Biasing a transition state search to locate multiple reaction pathways

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A variety of chemical systems exhibit multiple reaction pathways that adjoin to a common reactant state. In fact, any reaction producing side products or proceeding via a stable intermediate involves a species possessing at least two reaction pathways. Despite improvements in ab initio transition-state search algorithms it remains difficult to detect multiple reaction pathways. Typically, multiple reaction pathways can only be detected by intuitively varying the initial point in the transition-state search trajectory. This reliance on intuition limits the ability to discover new and unexpected chemistry using ab initio methods. This paper proposes a systematic and intuition-free method for biasing a transition-state search to identify multiple reaction pathways originating from a common reactant state. The method allows the successive location of transition states, with each successful search contributing to a cumulative bias potential for the following search. The method is applicable to all pseudo-Newton–Raphson-type transition-state searches. The procedure was tested for a model potential energy surface and for the thermal rearrangement of trans-1,4-dimethylcyclobutene. In the latter case, four reaction pathways were discovered: two exothermic conrotatory ring openings leading to hexadienes, an endothermic methyl migration pathway leading to a carbene, and an exothermic rearrangement leading to 3-methyl-1,4-pentadiene. In accordance with experiment, the calculations predict that the conrotatory pathway leading to trans,trans-2,4-hexadiene is the kinetically dominant pathway. The methodology was also used to compute selectivities for competitive pathways producing trans and cis trifluoropentadiene products in the thermal rearrangement of 3-trifluoromethyl-cyclobutene. Again, results were in accord with experimental observations. © 2003 American Institute of Physics. [DOI: 10.1063/1.1569906]

I. INTRODUCTION

Examples of multiple reaction pathways that originate from a common reactant state are abundant in virtually every branch of chemistry. This is especially true in heterogeneous catalysis where mechanisms often involve a complicated network of reaction pathways including dissociative adsorption, surface reaction, desorption, and gas phase reactions. If ab initio computational chemistry is to become a powerful tool in the design of catalysts, it must be able to reliably predict the relevant pathways associated with a given reactant state.

Present methods for locating reaction pathways can be partitioned into two groups.1 The first includes those based on transition path sampling.2–4 This category includes methods such as linear synchronous transit5 and the nudged elastic band.5,6 Such interpolation schemes have proven quite effective for a number of systems, but they have some disadvantages. The interpolated initial guess at a reaction pathway is often far from the correct pathway resulting in failed convergence of self-consistent field electronic structure calculations for unrealistic configurations along the path. Additionally, the search space is large, \( n(3N - 6) \), where \( N \) is the number of atoms and \( n \) is the number of interpolated states on the path. While these computational difficulties can be overcome by clever algorithms, there are fundamental shortcomings for transition-state searches based on interpolation schemes. Since the reaction products must be assumed, the method cannot reveal unexpected chemical pathways and products. Second, if multiple pathways exist between the assumed reactant-product pair only the one nearest the interpolated guess will be found. However, we note that schemes for sampling dynamic transition pathways do not suffer many of the shortcomings of interpolation schemes. Dynamic path sampling schemes are now under development for use with ab initio potential energy surfaces.5,7,8

A second group of methods for locating reaction pathways is particularly well suited for use with ab initio potential energy surfaces. These are the psuedo-Newton–Raphson (NR) methods,1,9–11 which are all similar to the Cerjan–Miller algorithm.9 The psuedo-NR methods search for a saddle point by a sequence of steps, each guided by the local gradient and curvature of the potential energy surface. Psuedo-NR searches are deterministic in the sense that the initial coordinate \( x_0 \) in the search trajectory determines which saddle point will be found. In many applications a number of searches initiated from different points \( x_0 \) lead to the same saddle point. When this occurs, computer time is
wasted since a known transition state is rediscovered. This paper presents a method for biasing a pseudo-NR search, the Cerjan–Miller (CM) algorithm, so that the region of a known pathway is avoided. The result is an improved method for exhaustively searching a stable basin for all relevant reaction pathways. Before discussing methods for biasing a saddle point search we give a brief review of the CM algorithm.

II. REVIEW OF THE CERJAN–MILLER ALGORITHM

Let the CM steps be numbered from the starting point, \( \mathbf{x}_0 \), until the step \( \mathbf{x}_i \), which first crosses the inflection surface, i.e., the boundary between the region where the Hessian is positive definite and that where the Hessian has one negative eigenvalue. The remaining steps are determined by a Newton–Raphson scheme. The crossover from Cerjan–Miller to Newton–Raphson steps is illustrated in Fig. 1.

The \((i+1)\)th CM step depends on the gradient and Hessian at the \(i\)th step, \( \partial \mathbf{V} / \partial \mathbf{x} \) and \( \partial^2 \mathbf{V} / \partial \mathbf{x}^2 \). The CM algorithm finds a stationary point on the local quadratic potential energy surface (PES) subject to a constraint of constant step size from \( \mathbf{x}_i \). The resulting step is expressed in terms of a Lagrange multiplier, \( \lambda \), the matrices of \( (i) \) eigenvalues, \( \mathbf{S} \), and eigenvalues, \( \mathbf{\Omega}^2 \), of the Hessian, and the gradient in the eigenvector basis, \( \mathbf{g} = \mathbf{S}^T \partial \mathbf{V} / \partial \mathbf{x} \). The step \( (\Delta \mathbf{x}) \) and the quadratic approximation to the change in energy \( (\Delta \mathbf{V}) \) for this step are

\[
\Delta \mathbf{x}(\lambda) = \mathbf{S}(\lambda \mathbf{I} - \mathbf{\Omega}^2)^{-1} \mathbf{g}
\]

and

\[
\Delta \mathbf{V}(\lambda) = \mathbf{g}^T \left( \lambda \mathbf{I} - \frac{1}{2} \mathbf{\Omega}^2 \right)^{-1} \mathbf{g}.
\]

Note that at \( \lambda = 0 \) the Newton–Raphson step is recovered.

Figure 2 shows the function \( \Delta \mathbf{V}(\lambda) \) and the value \( \lambda = \lambda_0 \) that is selected in the CM algorithm.

The choice of \( \lambda = \lambda_0 \) results in a step that is uphill along the eigenvector \( \mathbf{S}_1 \) corresponding to \( \omega_1^2 \), and downhill along all other eigenvectors for a net uphill step. Near the inflection surface one of the eigenvalues in \( \mathbf{\Omega}^2 \) (\( \omega_1^2 \)) is steadily decreasing with increasing energy and actually changes from positive to negative as the inflection surface is crossed in the uphill direction. For \( \mathbf{x}_i \) sufficiently close to the inflection surface, this \( k \)th eigenmode must be the smallest, as all other eigenvalues remain positive when the inflection surface is crossed (cf. Fig. 2). For a first-order saddle point the unstable mode points along the pathway, gradually becoming a stable mode as one follows the reaction pathway down from the saddle. Thus if a first-order saddle point exists uphill from the inflection surface, the uphill direction along this softest mode corresponding to \( \omega_1 \) should point the way.

III. BIASING A CERJAN–MILLER SEARCH

The CM algorithm is usually very effective for finding a first saddle point. Furthermore, simply changing the initial configuration \( \mathbf{x}_0 \) of the search trajectory often results in another saddle point. However, as pointed out earlier, many initial configurations \( \mathbf{x}_0 \) may lead to the same saddle point, providing no new information about possible reaction pathways. These wasted CM trajectories can be avoided using a bias potential to steer a CM search away from a known reaction pathway. In constructing the bias potential we assume the steepest descent reaction path, \( \mathbf{a}(s) \), has been computed and parametrized by its arclength, \( s \), measured from the saddle point, \( \mathbf{a}(0) \). We also assume that the projected Hessian has been computed and diagonalized along each known path yielding the “curved harmonic valley” PES of the reaction path Hamiltonian. The harmonic valley PES has the form

\[
V(s, \mathbf{q}) \approx V_0(s) + \frac{1}{2} \mathbf{q}^T \mathbf{\Omega}^2(s) \mathbf{q},
\]

where \( V_0(s) = V(\mathbf{a}(s)) \) is the potential for points on the path \( \mathbf{a}(s) \). \( \mathbf{\Omega}^2(s) \) is the diagonal matrix of squared transverse frequencies, and the vector \( \mathbf{q} \) measures displacement from \( \mathbf{a}(s) \) along each of the transverse eigenvectors which are the columns of \( \mathbf{L}(s) \). The assumption that all of this information is available can be relaxed to accommodate standard transition-state theory studies where the full reaction pathway is not computed. A recipe for the less descriptive, but computationally much less demanding bias potential is given in the Appendix.

A bias potential for preventing rediscovery of known reaction pathways must adhere to each of the following guidelines.
(i) If \( s_{\text{min}} \) and \( s_{\text{max}} \) are reaction coordinates corresponding to the ends of the path, i.e., the reactant and product minima, then the bias potential should be zero for \( s \notin [s_{\text{min}}, s_{\text{max}}] \).

(ii) As the displacement from the path \( a(s) \) increases, the bias potential should decay to zero. This decay should be commensurate with the width of the pathway in each direction of displacement to prevent distortion of the PES far away from the known pathway.

(iii) The bias potential should be constructed in a manner that allows superposition of an arbitrary number of known reaction pathways as shown in Fig. 3. As in an unbiased search algorithm, each step on the PES requires evaluation of the gradient and Hessian. Because of guidelines (i) and (ii), the superimposed bias potentials corresponding to the known pathways may vanish leaving only the electronic structure calculations to guide the search trajectory.

(iv) The Hessian of the bias potential, \( \partial^2 V_{\text{bias}} \), should have a sufficiently large positive component in the direction of the known pathway to ensure the uphill portion of the step is not along the known pathway. Recall the explanation of the CM algorithm and let \( a'(s) \) be the path tangent for the known pathway. If \( \omega_2^2 \) corresponds to the second softest mode obtained from the Hessian of the true potential, a bias potential satisfying

\[
a'(s)^T \partial^2 V_{\text{bias}} a'(s) > \omega_2^2
\]

results in a step that is downward in the direction of the known pathway. The biased Hessian should not increase the second derivative along directions perpendicular to the known path tangent, else the softest eigenmode may still be directed along the known path tangent.

(v) The bias potential should only depend on internal coordinates so that it has the same effect on the CM search trajectory irrespective of the translational and rotational orientation of the molecule.

A bias potential can be defined in terms of a system-specific set of internal coordinates. However, it is preferable to define the bias potential in terms of a generally applicable coordinate system that is convenient for describing a known reaction pathway. The most convenient coordinate system is that used in reaction path Hamiltonian studies, \((s, q)\). The reaction coordinate, \(s\), is defined as the arclength along the steepest descent path \( a(s) \). \( q \) measures displacements from the steepest descent path in the transverse eigenvector basis. The coordinate \((s, q)\) determines a Cartesian coordinate by the mapping

\[
x(s,q) = a(s) + L(s)q.
\]

To satisfy (v), we must be able to convert the Cartesian coordinate \( x \) to an internal coordinate \((s, q)\), evaluate the gradient and Hessian of the bias potential in variables \((s, q)\), and then change variables to obtain Cartesian representations of the bias potential gradient, \( \partial V_{\text{bias}} \), and Hessian, \( \partial^2 V_{\text{bias}} \). Calculations to obtain the gradient and Hessian of the bias potential proceed in the following order:

\[
x \rightarrow (s,q) \rightarrow \frac{\partial V_{\text{bias}}}{\partial (s,q)} \rightarrow \frac{\partial V_{\text{bias}}}{\partial x} = V_{\text{bias}},
\]

\[
\frac{\partial^2 V_{\text{bias}}}{\partial (s,q) \partial (s,q)} \rightarrow \frac{\partial^2 V_{\text{bias}}}{\partial x \partial x} = \partial^2 V_{\text{bias}}.
\]

The calculations depicted in Eq. (6) require an invertible mapping from \( x \) to \((s, q)\), i.e., Eq. (5) must be inverted.

For cluster models such as those used to model zeolite catalysts, the coordinates of some atoms at the periphery of the model are fixed into crystallographic positions to mimic the geometric constraints imposed on the active site by the crystal lattice. All allowed motions in a cluster model with fixed atoms are distortions of the internal coordinates because the fixed atoms do not allow free rotation and translation. Thus, for a cluster model, \( F \), the total number of degrees of freedom satisfies \( F = \text{rank}(L^T) + 1 \). The “one” is the reaction coordinate and \( \text{rank}(L^T) \) is the number of non-null eigenvectors in the projected Hessian. Because the dimensionality of \( x \) and \((s, q)\) are the same for a cluster model, Eq. (5) can be inverted numerically (only the free atom positions are listed in \( x \)). The inversion routine is as follows:

(1) \( s \) is chosen so that the distance from \( x \) to points on the known path \( a(s) \) is minimized. Here it is convenient to define \( x_s(x) = x - a(s) \), where \( s = s(x) \) is the reaction coordinate that minimizes the size of \( x_s \).

(2) The remaining displacement vector from the known path, \( x_s(x) \), is perpendicular to the path tangent \( a'(s) \) by construction. Thus \( x_s(x) \) can be resolved into the transverse eigenbasis to obtain \( q(x) = x_s^T(x) L(s(x)) \).

Systems without fixed atoms are significantly more difficult to handle. The center of mass coordinate can always be reset to zero for both \( a(s) \) and \( x \). However, a state \( x \) as used in the CM algorithm generally does not match the rotational orientation of states on the known reaction path \( a(s) \). An immediate solution is to rotate \( x \) while determining \( s(x) \) in step (1) so that the rotated \( x \), say \( x' \), matches the orientation of \( a(s) \). One could then compute \( \partial V \) and \( \partial^2 V \) for the rotated configuration and directly add the bias potential derivatives. However, this solution fails to produce bias potentials that can be superimposed, because the rotational orientations of the known paths, in general, do not match each other. The best solution is to rotate the path \( a(s) \) to match the orientation of \( x \) while determining \( s(x) \). Thus the inversion routine for systems that can rotate freely is as follows:
The remaining task is to construct a bias potential as a function of \( s \) and the Euler angles \( \phi, \theta, \) and \( \psi \) to get \( s(x) \) and \( \{ \phi, \theta, \psi \}(x) \). If the vector \( a(s) \) for an \( N \) atom system is written in the order \( (x_1(s), y_1(s), z_1(s), \ldots, x_N(s), y_N(s), z_N(s)) \), then the rotation matrix \( R_{\phi, \theta, \psi} \) has the block diagonal form

\[
\begin{pmatrix}
R_{\phi, \theta, \psi} & 0 \\
0 & R_{\phi, \theta, \psi}
\end{pmatrix}
\]

(7)

where \( R_{\phi, \theta, \psi} \) is a \( 3 \times 3 \) Euler rotation matrix and \( \mathbf{M} \) is the diagonal matrix of atomic masses,

\[
\mathbf{M} = \begin{pmatrix}
m_1 I_{3 \times 3} & 0 \\
0 & m_N I_{3 \times 3}
\end{pmatrix}
\]

(8)

Because of its block diagonal structure, \( \mathbf{M} \) commutes with the block diagonal rotation matrix. Thus the conversions from mass weighted coordinates \( (\mathbf{M}^{-1/2}) \) and back to mass weighted coordinates \( (\mathbf{M}^{1/2}) \) can be omitted in the definition of \( \mathcal{R}_{\phi, \theta, \psi} \). As was done for the cluster model, define the minimum displacement vector

\[
x_i(s) = x - \mathcal{R}_{\phi, \theta, \psi} (s) a(s(x)).
\]

(9)

(2) The remaining displacement from the path is perpendicular to the path tangent \( a'(s) \) and the rotational eigenvectors. To determine \( q(x) \), the transverse eigenvectors in \( \mathbf{L}(s) \) must first be rotated by the above-determined angles. Thus \( q(x) \) is given by

\[
q(x) = x^T(x) \mathcal{R}_{\phi, \theta, \psi} (s(x)) \mathbf{L}(s(x)).
\]

(10)

We now have a systematic and system-independent method for interconverting coordinates \( x \) and \( (s, q) \).

Using the coordinate transformation it is possible to differentiate \( V_{\text{bias}}(s, q) \) and write the derivatives in Cartesian coordinates to match the orientation of the molecule represented by \( x \). For convenience, define the rotated path tangent,\( t = \mathcal{R}_{\phi, \theta, \psi} (s(x)) a'(s(x)), \)

(11a)

and the rotated transverse eigenvectors at \( s(x) \),

\[
E = \mathcal{R}_{\phi, \theta, \psi} (s(x)) \mathbf{L}(s(x)).
\]

(11b)

Using the above-given definitions, a change of basis gives

\[
\partial V_{\text{bias}} = \partial V_{\text{bias}} / \partial x = (t, E) \frac{\partial V_{\text{bias}}}{\partial (s, q)}
\]

(12a)

and

\[
\partial^2 V_{\text{bias}} = \partial^2 V_{\text{bias}} / \partial x \partial x = (t, E) \frac{\partial^2 V_{\text{bias}}}{\partial (s, q)} \partial (s, q) (t, E)^T,
\]

(12b)

where \( (t, E) \) is the matrix of rotated (column) eigenvectors, \( E \), augmented by the rotated path tangent, \( t \). Equations (7)–(12) provide a computational framework for imposing a bias potential that depends only on \( (s, q) \), and moreover, for superimposing bias potentials from multiple known pathways. The remaining task is to construct a bias potential as a function of \( (s, q) \) coordinates that satisfies guidelines (i), (ii), and (iv). Recall that the harmonic valley PES approximately describes the PES in the vicinity of the known reaction pathway. The bias potential should decay more slowly in the soft directions, i.e., along the \( \mathbf{L}_i \) corresponding to small \( \omega_i^2 \), for which the known pathway is wide. One possibility is

\[
V_{\text{bias}}(s, q) = A(s) \exp \left( - \frac{1}{2A(s)} q \mathbf{L}(s) q \right),
\]

(13)

where \( A(s) \) can be chosen to satisfy guidelines (i) and (ii). The function \( A(s) \) used in this work is

\[
A(s) = \begin{cases} 
\frac{A_{\text{min}}}{2} (s - s_{\text{min}})^2, & s \in [s_{\text{min}}, 0] \\
\frac{A_{\text{max}}}{2} (s - s_{\text{max}})^2, & s \in [0, s_{\text{max}}] 
\end{cases}
\]

(14)

and \( A(s) = 0 \) otherwise. Parameters \( A_{\text{min}} \) and \( A_{\text{max}} \) were chosen larger than \( \omega_i^2 \) in reactant and product minima, respectively, to satisfy guideline (iv). Before discussing examples, we note that terms originating from the \( (DF - 1) \times (DF - 1) \) submatrix, \( [\partial^2 V_{\text{bias}} / \partial q \partial q] \), tend to introduce negative eigenvalues to the total Hessian. In all of the systems we have examined the best results were obtained by setting all matrix elements to zero except the \( \partial^2 V_{\text{bias}} / \partial s^2 \) element. In this respect the bias potential is used not as a true bias potential, but rather as a biased Hessian and gradient. Note that the biased portion of the Hessian still decays like the Gaussian, and thus the bias potential still satisfies all guidelines.

IV. EXAMPLES

A. The Muller–Brown potential

The Muller–Brown potential has been used as a test example in the development of several theoretical methods for chemical kinetics.\(^{13,16}\) As shown in Fig. 4, it has a stable intermediate connected via one pathway to “A” and by another...
other pathway to “B.” Figure 4 also shows an initial, unbiased CM search that found the pathway to basin A.

To test the biased search algorithm, a biased search was initiated from the same point as the unbiased search. Figure 5 is shaded according to the total potential, $V_{bias} + V$, but also shows the contour lines of the unbiased potential, $V$. Note that the bias potential has altered the potential energy surface only in the vicinity of the known reaction pathway. The biased CM search trajectory is shown in blue. After just two steps, the bias potential has turned the biased CM search trajectory away from the known pathway and toward the pathway leading to basin B.

B. Trans-1,4-dimethylcyclobutene rearrangement

The orbital symmetry rules of Woodward and Hoffman predict the thermal reaction pathways in substituted cyclobutenes. Trans-3,4-disubstituted cyclobutenes are known to undergo one of the conrotatory isomerizations shown below depending on the identities of $R$ and $R'$.

Letting $R$ and $R'$ be methyl groups, we initiated a series of searches from the configuration shown in Fig. 6. Note that the floppy methyl rotations impede the Cerjan–Miller algorithm because the algorithm walks uphill in the direction of the “softest mode.” To alleviate this problem, each methyl group was replaced by a 15 amu hydrogen during the Cerjan–Miller searches. All electronic structure calculations were performed using QCHEM2.0 as a subroutine that resides outside the main program and is called as needed during transition state searches.

The initial, unbiased search found a saddle point depicted by the middle configuration in Fig. 7. Calculation of the full steepest descent path revealed that the first pathway was that of reaction 1. The zero point corrected potential (black circles) along the steepest descent path and the free energy (red dots) as a function of this first reaction coordinate, $s_1$, are shown in Fig. 7.

The free energy is given by the harmonic approximation for vibrations and a rigid rotor approximation,

$$F(s) = V_0(s) - \frac{kT}{2} \ln \left( \pi \left( \frac{2kT}{\hbar^2} \right)^3 \text{det}[I(s)] \right)$$

$$+ \sum_{k=1}^{DF-1} \left[ \frac{\hbar \sigma_k(s)}{2} + k_B T \ln \left( 1 - \exp - \frac{\hbar \sigma_k(s)}{k_B T} \right) \right],$$

where $I(s)$ is the inertia tensor along $a(s)$, and $\sigma_k(s)$ is the angular frequency for the $k$th transverse mode. The barrier plot in Fig. 7 shows $F(s) = F(s_{\text{min}})$. When a transverse frequency becomes imaginary the quadratic approximation to the free energy as a function of the reaction coordinate breaks down. To guide the eye across these vanishing por-

FIG. 7. Zero point energy, free energy at 0 °C and stationary configurations on the steepest descent path for the initial pathway from the unbiased search. Trans-3,4-dimethylcyclobutene is denoted tr-dimeCB.
tions of the barrier plot, the potential along the steepest descent reaction path, \( V_0(s) \), has been included.

Experiments have shown that *trans, trans* hexadiene is the only product formed upon heating *trans*-dimethylcyclobutene.\(^{19,20}\) Thus, if any additional pathways for the conversion of *trans*-1,4-dimethylcyclobutene exist, they should possess higher activation barriers than the barrier for pathway 1.

Information from pathway 1 was used to bias a second transition-state search. The second transition-state search was initiated from the same configuration, \( x_0 \), to illustrate the effect of the bias potential. The second transition-state search found the saddle point along pathway 2, leading to *cis, cis*-2,4-hexadiene. The free energy profile and configurations along pathway 2 are shown in Fig. 8. The free energy barrier for pathway 2 is 14 kcal/mol greater than the barrier for pathway 1.

A third search was biased to avoid pathways 1 and 2. In contrast to pathways 1 and 2, pathway 3 represents a highly endothermic reaction pathway leading to a carbene species. The barrier for pathway 3 is 103 kcal/mol. The free energy profile and stationary point configurations for pathway 3 are shown in Fig. 9. Note that pathway 3 is a complicated path involving the concerted breaking of two bonds and formation of a new bond. Such complicated paths often have imaginary transverse frequencies at some points along the steepest descent path. (But not at the saddle point. All saddle points shown in this paper are true first-order saddle points.)

The fourth search, biased to avoid pathways 1, 2, and 3, found a slightly exothermic pathway leading to 3-methyl-1,4-pentadiene. The barrier along this pathway is 88.5 kcal/mol as shown in Fig. 10.

A fifth search, biased to avoid the first four pathways, failed to find a transition state. The fifth search trajectory became trapped in the vicinity of the dimethylcyclobutene minimum. Some initial conditions do result in yet another pathway leading to acetylene+2-butene. The barrier for this reaction was approximately 100 kcal/mol.

Figure 11 summarizes the four pathways found using the biasing algorithm. The calculated value of \( \Delta G^* \) is given for each pathway. The pathways are shown in order of ascending activation energy. Note that this is not the order in which they were found. There is no guarantee that the lowest en-
A biased transition-state search algorithm can be used to locate multiple reaction pathways from a stable intermediate in a series of reactions, or to predict competitive parallel reactions. Another aspect of this algorithm is its utility in exploring energy saddle points will be discovered first by an unbiased transition state search algorithm.

The effects of the bias potentials are best visualized by plotting the search trajectories and steepest descent paths in a coordinate system of the reaction coordinates for the various pathways. Thus, each configuration \( \mathbf{x} \) on a search or steepest descent trajectory determines a coordinate \( (s_1, s_2, s_3, \ldots) \) containing the reaction coordinates corresponding to \( \mathbf{x} \) for each known reaction pathway. Figure 12 shows the first three transition-state searches and resulting steepest descent paths in this “s-plot” format.

Figure 12 is useful for interpreting the effects of the bias potential on the search algorithm. However, it is important to note that the s-vectors in Fig. 12 were determined after all three of the pathways were computed. The initial search (red dots) found the pathway (red) to trans, trans-2,4-hexadiene without a bias potential. The bias potential from the first pathway then pushed the second search (blue dots) away from the red pathway. Once out of the red pathway, it found the second pathway (blue curve). The third search (green dots) was again pushed out of the red pathway because of the bias potential around pathway 1. The third search then briefly enters the region of the blue pathway, but exits because of the bias potential around pathway 2. Finally the third search is pushed away from both known pathways where it discovers a third pathway, 3 (green). Pathway 4 was found similarly, however, the fourth axis cannot be visualized simply.

Hydrogens in the saddle point geometries from pathways 1 and 2 of the previous study were replaced with flourines to obtain starting geometries for the new transition structures. The fluorinated transition structures were reoptimized at the B3LYP/6-31G* level. Figure 13 shows the calculated and experimental ratios of rate constants for the cis and trans pathways. The agreement between the experimental and calculated rate ratios illustrates that the method can be used to predict competition between parallel reactions and how the dominant pathway depends on substituents.

FIG. 13. Ratio of cis to trans rate constants for temperatures between 425 and 435 K. Experimental uncertainty is approximately the diameter of the points (Ref. 21).

V. SUMMARY

A biased transition-state search is a powerful tool for locating multiple reaction pathways from a common reactant state. The method we have developed allows the successive location of transition states, with each successful search contributing to a cumulative bias potential for subsequent searches. The method is system-independent and can be applied to any pseudo-Newton–Raphson search algorithm.

A biased transition state search algorithm can be used to locate multiple pathways from a stable intermediate in a series of reactions, or to predict competitive parallel reactions. Another aspect of this algorithm is its utility in exploring
various stable basins on the potential energy surface. For example once a pathway leading from a reactant A to product B is discovered, a biased search from B will avoid the pathway back to A, and reveal a new pathway from B to C.

In this paper the function \( A(s) \) was chosen to completely block the search from progressing in the direction of a known reaction pathway. The “trapped” behavior observed in the fifth search trajectory indicates that perhaps the function \( A(s) \) requires further optimization. An \( A(s) \) with a gradually increasing second derivative, \( A''(s) \), may have allowed the discovery of the fifth pathway from the initial configuration of Fig. 6. Nevertheless, the discovery of four reaction pathways from a single initial configuration is a testament to the capabilities of this methodology. The most effective use of the method would be to select various initial conditions for each search—perhaps points on a Monte Carlo trajectory. As evidenced by the discovery of a fifth pathway leading from trans-dimethyl-cyclobutene to acetylene and trans-2-butene, varying the initial conditions can prevent “trapping” of a search trajectory between bias potentials.

The biasing algorithm that we have described requires that the user modify the true gradient and Hessian as shown in Fig. 3 before they are used to compute a step on the PES. At the very least, the user must modify the gradient if a Powell updating procedure is used to approximate the Hessian.

In closing, we hope the biasing algorithm described in this paper will be used to study technologically relevant problems in homogeneous and heterogeneous catalysis.

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**APPENDIX: CONSTRUCTING A BIAS POTENTIAL WITHOUT COMPUTING AN ENTIRE PATHWAY**

In most applications of transition-state theory the saddle point is computed and a normal mode analysis is performed. The full pathway is usually not computed and thus cannot be used in the construction of a bias potential. A bias potential analogous to the one proposed in this paper can be constructed using only the saddle point geometry and the normal modes at the saddle point. In Eqs. (4)–(11) and (13), \( a(s) \) is replaced by \( a(0) + s \mathbf{u}_s \), where \( a(0) \) is the saddle point configuration and \( \mathbf{u}_s \) is the unstable eigenvector at the saddle point. This replacement makes \( a'(s) = \mathbf{u}_s \). The \( s \)-dependent transverse eigensystem, \( \mathbf{L}(s) \) and \( \mathbf{\Omega}^2(s) \), used in Eqs. (6)–(10), can be replaced by the stable eigenvectors and frequencies at the transition state. The arclengths \( s_{\text{min}} \) and \( s_{\text{max}} \) can be replaced with the signed, linear distances from the saddle point to the reactant and product minima, respectively. The resulting bias potential will not follow the curvature of the pathway or change width as the pathway width changes, but it should be accurate near known saddle points. An example of this simplified bias potential for the Muller–Brown surface is shown in Fig. 14.

Figure 14 shows that the bias potential based on the harmonic approximation fails to follow the steepest descent pathway as it curves toward the reactant and product minima. However, the bias potentials in (b) and (c) are very similar near the transition state.

8. A.F. Voter, Phys. Rev. B 57, 13985 (1998). While not a true path sampling technique, “parallel replicas” provide a fast means of exploring the topology of a complicated PES. In particular this methodology could be used to find initial dynamic routes through a number of different pathways for later use in transition path sampling.