Automated Transition State Searches without Evaluating the Hessian

Shaama Mallikarjun Sharada,[†] Paul M. Zimmerman,[†] Alexis T. Bell,*[,†] and Martin Head-Gordon*[,‡]

[†]Department of Chemical and Biomolecular Engineering and [‡]Department of Chemistry, University of California, Berkeley, Berkeley, California 94720, United States

ABSTRACT: Accurate and speedy determination of transition structures (TSs) is essential for computational studies on reaction pathways, particularly when the process involves expensive electronic structure calculations. Many search algorithms require a good initial guess of the TS geometry, as well as a Hessian input that possesses a structure consistent with the desired saddle point. Among the double-ended interpolation methods for generation of the guess for the TS, the freezing string method (FSM) is proven to be far less expensive compared to its predecessor, the growing string method (GSM). In this paper, it is demonstrated that the efficiency of this technique can be improved further by replacing the conjugate gradient optimization step (FSM-CG) with a quasi-Newton line search coupled with a BFGS Hessian update (FSM-BFGS). A second crucial factor that affects the speed with which convergence to the TS is achieved is the quality and cost of the Hessian of the energy for the guessed TS. For electronic structure calculations, the cost of calculating an exact Hessian increases more rapidly with system size than the energy and gradient. Therefore, to sidestep calculation of the exact Hessian, an approximate Hessian is constructed, using the tangent direction and local curvature at the TS guess. It is demonstrated that the partitioned-rational function optimization algorithm for locating TSs with this approximate Hessian input performs at least as well as with an exact Hessian input in most test cases. The two techniques, FSM and approximate Hessian construction, therefore can significantly reduce costs associated with finding TSs.

INTRODUCTION

The determination of transition structures (TSs), which are first order saddle points between reactants and products on potential energy surfaces, is a critical step in the analysis of reaction pathways and rates. TS searches typically involve two steps. The first step is determination of a guess for the TS based on the reactant and product configurations, while the second step is the refinement of the guess to precisely locate the saddle point. Owing to substantial computational costs associated with electronic structure calculations, traditionally, the TS guess is determined by hand.[1,2] The process involves using chemical intuition such as knowledge of the form of the TS in a system related to the one under study. If the guess is sufficiently good that it lies in the quadratic basin of the TS, or in other words has one negative Hessian eigenvalue, then it is likely that the TS can be successfully located. The principal advantage of this homologue-based approach is that it is computationally free and can be successful in systems that are either simple or very closely related to ones with known TSs. The disadvantage is that a rather large amount of human trial and error is required in many applications, particularly those where intuition fails and homology is not available. Unfortunately, this encompasses many complex systems, particularly those involved in catalytic processes, where multiple TSs, as well as intermediates that may not be observed, exist on intricate pathways between reactants and products.[3,4]

To overcome the limitations of either human or machine-based guessing, there has accordingly been growing effort to automatically identify a high-quality trial structure for the TS by characterizing the path(s) connecting a pair of known local minima, typically "reactant" and "product" structures. The result is a discretized path, which may approximate the intrinsic reaction coordinate (IRC) corresponding to the zero velocity trajectory linking the TS to reactants and products. There are a great variety of path searching methods in common use, most of which employ double-ended techniques such as the nudged elastic band (NEB),[5−9] the string method (SM),[10−14] the searching string method,[15] spline methods,[16] the growing string method (GSM),[17−21] and the freezing string method (FSM).[22] Given the discretized path, the geometry corresponding to the highest energy intermediate can be harvested as a high-quality TS guess. The second step involves refining the TS guess using algorithms such as the Berny optimization algorithm,[23] the dimer method,[24,25] partitioned-rational function optimization (P-RFO),[26−28] eigenvector following methods,[26,27,29−31] and global reaction route mapping (GRRM) combined with microiteration methods for large molecules.[32] Algorithms have been developed that combine double-ended interpolation methods with TS refinement.[33,34] Single-ended methods have also been developed, which require knowledge of only one local minimum.[35] Extensive reviews are available on TS finding techniques.[1,36]

Chain-of-states methods, such as the NEB and SM, involve the creation of a string of images between the reactant and product states, which are then relaxed to the reaction pathway. In the NEB, the forces on each image are projected along and perpendicular to the tangent direction, and energy is minimized perpendicular to this direction. Spring forces are artificially introduced between the images to maintain even spacing. String methods, on the other hand, use splines to calculate tangents and maintain node spacing via reparameterization. The main drawback of these methods is that multiple gradient

calculations must be performed on images located far away from the TS. To reduce the computational burden of such calculations for applications involving electronic structure theory, the GSM was developed. In this method, the search begins with only the reactant and product configurations, and the two string segments are "grown" independently until they join together. Once a new node is optimized with respect to the gradient in the direction perpendicular to the approximate reaction path, the string is reparameterized. In order to obtain a reasonable guess of the TS, the reparameterization and optimization steps are repeated for the completed string, or for a substring that contains the guess to the TS.

Very recently, we have introduced the freezing string method (FSM) as an algorithm that attempts to avoid the costs associated with both the reparameterization as well as the iterative steps of the GSM. In the FSM, the newly created nodes are optimized in a direction perpendicular to the reaction coordinate with a few conjugate gradient (CG) steps and are then irreversibly "frozen" in place from the path ends going inward until the ends meet. The FSM therefore is able to generate a guess for the transition state with significantly lower cost, quantified by the number of gradient calculations, compared to the GSM, as it sidesteps the iterative refinement of the fully grown string. As a consequence, the FSM does not reproduce the IRC and does not provide any guarantee that the TS guess will have the appropriate Hessian structure. However, in practical applications, the FSM has proved computationally highly efficient and satisfactorily robust. It is an open question, though, whether or not further improvements in the efficiency of the FSM are possible by modifying the perpendicular search protocol. The first purpose of this paper is to explore this question.

Turning to the second stage of a TS search, of the local TS refinement methods, partitioned-rational function optimization (P-RFO) is an efficient technique based on separation of the Hessian eigenvalues into modes with negative curvatures along which energy maximization is carried out, and all other modes along which the energy is minimized. Therefore P-RFO requires an initial Hessian with a single negative eigenvalue along the reaction coordinate in order to ensure convergence to the nearby TS. The P-RFO search may not lead to the desired TS if all the Hessian eigenvalues are positive, because the smallest positive eigenvalue is chosen as the mode for energy maximization, which may not correspond to the reaction coordinate. The same issue arises if the Hessian possesses multiple negative eigenvalues of similar magnitude, in which case the most negative eigenvalue is followed uphill even if it may not correspond to the reaction coordinate. Moreover, a P-RFO calculation may fail if the Hessian is not evaluated with high fidelity even if the TS guess is good, because errors in the sign of eigenvalues lead to the same ambiguity in identifying which mode to follow uphill. In routine calculations, therefore, the exact second derivative matrix is calculated for the TS guess as a reliable input to the P-RFO algorithm.

Just how severe is the requirement of obtaining the exact Hessian, or a finite difference approximation to it? The answer, of course depends on the type of PES that one is exploring: the answer can be very different for an empirical force field potential versus one based on quantum mechanics (QM) such as density functional theory (DFT).[37,38] Restricting ourselves to QM methods, it is well-known that the computational expense associated with evaluation of the Hessian typically scales one power of system size higher than the energy itself or the gradient.[39,40] Fundamentally, the scaling differences arise from the fact that responses of the unknowns are required with respect to each geometric distortion, whose number scales with the system size. Therefore, in practice, analytical Hessian or even finite difference Hessian evaluations become exceedingly expensive for systems containing a large number of atoms. It is highly desirable to remove the need for explicit evaluation of the Hessian, and that is the second purpose of this paper.

We describe here a modified version of the FSM that uses a quasi-Newton line search method for optimization in place of the existing conjugate gradient method. The enhancement in efficiency is measured in terms of the reduction in number of force calculations required to generate the TS guess. Information generated by the FSM is then directly incorporated into the construction of an approximate, but entirely appropriate, Hessian, which is utilized as input to the P-RFO method in lieu of an exact Hessian. The performance of the algorithm with the approximate Hessian is compared to that with the exact Hessian, in terms of computational time as well as number of optimization cycles. The overall objective is that, by amalgamating the FSM method with the approximate Hessian-based transition state search, we can obtain a low-cost, automated transition-state search technique that is particularly useful for studying reactions of large molecules, where exact Hessian calculations are prohibitively expensive.

■ METHODS

Modified Freezing String Method (FSM-BFGS). The algorithm for the freezing string method (FSM-CG) has been described in detail by Behn et al.[22] The string progresses by alternately adding nodes to two growing substrings that originate respectively from the reactant and product basins on the PES. The FSM terminates when the reactant and product string segments join together. Each node is created via an interpolation step followed by an optimization step.

The interpolation can either be done by a straight line Cartesian or a linear synchronous transit (LST)[41] method. The latter is much preferred since LST preserves internuclear distances on interpolation, whereas Cartesian interpolation may result in unrealistic bond stretches or bends[42] and, hence, very high energies. Tangent directions are determined at the innermost reactant and product nodes by fitting a spline through the images created by the LST.

In the optimization step, the energy is minimized along the negative perpendicular gradient to the interpolated geometry using the method of conjugate gradients (CG). When the convergence criterion is satisfied, or if maximum number of steps, N_{steps}, is reached, the optimization terminates, and the newly created node is "frozen" into place. The interpolation and optimization steps are repeated until the reactant and product side strings join.

A modified approach to the FSM is developed here. The original framework of the method, shown in Figure 1, remains unchanged. However, the conjugate gradient optimization step is replaced with a quasi-Newton line search method,[43] which, in addition to gradient information, builds and utilizes approximate Hessian information for optimization of the node in the direction perpendicular to the reaction coordinate. Since the line search is coupled with the Broyden−Fletcher−Goldfarb−Shanno (BFGS) method of updating the Hessian, this approach is termed FSM-BFGS.
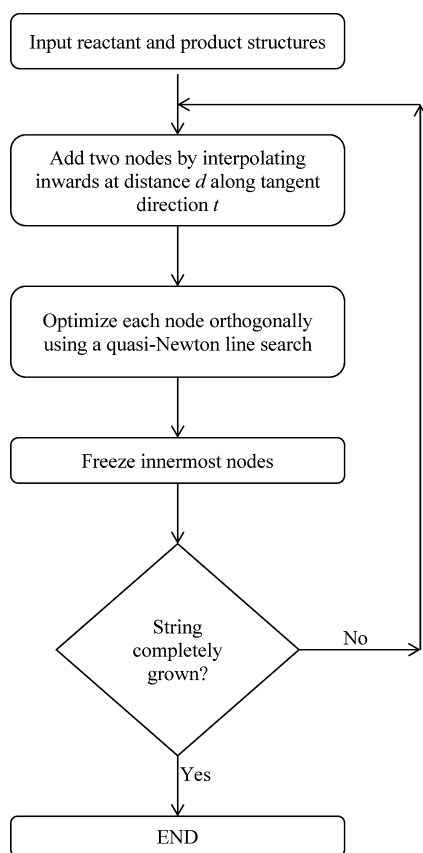
Figure 1. Algorithm for the freezing string method, where the conjugate gradient optimization (FSM-CG) step is replaced with the quasi-Newton line search technique (FSM-BFGS).

Figure 2. Algorithm for quasi-Newton line search optimization in the FSM-BFGS method.

The quasi-Newton line search procedure incorporated in the FSM is described in Figure 2. In this technique, the energy is minimized on the basis of the quadratic approximation:

$$E_{k+1} = E_k + \Delta x_k^T g_k^\perp + 1/2 \Delta x_k^T H_k \Delta x_k \tag{1}$$

Here, Δx_k is the stepsize, $g_k^\perp$ is the perpendicular gradient, and H_k is the approximate Hessian in the space perpendicular to the reaction coordinate. $g_k^\perp$ is given by

$$g_k^\perp = (I - tt^T) g_k \tag{2}$$

where t is the tangent direction determined in the interpolation step. This direction is not updated in the course of an optimization cycle. The quasi-Newton optimization algorithm consists of the following steps:

1. Determine the search direction, s_k, and normalize the direction

$$s_k = -\frac{H_k^{(-1)} g_k^\perp}{|H_k^{(-1)} g_k^\perp|} = -\frac{G_k g_k^\perp}{|G_k g_k^\perp|} \tag{3}$$

where G_k is the inverse of the approximate Hessian.

2. Determine the scaling factor for the step, α_k.
3. Take the minimization step by displacing atoms along the search direction in Cartesian coordinates.
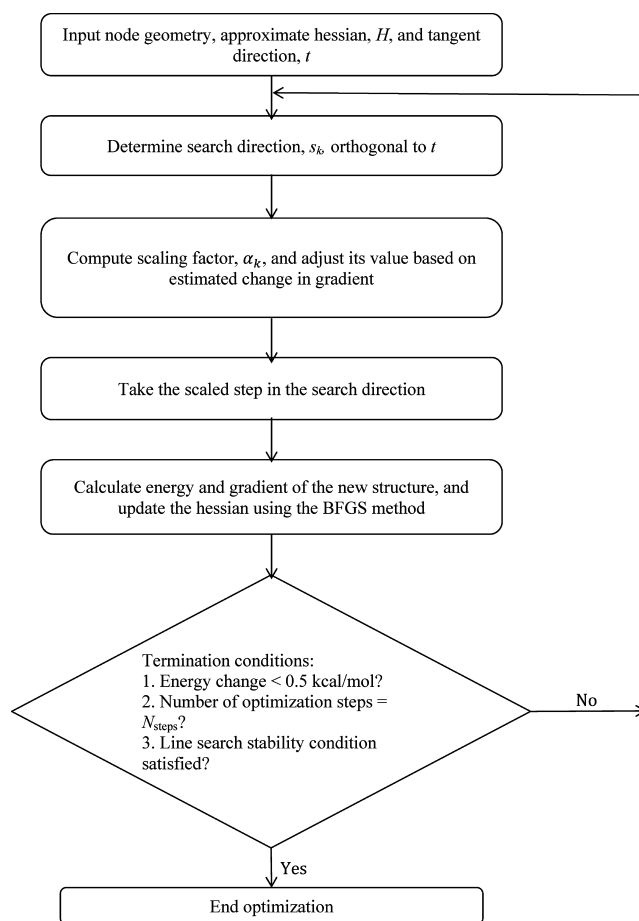
$$x_{k+1} = x_k + \alpha_k s_k \tag{4}$$

4. Update the inverse Hessian in the perpendicular direction, using the Broyden−Fletcher−Goldfarb−Shanno (BFGS) algorithm,[43] which preserves the positive definiteness of the matrix. At the start of the FSM algorithm, both reactant and product side Hessians are initialized to identity matrices.

$$\gamma_k = g_{(k+1)}^\perp - g_k^\perp$$

$$\delta_k = x_{k+1} - x_k$$

$$G_{k+1} = G_k + \left(1 + \frac{\gamma_k^T G_k \gamma_k}{\delta_k^T \gamma_k}\right) \frac{\delta_k \delta_k^T}{\delta_k^T \gamma_k} - \left(\frac{\delta_k \gamma_k^T G_k + G_k \gamma_k \delta_k^T}{\delta_k^T \gamma_k}\right) \tag{5}$$

In addition to the termination criteria specified by the FSM-CG algorithm, a condition associated with the stability of the line search is implemented. A line search factor $\sigma \in (0,1)$ is introduced.[43] The stability condition, shown below, ensures that in the limit of an exact line search, the gradient is perpendicular to the search direction.

$$|(g_{(k+1)}^\perp)^T s_k| \leq -\sigma (g_k^\perp)^T s_k \tag{6}$$

The line search terminates if this condition is satisfied. If σ is large, the condition is representative of a weak line search. In

Table 1. Test Suite of Reactions Used for Both Comparison between FSM-BFGS and FSM-CG as Well As the Contrast between a TS Search with the Approximate Hessian and That with the Exact Hessian

reaction	description	number of atoms	basis set	theory
formaldehyde decomposition	$H_2CO \leftrightarrow H_2 + CO$	4	6-31G	B3LYP
silane formation	$SiH_2 + H_2 \leftrightarrow SiH_4$	5	6-31G	B3LYP
ethanal rearrangement	$CH_3CHO \leftrightarrow CH_2CHOH$	7	STO-3G	HF
ethane dehydrogenation	$CH_3CH_3 \leftrightarrow CH_2CH_2 + H_2$	8	6-31G**	B3LYP
bicyclobutane ring-opening	bicyclobutane $\leftrightarrow CH_2CHCHCH_2$	10	STO-3G	HF
Diels−Alder Reaction	$CH_2CHCHCH_2 + CH_2CH_2 \leftrightarrow$ cyclohexene	16	6-31G	B3LYP
hexadiene ring formation	*cis,cis*-2,4-hexadiene $\leftrightarrow$ 3,4-dimethylcyclobutene	16	STO-3G	HF
alanine dipeptide rearrangement	$C_5 \leftrightarrow C_{7AX}$	22	6-31G	B3LYP
Ireland−Claisen rearrangement[53]	silyl ketene acetal $\leftrightarrow$ silyl ester	56	3-21G	B3LYP

the current implementation, the default value of σ is chosen to be 0.7.

The scaling factor α_k can in principle be determined by minimizing the objective function for the energy iteratively. This approach, however, is not feasible if expensive electronic structure calculations are involved. Therefore, a simple scaling factor evaluation is implemented. The ceiling value α_{max} is determined by imposing a constraint of 0.05 Å on the maximum possible step taken along any coordinate direction.[44]

$$\alpha_{max} |s_k^{max}| \leq 0.05 \tag{7}$$

where $|s_k^{max}|$ is the magnitude of the maximum component of the search direction vector. The FSM-CG algorithm also imposes a maximum step-size constraint of 0.05 Å. The scaling factor is then evaluated using the following expression:[43]

$$\alpha_k = -\frac{2\Delta E}{(g_k^\perp)^T s_k}$$

$$\Delta E = \max(E_{k-1} - E_k, \varepsilon) \tag{8}$$

Here, ε is an approximate lower limit on the desired change in energy and is a fixed parameter in the algorithm. The value of ε is fixed at 2.5 kcal/mol. However, in cases where the reactant and product structures are very similar in energy, the value of ε is set to this energy difference. The scaling factor is further refined by an a priori verification of whether the stability condition is satisfied. The Taylor series expansion for the gradient iterate is given by

$$g_{(k+1)}^{est} = g_k^\perp + \alpha_k G_k^{(-1)} s_k \tag{9}$$

By substituting the expression for s_k and taking the inner product with s_k on both sides

$$s_k^T g_{(k+1)}^{est} = s_k^T g_k^\perp \left(1 - \frac{\alpha_k}{|G_k g_k^\perp|}\right) \tag{10}$$

The expression in parentheses on the right-hand side must be less than σ. The value of α_k is adjusted accordingly. However, if the adjusted value exceeds α_{max}, the ceiling value itself is used to determine the step size. This step ensures that the scaling factor is neither too small nor too large in magnitude. If the search becomes unstable, it is immediately indicated by a negative value of the scaling factor and rectified by reinitializing the Hessian to an identity matrix.

Construction of an Approximate Hessian. The basis for construction of an approximate Hessian is that the tangent direction at the TS guess generated by any interpolation algorithm should be a reasonable approximation to the reaction coordinate at the TS. The second derivative of the energy with respect to the tangent direction is a good approximation to the single negative eigenvalue of the Hessian. This is already enough to separate the single maximization direction from the other degrees of freedom in which minimization is performed. Standard methods for guessing Hessians for minimization[45,46] can then be employed to yield a better guess for the remainder of the Hessian. For example, it is well-established that a unit Hessian constructed in delocalized internal coordinates[47] is usually substantially superior to a unit diagonal Hessian in Cartesian coordinates.

Specifically, beginning with an initial unit matrix constructed in delocalized internal coordinates,[47] the transformation to Cartesian coordinates is carried out using the B matrix,[48,49] according to

$$H_{cart} = B^T H_{int} B \tag{11}$$

where the B matrix transforms displacement in Cartesian coordinates to internal coordinates. The product, BB^T, generates the matrix in internal coordinates, H_{int}. The B matrix is constructed from the coordinates of the TS guess. The transformation to Cartesian coordinates is carried out since the tangent direction is available in this coordinate system. The eigenvalues of the matrix in Cartesian coordinates are all positive by construction. At this stage, we impose the correct structure on the approximate Hessian with no additional cost, by removing the component normal to the reaction coordinate from this matrix, followed by a rank-one update with the approximate curvature.

$$H = H_{cart} - (t^T H_{cart} t) t t^T + C t t^T \tag{12}$$

The update is carried out such that the curvature, C, is the expectation value of the resulting Hessian along the tangent direction. The value of C is obtained by a three-point finite difference interpolation between the TS guess and the two nodes closest and on either side of the guess along the FSM string, say nodes A and B, at distances a and b from the TS guess, respectively. The expression for curvature is given by[50]

$$C = \frac{2E_A}{a(a+b)} - \frac{2E_{TS}}{ab} + \frac{2E_B}{b(a+b)} \tag{13}$$

The approximate Hessian, therefore, has only one negative eigenvalue, as required. Therefore it is now compatible with automatic TS refinement via the P-RFO algorithm.

The performance of the P-RFO with the approximate Hessian input can be contrasted with that using an exact Hessian in terms of the number of optimization cycles as well as the total CPU time required for convergence. Since the

Table 2. Comparison between the FSM-CG and FSM-BFGS Techniques of Generating TS Guesses[a]

reaction	FSM-CG		FSM-BFGS		% increase in gradients from BFGS to CG
	gradients	negative eigenvalue	gradients	negative eigenvalue	
formaldehyde decomposition	94	−0.05	53	−0.27	77
silane formation	73	−0.24	41	−0.23	78
ethanal rearrangement	78	−0.48	61	−0.55	28
ethane dehydrogenation	74	−0.16	58	−0.05	28
bicyclobutane ring-opening	70	−0.10	47	−0.07	49
Diels−Alder reaction	72	−0.05	57	−0.04	26
hexadiene ring formation	78	−1.10	55	−1.00	42
alanine dipeptide rearrangement	94	−0.003	53	−0.003	77
Ireland−Claisen rearrangement	78	−0.25	53	−0.06	47

[a]The two methods are contrasted, using identical input parameters ($ngrads = 3$, $nnodes = 18$), based on the total number of gradient calculations required to obtain the string, as well as the magnitude of the eigenvalue corresponding to the reaction coordinate, obtained from a frequency calculation on the TS guess structure. Barring the exception of ethane dehydrogenation, where the exact Hessian for the TS guess generated using FSM-CG and FSM-BFGS contains three and two negative eigenvalues, respectively, all the TS guesses have the correct structure for the Hessian, with one large negative eigenvalue. The eigenvalues are in atomic units (Ha/Bo^2).

approximate Hessian is determined with no additional electronic structure calculations, the cost of calculating this Hessian compared to the exact Hessian is nearly zero.

■ COMPUTATIONAL DETAILS

A test suite consisting of nine reactions was chosen for this study, as summarized in Table 1. The broad categories of bond formation or dissociation, rearrangement, ring-opening or formation, and isomerization reactions are encompassed in this test set. The size of the test system ranges from 4 to 56 atoms. Basis sets ranging from STO-3G to 6-31G** are used along with either wave function theory (HF) or density functional theory (B3LYP). The reactions in Table 1, listed in order of increasing system size, are used to test both the efficiency of FSM-BFGS as well as the performance of the transition state search using the approximate Hessian relative to the exact Hessian. The efficiency of FSM-BFGS relative to FSM-CG is evaluated in both of the steps of TS search. In the TS guess generation step, the methods are contrasted on the basis of the number of gradient calculations required to generate the guess, as well as the number of negative eigenvalues of the exact Hessian at the guess, which indicates the quality of the guess structure. In the TS refinement step, the performance of the P-RFO method with the approximate and exact Hessians at the TS guess are contrasted for the guess structures generated by both FSM-CG and FSM-BFGS. The two FSM methods are compared on the basis of the number of optimization cycles required by the P-RFO to converge to the true TS structure. The efficiency of the approximate Hessian is evaluated on the basis of the computational time saved by sidestepping the exact Hessian computation.

All calculations were performed with a developmental version of Q-Chem.[51] The FSM requires optimized reactant and product structures as input. In addition, the user can specify both the desired number of maximum steps per optimization, given by *ngrads*, and the node spacing, given by *nnodes*. The node spacing is determined by dividing the distance between reactant and product structures by this number. For all the reactions studied, *ngrads* is set to 3 and *nnodes* is set to 18. These values are chosen such that sufficiently smooth strings and reasonable TS guesses are generated for all the test systems. The inputs to the P-RFO algorithm for TS refinement consist of the TS guess structure, the exact or approximate Hessian, and a user-defined ceiling on

the optimization step size, which is set to a default value of 0.05 Bo.

■ RESULTS AND DISCUSSION

Modified Freezing String Method. The efficiency of FSM-BFGS is measured on the basis of the number of gradients required to obtain a string similar to that generated by FSM-CG. The quality of the guess generated, indicated by the number and magnitude of negative eigenvalues in the exact Hessian, is also contrasted for the two methods. The results are shown in Table 2. Irrespective of the size of the system, level of theory, or reaction involved, both techniques require less than 100 gradient calculations to produce a complete string. This is already a substantial improvement over iterative NEB or string methods.[52] Barring the exception of ethane dehydrogenation where the exact FSM-CG Hessian has three negative eigenvalues and the FSM-BFGS Hessian has two, both methods generate guess structures whose Hessians have single negative eigenvalues. As already discussed, this is highly desirable to ensure that the subsequent P-RFO refinement of the TS is successful. The magnitudes of the eigenvalues corresponding to the reaction coordinate are similar in most cases, indicating the similarity of the TS guesses generated by the two methods. From Table 2, it can also be observed that the FSM-BFGS method requires far fewer gradient calculations than the FSM-CG technique to generate a similar guess structure using identical input parameters. For the reactions in the test set, the existing FSM-CG method requires 50% more gradients on average compared to the new FSM-BFGS variant.

The quasi-Newton optimization method can determine step sizes more effectively than the conjugate gradient method since approximate Hessian information is also incorporated in the line search in addition to gradient information. A moderate line search stability condition, which uses a default value of 0.7 for σ, is sufficient to generate a smooth string in all cases. As a result, the termination condition for the line search is usually satisfied in fewer steps than the enforced upper limit. The FSM-BFGS technique, therefore, reduces computational effort relative to the FSM-CG method for generating the TS guess. The quality of the TS guess generated by each method is also examined by testing the performance of the approximate Hessian for TS refinement.

Transition State Search with an Approximate Hessian. The quality of the approximate Hessian is tested on the basis of

5170

dx.doi.org/10.1021/ct300659d | J. Chem. Theory Comput. 2012, 8, 5166−5174

Table 3. Comparison between the Performance of P-RFO Algorithm with an Exact Hessian and That with an Approximate Hessian, Using the TS Guess and Hessian Generated by the FSM-BFGS Algorithm[a]

	exact Hessian			approximate Hessian			
reaction	negative eigenvalue	cycles	CPU time (s)	|overlap|	negative eigenvalue	cycles	CPU time (s)	reduction in CPU time (%)
formaldehyde decomposition	−0.27	50	56.1	0.7	−0.29	44	43.9	22
silane formation	−0.23	5	13.6	0.6	−0.45	12	14.2	−4
ethanal rearrangement	−0.55	74	15.9	0.0	−2.63	54	11.1	30
ethane dehydrogenation	−0.05	63	459.8	0.5	−0.26	148	906.2	−97
bicyclobutane ring-opening	−0.07	129	37.5	0.7	−0.30	147	41.1	−10
Diels−Alder reaction	−0.04	63	1366.9	0.6	−0.23	63	1033.6	24
hexadiene ring formation	−1.00	61	45.1	0.8	−1.68	67	44.1	2
alanine dipeptide rearrangement	−0.003	43	2538.3	0.7	−0.02	51	1889.7	26
Ireland−Claisen rearrangement	−0.06	88	13 567.2	0.3	−2.65	153	12 980.3	4

[a]Contrast is made between the number of optimization cycles required to converge to the TS, as well as the total CPU time. The CPU time in the case of the exact Hessian is the sum of the time required to calculate the Hessian and the time required for the TS search. The overlap is calculated as the scalar product magnitude between the eigenvectors corresponding to the reaction coordinate in the exact and approximate Hessians.

Table 4. Comparison between the Performance of P-RFO Algorithm with an Exact Hessian and That with an Approximate Hessian, Using the TS Guess and Hessian Generated by the FSM-CG Algorithm

	exact Hessian			approximate Hessian			
reaction	negative eigenvalue	cycles	CPU time (s)	|overlap|	negative eigenvalue	cycles	CPU time (s)	reduction in CPU time (%)
formaldehyde decomposition	−0.05	59	65.1	0.6	−0.15	64	63.9	2
silane formation	−0.24	5	13.6	0.7	−0.48	12	14.2	−4
ethanal rearrangement	−0.48	66	14.3	0.8	−0.22	65	13.4	6
ethane dehydrogenation[a]	−0.16	193	1255.8	0.1	−1.20			
bicyclobutane ring-opening	−0.1	114	33.3	0.6	−0.31	117	32.7	2
Diels−Alder reaction	−0.05	83	1695.0	0.4	−0.20	85	1394.5	18
hexadiene ring formation	−1.1	54	40.4	0.5	−1.85	77	50.7	−25
alanine dipeptide rearrangement	−0.003	36	2278.9	0.4	−0.007	51	1889.7	17
Ireland−Claisen rearrangement	−0.25	364	36 982.7	0.1	−0.27			

[a]The TS search with the exact Hessian required a smaller step to converge to the correct TS. The ceiling on stepsize in this case is 0.025 Bo.

the total time required for the algorithm to converge to the correct transition state. For the TS search conducted with an exact Hessian, the total time includes the time required to evaluate the Hessian itself. In addition, the most negative eigenvalue is compared between the approximate and exact Hessian. The overlap of the approximate and exact eigenvectors corresponding to the reaction coordinate is determined by calculating their scalar product. The efficiency of the P-RFO search algorithm with these Hessians is compared in delocalized internal coordinates.[47]

The contrast between searches carried out with the exact and approximate Hessians with the TS guess generated by the FSM-BFGS algorithm is reported in Table 3. The best possible input for a P-RFO search should be the exact Hessian. The expectations for relative efficiency of searches performed with an approximate Hessian therefore should not be too high since the primary purpose of the approximate Hessian is to avoid expensive exact Hessian evaluations in large systems. The trends are not uniform since the quality of both Hessians depends on the nature of the TS guess. In addition, the constructed Hessian is based on an approximate reaction coordinate and an interpolated curvature. However, the overall results are promising.

One measure of the quality of the approximate Hessian is the overlap between the eigenvector corresponding to the reaction coordinate in the exact Hessian with the corresponding vector in the approximate Hessian. This overlap is greater than 0.5 in

most of the test reactions studied, with a fair match between the eigenvalues as well. In general, with the exception of ethane dehydrogenation, the transition-state search performs remarkably well with an approximate Hessian input, both in terms of the number of optimization cycles as well as the total CPU time required for convergence. In the case of ethane dehydrogenation, it is observed that the exact Hessian has two negative eigenvalues of similar magnitude. This indicates that the TS guess is not close to the region of the true saddle point, and therefore, the approximate tangent direction may not be effective in guiding the P-RFO. However, the algorithm does converge to the true TS within 150 optimization cycles since the approximate Hessian possesses the desired structure of a single negative eigenvalue. The utility of an approximate Hessian in saving computational time, however, is distinctly visible for large systems. For systems containing 16 atoms or higher, the exact Hessian calculation costs between 10% of the total CPU time in the case of hexadiene ring formation to 45% in the case of Ireland−Claisen rearrangement. In these cases, the reduction in cost associated with sidestepping the exact Hessian clearly outweighs the increase in cost of gradients associated with the use of an approximate Hessian.

On similar lines, the performance of the approximate Hessian using the TS guess generated by the FSM-CG method is also evaluated. The results are shown in Table 4. In most cases, the approximate Hessian generated using the FSM-CG algorithm performs just as effectively as that using the FSM-BFGS
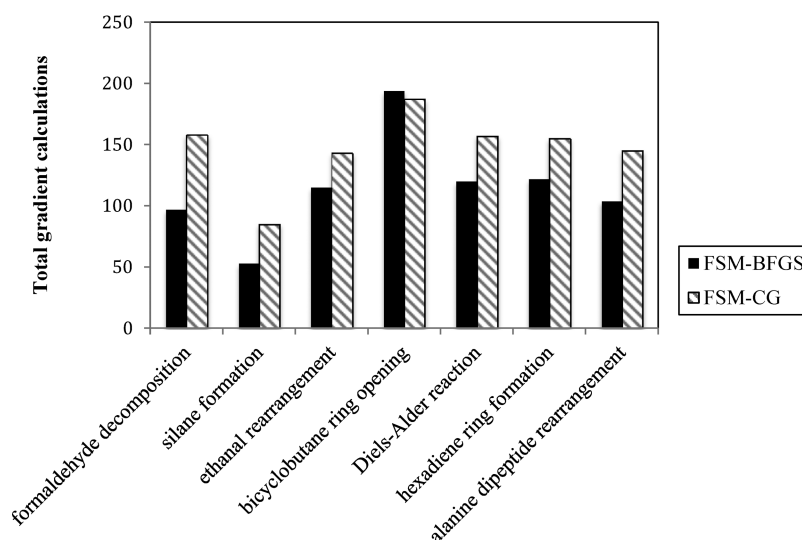
Figure 3. Performance of the combination of a string method with an approximate Hessian-based TS search. Comparison between FSM-CG and FSM-BFGS is carried out on the basis of the total number of gradients required to achieve convergence beginning with reactant and product configurations. Ethane dehydrogenation and Ireland−Claisen rearrangement are not shown since the FSM-CG guess does not converge to the correct saddle point.

algorithm, demonstrating the transferability of the approximate Hessian construction procedure to any interpolation algorithm. The overlap between the exact and approximate reaction coordinates, however, is slightly poorer on average compared to the FSM-BFGS method. Particularly, in the instances of ethane dehydrogenation and Ireland−Claisen rearrangements, the TS searches with the approximate Hessian converge to first order saddle points, which do not lead to the correct reactant and product structures. The TS guesses converge to the true TS with the exact Hessian input for these reactions, indicating that the FSM-CG generates a good structure for the TS guess. However, for the same input parameters, the approximate reaction coordinate generated by the BFGS method is better than the CG direction for these reactions.

The approximate Hessian calculated using the information generated by the FSM algorithm, therefore, effectively eliminates the need for computation of an exact Hessian for TS search. The requirement of an exact Hessian for an accurate transition state search has been a massive obstacle to determining TSs for systems consisting of hundreds of atoms. While the largest system in this study, the Ireland−Claisen rearrangement, has only 56 atoms, the impact of exact Hessian evaluation in that case is already significant. The exact Hessian calculation constitutes about 45% of the entire job time when the search is carried out in internal coordinates. If one then doubles the system size, the energy and gradient calculations will scale up by approximately a factor of 4 for these DFT calculations, while the exact Hessian calculation will increase by approximately a factor of 8.[39,40] This illustrates how exact Hessian evaluation progresses from being computationally insignificant in the small reactions toward being a severe bottleneck in large systems. The virtue of the approximate Hessian approach is the removal of this bottleneck without unduly affecting the convergence of the TS refinement by the P-RFO algorithm.

The overall performance of the combined FSM and approximate Hessian-based method, described by the total gradient calculations required for both steps of TS finding, is shown in Figure 3. It can be observed that the FSM-BFGS

performs better in terms of both accuracy as well as efficiency of finding the TS. Most of the improvement in efficiency arises from the improvement in the string method itself, since the TS guesses generated and the constructed approximate Hessians are similar.

CONCLUSIONS

The aim of this study was to develop a set of computational techniques that determines transition structures rapidly and accurately, given only reactant and product structures. We have made progress in addressing two of the key bottlenecks in finding transition states: generating the guess to the transition state and calculating the exact Hessian.

The cost of automatically generating an initial guess is reduced by replacing the conjugate gradient technique used in the optimization step of the freezing string method (FSM) with a quasi-Newton line search coupled with a BFGS Hessian update. This approach enhances the computational efficiency of the FSM by 50% on average for the test suite consisting of a diverse range of reaction types and system sizes. It must be noted, however, that interpolation methods do not follow the reaction path exactly. Therefore, convergence to the correct TS cannot be rigorously guaranteed. The FSM-BFGS method with the current set of parameters may fail in systems more complex than the current test set. In such cases, however, it is possible to tighten the line search using a lower value of σ, in order to follow the true reaction path more accurately.

The second bottleneck, the exact Hessian calculation, is addressed by constructing an approximate Hessian using the output of the FSM-BFGS or FSM-CG method, which is then used as an input to the P-RFO algorithm instead of the exact Hessian. In addition to the computational benefit of avoiding an expensive exact Hessian calculation, the approximate Hessian by design possesses the desirable property of a single negative eigenvalue. This means that it can in fact be more appropriate than the exact Hessian in cases where the latter does not initially have the correct structure. Despite being approximate, the numerical performance of P-RFO refinements is not degraded by its use. Furthermore, an approximate

5172

dx.doi.org/10.1021/ct300659d | *J. Chem. Theory Comput.* 2012, 8, 5166−5174

Hessian-based search in delocalized internal coordinates helps to make the study of reactions of large molecules more computationally viable using electronic structure methods.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: mhg@bastille.cchem.berkeley.edu (M.H.-G.); bell@cchem.berkeley.edu (A.T.B.).

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Schlegel, H. B. Exploring Potential Energy Surfaces for Chemical Reactions: An Overview of some Practical Methods. *J. Comput. Chem.* **2003**, *24*, 1514−1527.

(2) Berti, P. J; Schramm, V. L. Transition State Structure of the Solvolytic Hydrolysis of NAD$^+$. *J. Am. Chem. Soc.* **1997**, *119*, 12069−12078.

(3) Bell, A. T.; Head-Gordon, M. Quantum Mechanical Modeling of Catalytic Processes. *Annu. Rev. Chem. Biomol. Eng.* **2011**, *2*, 453−477.

(4) Keil, F. J. Multiscale Modelling in Computational Heterogeneous Catalysis. *Top. Curr. Chem.* **2012**, *307*, 69−108.

(5) Mills, G.; Jonsson, H. Quantum and Thermal Effects in H_2 Dissociative Adsorption: Evaluation of Free Energy Barriers in Multidimensional Quantum Systems. *Phys. Rev. Lett.* **1994**, *72*, 1124−1128.

(6) Henkelman, G.; Jonsson, H. Improved Tangent Estimate in the Nudged Elastic Band Method for finding Minimum Energy Paths and Saddle Points. *J. Chem. Phys.* **2000**, *113*, 9978−9985.

(7) Henkelman, G.; Uberuaga, B. P.; Jonsson, H. A Climbing Image Nudged Elastic Band Method for Finding Saddle Points and Minimum Energy Paths. *J. Chem. Phys.* **2000**, *113*, 9901−9904.

(8) Trygubenko, S. A.; Wales, D. J. A Doubly Nudged Elastic Band Method for finding Transition States. *J. Chem. Phys.* **2004**, *120*, 2082−2094.

(9) Chu, J.; Trout, B.; Brooks, B. A Super-Linear Minimization Scheme for the Nudged Elastic Band Method. *J. Chem. Phys.* **2003**, *119*, 12708−12717.

(10) E., W.; Ren, W.; Vanden-Eijnden, E. String Method for the Study of Rare Events. *Phys. Rev. B* **2002**, *66*, 052301−052304.

(11) E., W.; Ren, W.; Vanden-Eijnden, E. Finite Temperature String Method for the Study of Rare Events. *J. Phys. Chem. B* **2005**, *109*, 6688−6693.

(12) Ren, W.; Vanden-Eijnden, E. Simplified and Improved String Method for Computing the Minimum Energy Paths in Barrier-Crossing Events. *J. Chem. Phys.* **2007**, *126*, 164103−164110.

(13) Burger, S. K.; Yang, W. Quadratic String Method for Determining the Minimum-Energy Path based on Multiobjective Optimization. *J. Chem. Phys.* **2006**, *124*, 054109−054121.

(14) Burger, S. K.; Yang, W Sequential Quadratic Programming Method for Determining the Minimum Energy Path. *J. Chem. Phys.* **2007**, *127*, 164107−164113.

(15) Chaffey-Millar, H.; Nikodem, A.; Matveev, A. V.; Krüger, S.; Rösch, N. Improving Upon String Methods for Transition State Discovery. *J. Chem. Theory Comput.* **2012**, *8*, 777−786.

(16) Granot, R.; Baer, R. A Spline for your Saddle. *J. Chem. Phys.* **2008**, *128*, 184111−184119.

(17) Peters, B.; Heyden, A.; Bell, A. T.; Chakraborty, A. A Growing String Method for Determining Transition States: Comparison to the Nudged Elastic Band and String Methods. *J. Chem. Phys.* **2004**, *120*, 7877−7886.

(18) Quapp, W. A Growing String Method for the Reaction Pathway defined by a Newton Trajectory. *J. Chem. Phys.* **2005**, *122*, 174106−174116.

(19) Goodrow, A.; Bell, A. T.; Head-Gordon, M. Development and Application of a Hybrid Method Involving Interpolation and ab initio Calculations for the Determination of Transition States. *J. Chem. Phys.* **2008**, *129*, 174109−174120.

(20) Goodrow, A.; Bell, A. T.; Head-Gordon, M. Transition State-Finding Strategies for use with the Growing String Method. *J. Chem. Phys.* **2009**, *130*, 244108−244121.

(21) Goodrow, A.; Bell, A. T.; Head-Gordon, M. A Strategy for Obtaining a More Accurate Transition State Estimate using the Growing String Method. *Chem. Phys. Lett.* **2010**, *484*, 392−398.

(22) Behn, A.; Zimmerman, P. M.; Bell, A. T.; Head-Gordon, M. Efficient Exploration of Reaction Paths via a Freezing String Method. *J. Chem. Phys.* **2011**, *135*, 224108−224116.

(23) Schlegel, H. B. Optimization of Equilibrium Geometries and Transition Structures. *J. Comput. Chem.* **1982**, *3*, 214−218.

(24) Henkelman, G.; Jonsson, H. A Dimer Method for Finding Saddle Points on High Dimensional Potential Surfaces using only First Derivatives. *J. Chem. Phys.* **1999**, *111*, 7010−7022.

(25) Heyden, A.; Bell, A. T.; Keil, F. J. Efficient Methods for Finding Transition States in Chemical Reactions: Comparison of Improved Dimer Method and Partitioned Rational Function Optimization Method. *J. Chem. Phys.* **2005**, *123*, 224101−224114.

(26) Cerjan, C. J.; Miller, W. H. On Finding Transition States. *J. Chem. Phys.* **1981**, *75*, 2800−2806.

(27) Simons, J.; Jorgensen, P.; Taylor, H.; Ozment, J. Walking on Potential Energy Surfaces. *J. Phys. Chem.* **1983**, *87*, 2745−2753.

(28) Baker, J. An Algorithm for the Location of Transition States. *J. Comput. Chem.* **1986**, *7*, 385−395.

(29) Wales, D. J. Basins of Attraction for Stationary Points on a Potential-energy Surface. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 653−657.

(30) Wales, D. J. Locating Stationary Points for Clusters in Cartesian Coordinates. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1305−1313.

(31) Munro, L. J.; Wales, D. J. Defect Migration in Crystalline Silicon. *Phys. Rev. B* **1999**, *59*, 3969−3980.

(32) Maeda, S.; Ohno, K.; Morokuma, K. An Automated and Systematic Transition Structure Explorer in Large Flexible Molecular Systems Based on Combined Global Reaction Route Mapping and Microiteration Methods. *J. Chem. Theory Comput.* **2009**, *5*, 2734−2743.

(33) Ayala, P. Y.; Schlegel, H. B. A Combined Method for Determining Reaction Paths, Minima, and Transition State Geometries. *J. Chem. Phys.* **1997**, *107*, 375−384.

(34) del Campo, J. M.; Koster, A. M. A Hierarchical Transition State Search Algorithm. *J. Chem. Phys.* **2008**, *129*, 024107−024118.

(35) Cancès, E.; Legoll, F.; Marinica, M. C.; Minoukadeh, K.; Williame, F. Some Improvements of the Activation-Relaxation Technique Method for Finding Transition Pathways on Potential Energy Surfaces. *J. Chem. Phys.* **2009**, *130*, 114711−114716.

(36) Schlegel, H. B. Geometry Optimization. *WIREs Comput. Mol. Sci.* **2011**, *1*, 790−809.

(37) Hohenberg, P.; Kohn, W. Inhomogeneous Electron Gas. *Phys. Rev.* **1964**, *136*, B864−B871.

(38) Kohn, W.; Sham, L. J. Self-Consistent Equations Including Exchane and Correlation Effects. *Phys. Rev.* **1965**, *140*, A1133−A1138.

(39) Johnson, B. G.; Fisch, M. J. An Implementation of the Analytical Second Derivatives of the Gradient-corrected Density Funtional Energy. *J. Chem. Phys.* **1994**, *100*, 7429−7442.

(40) Amos, R. D.; Rice, J. E. Implementation of Analytical Derivative Methods in Quantum Chemistry. *Comput. Phys. Rep.* **1989**, *10*, 147−187.

(41) Halgren, T. A.; Lipscomb, W. N. The Synchronous-Transit Method for Determining Reaction Pathways and Locating Molecular Transition States. *Chem. Phys. Lett.* **1977**, *49*, 225−232.

(42) Behn, A.; Zimmerman, P. A.; Bell, A. T.; Head-Gordon, M. Incorporating Linear Synchronous Transit Interpolation into the

Growing String Method: Algorithm and Applications. *J. Chem. Theory Comput.* **2011**, *7*, 4019−4025.

(43) Fletcher, R. *Practical Methods of Optimization Vol 1: Unconstrained Optimization*; Wiley: New York, 1980; pp 10−60.

(44) Head, J. D.; Zerner, M. C. A Broyden-Fletcher-Goldfarb-Shanno Optimization Procedure for Molecular Geometries. *Chem. Phys. Lett.* **1985**, *122*, 264−270.

(45) Schlegel, H. B. Estimating the Hessian for Gradient-type Geometry Optimizations. *Theor. Chim. Acta (Berlin)* **1984**, *66*, 333−340.

(46) Lindh, R.; Bernhardsson, A.; Karlstrom, G.; Malmqvist, P. On the use of a Hessian Model Function in Molecular Geometry Optimizations. *Chem. Phys. Lett.* **1995**, *241*, 423−428.

(47) Baker, J.; Kessi, A.; Delley, B. The Generation and Use of Delocalized Internal Coordinates in Geometry Optimization. *J. Chem. Phys.* **1996**, *105*, 192−212.

(48) Pulay, P.; Fogarasi, G. Geometry Optimization in Redundant Internal Coordinates. *J. Chem. Phys.* **1992**, *96*, 2856−2860.

(49) Wilson, E. B.; Decius, J. C; Cross, P. C. *Molecular Vibrations*; McGraw-Hill: New York, 1955; pp 54−61.

(50) Anoshkina, E. V.; Belyaev, A. G.; Seidel, H.-P. Asymptotic Analysis of Three-Point Approximations of Vertex Normals and Curvatures. In *Proceedings of Vision, Modeling, and Visualization (VMV)*, Erlangen, Germany, November 20−22, 2002; Aka GmbH: Aachen, Germany, 2002.

(51) Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C. P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. Advances in Methods and Algorithms in a Modern Quantum Chemistry Program Package. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172−3191.

(52) Peters, B.; Heyden, A.; Bell, A. T.; Chakraborty, A. A Growing String Method for Determining Transition States: Comparison to the Nudged Elastic Band and String Methods. *J. Chem. Phys.* **2004**, *120*, 7877−7886.

(53) Gul, S.; Schoenebeck, F.; Aviyente, V.; Houk, K. N. Computational Study of Factors Controlling the Boat and Chair Transition States of Ireland-Claisen Rearrangements. *J. Org. Chem.* **2010**, *75*, 2115−2118.