J. Phys. Chem. A **2000,** *104,* 2191−2194

Predicting Unexpected Chemical Reactions by Isopotential Searching

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Received: July 23, 1999; In Final Form: October 19, 1999

The reactions of a chemical system are dictated by the corresponding potential energy surface (PES). Since reasonably accurate PESs are now available from quantum chemical calculations, a great deal of chemistry can, in principle, be predicted using existing techniques. We describe a few algorithms for finding low-energy exit channels from a well in a PES without foreknowledge of the products. Several illustrative applications are provided, including (1) unimolecular rearrangement of benzocyclohex-1-en-3-yne and (2) bimolecular reaction between ammonia and dichlorosilane. These two systems were chosen because their reactions were previously found to have been predicted incorrectly. In both cases, the correct mechanisms are recovered using isopotential searching strategies.

Introduction

Ab initio methods and computational hardware are sufficiently advanced that many chemical problems can now be solved accurately by computation.[1,2] As theory and technology continue to improve, increasingly many quantitative problems may be considered solved. For example, standard methods can be used to compute the gas-phase reaction enthalpy and rate constant if the reactants and products are known.[2] In contrast, qualitative chemistry is not easily predicted. Expert systems have been designed to exploit the large knowledge base in organic chemistry[3] but cannot predict entirely new types of reaction. This remains in the domain of experimental laboratories and of creative humans. Contributions from theory are restricted to cases where clever ideas are merely substantiated using computational methods.[4]

There are some counterexamples. “Direct” dynamics, in which atoms move classically along a quantum-chemical, Born−Oppenheimer potential energy surface, occasionally leads to unexpected reactions or structures. For example, Ziegler and co-workers recently discovered a stable cationic, titanium dihydrogen complex that they had not anticipated.[5] Likewise, Sato and Ohmine[6] found a transition state for the reaction between dichlorosilane and ammonia that is more than 200 kJ/mol lower than had been previously calculated. In our laboratory, we investigated such a dynamical approach to predicting reactivity but were dissatisfied with its efficiency. We have had more success searching isopotential surfaces directly, as described below.

Concept and Methods

The potential energy surface (PES) for a set of atoms describes how the system’s energy changes as the atoms move. A stable molecule corresponds to a local minimum on the PES, and a transition state corresponds to a first-order saddle point. Chemical reactions are trajectories on a PES. A popular analogy, for a two-coordinate model system, is with geographic topography. A stable molecule lies in a basin; a transition state lies atop a mountain pass. A chemical reaction is a path from one basin (reactants), over a mountain pass (transition state), and into another basin (products). Thus, finding low-energy reactions is analogous to finding low-lying passes through the mountains surrounding the first basin.

Imagine filling the basin (reactants) with water to form a lake. As the water rises, it will begin to pour through the mountain passes into neighboring basins. We seek the places where water is draining from the lake. A molecular dynamics approach corresponds to piloting a motor boat back and forth, across the surface of the lake, looking for waterfalls. Most of the time is spent passing over the deeper water of the lake, while the interesting features are at the water’s edge. Instead, we prefer to keep our boat near the shore (isopotential contour on the PES); any waterfall encountered will be recognized easily! Once an interesting reaction is identified, standard techniques of quantum chemistry can be used to obtain the thermochemistry and kinetics.

For two coordinates, as in the geographic analogy, such a technique will find all exit channels. For more dimensions, as in real chemical systems, this cannot be guaranteed. Thus, these methods are intended only as a creativity tool to supplement a chemist’s intuition. Since isopotential searching is only intended to identify qualitative features on the PES, the underlying theory only needs to be qualitatively correct. Thus, simple theories are often adequate and the computational expense modest.

We have tried several algorithms for isopotential searching. They are illustrated with the general flowchart in Figure 1. In block 1 we perform an energy minimization of the reactant(s) to give a minimum energy (E_0) and geometry. The target energy (E_{target}) specifies which isopotential hypersurface is to be searched, typically between 200 and 600 kJ/mol above E_0. In block 2 we choose one or more initial points near the minimum energy geometry. In blocks 3, 4, and 5 we adjust the geometry to reach the desired isopotential. This is done by moving parallel to the energy gradient ($\vec{\nabla}E$), typically in steps of length $\Delta E/|\vec{\nabla}E|$, where ΔE is the desired adjustment in energy. The computationally expensive part is block 3, in which the energy and its gradient are computed using a quantum-chemical method. In block 4 we compare the calculated energy with E_{target} and

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10.1021/jp992557a CCC: $19.00

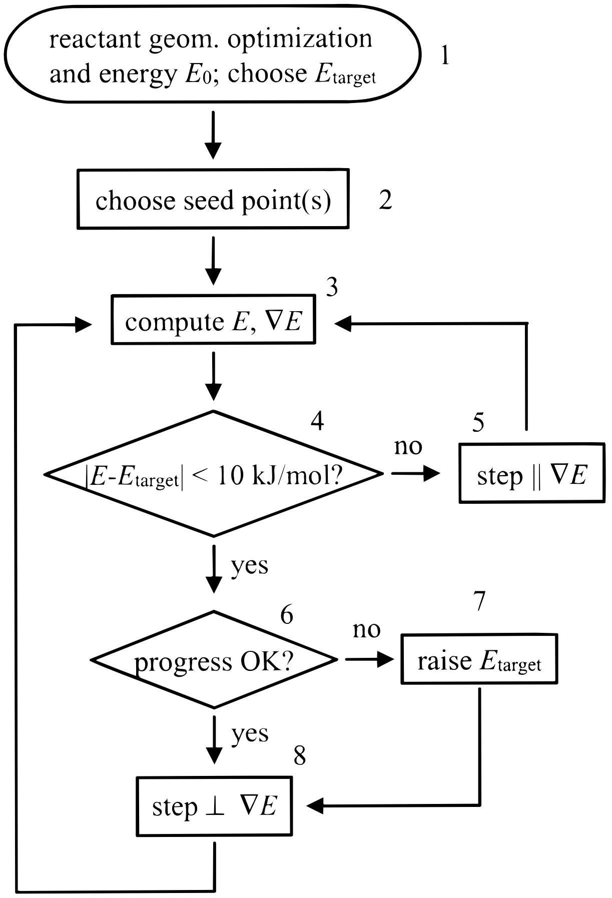

Figure 1. Flowchart indicating our general strategy for isopotential searching.

move toward the E_{target} isopotential (block 5) if necessary; our arbitrary threshold is 10 kJ/mol. In block 6 we check for interesting chemistry. This is done by examining the molecular geometries visually, or by performing a Mulliken bond analysis and looking for a change in bonding. If progress after many steps is unsatisfactory, we move to a higher-energy contour by raising E_{target} in block 7; this widens all "waterfalls." We return to block 3 after taking a step along the isopotential (block 8). How we choose this step differs for each algorithm, but always involves moving perpendicular to $\vec{\nabla} E$.

In the simplest algorithm, forward isopotential searching (FIS), block 8 involves straight, uniform steps under the constraint of remaining on the isopotential (i.e., walking perpendicular to the force). Kinematic isopotential searching (KIS) incorporates atomic masses and a kinetic temperature to govern the details of the forward motion. An origin-fleeing method (OFIS) steps away from the initial local minimum (in Cartesian space). Specular reflection (SRIS) has two walkers that leapfrog each other by reflecting from the mirror planes defined by the force vectors. SRIS is intended to follow curved paths efficiently; it will follow a circular arc exactly. The "no-return" procedure (NRIS) avoids proximity to all points that were visited previously. Our final algorithm, designed for "embarrassingly parallel" computation, involves many walkers ($\sim 6N$ for N atoms) each moving away from the average of all the others but still on the isopotential (many repulsive walkers, MRWIS). The MRWIS, NRIS, and OFIS algorithms all require a unique definition of the distance between two structures. We adopt simply the length of the Cartesian $3N$-dimensional vector representing the displacement between the two structures. To avoid overall rotation and translation, which are not chemically interesting, three atoms are also chosen to define a fixed reference plane.

All of these strategies have two major sources of inefficiency in varying degrees: (1) wandering in "unproductive" parts of coordinate space and (2) straying from the desired isopotential. The first problem can be alleviated by biasing the search, but only at the danger of reducing the chance of finding novel reactivity. The second problem can be costly because many steps may be needed to return to the isopotential. Using a small step size makes it easier to stay at the correct potential, but requires more steps to cover a given region of space. Likewise, a liberal margin of error for the potential energy will reduce the number of steps required to reach the desired energy window. In most of our searches we use an energy tolerance of ±10 kJ/mol. Other problems, such as moving in circles or taking very small steps, are remedied by applying random displacements periodically or by enforcing a minimum step size. Often it is helpful to move to increasingly higher isopotentials to encourage reactions to "occur". It is easier to find reactions on a higher isopotential because exit "holes" are correspondingly larger (relative to the step size). Note that the total energy must usually be substantially higher than the threshold for the (unknown) process of interest, since energy is distributed among all $3N - 6$ degrees of freedom.

Examples of Applications

Many tests were run to learn how the various methods perform. Often a run produces no reactions. Since the initial conditions are random, such a failed run may succeed when repeated. It may also be beneficial to try more than one algorithm. We present some successful examples here. As mentioned earlier, there is no guarantee that any reactions will be discovered by any of these procedures. A few systems yielded nothing interesting after repeated efforts, and provided only obvious reactions such as simple bond cleavage. We believe that such failures are acceptable if unexpected, new reactions or mechanisms can sometimes be discovered. We emphasize that isopotential searching is not intended to replace chemical intuition, but to supplement it. Also, as with any calculation, the results can be no more reliable than the underlying theoretical method that is used to generate energies.

Phenoxyl Radical. Under combustion conditions, the phenoxyl radical is known to decompose unimolecularly to yield carbon monoxide and a cyclopentadienyl radical ($C_6H_5O \rightarrow C_5H_5 + CO$). As summarized in recent theoretical papers,[7,8] the reaction proceeds through a bicyclic intermediate (6-oxobicyclo[3.1.0]hex-3-ene-2-yl) and then a C−C cleaved intermediate (2,4-cyclopentadienoyl) before releasing products. We applied the SRIS algorithm to the PM3 semiempirical PES for phenoxyl. The initial isopotential was at 200 kJ/mol above the minimum energy. This was raised periodically; the first intermediate was observed while exploring the isopotential at 350 kJ/mol. Note that this is much higher than the transition state that leads to the intermediate, which is only at +210 kJ/mol on the PM3 surface. Carbon monoxide was expelled soon after increasing the energy by an additional 50 kJ/mol, to 400 kJ/mol. Again, this is much higher than the minimum energy required to reach the appropriate transition state, which is also (coincidentally) at +210 kJ/mol on the PM3 PES. Thus, the observed products and currently accepted mechanism were both recovered during this run, which involved about 2600 gradient calculations (using the *Gaussian 98* quantum chemistry package)[9] and consumed about 5 h on a personal computer (400 MHz Intel Pentium II processor running the Linux operating system).[10]

Dichlorosilane and Ammonia. The isopotential searching algorithms can be extended to bimolecular reactions by constraining the distance between the geometric centers of the reactants. Applying an artificial restoring force works poorly because it encourages the reactants merely to orbit each other on the artificial isopotential. We chose the bimolecular reaction between SiH_2Cl_2 and NH_3 as an example because recently, using direct molecular dynamics on a PM3 PES, it was discovered that the previously proposed[11] activation energy is four times too high![6] Isopotential searching would have been helpful at an early stage in the earlier work, when possible reaction mechanisms were being listed for subsequent quantitative evaluation. Here we have applied the SRIS procedure on the PM3 PES, at 100 kJ/mol above the potential minimum, which is a complex bound by 18 kJ/mol at the PM3 level. The distance between the geometric centers of the silane and ammonia fragments was constrained to be $\leq$ 2.5 Å (the equilibrium distance) to encourage bimolecular chemistry. The products $H_2ClSiNH_2$ + HCl were generated after about 300 gradient calculations (*Gaussian 98*) and about 35 min on the personal computer described above.[10] At the PM3 level, the corresponding transition state (1,2-elimination of HCl from a hypervalent complex) lies at +13 kJ/mol. If quantitative energetics is desired, the PM3 results must be refined using standard, correlated, ab initio methods, as was done by Sato and Ohmine.[6]

Methylene Chloride and Ammonia. The reaction between SiH_2Cl_2 and NH_3, described above, has a very low barrier. We wondered whether the analogous reaction between CH_2Cl_2 and NH_3 would yield the analogous products, chloromethylamine (H_2ClCNH_2) and HCl. The NRIS method and a distance constraint of 2.5 Å were applied as above. In anticipation of a larger barrier than in the silane reaction, the initial energy was set to 300 kJ/mol. In the weakly bound (5 kJ/mol at the PM3 level) complex, a C−H bond is pointed directly at the nitrogen lone pair. Thus, attempting to satisfy the distance constraint causes the molecules to collide, exceeding the target energy and failing to obtain a seed point on the target isopotential. A successful ad hoc solution was to use the geometry of the analogous silane complex (above) as the starting geometry, which rapidly provided a point on the desired contour. The analogous reaction was indeed generated, leading to chloromethylamine and HCl. 1,1-Elimination to form HCl + CHCl + NH_3 was also indicated. In one run, ammonia appeared to catalyze the 1,1-elimination by means of an ion-pair intermediate, $[CHCl_2^-][NH_4^+]$. In a dedicated study, the corresponding transition states would be located and refined; comparing the calculated rates would then lead to a prediction for the products and mechanism of the bimolecular reaction. These quantitative details are not of interest here; we wish to illustrate only the utility of isopotential searching for suggesting chemical reactions and their mechanisms.

Benzocyclohex-1-en-3-yne. Lu and Jones recently prepared this cyclohexyne derivative at high temperature and reported its interesting chemistry.[12] Labeling studies were done to construct a mechanism for conversion to naphthalene and to methyleneindene. The mechanism was not what they had anticipated. We choose this example here to illustrate how isopotential searching can profitably supplement even very well educated mechanistic predictions. Reactions of benzocyclohex-1-en-3-yne (**1**) were sought using the MRWIS algorithm on an AM1 semiempirical PES. The initial energy was 400 kJ/mol above the energy minimum. Isomerization to **5** and subsequently to **6** (numbering as in ref 12) were both indicated, as inferred by Lu and Jones. An independent SRIS/AM1 exploration, starting with **6** at 500 to 600 kJ/mol above its minimum energy, suggested extensive rearrangement leading to **5**, to **7**, to **4** (product), and to further decomposition. The candidate reactions that were identified using isopotential searching are summarized in Figure 2. This includes most of Scheme 5 of ref 12, which was not anticipated prior to the isotopic labeling experiments. An additional SRIS/AM1 study of compound **8** revealed a reaction that was not considered in ref 12. The new reaction is indicated in the upper part of Figure 3, where an asterisk indicates a carbon position labeled with ^{13}C. If it is indeed the preferred route, then the deuterium-labeling experiments can still be rationalized by invoking the intermediacy of **8**, but only by contradicting the ^{13}C-labeling results. This suggests that **8** is not an important intermediate after all and leaves no explanation for the deuterium results. Both MRWIS/AM1 and SRIS/AM1 interrogations of compound **6** suggested an alternative. This is presented in the lower part of Figure 3, where the question mark indicates a step that is plausible but was not generated computationally and thus may not be important. However, intermediate **12** would permit the methylene groups to become equivalent, as required by the deuterium experiments, and is also consistent with the ^{13}C results. Although it is beside

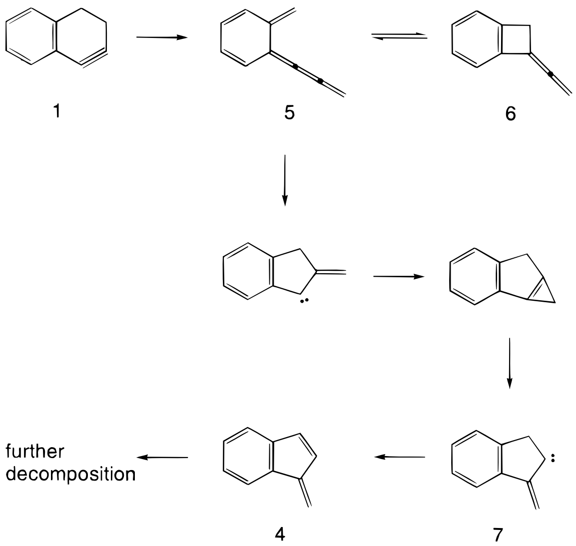

Figure 2. Unimolecular reactions of compound **1** generated computationally by isopotential searching.

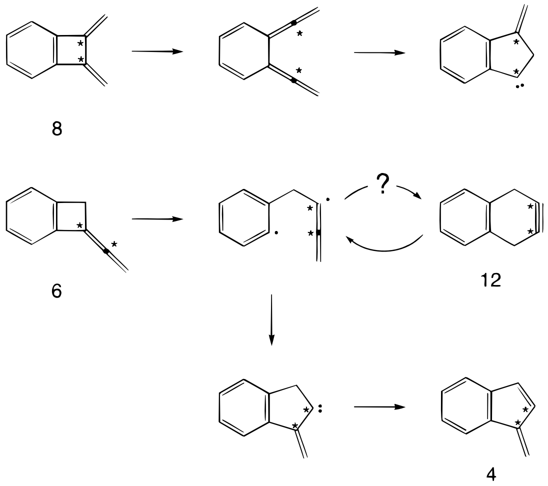

Figure 3. Computationally assisted evaluation of candidate mechanisms that rationalize the results of isotopic labeling experiments.

the point of the present paper, established ab initio methods could be applied to transform the qualitative suggestions into quantitative mechanistic predictions.

Summary

Isopotential searching is an effective strategy for identifying reasonable chemical reactions. The illustrations presented above are for neutral unimolecular and bimolecular reactions in the gas phase. No algorithmic changes are necessary for applications to ionic reactions (i.e., mass spectrometry) or for reactions in solution when using continuum solvation models. The bimolecular strategy can be extended to multimolecular reactions to accommodate discrete solvation models or condensed phase chemistry. Applications to photochemistry (i.e., electronically excited states) may be limited because a single isopotential is unrealistic when state crossing is important. Of course, isopotential searching is only worthwhile on a potential energy surface that is qualitatively correct. Thus, applications to transition metal chemistry may be limited by computational expense, because density functional theory may be required and is much more expensive than the semiempirical theories used in the examples above. Because of the high dimensionality of the potential energy surface, there can be no guarantee that the lowest exit channel will be found. Nonetheless, isopotential searching promises to become an important supplement to traditional "head-scratching" for writing candidate reactions and mechanisms, which can then be quantified using standard ab initio methods.

Acknowledgment. The idea for this project grew from challenging questions posed by Wing Tsang (NIST) during lunchtime conversations.

References and Notes

(1) *Quantum Mechanical Electronic Structure Calculations with Chemical Accuracy*; Langhoff, S. R., Ed.; Kluwer Academic: Dordrecht, 1995.

(2) *Computational Thermochemistry: Prediction and Estimation of Molecular Thermodynamics*; Irikura, K. K., Frurip, D. J., Eds.; ACS Symposium Series 677; American Chemical Society: Washington, D.C., 1998.

(3) Chen, L.; Gasteiger, J. *J. Am. Chem. Soc.* **1997**, *119*, 4033−4042.

(4) Rappé, A. K.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1982**, *104*, 448−456.

(5) Margl, P. M.; Woo, T. K.; Blöchl, P. E.; Ziegler, T. *J. Am. Chem. Soc.* **1998**, *120*, 2174−2175.

(6) Sato, Y.; Ohmine, T. *Computational Quantum Chemistry and Experimental Research on the Gas-Phase Reaction of* SiH_2Cl_2 *and* NH_3; American Institute of Chemical Engineers; Annual Meeting 1998, Miami Beach; paper 51a.

(7) Olivella, S.; Solé, A.; García-Raso, A. *J. Phys. Chem.* **1995**, *99*, 10549−10556.

(8) Liu, R.; Morokuma, K.; Mebel, A. M.; Lin, M. C. *J. Phys. Chem.* **1996**, *100*, 9314−9322.

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(10) Certain commercial materials and equipment are identified in this paper in order to specify procedures completely. In no case does such identification imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the material or equipment identified is necessarily the best available for the purpose.

(11) Koseki, S.; Ishitani, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3174−3176.

(12) Lu, P. J.; Pan, W.; Jones, M., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 8315−8318.