{\text{relA}} + 1 + D_{\text{relB}} + 1) \quad (3)$$

and the energy depends on both the atomic deformabilities. Substituting in eq 2 the minimum interaction energy and solving for R gives the minimum interaction distance. (As the equation contains both linear and exponential terms, the solution is searched for numerically.) In a similar way it is possible to calculate the minimum interaction distance between two atoms solving eq 3. This distance is the quantity used from now on and it will be called DIST.

Potential Sphere Construction. Having DIST available, the second step of the model begins. It consists of the construction of a potential sphere around each interacting atom.

The sphere radius is taken equal to DIST, and a grid of points is calculated on the sphere. The grid is obtained by adding two sets of circles. Each set contains N equidistant parallel circles with decreasing radius, and the two sets are perpendicular to each other. Each circle contains a set of equidistant points. The distance between circles and between points is approximately similar, and this distance depends on the dimension of the sphere.

The potential for each point of the sphere is then calculated by using eq 2 modified for potential calculation. The potential depends on all the atoms in the molecule that could "see" the point.

The visibility of an atom is determined considering each atom as a sphere with the radius equal to r_{cov} and controlling if the sphere of the atom is visible from the point, i.e., it is not hindered by some other atom.

The next operation is the search for the areas on the potential sphere where the maxima potentials are concentrated. This is done by a mapping procedure that is divided into two phases: (1) once the maximum negative and positive potential

are determined, the sphere is scanned and all the points with a potential greater or equal to 80% of the maxima are chosen; (2) the geometric areas containing the points are evaluated together with the mass center of the point sets, and if necessary, the areas are balanced around the mass center eliminating all the points that are outside the new calculated areas.

The midpoints of the two areas are considered as representing the optimal disposition of the molecule for a possible interaction.

The calculation is repeated for both the molecules and these are oriented accordingly.

Cylinder Construction and Molecule Movements. The third phase of the procedure consists of the construction of the potential cylinder and the relative movement of the two molecules.

The starting point of the movement is obtained by positioning the two molecules with the midpoints of opposite polarities facing each other and by translating one of the molecules into a position of space where the two molecules do not touch and where the distance between the interacting atoms is greater than DIST.

Then the real interaction simulation begins. It is divided into three operations: (1) the best orientation of the two molecules at the actual distance is calculated; (2) one of the molecules is moved toward the other by a fixed distance (0.3 Å); (3) a check is done to verify the contact possibility between the two molecules, and if this contact is verified, a minimum translation is done to eliminate the contact; all steps are repeated until the two molecules reach the distance where the reaction begins. The three operations are described below.

(1) As anticipated, a circle perpendicular to the movement direction and with a radius equal to DIST is built, and 20 points are identified on it.

The potential interaction energy of the two molecules at these points is calculated for each possible orientation obtained by rotating one of the molecules with respect to the other in the 20 possible orientations.

Obviously if the rotation is hindered by a contact (see *infra*), the orientations in that direction are not considered. The best of these orientations is then considered the best possible one at that particular distance, and the molecules are oriented accordingly.

(2) This operation consists simply in a translation along the approaching direction. The magnitude of the translation is fixed and can be varied at will, but the present amount seems sufficient to map the interaction space.

(3) After each translation the possibility of contacts among the atoms of the two molecules is checked.

A contact happens any time two atoms are found at less than the sum of their covalent radii. This approximation differs from the use of considering the atomic dimension at the limit of the van der Waals radius. The difference is important, but the present approximation is less drastic because an atom with a rigid behavior at its van der Waals limit is without any foundation, whereas the rigidity of atoms at their covalent radius is conceivable because at this distance the bonding process is complete. A future objective is, however, to simulate an elastic behavior of the atoms just by using the atomic deformability introduced in this paper.

If a contact is present, one of the molecules is translated in the four directions perpendicular to the approaching line. The amount of the translation is calculated equal to that required to eliminate the contact. If all the contacts disappear during the translations the procedure continues, otherwise the approach is considered impossible.

With this operation the phase is concluded and the entire procedure is complete. The possibility of a different approaching direction is also considered and the whole procedure

is repeated starting with the two molecules positioned exactly at the point on the opposite side of the main approaching direction. This choice is a first approximation and in a future version the other approaching direction(s) will be chosen on the basis of the potential situation present in the sphere excluding the areas already considered.

The procedure has been transformed in a computer program (named CESIRA⁷), written in Fortran 77 and implemented on a Bull X-20 (using SVS Fortran compiler and Unix o.s.).

RESULTS AND DISCUSSION

The procedure just described has been applied to a particular reaction problem: the accessibility by alkyllithium derivatives with different bulk to some carbonyls with increasing steric congestion.

The choice of this addition reaction has been made for two reasons: (1) the addition reaction can be considered as a bipolar reaction where four atoms with opposite polarities interact to give the product, and the reaction is also easily analyzable from two complementary directions; (2) there exists the possibility of comparing the results with some of the results reported by Wipke.³

The results obtained will be shown and discussed in three sections: in the first, the complete set will be considered and the general trend shown; in the second, a comparison of some results will be made with semiempirical calculations; and in the third, one example taken from Wipke will be solved by both the present method and a semiempirical approach.

Table I shows the results obtained by using the procedure. The results cover the addition of methylolithium (MeLi), *tert*-butyllithium (*tert*-BuLi), and neopentylolithium (neopentLi) to a group of carbonyl compounds where at each step a hydrogen atom is substituted with a methyl group, starting from formaldehyde and finishing with di-*tert*-butyl ketone.

As mentioned above, the addition is simulated starting from two opposite sides of the carbonyl group; these two positions are not always exactly perpendicular to the C=O double bond because they only depend on the potential sphere around the interacting atoms and the positions are modified for each compound.

The second common observation concerns the rigidity of the molecules. In fact, they are approached without allowing rotations around bonds (no dihedral angle variations), and this restriction causes some results that could appear illogical; this first version, however, is only aimed at elucidating the possibilities of the procedure to simulate the steric behavior of molecules during their interaction. It is obvious that the introduction of some mobility into the structures can in certain cases suffice to overcome many obstacles.

It is also possible to observe a common trend in the interaction distances calculated for all the compounds. The increase in alkyl substitution determines a decrease in the distances; this is due to the greater positive congestion around the negative centers. (Compare the series formaldehyde, acetaldehyde, and acetone and the series MeLi, neopentLi, and *tert*-BuLi.)

The results will now be commented on considering pairs of neighboring structures.

Formaldehyde versus Acetaldehyde. Both molecules are relatively unhindered and all the reactions would proceed. The neopentLi molecule, however, has a curious behavior: it gives the usual reaction with acetaldehyde (but from the side opposite *tert*-BuLi) and no reaction with formaldehyde. This lack of reaction is related to the particular approaching direction where a proton lies directly in the pathway between the molecules, thus precluding the approach.

Acetaldehyde versus Acetone. In this case the increase in steric hindrance is very easily reproduced, precluding any

Table I. Accessibility Results by CESIRA for RLi Addition on Carbonyl Moieties

1 ^a	2 ^b	reacting distance C1-C1 ^c	reacting distance O-Li ^c	starting distance C1-C1 ^{c,d}	starting distance O-Li ^{c,d}	direct approach ^d	no. of contacts ^d
A	A'	2.61	8.93	3.09 [3.17]	2.63 [2.63]	Y [Y]	0 [1]
B	A'	2.47	8.99	2.52 [2.52]	2.71 [2.71]	N [N]	M [M] ^e
C	A'	2.35	9.05	2.72 [2.75]	2.94 [2.90]	Y [Y]	1 [2]
A	B'	3.21	8.82	4.43 [4.97]	3.52 [4.69]	Y [Y]	-1 [5]
B	B'	3.04	8.88	3.36 [3.14]	3.06 [3.47]	N [Y]	M [2]
C	B'	2.91	8.94	3.25 [2.92]	2.96 [3.29]	Y [N]	1 [M]
A	C'	3.70	8.50	4.52 [4.49]	3.98 [3.98]	Y [Y]	4 [3]
B	C'	3.52	8.55	3.72 [3.72]	3.69 [3.72]	N [N]	M [M]
C	C'	3.38	8.62	3.43 [3.40]	3.38 [3.39]	N [N]	M [M]
A	D'	3.72	8.50	6.41 [4.94]	6.18 [4.13]	Y [Y]	2 [0]
B	D'	3.54	8.55	4.53 [4.06]	4.76 [3.74]	N [N]	M [M]
C	D'	3.40	8.62	3.86 [3.75]	4.07 [3.42]	Y [Y]	3 [3]
A	E'	3.91	8.74	6.31 [5.35]	6.02 [4.41]	N [Y]	M [0]
B	E'	3.72	8.80	4.07 [4.31]	4.33 [3.94]	N [N]	M [M]
C	E'	3.58	8.86	3.67 [4.00]	3.93 [3.98]	N [Y]	M [1]
A	F'	3.94	8.71	5.49 [5.40]	5.16 [4.98]	Y [Y]	2 [3]
B	F'	3.76	8.77	4.68 [4.69]	4.82 [4.88]	N [N]	M [M]
C	F'	3.62	8.84	4.83 [4.79]	5.01 [4.91]	Y [Y]	6 [6]
A	E'	3.91	8.74	6.31 [5.35]	6.02 [4.41]	N [Y]	M [0]
B	E'	3.72	8.80	4.07 [4.31]	4.33 [3.94]	N [N]	M [M]
C	E'	3.58	8.86	3.67 [4.00]	3.93 [3.98]	N [Y]	M [1]
A	F'	3.94	8.71	5.49 [5.40]	5.16 [4.98]	Y [Y]	2 [3]
B	F'	3.76	8.77	4.68 [4.69]	4.82 [4.88]	N [N]	M [M]
C	F'	3.62	8.84	4.83 [4.79]	5.01 [4.91]	Y [Y]	6 [6]
A	G'	3.92	8.71	5.13 [7.19]	4.11 [7.09]	Y [N]	0 [M]
B	G'	3.73	8.77	4.17 [5.06]	3.74 [5.53]	N [N]	M [M]
C	G'	3.59	8.84	4.05 [4.95]	3.65 [5.42]	Y [N]	3 [M]
A	H'	3.82	8.71	4.72 [4.64]	4.53 [3.86]	Y [Y]	2 [1]
B	H'	3.63	8.77	3.63 [3.89]	4.07 [3.65]	N [N]	M [M]
C	H'	3.49	8.84	3.59 [3.96]	4.06 [3.71]	Y [Y]	2 [1]

^aCompound 1A is MeLi, 1B is neopentLi, and 1C is *tert*-BuLi. ^bCompound 2A' is formaldehyde, 2B' is acetaldehyde, 2C' is acetone, 2D' is methyl isopropyl ketone, 2E' is methyl *tert*-butyl ketone, 2F' is di-*tert*-butyl ketone, 2G' is camphor, and 2H' is fenchone. ^cDistances are in angstroms. ^dResults for the reverse approaching direction are reported in square brackets. ^eM represents the maximum number of contacts available.

reaction between acetone and neopentLi or *tert*-BuLi. As the two molecules are easy to compare, the results are as expected: the introduction of one methyl group is sufficient to prevent the reaction but does not modify the approaching direction.

Acetone versus Methyl Isopropyl Ketone. The presence of the isopropyl group is sufficient to modify the approaching direction, thus *tert*-BuLi can reach the carbonyl group from one side. The asymmetry of the potential sphere is also shown by the preferred reactive side, i.e., the isopropyl and not the methyl one, again showing the limitations due to molecular rigidity.

Methyl Isopropyl Ketone versus Methyl *tert*-Butyl Ketone. These two molecules also show a gradual increase in steric demand. The *tert*-butyl group causes such a symmetric hindrance that the approaching molecules can reach the carbonyl only from the methyl side. NeopentLi is unreactive.

Methyl *tert*-Butyl Ketone versus Di-*tert*-butyl Ketone. The di-*tert*-butyl ketone is the most hindered molecule considered in Table I and it can hardly react. This is verified in the case of neopentLi, but both MeLi and *tert*-BuLi seem to reach the necessary reactive distance. This is surprising when considering the situation of the methyl *tert*-butyl ketone, the approach from the *tert*-butyl side being nearly precluded. On the other hand, on analyzing the obtained output it is possible to observe a large number of collisions in the approach and also the high symmetry of the potential sphere that orients the reactant molecule nearly perpendicular to the carbonyl double bond, i.e., from the less hindered direction, thus allowing the correction of the colliding situations.⁸

The reactions of formaldehyde, methyl *tert*-butyl ketone, and camphor with MeLi were chosen to compare CESIRA results with those from semiempirical calculations. In the case of camphor, the results are also compared with those from Wipke³ as well as with experimental data.⁹

For this purpose the MM2-optimized geometries with the

Table II. Reaction of Formaldehyde with Methyllithium; Fully Optimized Conformation in the Direct Approach^{a,c,e}

C1-C1' ^b	C1-O	C1'-Li	O-Li	α^d	β^d	E
3.09	1.24	2.20	4.10	18.00	10.73	-647.67334
[0.00]	[1.94]					
2.90	1.23	2.08	5.71	74.17	52.24	-648.03441
[0.01]	[1.94]					
2.60	1.23	2.10	5.21	80.12	79.90	-648.04239
[0.04]	[1.91]					
2.30	1.24	2.17	4.90	86.21	84.06	-647.92488
[0.12]	[1.83]					
2.00	1.29	3.70	2.47	97.21	100.84	-648.48689
[0.69]	[1.33]					
1.70	1.32	4.22	2.36	103.81	109.95	-649.4015
[0.86]	[1.19]					
1.40	1.35	4.59	2.32	108.86	115.45	-649.3542
[0.97]	[1.31]					

^aDistances are in angstroms. Angles are in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1'-C1-O}$; $\beta = \text{C1'-C1-O-H}$. ^eEnergies are in eV.

CESIRA relative spatial orientations of the two reactant molecules have been used as starting points and elaborated with the AM1¹⁰ program in two different ways: (a) the C-C bond which is presumed to form in the reaction is chosen as the reaction coordinate, and the two reactants are fully optimized; (b) keeping the same reaction coordinate, the mutual orientation of the nucleophilic carbon (MeLi) and the carbonyl moiety has been chosen as an optimization constraint.

The results obtained are reported in the Tables II-IX and are discussed individually for each substrate.

Formaldehyde. In the fully optimized situation (case a), the reaction proceeds fairly easily in both the direct and the reverse approach even if in the former an earlier stabilization occurs (2.0 Å vs 1.7 Å) due to a stronger bonding interaction (0.69 vs 0.41) between the C1-C1' carbons.

Table III. Reaction of Formaldehyde with Methyl lithium; Fully Optimized Conformation in the Reversed Approach^{a,c,e}

C1-C1' ^b	C1-O	C1'-Li	O-Li	α^d	β^d	E
2.60	1.23	2.10	5.17	81.80	74.19	-648.04359
[0.04]	[1.92]					
2.30	1.24	2.18	4.90	86.67	84.24	-647.92327
[0.12]	[1.83]					
2.00	1.26	2.49	4.73	94.42	96.90	-647.65238
[0.41]	[1.60]					
1.70	1.32	4.36	2.35	54.74	123.50	-649.40306
[0.86]	[1.19]					
1.40	1.35	4.08	2.32	108.84	115.54	-649.35403
[0.97]	[1.13]					

^aDistances are in angstroms. Angles are in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1'-C1-O}$; $\beta = \text{C1'-C1-O-H}$. ^eEnergies are in eV.

Table IV. Reaction of Formaldehyde with Methyl lithium; Conformation with Optimization Constraints in the Direct Approach^{a,c,e}

C1-C1' ^b	C1-O	C1'-Li	O-Li	α^d	β^d	E
3.09	1.23	2.13	4.41	-13.50	-170.33	-647.81255
[0.00]	[1.94]					
2.90	1.24	2.20	4.06			-647.64667
[0.02]	[1.93]					
2.60	1.25	3.78	3.11			-647.99902
[0.03]	[1.86]					
2.30	1.26	3.67	3.07			-647.10538
[0.09]	[1.79]					
2.00	1.28	3.71	2.96			-644.62423
[0.17]	[1.67]					
1.70	1.31	3.90	2.71			-639.48326
[0.32]	[1.46]					
1.40	1.36	4.20	2.42			-629.614784
[0.65]	[1.19]					

^aDistances are in angstroms. Angles are in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from Mulliken population analysis. ^d $\alpha = \text{C1'-C1-O}$; $\beta = \text{C1'-C1-O-H}$. Both are kept fixed. ^eEnergies are in eV.

Table V. Reaction of Formaldehyde with Methyl lithium; Conformation with Optimization Constraints in the Reversed Approach^{a,c,e}

C1-C1' ^b	C1-O	C1'-Li	O-Li	α^d	β^d	E
2.6	1.23	2.15	4.91	137.27	3.53	-647.30715
[0.00]	[1.96]					
2.3	1.22	2.21	4.50			-646.35500
[0.01]	[1.95]					
2.0	1.22	2.28	4.34			-644.55713
[0.04]	[1.94]					
1.7	1.32	4.28	2.39			-645.22303
[0.87]	[1.25]					

^aDistances are in angstroms. Angles in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1'-C1-O}$; $\beta = \text{C1'-C1-O-H}$. Both angles are kept fixed. ^eEnergies are in eV.

In case b the reaction proceeds equally well with C1-C1' bond formation at 1.7 Å in the reverse approach, whereas in the direct one the imposed optimization constraints force the C1' carbon far too close to one of the formaldehyde hydrogen and the AM1 results are no more reliable.

These results are in agreement with those by CESIRA. In particular the results in case a show that the C1-C1' interaction begins around 2.6 Å in both approaches (direct and reverse): a value comparable with CESIRA distance (2.61 Å). In case b the results are again similar to CESIRA's also for the presence of a hydrogen on the reaction path in the direct approach.

Methyl *tert*-Butyl Ketone. In the fully optimized situation the reaction proceeds easily in both approaches, an unexpected result because one (the direct one) must suffer a very different

Table VI. Reaction of Methyl *tert*-Butyl Ketone with Methyl lithium; Fully Optimized Conformation in the Direct Approach^{a,c,e}

C2-C1' ^b	C2-O	C1'-Li	O-Li	α^d	β^d	E
6.31	1.21	1.81	6.44	103.35	-154.07	-1426.88790
[0.00]	[1.91]					
5.00	1.24	2.07	7.98	50.56	173.58	-1426.96460
[0.00]	[1.90]					
4.70	1.24	2.07	7.86	50.87	159.83	-1426.99030
[0.00]	[1.90]					
4.40	1.24	2.08	7.63	47.73	153.80	-1427.01420
[0.00]	[1.90]					
4.10	1.24	2.09	7.29	50.04	148.53	-1426.96770
[0.01]	[1.89]					
3.80	1.24	2.08	6.13	67.96	110.49	-1426.97520
[0.00]	[1.89]					
3.50	1.24	2.08	5.13	78.05	90.08	-1426.97470
[0.00]	[1.89]					
3.20	1.24	2.09	4.88	82.03	94.89	-1426.9181
[0.00]	[1.89]					
2.90	1.24	2.10	4.84	88.54	91.50	-1426.7777
[0.00]	[1.89]					
2.60	1.24	2.11	4.77	89.08	89.66	-1426.6620
[0.00]	[1.88]					
2.30	1.24	2.21	4.71	92.07	98.66	-1426.37374
[0.14]	[1.78]					
2.00	1.30	3.88	2.49	97.72	110.88	-1426.97874
[0.71]	[1.30]					
1.70	1.34	4.34	2.40	103.40	117.34	-1427.828630
[0.86]	[1.19]					
1.40	1.36	4.38	2.39	108.32	123.35	-1427.633892
[0.96]	[1.14]					

^aDistances are in angstroms. Angles are in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1'-C2-C1}$; $\beta = \text{C1'-C2-C1-O}$. ^eEnergies are in eV.

Table VII. Reaction of Methyl *tert*-Butyl Ketone with Methyl lithium; Fully Optimized Conformation in the Reversed Approach^{a,c,e}

C2-C1' ^b	C2-O	C1'-Li	O-Li	α^d	β^d	E
5.35	1.24	2.07	4.16	131.16	-75.58	-1426.93400
[0.00]	[1.89]					
4.70	1.24	2.08	4.05	109.41	-76.64	-1426.92420
[0.00]	[1.89]					
4.40	1.24	2.08	4.18	100.33	-85.24	-1426.94110
[0.00]	[1.89]					
4.10	1.24	2.08	4.64	69.94	-86.71	-1426.97060
[0.00]	[1.89]					
3.80	1.24	2.08	4.52	74.34	-86.07	-1426.97540
[0.00]	[1.89]					
3.50	1.24	2.08	4.59	79.56	-89.15	-1426.97960
[0.00]	[1.89]					
3.20	1.24	2.09	4.40	84.09	-89.97	-1426.92280
[0.00]	[1.89]					
2.90	1.24	2.09	4.51	85.46	-85.25	-1426.83850
[0.01]	[1.89]					
2.60	1.24	2.11	4.58	86.64	-88.92	-1426.66770
[0.03]	[1.87]					
2.30	1.25	2.21	4.64	91.31	-98.31	-1426.36680
[0.14]	[1.78]					
2.00	1.30	3.87	2.48	97.89	-110.84	-1426.973767
[0.71]	[1.30]					
1.70	1.33	4.34	2.41	103.44	-117.34	-1427.828702
[0.86]	[1.19]					
1.40	1.36	4.37	2.39	108.35	-123.49	-1426.633934
[0.96]	[1.14]					

^aDistances are in angstroms. Angles are in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1'-C2-C1}$; $\beta = \text{C1'-C2-C1-O}$. ^eEnergies are in eV.

steric congestion. In fact the first operation done by AM1 is to move the MeLi on the methyl side of the ketone, as in the reverse approach but on the other side of the carbonyl plane.

In case b the reaction proceeds in the direct approach whereas in the reverse one the C1' carbon comes too close to

Table VIII. Reaction of Camphor with Methylithium; Fully Optimized Conformation in the Direct Approach^{a,c,e}

C2-C1' ^b	C2-O	C1'-Li	O-Li	α^d	β^d	E
5.10	1.23	2.07	7.04	22.55	68.96	-1993.87237
[0.00]	[1.91]					
4.8	1.23	2.07	7.27	25.19	88.40	-1993.87420
[0.00]	[1.91]					
4.5	1.23	2.07	6.59	46.29	144.02	-1993.88852
[0.00]	[1.91]					
4.2	1.23	2.07	6.11	55.60	118.96	-1993.88739
[0.00]	[1.91]					
3.9	1.23	2.07	5.44	63.35	124.13	-1993.88287
[0.00]	[1.91]					
3.6	1.23	2.07	4.76	71.40	132.22	-1993.83075
[0.00]	[1.92]					
3.3	1.23	2.07	4.48	79.41	130.46	-1993.79440
[0.00]	[1.91]					
3.0	1.23	2.09	4.21	85.08	129.97	-1993.70324
[0.00]	[1.92]					
2.7	1.23	2.11	4.07	90.44	128.43	-1993.49582
[0.01]	[1.90]					
2.4	1.24	2.18	4.30	94.81	129.37	-1993.13693
[0.08]	[1.83]					
2.1	1.29	3.71	2.52	104.22	119.92	-1993.51945
[0.66]	[1.35]					
1.8	1.32	4.24	2.43	107.58	120.76	-1993.37786
[0.83]	[1.23]					
1.5	1.34	4.37	2.42	111.13	121.19	-1994.93981
[0.93]	[1.17]					

^aDistances are in angstroms. Angles in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1}'\text{-C2-C3}$; $\beta = \text{C1}'\text{-C2-C3-C4}$. ^eEnergies are in eV.

Table IX. Reaction of Camphor with Methylithium; Fully Optimized Conformation in the Reversed Approach^{a,c,e}

C2-C1' ^b	C2-O	C1'-Li	O-Li	α^d	β^d	E
5.10	1.23	2.07	4.43	104.35	-96.70	-1993.87909
[0.00]	[1.90]					
4.80	1.23	2.08	4.15	103.53	-97.54	-1993.88138
[0.00]	[1.90]					
4.50	1.23	2.08	4.26	81.47	-100.28	-1993.89018
[0.00]	[1.90]					
4.20	1.23	2.08	4.19	81.28	-100.83	-1993.89657
[0.00]	[1.90]					
3.90	1.23	2.09	4.07	83.03	-102.09	-1993.89512
[0.00]	[1.90]					
3.60	1.23	2.09	4.15	81.47	-104.48	-1993.87940
[0.00]	[1.90]					
3.30	1.23	2.09	4.33	80.40	-106.36	-1993.82678
[0.00]	[1.90]					
3.00	1.23	2.08	4.23	95.19	-166.67	-1993.71886
[0.00]	[1.90]					
2.70	1.23	2.10	4.54	90.73	-115.21	-1993.57713
[0.01]	[1.91]					
2.40	1.23	2.16	4.55	95.18	-115.49	-1993.30790
[0.08]	[1.84]					
2.10	1.26	2.44	4.54	99.73	-115.55	-1992.99035
[0.36]	[1.63]					
1.80	1.31	4.11	2.44	105.36	-116.54	-1994.44115
[0.81]	[1.23]					
1.50	1.34	4.24	2.42	109.39	-115.94	-1994.99615
[0.93]	[1.17]					

^aDistances in angstroms. Angles in degrees. ^bReaction coordinate. ^cThe values in brackets refer to the bond orders from the Mulliken population analysis. ^d $\alpha = \text{C1}'\text{-C2-C3}$; $\beta = \text{C1}'\text{-C2-C3-C4}$. ^eEnergies are in eV.

the methyl carbon (1.93 Å at 2.9 Å for C1'-C1) precluding the expected reaction. CESIRA gives the opposite results. However, keeping the lithium position fixed with respect to the carbonyl moiety the expected reaction does not occur in either approach due to a collision of the MeLi with one of the ketone hydrogens; this collision occurs at a shorter distance for the reverse approach, and, what is more, at a distance much shorter than the one calculated by CESIRA for the interaction

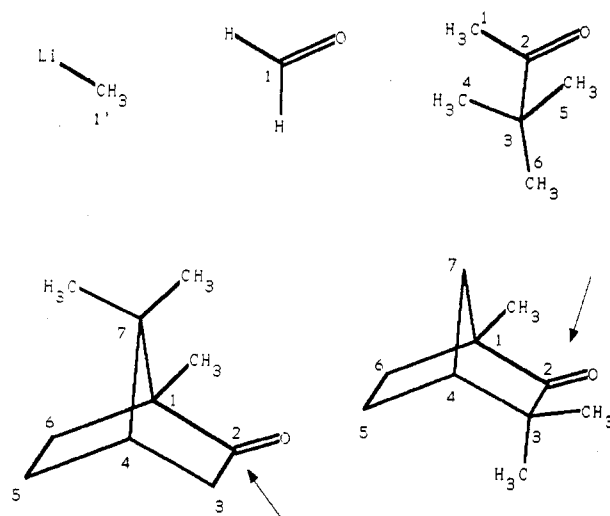


Figure 2. Structures used in AM1 calculations together with the atom numbering used (methylithium, formaldehyde, methyl *tert*-butyl ketone, camphor, and fenchone). The successful approaching directions are evidenced for camphor and fenchone (the arrows point to that side of the molecule where MeLi addition is calculated to proceed).

(deformation) to begin. A full optimization would overcome this problem through conformational modifications and allow the reaction to proceed.

Camphor. In the fully optimized situation the reaction proceeds easily in both approaches. As in the case of methyl *tert*-butyl ketone, MeLi in the most hindered direction of approach (here the reverse one) is moved toward the "overt" side of the camphor molecule, the same side involved in the direct approach.

In case b the reaction does not proceed in both the approaches: at a reaction coordinate around 4.5–4.2 Å the passage of the C1' "near" one carbon of the camphor skeleton (C3 or C7) causes an interaction between the carbons and deviates the reaction from the expected path. This effect is probably related to the treatment of the C-Li bond as an ion pair by AM1. As in the previous example, a full optimization would overcome this problem through conformational modifications and allow the reaction to proceed.

CESIRA gives different results, allowing the reaction only in the direct approach. This behavior is in qualitative agreement with that reported by Wipke and obtained by experiment. The agreement is also confirmed in the case of fenchone where the successful direction of approach is the opposite (reverse) one (see Figure 2).

CONCLUSION

This paper reports a procedure for the evaluation of the accessibility to reaction centers. Some of the results are discussed and compared with those obtained by a semi-empirical approach, by the procedure described by Wipke, and by experiment. Considering the present level of development of the procedure, it is possible to affirm that CESIRA is already giving good answers to the problem of accessibility. The two principal requirements for a model for steric hindrance are present: (1) a completely general treatment of steric hindrance as an electrostatic force; (2) a procedure for calculating both the approaching direction and the optimum molecular spatial disposition at each step.

Some problems still remain: (1) the necessity of considering more spatial movements for solving the collision states; (2) the possibility to calculate the energy cost of these movements, thus obtaining a method for evaluating the relative reaction rates and the product percentages by alternative approaches; (3) the need to consider the molecular conformational space

in a different perspective. Points 1 and 2 are sufficiently easy to solve and are presently being studied; point 3 is much more complex, requiring greater effort and much thinking before reaching a solution.

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- (7) CESIRA is not an acronym but the name of the wife of a mole in a comic strip.
- (8) It is noteworthy that the reaction is reported to proceed. See: Tidwell, T. T. Sterically Crowded Organic Molecules: Synthesis, Structure and Properties. *Tetrahedron* **1978**, *34*, 1855-1868.
- (9) See references cited in ref 3 for experimental value comparison.
- (10) *Ampac: Austin Method 1 Package*; QCPE Program No. 527.