

VADER: New Software for Exploring Interconversions on Potential Energy Surfaces[†]

Martin Černohorský,^{‡,§} Sofiane Kettou,^{§,||} and Jaroslav Koča*,^{§,||}

Institute of Computer Science, Masaryk University, 602 00 Brno, Czech Republic, Department of Organic Chemistry, Faculty of Science, Masaryk University, 611 37 Brno, Czech Republic, and Laboratory of Biomolecular Structure and Dynamics, Faculty of Science, Masaryk University, 611 37 Brno, Czech Republic

Received December 24, 1998

A new computer program for investigating both reaction and conformational potential energy surfaces (PES's) based on the utilization of the extended single coordinate driving technique is presented. The program is called *VADER*—advanced variation of driver. It uses an external quantum mechanics program to calculate the energy of the studied system and also for the minimization procedure. On simple examples it is shown that the program is capable of studying the reactivity of small organic molecules and biomolecules. *VADER* is probably the first software that is able to generate the topology of a reaction PES using quantum chemistry in an automated way. The program will be made available.

INTRODUCTION

The behavior of a chemical system can be described by its energy as the function of its coordinates. For the majority of systems containing n atoms, it is possible to express the energy as a function

$$E = f(x_1, x_2, \dots, x_{3n-6})$$

This function is not known analytically (for nontrivial systems), and thus the energy must be calculated for given coordinates $x_1 \dots x_{3n-6}$ by a quantum mechanics^{1,2} or force field method.³ The geometrical interpretation of the above function calculated within the Born–Oppenheimer approximation is called the potential energy surface, PES. There are two categories of interesting points on the PES:

1. Local minima—critical points of zero index⁴ representing stable structures (reactants, products, conformers, etc).
2. Saddle points—critical points of index 1, representing the highest energy points on lowest energy pathways connecting two minima (transition states).

Many techniques (for example, refs 5, 6 and others) are described in the literature which lead to an analysis of PES in terms of stationary points. Looking for a minimum is a relatively simple task as it is the usual result of the majority of minimization techniques. The solution is much more complicated when one is looking for a saddle point. The real problem is not to prove that a stationary point is a saddle (this is done by calculating eigenvalues of the Hessian) but to find the saddle.

Most techniques for finding saddle points work well only under the condition that the starting point for transition state optimization lies close to the saddle point,^{7–10} or they require the knowledge of both starting and ending minima.^{11,8,12} All these techniques are computationally expensive except for

the technique described in ref 12, which works extremely fast but sometimes fails to find the transition state. An overview of these methods may be found, for example, in refs 13 and 14. None of these methods are designed for the global analysis of the PES, which is the key problem in the study of conformational behavior and chemical reactivity.

One way to obtain a global view of PES is to use a multidimensional variation of the GRID SEARCH (GS) technique, but this approach is computationally very expensive and has several serious drawbacks. Sometimes it produces, artifactually, areas of PES where the energy function is discontinuous. These areas can have a significant negative influence on analysis of other parts of the PES.¹⁵ Furthermore, in order to estimate reaction pathways from the results of GS, it is necessary to process the obtained data further, which is simple on two-dimensional GS results but is more complicated for higher dimensions. Another problem of the GS technique is the large amount of data which is necessary to describe the selected part of the PES.

There is a modification of the GS technique called ValleyScan (VS)¹⁶ which avoids several of the problems of GS discussed in ref 15. This approach calculates only those points on the grid that lie under a specified energy limit and thus not only avoids the problems mentioned above but also saves some CPU time.

Another possible way to analyze the PES is the so-called single coordinate driving technique (SCD), which has some advantages in comparison with the GS and VS. Both VS and GS are much more dependent on the dimensionality of the calculated system than is SCD. It is especially remarkable for GS, for which m^n constrained minimizations are necessary, where m is the number of steps in the grid and n is the dimensionality of the system. In contrast, the SCD can be optimized to require only $m \cdot n \cdot p$ constrained minimizations, where p is the distance from the starting structure measured as the minimum number of elementary interconversions, i.e., pathways minimum-transition state and vice versa. In reality, SCD produces an approximation of the reaction pathway.

[†] Dedicated to Professor Milan Kratochvíl on the occasion on his 75th birthday.

* Corresponding author. E-mail: jkoca@chemi.muni.cz.

[‡] Institute of Computer Science.

[§] Department of Organic Chemistry.

^{||} Laboratory of Biomolecular Structure and Dynamics.

Another method, which can also be used for locating a reaction pathway starting from a single minimum, is the gradient extremal walking algorithm (GEWA).⁹ However, GEWA appears more like a method to search transition states while our method has, in the current stage, been designed especially to search for important minima on PES. Additionally, GEWA is not a fully systematic method as the search starts in the direction of minimal gradient. Moreover, we find this method to be more computationally expensive as the Hessian must be calculated many times. SCD and GEWA should be understood as complementary methods rather than competing ones.

The theoretical background of SCD is described in refs 17 and 18. This theory is implemented in the program CICADA,¹⁹ which is routinely used for studying conformational behavior of small and middle sized systems employing molecular mechanics. Our intention with this work is to extend the SCD methodology to the PES describing chemical reactions. The task requires employing quantum mechanics programs for calculating PES. Conformational analysis using both semiempirical and ab initio quantum mechanics is possible as well.

TOPOLOGICAL DESCRIPTION OF ENERGY SURFACES

PES's, despite being multidimensional bodies, can be visualized and understood very clearly by a topological approach. The theory has been introduced by Mezey^{20,21} and summarized in his excellent book.⁴ One of the clearest representations is offered by graph theory. For conformational PES, it is believed that a full understanding of the conformational space requires the identification of the complete network of conformational interconversions (NCI) within a thermodynamically suitable energy window¹⁴ or a graph of conformational PES ($^1G_{\text{PES}}$) introduced in refs 17 and 18. The basic units of such a description are the directly connected *minimum–saddle–minimum* triads¹⁴ which represent single conformational interconversions. The theory can also be applied to reaction PES without any changes. The only difference will be, however, that the thermodynamic energy window will be much larger in a majority of cases. The graph will be called the network of interconversions (NI). An example of NI for the system *tert*-butyl chloride + water is shown in Figure 1. It is clear, however, that only a very small part of the entire NI for the PES of *tert*-butyl chloride + water is pictured.

COMPUTER PROGRAM VADER

It has been shown²² that the above-mentioned SCD procedure, modification of which is described further in the paper, can successfully be used to generate NCI's. Therefore, we have also decided to use SCD for reaction PES's analysis in order to generate NI. The algorithm has been implemented in the computer program VADER (advanced variation of driver). The output of the newly written software is the graph of interconversions on the PES, the so-called convertibility graph. The convertibility graph is a graph theory representation of NI. The vertices in the graph represent the minima, saddle point structures, and other special geometries described further. The edges represent the interconversions between vertices. The graph is created using methodology based on a modified SCD approach^{23,24} applied in the

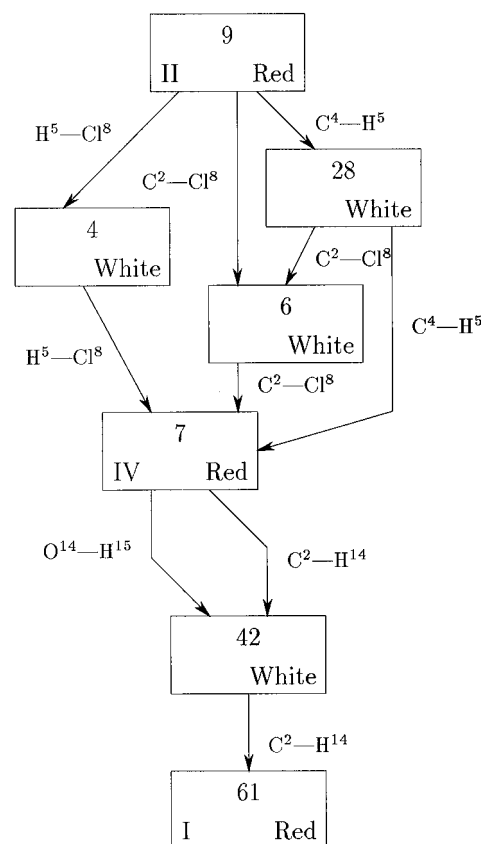


Figure 1. Part of the graph of interconversions on the PES of *tert*-butyl chloride and water. For numbering of atoms, see Figure 5. The vertex number (middle top in each frame) denotes the number assigned to the structure by VADER (see further text). The structure number (bottom left) refers to the numbering used in Table 2. The category of each vertex (for example, a minimum = red, a saddle point = yellow, etc.; for details see the algorithm) is expressed by its color (bottom right). The edges have the assigned RCSE's which have been used by VADER to create them. For the definition and further description of RCSE's, see the next chapter. Full electronic data about the PES's analyzed in this paper will be made available upon request.

program CICADA.¹⁹ By default, the format of the graph of interconversions on the PES produced by VADER is the same as that produced by CICADA, so it can be processed by tools linked to the program CICADA.^{25,26}

To extend the SCD approach to reaction PES, we define the term "reaction coordinate structure element" (RCSE) referring to one or more chosen internal coordinates. More than one internal coordinate is sometimes necessary because of the nature of many chemical reactions, which cannot be described by a single internal coordinate. The following RCSE types are used in the current implementation:

- single interatomic distance,
- an angle formed by three atoms,
- a torsion angle formed by four atoms, and
- two interatomic distances.

The algorithm usually starts from a single structure, which requires one or more RCSE's associated with it. These are defined by the user. The usual way is to include atoms and geometry parameters of assumed reaction centers. At least one RCSE must be active. Any calculation which starts with more structures is treated as a restart.

In the case of reactions where two or more molecules/particles are involved, the starting configuration should be

generated in such a way that the shortest atomic distance between these molecules/particles is greater than the covalent distance of the atoms multiplied by a constant k . This parameter is used by the program to decide whether the atoms are bonded or not and its value may be defined by the user. The shortest starting atomic distance should never be smaller than, say, the covalent distance multiplied by 2.5. On the other hand, when the starting distance is too high, many driving steps are necessary before the molecules/particles approach each other to generate an interaction, thus making the calculation longer. When the QM program used puts the molecules/particles too far away from each other, the energy gradient parameter must be changed within the QM program.

The computational algorithm is as follows:

1. From the list of vertices (i.e., structures) select a vertex which still has at least one active, unused RCSE associated with it. If there are more than one of such vertices, then select the oldest one.
2. Change the selected RCSE by a predefined step and constrain it on this value.
3. Minimize the structure (constrained minimization) and record the energy.
4. Repeat steps 2 and 3. Check if one or more of the conditions introduced in the following list are met. If yes, go to step 5.
 - (a) The energy exceeds a predefined limit.
 - (b) The energy profile shows a minimum or a maximum.
 - (c) At least one of the values of the RCSE's differs more than a predefined limit compared to the previous step. (An example of such a situation is shown in Figure 2.)
 - (d) The topology of the system has changed. (i.e., a new bond was formed or an existing bond vanished.)
 - (e) At least one element of the distance matrix differs more than a predefined limit compared to its value in the previous step.
5. If the geometry obtained in the previous step is a minimum on the pathway, minimize the geometry without any constraints and insert it as a new vertex (colored by red) in the graph. If the obtained energy profile shows a maximum, insert the geometry in the graph (without minimization) as a yellow colored vertex, estimating geometry of the transition state, and go to step 4 (i.e., continue travelling along PES using the same RCSE). In all other cases take the structure from the previous step and insert it in the graph without minimization as a white colored vertex. Minimize the structure from the last step and insert it in the graph as a red colored vertex.
6. If the new vertex was found using either the d or e conditions mentioned in step 4, add a new RCSE which is the coordinate that caused the situation. If the new vertex was found using the condition c, mark the excessively differing RCSE's as active (if they are not already).
7. Repeat steps 2–6 for each active RCSE. If the RCSE is an angle, repeat the steps for both directions of driving.
8. Perform graph cleaning if required (see further).

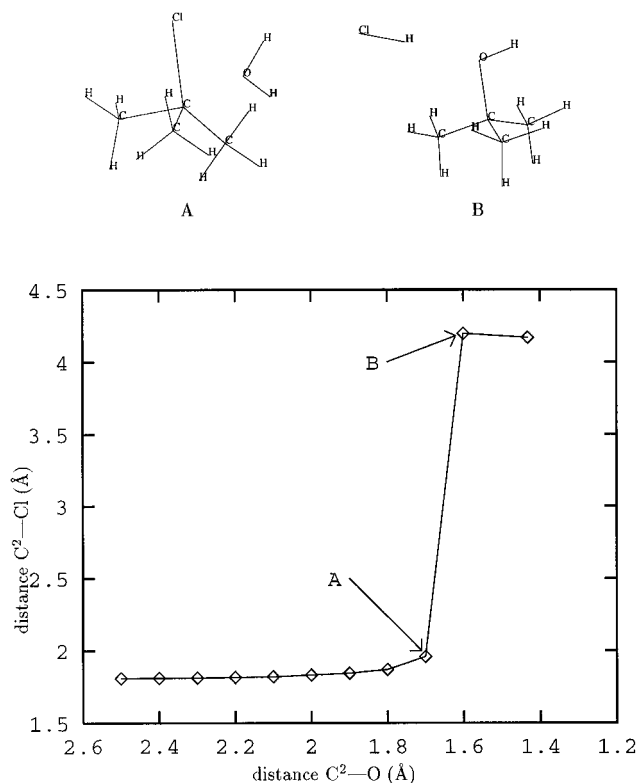


Figure 2. Illustration of applying condition c in step 4 of the algorithm. For atom numbering, see Figure 5. Let us consider that both C^2-O and C^2-Cl are RCSE's. While decreasing the distance C^2-O by the driver (trying to form a new bond), the distance C^2-Cl is also monitored. After the step leading from A to B, the condition c is met because the distance C^2-Cl changed substantially. In this particular case, structure A is recorded as a new vertex in the graph. Moreover, the structure A will have assigned the distance C^2-Cl as an active RCSE. The structure B will be fully minimized leading to the real product of substitution. This final structure will again be included into the graph.

9. If any interesting vertex remains, go to step 1. Otherwise stop the procedure.

In the graph, the regular minima and transition states are colored by red and yellow, respectively, while the structures found using the conditions c, d, and e are usually colored by white, so it is possible to distinguish the cases.

Graph cleaning can be performed using one or more of the following rules.

- If the topologies of the two compared vertices are identical, the vertices are considered identical. (Not used for conformational PES analysis.)
- If the values of all RCSE's of the two compared vertices differ less than predefined constants, the vertices are considered identical.
- If all the internal coordinates of the two compared vertices differ less than predefined constants for interatomic distances, angles and torsion angles, the vertices are considered identical.
- If the values of all the elements of the distance matrices of the two compared vertices differ less than a predefined constant, the vertices are considered identical.

If at least one of the selected conditions is met (which means that the two compared vertices are considered identical), the vertex with a higher energy is removed and all edges incident with it are redirected to the energetically

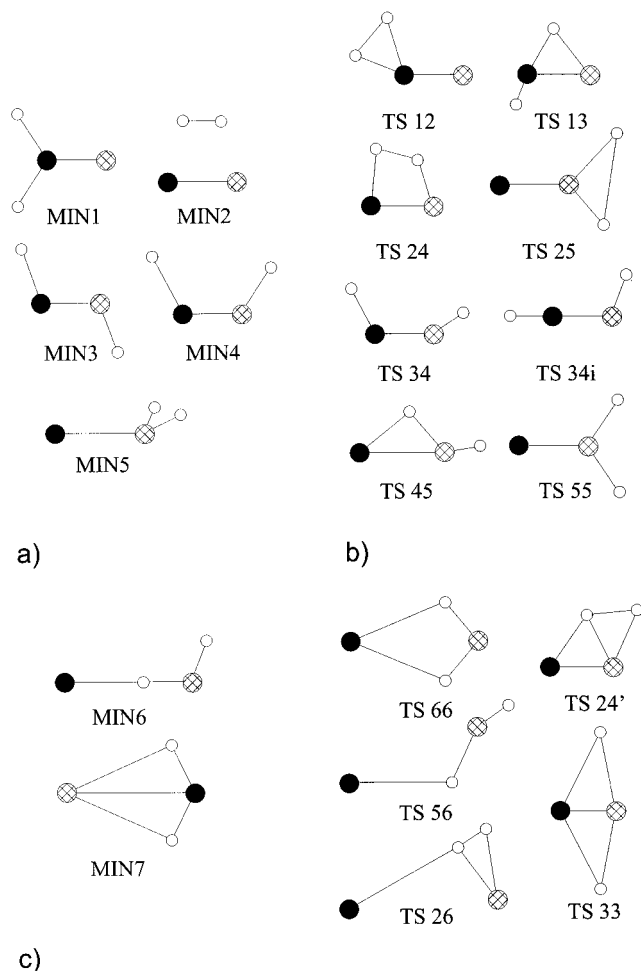


Figure 3. PES of the HCHO system as described by *VADER*: Optimized minima (a) and transition states (b) and minima together with transition states which were not found by our approach (c).

lower one. Under normal circumstances, only red vertices (the minima on the pathways) are involved in graph cleaning.

VADER can be interfaced with various quantum mechanics programs, usually without recompilation. Currently the interfaces with semiempirical programs MOPAC¹ and VAMP²⁷ and ab initio programs Gaussian 94² and Turbomole²⁸ are supported.

These external QM programs are used for energy calculation, for constrained minimization, for full optimization of a minimum, and when the smooth transition states (TS) search is required, for a full TS optimization and Hessian calculation. No optimization routine is included in *VADER* itself. It should be stressed again that SCD is *not* a methodology for exact localization of a TS, but rather a routine for finding areas on the PES where a TS can be expected.

There is an option in *VADER* which allows for full optimization of yellow vertices which are an approximation of true transition states. When this option is turned on, the geometry is optimized and the resulting structure is subjected to the recalculation of the Hessian. In the case that it does not represent a stationary point of first order on the PES, the corresponding vertex is recolored to white and the original nonoptimized geometry is used. With this option switched on, it is also possible to include the yellow vertices into the graph cleaning algorithm.

Table 1. Summarized Results of *VADER* Analysis of the HCHO PES^a

	energy [kcal/mol]	starting geometry for the optimization
Minima Found		
MIN1 ^{b,c}	0	1 ^{b,c}
MIN2 ^{b,c}	7	2023 ^{b,c}
MIN3 ^{b,c}	48	751 ^{b,c}
MIN4 ^{b,c}	53	2133 ^{b,c}
MIN5 ^{b,c}	173	24 ^{b,c}
Transition States Found		
TS12 ^{b,c}	141	913 ^{b,c}
TS13 ^{b,c}	119	2670 ^{b,c}
TS24 ^b	158	180 ^b
TS25 ^c	239	114 ^c
TS34 ^{b,c}	77	1087 ^{b,c}
TS34i ^{b,c}	130	711 ^{b,c}
TS45 ^{b,c}	193	391 ^{b,c}
TS55 ^b	174	114 ^b
Minima and Transition States Which Were Not Found by <i>VADER</i>		
MIN6	184	
MIN7	201	
TS66	186	
TS56	186	
TS24'	265	
TS33	280	
TS26	304	

^a The numbering of starting geometries (left) was generated by *VADER*. Energy is relative with respect to the lowest energy minimum, and it is calculated on the RHF/STO-3G level. ^b Optimized by SPARTAN.³³ ^c Optimized by Gaussian 94.²

Our experience shows that this TS optimization option should be used very carefully as such a procedure can result in very "bizarre" geometries having harmonic analyses different than that of a true TS. Additionally, such an optimization is sometimes very time consuming. An improvement of *VADER* for a TS search and optimization is the task we plan for the near future.

VADER can be used for both conformational and reaction PES analysis. It has been tested on the conformational analysis of boron analogues of amino acids.²⁹ Here we present the results obtained for reaction PES.

POTENTIAL ENERGY HYPERSURFACE (PES) OF THE HCHO SYSTEM

To compare results obtained by *VADER* with other methods, we have calculated the PES of HCHO, which has recently been studied in literature^{30–32} using other techniques and which is simple enough to allow the use of ab initio methods. There are six possible interatomic distances for four atoms, all of which were assigned as active RCSE's. The energy cutoff was set to 300 kcal/mol to ensure that high energy barriers on the PES would be overcome. The calculations were performed on a Pentium Pro/267 based computer (starting inspection of PES), and a SGI Indigo² R4400/250 (optimization of TS's and ab initio single point energy calculations). The starting inspection of the PES was performed at the semiempirical AM1 level. Minima and estimated transition states were then reoptimized at the RHF/STO-3G level to be comparable with literature data. The resulting minima and transition states are shown in Figure 3 and collected in Table 1.

It is revealed that five energy minima found by other methods are also generated by *VADER*. Two minima

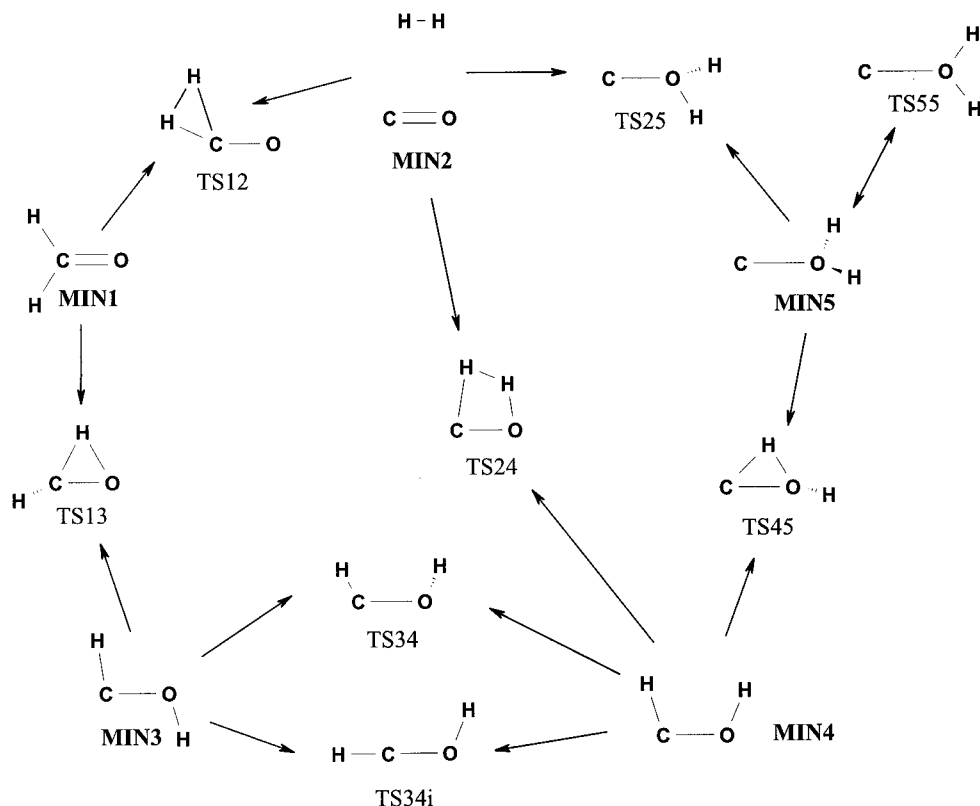


Figure 4. The interconvertibility network on HCHO PES found by VADER. The minima and transition states are denoted by MIN and TS, respectively.

described in ref 32 were not generated by VADER. These are weak van der Waals complexes. There may be two reasons why they were not found: (i) the minima are too shallow, so the driver step should be smaller to find them; (ii) the energy of the minima is too high, so it is realistic to expect that the search stopped before the part of PES with the minima was really searched.

Optimization of estimated transition states (yellow vertices) did not always lead to a true transition state or a second order transition state. Sometimes a true minimum was generated by such an optimization. Five of the literature transition states were not found by our approach (see Figure 3c). There are at least two reasons for this: (i) as before, the calculation was stopped too soon (there is no indicator to ensure that the entire PES has been explored so the calculation may stop); (ii) the current version of the software is designed to find all important minima on the PES and only to estimate the geometry of transition states. When the approximation is not good, the consequential optimization may fail. A new version of VADER will be developed in the future that can focus more precisely on the location of transition states.

The basic interconversions on the HCHO PES as generated by VADER are shown in Figure 4.

APPLICATION ON THE *tert*-BUTYL HALIDE SYSTEM

To demonstrate the ability of the program to investigate the reaction PES, we have selected a system on which we have not been successful when applying other methods.¹⁵ The system chosen was *tert*-butyl halide and water (see Figure 5).

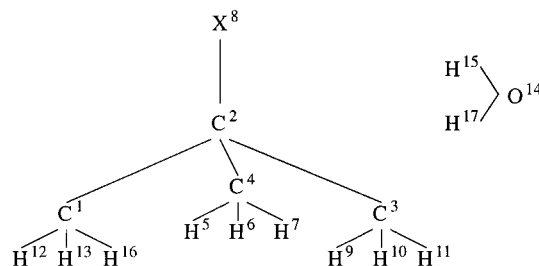


Figure 5. Numbering of atoms in the analyzed system (X = Cl, Br, I).

All the calculations were done using the AM1 Hamiltonian as implemented in MOPAC 6.0 and were performed on the SGI Power Challenge R10000 computer.

The following RCSE's were used: C⁴–H⁵, H⁵–X⁸, C²–O¹⁴, O¹⁴–H¹⁵, C¹–O¹⁴. All of these RCSE's were set as active, and all of them are of the interatomic distance type. In all calculations, the step size was set to 0.1 Å, and the limit of relative energy was set to 150 kcal/mol. The tests for topology change were performed during the calculations.

All results were analyzed on two levels: with and without graph cleaning. All calculations were stopped after the predefined number of edges (1000) in the graph of reaction interconversions on PES was reached.

The structures generated by the calculations are shown in Tables 2, 4, and 6 and some convertibilities found are collected in Tables 3, 5, and 7. These tables show how the values of energy barriers may be overestimated when no optimization of the yellow vertices is performed. The optimization was performed on all yellow vertices obtained (263 for chloride, 262 for bromide, and 271 for iodide), and it was successful in 189, 153, and 164 cases, respectively.

Table 2. Structures Found by the Analysis of the PES of *tert*-Butyl Chloride and Water^a

no.	structure	ΔH_f (kcal/mol)	E_{rel} (kcal/mol)
I*	(CH ₃) ₃ C-OH + HCl	-100.2	0.0
II*	(CH ₃) ₃ C-Cl + H ₂ O	-96.2	4.0
III	(CH ₃) ₂ C-O-CH ₃ + HCl	-91.3	8.9
IV*	(CH ₃) ₂ C=CH ₂ + H ₂ O + HCl	-90.5	9.7
V*	(CH ₃) ₂ CH-OH + CH ₃ Cl	-90.1	10.1
VI*	(CH ₃) ₂ CH-Cl + CH ₃ OH	-89.6	10.6
VII	CH ₃ -CH ₂ -CO-CH ₃ + HCl + H ₂	-89.3	10.9
VIII*	(CH ₃) ₂ C=O + HCl + CH ₄	-86.8	13.4
IX	(CH ₃) ₂ C(OH)-CH ₂ -Cl + H ₂	-85.3	14.9
X	CH ₃ -CH ₂ -CH=O + HCl + CH ₄	-85.2	15.0

^a Structures marked with an asterisk (*) were also obtained in calculations without graph cleaning.

Table 3. Energy Barriers for Selected Reactions Found by the Analysis of the PES of *tert*-Butyl Chloride and Water^a

reaction	E_a (kcal/mol)
(CH ₃) ₃ C-Cl + H ₂ O → CH ₂ =C(CH ₃) ₂ + H ₂ O + HCl	41 41
(CH ₃) ₃ C-Cl + H ₂ O → (CH ₃) ₃ C-OH + HCl	58 58

^a The first and second energies denote the barriers for the direction from left to right before and after the TS optimization, respectively.

The optimization gave, respectively, 106, 88, and 71 true transition states (configurations with exactly one negative eigenvalue of the Hessian).

Reactions of the System *tert*-Butyl Chloride and Water.

The results are shown in Table 2. In the calculation with "graph cleaning" turned on, all structures presented in the table were found while only structures marked with an asterisk (*) were generated in the run without graph cleaning.

This shows that the diversity of solutions is higher when graph cleaning is performed during the calculations. The reason is that for uncleaned graphs the progress in calculation is much slower as many motives are repeated.

The results are in good qualitative agreement with experimental data. According to ref 34, *tert*-butyl chloride undergoes both elimination and substitution reactions in water. At 25°, it forms a mixture of 80% of the substitution product (I) and 20% of the elimination product (IV).

Another realistic reaction found is the addition of water to the olefine (reaction IV→I). Although the energy barrier extracted from the calculated data is quite high, the predicted reaction itself is in agreement with the Markovnikov rule which shows that the predictions are in qualitative agreement with reality.

Reactions of the System *tert*-Butyl Bromide and Water.

The structures found are shown in Table 4. In the calculation with graph cleaning turned on, all structures presented in the table were found, while in the run without graph cleaning only those marked with an asterisk (*) were found. Selected reactions are collected in Table 5.

The results show some similarity with the reactions of the *tert*-butyl chloride system, even in the area of structures with higher relative energy. The pairs of structures VI and XV, VII and XVIII, VIII and XIX, III and XIV in fact, describe the behavior of the isopropyl system, not the *tert*-butyl system.

The apparent similarity in the behavior of *tert*-butyl chloride and the bromide system is in accordance not only

Table 4. Structures Found by the Analysis of the PES of *tert*-Butyl Bromide and Water^a

no.	structure	ΔH_f (kcal/mol)	E_{rel} (kcal/mol)
XI	(CH ₃) ₂ CH-CH ₂ -OH + HBr	-89.4	0.0
XII*	(CH ₃) ₃ C-OH + HBr	-85.4	4.0
XIII*	(CH ₃) ₃ C-Br + H ₂ O	-82.0	7.4
XIV	(CH ₃) ₂ CH-O-CH ₃ + HBr	-76.4	13.0
XV*	(CH ₃) ₂ CH-Br + CH ₃ OH	-76.0	13.4
XVI	CH ₃ -CH(CH ₂ -OH)-CH ₂ -Br + H ₂	-75.2	14.2
XVII*	(CH ₃) ₂ C=CH ₂ + H ₂ O + HBr	-75.1	14.3
XVIII	CH ₃ -CH ₂ -CO-CH ₃ + HBr + H ₂	-74.3	15.1
XIX*	(CH ₃) ₂ C=O + HBr + CH ₄	-72.0	17.4
XX	(CH ₃) ₂ C(OH)-CH ₂ -Br + H ₂	-71.5	17.9

^a Structures marked with an asterisk (*) were also obtained in calculations without graph cleaning.

Table 5. Energy Barriers for Selected Reactions Found by the Analysis of the PES of *tert*-Butyl Bromide and Water^a

reaction	E_a (kcal/mol)
(CH ₃) ₃ C-Br + H ₂ O → CH ₂ =C(CH ₃) ₂ + H ₂ O + HBr	54 54
(CH ₃) ₃ C-Br + H ₂ O → CH ₂ =C(CH ₃)-CH ₂ Br + H ₂ O + H ₂	102 76

^a The first and second energies denote the barriers for the direction from left to right before and after the TS optimization, respectively.

Table 6. Structures Found by the Analysis of the PES of *tert*-Butyl Iodide and Water^a

no.	structure	ΔH_f (kcal/mol)	E_{rel} (kcal/mol)
XXI ²	CH ₃ -CH ₂ -CH ₂ -CH ₂ -I + H ₂ O	-75.3	0.0
XXII ^{1,2}	(CH ₃) ₃ C-I + H ₂ O	-69.3	6.0
XXIII ^{1,2}	(CH ₃) ₃ C-OH + HI	-66.0	9.3
XXIV ²	(CH ₃) ₂ CH-OH + CH ₃ I	-64.8	10.5
XXV ^{1,2}	(CH ₃) ₂ CH-I + CH ₃ OH	-64.0	11.3
XXVI ²	(CH ₃) ₂ CH-O-CH ₃ + HI	-57.3	18.0
XXVII ¹	(CH ₃) ₃ CH + I-OH	-56.7	18.6
XXVIII ^{1,2}	(CH ₃) ₂ C=CH ₂ + H ₂ O + HI	-56.3	19.0
XXIX ¹	CH ₂ =C(CH ₃)-CH ₂ -I + H ₂ O + H ₂	-52.3	23.0

^a Structures marked with a superscript "1" were found in calculations without graph cleaning, while structures marked with a superscript "2" were found in calculations with graph cleaning.

with the homology rules in the periodic table but also with some calculations^{15,35} where the chlorine and bromine behave as more similar substituents than other halogens.

The most apparent difference in the *tert*-butyl chloride system is the isomerization of *tert*-butyl alcohol to 2-methyl-1-propanol (reaction XII→XI). An intermediate structure with a relative energy about 70 kcal/mol would lead to a mechanism of migration of the hydroxyl group, but the elimination-addition mechanism is also possible (this can be supported by the findings of two edges connecting vertices having structure XI, created by the movement along the RCSE 2 (H⁵-I⁸) and 3 (C²-O¹⁴)).

Reactions of the System *tert*-Butyl Iodide and Water.

The structures found by the program are shown in Table 6. Selected reactions of this system are displayed in Table 7.

Although the general behavior of this system is, again, similar to the other ones, there are some significant differences. The systems with the lowest energy are *n*-butyl iodide and *tert*-butyl iodide, both with a lower energy than *tert*-butyl alcohol. In reality, the equilibrium of the hydrolytic reaction would be shifted to the other side (i.e., the side of the butyl iodide). According to ref 34, the ratio of substitution

Table 7. Energy Barriers for Selected Reactions Found by the Analysis of the PES of *tert*-Butyl Iodide and Water^a

reaction	E_a (kcal/mol)	
$(\text{CH}_3)_3\text{C-I} + \text{H}_2\text{O} \rightarrow \text{CH}_2=\text{C}(\text{CH}_3)_2 + \text{H}_2\text{O} + \text{HI}$	82	31
$(\text{CH}_3)_3\text{C-I} + \text{H}_2\text{O} \rightarrow (\text{CH}_3)_3\text{C-OH} + \text{HI}$	75	57

^a The first and second energies denote the barriers for the direction from left to right before and after the TS optimization, respectively.

to elimination products in solvolysis is determined mostly by the environment and not by the leaving group. However, in our calculations the environment was not involved.

Another interesting difference is the structure XXVII, containing isobutane and the hypoidous acid (HIO). This acid is very soft, it is amphoteric, and it disproportionates even at room temperature. It is difficult to explain the formation of this structure because there was no transition state identified in the reaction leading to structure XXVII. If we assume that the microscopic reversibility principle is valid here, then the interpretation of this step would be the disproportionation of HIO to I^+ and OH^- .

All reactions with hydrogen elimination (i.e., structure XXIX in this case) can be considered unrealistic. The reaction barrier is very high, and the thermodynamic aspect doesn't support it. But again, in the framework of the microscopic reversibility principle, this reaction can be interpreted as an addition of hydrogen to an appropriate molecule (in the case of structure XXIX, it is an addition to 2-methyl-3-iod-1-propen).

DISCUSSION

The results of the above-mentioned calculations show that the program *VADER* can be used as a tool for the investigation of reaction PES's, both for mechanism studies and for initial stages of synthesis design. However, the results show that there may be significant differences between the reactions proposed by the program and the situation in reality. These differences are mostly explained by the following factors.

Firstly, the ability to predict qualitative and semiquantitative data for the studied reactions is heavily influenced by the quantum mechanical method used. It is obvious that for many reactions, like the previously mentioned substitution and elimination reactions, it is possible to use—with a realistic degree of approximation—the semiempirical AM1 or PM3 method. For many other classes of reactions (like all radical reactions, photochemical reactions, etc.) it is necessary to use at least the unrestricted Hartree–Fock semiempirical method or, better still, some *ab initio* technique with an appropriate basis set. The method chosen for the calculation completely depends on the reacting system.

Another important influence is the solvation. All the above-mentioned examples were calculated without solvation. There are very few reactions of practical importance that can be calculated with a high level of accuracy without the environment. Fortunately, there are ways of including the solvent in the calculations. The first and simplest method is to simulate the environment using a continuum solvation model. However, the results of this method are not always reliable. Another way is to use so-called sparkles (charged points, dipoles, etc.) to mimic the solvent. The most exact method is to create a cluster of solvent molecules (usually

water) and perform the reaction inside this cluster. This, of course, heavily increases the computational demands and thus usually limits the model to semiempirical Hamiltonians. Moreover, our unpublished results indicate that this method also has some inherent problems, which strongly limit its use today.

The last problem which should be mentioned here is the criterion for ending or stopping the calculation. Except for trivial tasks, the calculation does not finish by exhausting the active RCSE's on all vertices.

When only searching in a neighborhood of the starting vertex until certain graph distance (say n) is required, the halt criterion is then clearly defined. In this case the calculation stops when no vertex with active RCSE's is present for which the shortest pathway connecting it with the starting vertex includes less than $n - 1$ red vertices. However, when this distance condition is not specified, the question "When to stop the search?" is much more difficult to answer.

CONCLUSIONS

The new computer program *VADER* for investigation of both conformational and reaction PES's has been developed. The program is based on an extension of the single coordinate driving (SCD) methodology. Several quantum mechanics programs are currently working with *VADER*, and others can easily be interfaced. The program can be seen as the next step toward nonempirical synthesis design.

It has been shown in this paper that the technology used still has several drawbacks and the results are not always in full agreement with reality. The reasons for such a disagreement have been pointed out in the paper and will be considered during further improvement of the program. It should be highlighted that the program is probably the first in the category of software for generating a topology of reaction PES's using quantum chemistry in an automated way.

In this stage of our research we only concentrate on finding all important minima on PES and just the first approximation of transition states. From this point of view, the results are somewhat satisfactory. Our future research will be focused on implementing more precise methods to refine transition states within the SCD approach we have used in this paper.

Binary executable installations will be made available upon request from the e-mail address cerno@ics.muni.cz. The binaries are available for the following platforms: SGI workstations running IRIX 6.2 and later, Sun Sparc workstations running SunOS 5.5 and later, DEC Alpha workstations running Digital UNIX V4.0 or later, and Intel-based personal computers running either NetBSD 1.3 or Linux 2.0. Full electronic data about the PES analyzed in this paper will also be made available.

ACKNOWLEDGMENT

This paper is dedicated to Professor Milan Kratochvíl who has been a pioneer in the study of organizing huge amounts of information. The presented paper is just a continuation of his ideas presented many years ago. The authors thank the Czech Academic Supercomputer Centre in Brno for providing them with access to the computer facilities. The research has partially been supported by the Grant Agency

of the Czech Republic, Grant 203/94/0522, and by the Ministry of Education, Grant VS 96095. The financial support is gratefully acknowledged. The authors are grateful to Mr. Laurence Benjamin, B.A., for language corrections.

REFERENCES AND NOTES

- (1) Stewart, J. J. P. *MOPAC*; F. J. Seiler Res. Lab.: Colo. Springs, QCPE No. 455.
- (2) Frisch, M. J.; et al. *Gaussian 94*; Gaussian, Inc.: Pittsburgh, PA, 1995.
- (3) Allinger, N. L.; Burkert, U. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.
- (4) Mezey, P. G. *Potential Energy Hypersurfaces*; Elsevier: Amsterdam, 1987.
- (5) Shano, D. F. J. *Opt. Theor. App.* **1985**, 46, 87.
- (6) Baker, J. J. *Comput. Chem.* **1986**, 7, 385.
- (7) Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Chem. Soc., Faraday Trans. 2* **1984**, 80, 227.
- (8) Halgren, T. A.; Lipscomb, W. N. *Chem. Phys. Lett.* **1977**, 49, 225.
- (9) Jorgensen, P.; Jensen, H. J. A.; Helgaker, T. *Theor. Chim. Acta* **1988**, 73, 55.
- (10) McIver, J. W.; Komornicki, A. *Chem. Phys. Lett.* **1971**, 10, 303.
- (11) Muller, K.; Brown, L. D. *Theor. Chim. Acta* **1979**, 53, 75.
- (12) Jensen, F. *J. Am. Chem. Soc.* **1992**, 114, 1596.
- (13) Müller, K. *Angew. Chem.* **1980**, 19, 1.
- (14) Kolossvary, I.; Guida, W. C. *J. Am. Chem. Soc.* **1993**, 115, 2107.
- (15) Černohorský, M.; Kutý, M.; Koča, J. *Comput. Chem.* **1996**, 21, 35.
- (16) Bringmann, G.; Gusseren, S.; Holger, B. *J. Comput.-Aided Mol. Design* **1992**, 6, 505.
- (17) Koča, J. *Theor. Chim. Acta* **1991**, 80, 29.
- (18) Koča, J. *Theor. Chim. Acta* **1991**, 80, 51.
- (19) Koča, J. *J. Mol. Struct.* **1994**, 308, 13.
- (20) Mezey, P. G. *Theor. Chim. Acta (Berlin)* **1982**, 60, 409.
- (21) Mezey, P. G. *Int. J. Quantum Chem. Quantum Chem. Symp.* **1984**, 18, 675.
- (22) Koča, J. *Prog. Biophys. Mol. Biol.* **1998**, 70, 137.
- (23) Fadrná, E.; Koča, J. *J. Phys. Chem. B* **1997**, 101, 7863.
- (24) Fadrná, E.; Koča, J. *J. Mol. Struct. (Theochem.)* **1997**, 398–399, 523.
- (25) Koča, J. *J. Mol. Struct.* **1993**, 291, 255.
- (26) Koča, J. *J. Mol. Struct.* **1995**, 343, 125.
- (27) Rauhut, G.; A, A.; Chandrasekhar, J.; Steinke, T.; Sauer, W.; Beck, B.; Clark, T. *VAMP, v. 6.1*; Erlangen: 1995.
- (28) *Turbomole*; Biosym/MSI: 9685 Scranton Road, San Diego, CA 92121-3752, 1994.
- (29) Černohorský, M.; Vaultier, M.; Koča, J. *J. Mol. Struct. (Theochem.)* **1999** (in press).
- (30) Jensen, F. *Theor. Chem. Acc.* **1998**, 99, 295.
- (31) Bondensgaard, K.; Jensen, F. *J. Chem. Phys.* **1996**, 104, 8025.
- (32) Quapp, W.; Hirsch, M.; Imig, O.; Heidrich, D. *J. Comput. Chem.* **1998**, 19, 1087.
- (33) *SPARTAN v4.1*; Wavefunction, Inc.: Irvine, CA, 1993.
- (34) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987.
- (35) Kutý, M. Unpublished results, 1993.

CI9804138