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Locating Minima on Seams of Intersecting Potential Energy Surfaces. An Application to Transition Structure Modeling

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Abstract: It is proposed that the equivalent of a transition structure within a force field model can be defined as the lowest energy structure on the seam of the two intersecting potential energy surfaces valid for the reactant and product. The present paper describes a method for locating such minima and compares the obtained results with ab initio transition structures and with experimental activation energies for closely related systems. Using Allinger's MM2 force field, it is shown that the method generates transition structures with overall features close to those obtained by ab initio calculations, and trends in activation energies are also reproduced reasonably well.

Introduction

The structure and energy of transition structures (TS) are of prime importance in theoretical studies of chemical reactions. Improvements in optimization algorithms during recent years have made the location of TS's relatively routine. If the energy-generating function is taken to be of the ab initio type, the TS can in principle be refined to any desired accuracy, although practical considerations usually put rather strict limits on both the size and the level of sophistication. Semiempirical methods can be used for somewhat larger systems, but in this case only comparison with experiments or accurate ab initio calculations can be used to judge the quality of the results.

In many applications it is not the prediction of absolute values of activation parameters that is of primary concern, but rather how these vary for closely related systems. Synthetic sequences are often dependent on two or more reaction pathways having activation energies differing by only a few kcal/mol, and in such cases the desired reaction can often be favored by a careful selection of substituents at specific sites in the substrates. Substituents can be divided into two limiting cases according to the influence they have on a reaction: those which primarily are of "structural" or "steric" nature and those which mainly exert "electronic" influence. While the latter certainly requires an explicit description of the electrons in the system, there is some hope that the former can be modeled by less rigorous theoretical methods. Of course, the above classification of substituents will depend on the given reaction.

The modeling of substituent effects on transition structures by force field methods, which by nature cannot cope with electronic effects, has been pionered by Houk and co-workers;[1-3] however, their method has been criticized by Menger and Sherrod.[4,5] The approach utilized by Houk consists of performing ab initio calculations on the TS for a suitable model reaction and transferring structural parameters to the force field environment. The TS is here treated as a minimum on the potential energy surface (PES), and relative energies of TS's for more complex systems are evaluated by regular geometry optimization. Typically the model TS is optimized at the SCF level of theory with a medium-size basis set, and the relevant bond lengths and angles then define the "natural" or "equilibrium" parameters in the force field. The corresponding force constants can be estimated by ab initio calculations or more often simply given "reasonable" values based on chemical intuition. Similarly, the constants needed for evaluating torsional and Coulomb energies are usually estimated or simply set equal to zero. For a given reaction the number of new parameters to be defined are typically on the order of 20–40. While results from this approach have been shown to give respectable agreement with experimental data, it must be noted that the number of points used for comparison in each case is small, typically on the order of 10. Menger and Sherrod have criticized the procedure for its lack of rigor and pointed out that any agreement between calculated and experimental data may not stem from the physical significance of the parameters but simply from the closeness of the parameters to those that could be obtained by a least-squares fit; i.e., using 20–40 parameters in a model to reproduce 10 experimental data gives a certain degree of flexibility in any model.[4,5]

A more fundamental problem with the Houk approach is the treatment of the TS as a minimum on the PES. A TS is characterized as being a maximum on the PES in one direction (the reaction coordinate) and a minimum in all other, and these directions can in general be written as linear combinations of internal or Cartesian coordinates. Three different strategies can be employed in transferring the ab initio structure to the force field model: (1) a "fixed atom" procedure where the atoms directly involved in the reaction are frozen by fixing their Cartesian coordinates; (2) a "fixed parameter" procedure where certain internal coordinates are constrained by assigning large force constants to these variables; (3) a "flexible parameter" procedure where all atoms are allowed to move. The first approach assumes that the essence of the TS does not change with substituents; i.e., the TS is not allowed to "relax". The second approach assumes that the reaction coordinate is dominated by a few internal variables and the motion along the reaction coordinate is frozen by keeping these variables constant. This approach is less restrictive than the first since all atoms are allowed to move and only certain relationships among them are required to hold (e.g., fixed bond lengths and angles). Of course, this also puts restrictions on the optimization along directions other than the reaction coordinate, especially those where the frozen internal coordinates make a significant contribution. The third, usually preferred, approach treats the motion along the reaction coordinate on equal footing with all other directions and allows the TS to relax; however, the change in geometry along the reaction coordinate is in the wrong direction since the TS is treated as a minimum on the PES, not as a maximum.[3,6]

One may ask why it is necessary to resort to modeling the TS by the above methods; why not simply locate the real TS? The

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(1) (a) Houk, K. N.; Duh, H.; Wu, Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (b) Dorigo, A.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2195. (c) Wu, Y.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. (d) Mukherjee, D.; Wu, Y.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328.

(2) (a) Dorigo, A.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698. (b) Dorigo, A.; Houk, K. N. *Adv. Mol. Model.* **1988**, *1*, 135.

(3) For other reactions modeled by force field methods treating the TS as a minimum, see: (a) DeTar, D. F. *J. Am. Chem. Soc.* **1974**, *96*, 1255. (b) DeTar, D. F.; McMullen, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1978**, *100*, 2484. (c) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. (d) Gleicher, G. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 4628.

(4) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8071.

(5) Sherrod, M. J.; Menger, F. M. *J. Am. Chem. Soc.* **1989**, *111*, 2611.

(6) If the reactions in a series happen to have TS's determined by symmetry, as the S_N2 reaction of X^- with RX, there is no change in geometry along the reaction coordinate, and consequently treating the TS as a minimum does not introduce any errors.

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problem is that few reactions have a well-defined TS when the energy function is of the force field type. In order to calculate the energy of a molecule by these methods, the structure must be defined in terms of atom types and connectivity, and for a general reaction these will usually be different for the reactant and product. Only when the structure for the whole reaction can be described by the same set of atom types and connectivity is the TS well defined, and it can be located by usual techniques for geometry optimization. Examples of such reactions will typically be of a conformational nature, e.g., bond rotations and atom inversions. When the connectivity and/or atom types change during the reaction, one has the problem that two different PES's can be generated from the same set of Cartesian coordinates, one that has a minimum corresponding to the reactant but not the product and one where the reverse is true. One strategy could be to smoothly change one set of parameters into the other as the reaction proceeds; however, the lack of guidelines for choosing the interpolating function makes such an approach rather arbitrary.

Alternatively, the *equivalent* of a TS in a force field environment can be defined as the lowest energy structure linking the reactant and product. When different sets of parameters are needed for describing the two end points, the TS equivalent is thus the lowest energy structure on the seam of the intersecting PES's. The present paper describes how such points can be located and evaluates how the predictions of this model compares with ab initio structures and experimental data. We will loosely refer to the minimum energy structure on the seam of the intersecting PES's as the (force field) TS. The advantage of the current strategy over Houk's TS modeling is that only information regarding the two minima (reactant and product) on the PES is needed, and such data are in principle accessible by experiments. The disadvantage is that the functional form of the energy must be reasonably accurate over a wider range of geometries than just near the minimum. It is also clear that the calculated activation energies will be too high (see below), but this is of no major concern if only relative values are of interest.

Connection with Other Work and Model Limitations

To the author's knowledge the present work is the first where multidimensional surface crossing is combined with molecular modeling methods for investigating reactivity. However, surface crossings have been used extensively over the years to explain chemical reactions. Below are given some of the more important contributions that relate to this work.

In the simplest form, where the reaction is depicted to occur in one dimension, Bell, Evans, Polanyi,[7] and Hammond[8] have postulated how the structure of the TS should vary if the overall reaction energy changes. More recently these concepts have been shown to be closely connected with the Marcus equation,[9] which again is a consequence of a "square" relationship between the symmetric and asymmetric component of the reaction barrier.[10] Subsequent work by More O'Ferrall, Thornton, Jencks, Kresgee, and others extended the treatment to allow the reaction to proceed in two dimensions, a reaction and a perpendicular coordinate connecting (possibly hypothetical) intermediates; for a review, see ref 11. Upon going to two dimensions, the one-to-one correspondence between the activation energy, the position of the TS, and exothermicity is lost, since displacement along the perpendicular coordinate can significantly influence both the structure and energy of the TS. However, for closely related systems it is usually assumed that only little motion occurs along the perpendicular coordinate(s), in which case the Bell-Evans-Polanyi treatment should be valid. The one-dimensional treatment often considers model potentials and assumes that the TS can be represented by the intersection of the reactant and product curves. If the potentials are taken to be simple harmonics, the barrier heights of a reaction series are connected by the Marcus equation.[10] Within this context, the present method can be considered as the full multidimensional extension where the potentials are given by the chosen force field.

The principle of least nuclear motion[12] (PLNM) also bears resemblance with the present work. The PLNM states that, for reactions experiencing the same degree of electronic stabilization, the one which involves the least nuclear reorganization between reactant and product will occur fastest. Taking instead the PLNM to hold between the reactant and the TS, and weighting the distances by appropriate force constants, this is the present model.

Within electronic structure calculations surface crossings have been widely used for interpreting reactions, especially in photochemical reactions where several electronic states usually are involved.[13] The idea that the activation barrier for a thermal reaction can be thought of as arising from the crossing of wave functions for the reactant and product, and a quantum mechanical resonance term, has been advocated by Shaik and Pross.[14] The early work in this area concentrated on recovering qualitative trends in reactivity when the electronic structure of the reactant(s) was varied, and how these relate to reactant/product properties. This model discusses barriers in terms of an (unspecified) one-dimensional reaction coordinate and formal valence bond (VB) structures.[15] Lately these ideas have been quantified for some reaction types by carrying out ab initio VB calculations.[16] The reactant and product wave functions are written as small linear combinations of VB determinants yielding classical Lewis structures. The reactant wave function at the product geometry corresponds to an excited state of the product wave function, and vice versa. Given a suitable reaction coordinate, the surface crossing point for these two VB wave functions can be located. An adequate description of the wave function for the TS will in general require not only VB structures for the reactant and product but also zwitterionic structures. By including these, and performing a variational calculation, the quantum mechanical resonance integral can be identified as the difference between the TS energy and that of the surface crossing point. So far these calculations have been limited to systems where the TS and the surface crossing point are determined by the symmetry of the reaction, e.g., linear X_3 species and S_N2 reactions of the type $X^- + CH_3X$. By making suitable assumptions regarding the reactions coordinate (e.g., conservation of bond order[16b]), these systems can be treated as one-dimensional.[17]

The work by Shaik and Pross concentrates on obtaining a more detailed understanding of how *electronic* changes in the reactant/product influence the height of the reaction barrier. Dif-

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(7) (a) Bell, R. P. *Proc. R. Soc. London, Ser. A* **1936**, *154*, 414. (b) Evans, M.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875. (c) Evans, M.; Polanyi, M. *Trans. Faraday Soc.* **1936**, *32*, 1333. (d) Evans, M.; Polanyi, M. *Trans. Faraday Soc.* **1937**, *33*, 448. (e) Evans, M.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11. (f) Evans, M.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 49. (g) Leffler, J. E. *Science* **1953**, *117*, 340. (h) Agmon, N.; Levine, R. D. *Chem. Phys. Lett.* **1977**, *52*, 197. (i) Agmon, N. *J. Am. Chem. Soc.* **1984**, *106*, 6960. Miller, A. R. *J. Am. Chem. Soc.* **1978**, *100*, 1984.

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(13) See, e.g.: (a) Salem, L. *J. Am. Chem. Soc.* **1974**, *96*, 3486. (b) Dauben, W. G.; Salem, L.; Turro, N. J. *Acc. Chem. Res.* **1975**, *8*, 41.

(14) (a) Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3692. (b) Pross, A.; Shaik, S. S. *Acc. Chem. Res.* **1983**, *16*, 363. (c) Pross, A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99. (d) Shaik, S. S. *Pure Appl. Chem.* **1991**, *63*, 193.

(15) (a) Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 187. (b) Mitchell, D. J.; Schlegel, H. B.; Shaik, S. S.; Wolfe, S. *Can. J. Chem.* **1985**, *63*, 1642. (c) Cohen, D.; Bar, R.; Shaik, S. S. *J. Am. Chem. Soc.* **1986**, *108*, 231. (d) Buncel, E.; Shaik, S. S.; Um, I.-H.; Wolfe, S. *J. Am. Chem. Soc.* **1988**, *110*, 1275. (e) Shaik, S. S.; Pross, A. *J. Am. Chem. Soc.* **1982**, *104*, 2708. (f) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 187. (g) Shaik, S. S. *J. Am. Chem. Soc.* **1983**, *105*, 4359.

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(17) The development of methods for locating seams of intersecting surfaces, as described by Farazdel and Dupuis (ref 26) and in this work, may help advance the curve crossing VB calculations to also treat true multidimensional systems.

ferences in reactivity due to "steric" factors cannot be handled, and in this respect the present force field method is complementary. In the force field model the surface crossing point is equated to the TS and the "resonance" contribution is totally neglected. The success or failure of the present method thus depends critically on the assumption that the resonance integral is constant (or proportional to the height of the surface crossing point) within a reaction series.[18] The variation of the TS along or perpendicular to the reaction coordinate will be adequately modeled (within the accuracy of the force field) as long as the perturbations are sterically steric; force fields are by nature unable to handle electronic effects. Differences in reactivity due to electronic factors, such as symmetry-forbidden or -allowed pathways, are often known in advance, and the force field method concentrates on recovering more subtle details between closely related systems. Whether the above assumptions are too drastic or hold sufficiently close for acquiring useful results will have to be settled by actual calculations.

Force Field Considerations

In the present investigation the force field used was Allinger's MM2,[19] which is one of the most popular for medium-size organic systems due to the variety of functional groups it includes. In MM2 the energy is given as a sum of bond stretch, bond angle, torsional, and nonbonded interactions (van der Waal and dipole–dipole terms). The bond stretch term has the form:

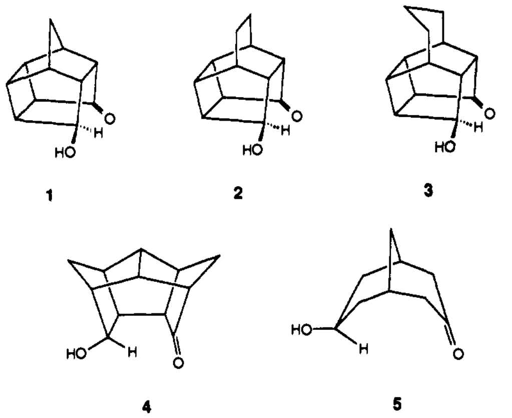
$$E_{\mathrm{str}} = k(r - r_0)^2(1 - c(r - r_0)) \qquad (1)$$

where k is the force constant for the given bond type and c is a cubic stretch constant which introduces some anharmonicity in the potential. In MM2 c has a constant value of 2.0 (Å^{-1}) for all bonds and has been included for improving geometries of strained structures. In the present application where the desired geometries have bonds stretched significantly beyond their natural values, the above form may not be physically realistic since it inverts at $r - r_0 = 2/3c$. With $c = 2.0$, this limits the physically acceptable region of (1) to $r - r_0 < 0.33$ Å. Neglecting the cubic term clearly will produce TS geometries that are too "tight" since the potential raises too sharply with increasing bond length. As a compromise a value of $c = 0.8$ has been used unless noted otherwise, which, as shown below, gives quite reasonable geometries. Alternatively the functional form of (1) can be discarded and a more realistic description such as a Morse potential can be substituted.

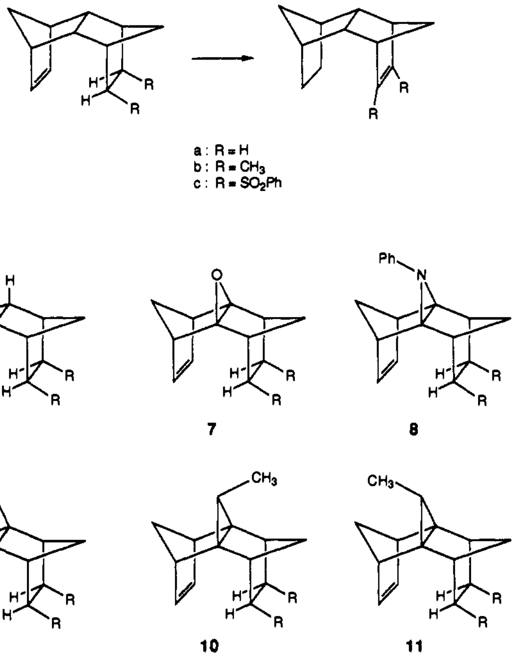
In addition to comparing MM2 TS's with ab initio TS's for small systems, four test cases have been chosen for probing whether the present method is capable of reproducing experimental trends in reactivity for closely related systems. For each of the series the change in structure is not immediately connected with the reaction center, and as the structures are very similar it is expected that differences in rate are mainly due to differences in activation enthalpies and not of entropic origin. In no case have solvent effects been explicitly considered, although the structural similarity should make this a relatively small contribution. For some of the systems additional MM2 parameters had to be defined; these were taken either from experimental data or from ab initio calculations at the SCF level using basis sets of at least DZP quality. Extra parameters and source are given below; numerical values are provided as supplementary material.

The S_N2 reaction of alkyl halides is a textbook example of the influence of steric effects on reactivity; as a specific example, the exchange of bromide ions in methyl, ethyl, propyl, isopropyl, isobutyl, neopentyl, and *tert*-butyl bromide has been taken. Experimental rates at 25 °C in acetone have been obtained by de la Mare.[3b,20]

Scheme I



Scheme II



The second reaction is a hydride transfer in the anions of hydroxy ketones (Scheme I); activation energies have been measured by NMR coalescence of the sodium salts in DMSO.[21] The alkoxy oxygen was modeled as an alcohol oxygen modified such that the natural bond length was shorter and the bond dipole moment larger than those for a regular alcohol oxygen. Numerical values were obtained from HF/6-311+G* calculations on CH_3O^-.

Paquette et al. have studied the double hydrogen transfer in *syn*-sesquinorbornenes of the general structure shown in Scheme II and measured the rates by NMR.[22] The transfer distance was varied by introducing suitable functional groups across the 9- and 10-positions and determined by X-ray crystallography. As few parameters exist for unsaturated sulfones, calculations have been

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(18) Calculations for S_N2 reactions of the type $X^- + CH_3X$ have shown that the difference between the activation energy and that required to distort the reactant to the TS geometry is constant to within 3–4 kcal/mol for a variety of X; see ref 15b.

(19) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. The updated MM2 parameter set from 1987 has been used.

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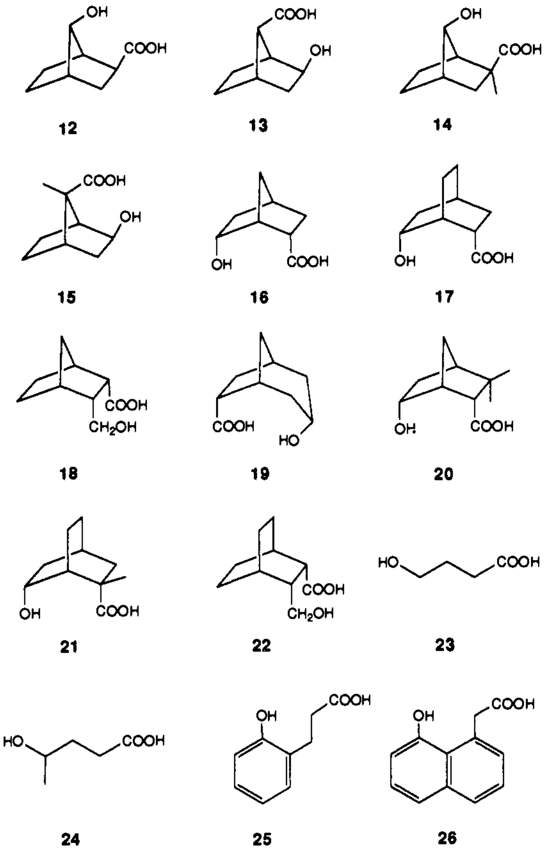
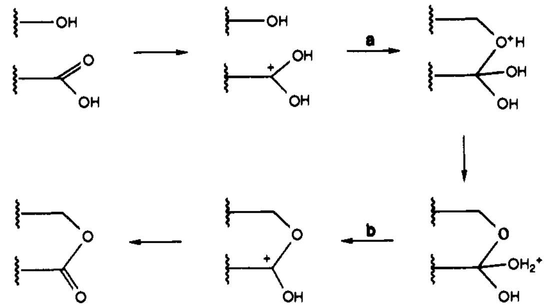
Scheme III



Scheme IV



performed on the corresponding systems where either hydrogens or methyl groups replace the phenyl sulfone groups. Additional parameters for this group were angle bend constants for the epoxides and aziridines, which were taken from experimental data, and parameters for the phenyl ring were those given by Becknaus.[23]

The acid-catalyzed lactonization of the hydroxy acids shown in Scheme III has been one of the points of dispute between Houk and Dorigo[2] and Menger and Sherrod.[4] The interpretation of relative rates for this system is complicated by the fact that it is a multistep reaction, and thus rates of reaction may not readily reflect differences in individual rate constants. The accepted reaction mechanism is illustrated in Scheme IV, and it has been argued that the rate-determining step is the decomposition of the tetrahedral intermediate.[24] To conform with previous transition-state modeling, calculations have been performed both on the formation of the dihydroxy ether and on the subsequent loss of water (i.e., either reaction **a** or **b** being rate determining). Parameters for modeling a protonated carbonyl group and a protonated dihydroxy ether were assigned based on HF/6-31G* calculations.

Theoretical Section

Consider two different energy functionals defined by the atom types and connectivity of the reactant and product which, for a given set of Cartesian coordinates, will produce energies E_r and E_p. Starting from a suitable trial structure, a geometry is sought where $E_r = E_p$ and where E_r (or E_p) has a minimum. An algorithm for locating such points within electronic structure calculations has previously been considered by Koga and Morokuma,[25] and during the course of this work a more general algorithm was published by Farazdel and Dupuis.[26] These workers transformed the restricted optimization to an unrestricted one by defining an objective function of the form $L = (c_aE_r + c_bE_p) - \lambda(E_r - E_p)$, where λ is a suitable Lagrange multiplier. The minimization of L is then accomplished by a quasi-Newton method combined with a line search.[26]

In the present work, slightly different objective functions of the general type $L_n = (E_r + E_p)^n + (E_r - E_p)^2$ have been used. For $n = 1$ this can be considered a special case of the Farazdel–Dupuis function with $c_a = c_b = 1$ and $\lambda = E_p - E_r$. In the initial stages of the optimization, n is set equal to 2 which rapidly produces a geometry close to the desired. As L_2 puts equal weight on the $E_r = E_p$ condition and $E_r + E_p$ having a minimum, it will usually locate a point where E_r is too different from E_p to be considered converged. By switching to the $n = 1$ or $^1/_2$ function, the equality condition is strengthened and $L_{1/2}$ is normally capable of giving acceptable accuracy.

The actual minimization algorithm employed is of the augmented Hessian type, borrowing ideas from Cerjan and Miller,[27] Simons,[28] and Baker.[29] Assuming both the first and second derivatives of E_r and E_p with respect to all coordinates are available, the corresponding derivatives of the L_n functions can easily be calculated, and L_n can be Taylor expanded to second order around the current geometry. In the present applications the Hessians of E_r and E_p were calculated as numeric differences of analytical gradients at the initial geometry and updated at subsequent points using the Powell scheme.[30] Rotational and translational degrees of freedom were projected out using the method of Miller, Handy, and Adams.[31]

Denoting the eigenvalues of the Hessian of L_n as b_i and the gradients along the Hessian eigenvectors as f_i, an attempt is first made to find a RFO geometry step[28a,29] within the current trust radius R (initial value = 0.5 Å) from a shift parameter λ determined by solving eq 2:

$$\sum_i f_i^2/(\lambda - b_i) = \lambda \tag{2}$$

The geometry step is then calculated from:

$$\Delta x = \sum_i f_i/(\lambda - b_i) \tag{3}$$

If the predicted step is larger than the trust radius, a new λ is found which produces the best step on the hypersphere[27] with radius R by solving eq 4:

$$\sum_i f_i^2/(\lambda - b_i)^2 = R^2 \tag{4}$$

Using the appropriate λ in (3), the trial step is added to the current geometry and the function L_n is calculated. If the value of L_n is lowered, the step is accepted, gradients and Hessians are

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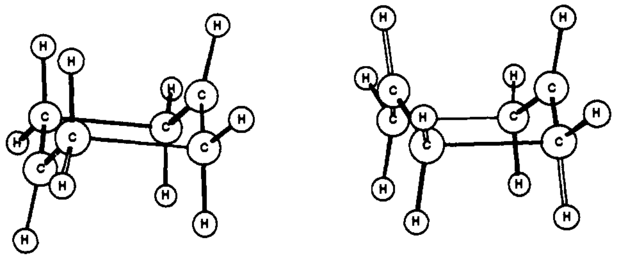

Figure 1. MM2 chair and boat transition structures for the Cope rearrangement of 1,5-hexadiene.

evaluated at the new geometry, and a new trial step is determined. If the value of L_n rises, the step is rejected, the trust radius is reduced by a factor of 2, and a new λ is formed from (4). Iteration is continued until the difference $|E_r - E_p|$ is less than 10^{-2} kcal/mol and the drop in $(E_r + E_p)$ from previous iteration is less than 10^{-3} kcal/mol. If these criteria could not be satisfied with function L_2 (L_1) and the thrust radius dropped below 10^{-4} Å, the optimization was switched to L_1 ($L_{1/2}$). For the present calculations the starting geometry was simply taken to be that of either the reagent or product. As usual in optimizations, one faces the problem of multiple (local) minima; however, the present systems have few degrees of freedom and we believe that the global minimum has been located in each case.

Results and Discussion

Comparison with ab Initio Structures. In order to compare the force field TS's with those from ab initio methods, calculations have been performed on the S_N2 reaction of chloride ion with methyl chloride, the hydride transfer between methoxide and formaldehyde, the Cope rearrangement in 1,5-hexadiene, the Claisen rearrangement of allyl vinyl ether, and the Diels–Alder reaction of ethylene with butadiene. In each case main features of the structures obtained with values of the cubic stretch constant of 0.0, 0.5, and 0.8 are given in order to illustrate the effect of the last term in eq 1.

The S_N2 reaction of chloride ion with methyl chloride has been studied several times; one of the most recent investigations predicts a C–Cl bond distance at the TS of 2.315 Å at the MP2/6-31+G* level and 2.302 Å with the 6-31G** basis set.[32] When the chloride ion is modeled as a chlorine atom, the MM2 TS C–Cl bond length is calculated to be 2.117 Å when the cubic stretch term is neglected, 2.174 Å when c is set to 0.5, and 2.272 Å for $c = 0.8$. Larger values for c caused the structure to "explode" due to the inversion of the bond stretch term as discussed above. A value of 0.8 was in general found to be close to the maximum anharmonicity that could be used in the present force field.

The hydride transfer between methoxide and formaldehyde has served as the model for transition state modeling by Sherrod and Menger.[5] The distance from the migrating hydride to the carbon at the TS is calculated to be 1.463 Å at the HF/3-21G level and 1.422 Å with the 6-31G basis set. The C–O bond length is elongated by 0.050 and 0.062 Å upon going to the TS at the two levels.[5] The values calculated for the MM2 TS are 1.377 Å with $c = 0.0$, 1.410 Å with $c = 0.5$, and 1.447 Å with $c = 0.8$. For the latter value of c, the C–O bond length is elongated by 0.044 Å upon going to the TS. For this reaction the MM2 method fails to predict a bent hydride transfer; i.e., while the ab initio methods give a hydride transfer angle around 150°, the MM2 TS transfer angle is 180°. This is most likely due to the neglect of the resonance energy.

The chair-like TS for the Cope rearrangement in 1,5-hexadiene has been calculated at the MCSCF level with the 3-21G basis to have breaking/forming C–C bond distances of 2.086 Å.[33] The corresponding MM2 TS distances for the three values of the cubic stretch constant are 1.807, 1.860, and 1.950 Å. The other C–C bond distances are predicted to be 1.401 Å at the ab initio level while the MM2 values are 1.401, 1.404, and 1.405 Å for the three values of c. A second MM2 TS having a boat conformation could also be located; the calculated energy difference of 6.4 kcal/mol is almost identical with the MCSCF value of 6.6 kcal/mol but somewhat lower than the experimental value of 11.1 kcal/mol.[34] The breaking/forming C–C bond for the boat TS is 1.966 Å with $c = 0.8$, i.e., only 0.016 Å longer than for the chair TS in contrast to 0.230 Å found by the MCSCF calculations. Both structures are shown in Figure 1.

Table I. Geometrical Features of the Chair-Like TS for the Claisen Reaction (Å)

	$\|O_1C_2\|$	$\|C_2C_3\|$	$\|C_3C_4\|$	$\|C_4C_5\|$	$\|C_5C_6\|$	$\|O_1C_6\|$
$c = 0.0$	1.274	1.399	1.830	1.398	1.404	1.645
$c = 0.5$	1.276	1.404	1.885	1.402	1.407	1.687
$c = 0.8$	1.276	1.408	1.974	1.405	1.406	1.748
RHF/6-31G*[a]	1.261	1.374	2.264	1.376	1.390	1.917

[a] RHF/6-31G* data taken from ref 36.

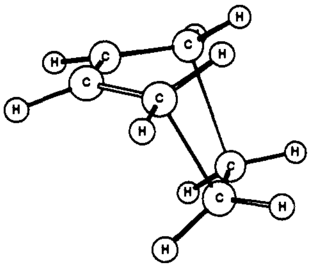

Figure 2. MM2 transition structure for the Diels–Alder reaction of ethylene with butadiene.

For the Claisen reaction there is the complication that the reaction is no longer thermoneutral. In MM2 language this means that heats of formation in contrast to just steric energies have to be employed. MM2 predicts the reaction to be exothermic by 16.1 kcal/mol, in good agreement with the experimental value of 17.0 kcal/mol.[35] The ab initio chair-like TS has been calculated at the RHF/6-31G* level[36] and selected geometrical features are collected in Table I. For this reaction the MM2 method predicts breaking/forming bond distances that are too short by 0.17 and 0.29 Å, respectively, with $c = 0.8$. The other distances are slightly too long. The use of steric energies only, which corresponds to the reaction being almost thermoneutral, give breaking/forming bond distances of 1.765 and 1.943 Å with $c = 0.8$; i.e., the model reproduces in this case the Hammond postulate[7] that a more exothermic reaction has an earlier TS.

The Diels–Alder reaction of ethylene with butadiene illustrates a couple of additional problems that can be encountered. The presence of conjugated double bonds requires special attention in MM2; in the present case the parameters for the central C–C bond in butadiene were modified such that the experimental geometry and torsional barrier are reproduced.[37] The other problem is that the exothermicity of the reaction is overestimated by MM2, 66.4 kcal/mol compared to 40.4 kcal/mol that can be calculated from experimental data.[38] In such cases, or when the force field contains insufficient formation for converting steric energies into heat of formations, a constant factor must be added to one of the structures in order to obtain energies comparable for the reactant and product.

The best ab initio calculations on the Diels–Alder TS are MCSCF/4-31G results reported by Bernardi et al.[39] They predict

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Table II. Results for the S_N2 Reaction of Alkyl Bromides with Bromide Ion[a]

alkyl	R_{C-Br}	ΔE(MM2)	ΔE_s(exp)	ΔE_g(exp)
methyl	2.422	0.00	0.00	0.0
ethyl	2.451	3.93	1.56	3.3
propyl	2.453	3.52	1.41	2.0[b]
isobutyl	2.461	5.84	3.07	
isopropyl	2.494	8.24	3.77	7.6
neopentyl	2.474	10.91	5.55	8.2
tert-butyl	2.657	20.63		

[a] R_{C-Br} is the breaking/forming C–Br bond length (Å) at the TS. ΔE's are relative activation energies (kcal/mol). ΔE_s(exp)'s refer to solution-phase data for the $Br^- + RBr$ reaction.[3b,20] ΔE_g(exp)'s refer to gas-phase data for the $Cl^- + RBr$ reaction.[40] [b] Data for *n*-butyl.

Table III. MM2 Geometrical Features for the Hydride Transfer in Substrates **1–5**[a]

	|C–C|		|C–H|		
structure	GS	TS	GS	TS	α_{CHC} TS
1	2.65 (2.67)	2.45	2.63	1.52	108.2
2	2.59 (2.53)	2.43	2.53	1.51	107.2
3	2.54 (2.48)	2.41	2.45	1.51	106.5
4	2.65 (2.58)	2.54	2.35	1.47	119.2
5	3.04 (2.97)	2.77	2.54	1.48	138.4

[a] \|C–C\| is the distance (Å) between the two carbons where the hydride transfer takes place, (experimental values in parentheses[21]). \|C–H\| is the distance between the migrating hydrogen and the distant carbon. α_{CHC} is the angle around the migrating hydrogen at the TS (degrees).

Table IV. Relative Activation Energies for the Hydride Transfer in Substrates **1–5**[a]

structure	ΔE(MM2)	ΔE(exp)	ΔE(3-21G)
1	0.0	0.0	0.0
2	−1.9	−2.7	−2.0
3	−3.6	−4.4	−3.4
4	−10.5	−8.0	−6.2
5	−14.0	−2.3	+1.4

[a] ΔE(MM2)'s are relative activation energies (kcal/mol) as calculated by the present MM2 model. ΔE(exp)'s are experimental values[21] and ΔE(3-21G)'s are those predicted from a TS modeling using HF/3-21G data.[5]

Table V. MM2 Geometrical Features for the Double Hydrogen Hydride Transfer in Substrates **6–11b**[a]

	|C–C|		|C–H|	
structure	GS	TS	GS	TS
7b	3.10	2.73	2.37 (2.53)	1.47
6b	3.08	2.74	2.37 (2.41)	1.47
8b	3.02	2.72	2.31 (2.40)	1.47
9b	3.04	2.73	2.33 (2.32)	1.47
10b	3.01	2.71	2.30 (2.28)[b]	1.46
11b	3.01	2.71	2.30 (2.28)[b]	1.46

[a] \|C–C\| is the distance (Å) between two carbons where a hydrogen transfer takes place (experimental values for structures labeled **c** in parentheses[22]). \|C–H\| is the distance between a migrating hydrogen and the distant carbon. [b] Average value for structures **10c** and **11c**.

a forming C–C distance of 2.244 Å while the corresponding MM2 values are 1.932 Å, 1.976 Å, and 2.034 Å with $c = 0.0$, 0.5, and 0.8, respectively. The other C–C distances are 1.376, 1.389, and 1.398 Å at the ab initio level, compared to values of 1.407, 1.395, and 1.414 Å with the MM2 method ($c = 0.8$). A drawing of the MM2 TS is shown in Figure 2.

Comparison with Experimental Results. In the S_N2 bromide exchange in alkyl bromides it is generally agreed that the effect of different alkyl substituents is of steric nature,[20b] and the basic premise for the model calculations is thus fulfilled. For this reaction a value of 0.6 for *c* had to be used since larger values had the "inversion" problem for the *tert*-butyl system. This value most likely generates structures with too short C–Br bonds and consequently the steric effects are overestimated. Experimental data for this reaction have been obtained in acetone solutions by de la Mare,[3b,20] and gas-phase results for the $Cl^- + RBr$ reaction has been reported by Caldwell et al.[40] As seen in Table II the calculated effects appear to be too high; however, the trend is reproduced quite nicely. Note also that the solution-phase data indicate a lower sensitivity to steric effects relative to the gas phase. The almost lack of variation in the breaking/forming C–Br bond length may be surprising at first sight; however, ab initio calculations for the $Cl^- + RBr$ reaction at the HF/MINI level with R = Me, Et, *i*-Pr also show a near-constant C–Br bond length at the TS (calculated values are 2.418, 2.442, and 2.410 Å).[41] Whether this feature also holds at better levels of theory, and for the other alkyl groups, remains to be investigated, although it would appear that the MM2 bond length for the *tert*-butyl system probably is too long.

The degenerate hydride transfer in the anions of the hydroxy ketones shown in Scheme I has been studied by Watt et al.,[21] and Sherrod and Menger[5] have used the data in their criticism of Houk's transition-state modeling. Table III shows geometrical features obtained by MM2 and Table IV compares relative activation energies with experimental data and results obtained by transition-state modeling using data from HF/3-21G calculations.[5] Hydroxy ketones **1–3** have very similar structures, and the only major difference is the decreasing distance the hydride has to travel during the reaction. The relative activation energies predicted by MM2 for these three molecules are slightly lower than the experimental values but show the correct trend. Structure **4** has nearly the same distance between the carbons where the migration takes place as **1**; however, the hydrogen is turned more "inwards", and the distance from the migrating hydrogen to the receiving carbon is almost 0.3 Å less. The predicted change in activation energy by MM2 is somewhat overestimated. The calculated change in activation energy for structure **5** is −14.0 kcal/mol, in poor agreement with the observed value of −2.3 kcal/mol. The other modeling method based on HF/3-21G calculations predicts an increase in activation energy of 1.4 kcal/mol; thus structure **5** may simply be too different from the other structures for force field modeling to work, or the experimental value reflects differences in solvation rather than purely structural effects.[21g] It is significant that the systems **1–5** all show a bent hydrogen transfer, although the transfer in the methoxide/formaldehyde system is linear. This indicates that the origin of the angular transfer is not purely electronic in nature.

The double hydrogen transfer in *syn*-sesquinorbornenes **6–11c** has been studied by Paquette et al.[22] As MM2 parameters for sulfone groups are scarce, one has the choice of either entering the lacking parameters more or less ad hoc, or substitute the phenyl sulfone group with another substituent for which parameters exist. In the present case the latter has been chosen, with either hydrogens or methyl groups replacing the phenyl sulfone groups. An additional complication is that MM2 does not contain enough parameters for converting steric energies into heats of formation for structures **7–11**. The exothermicity for compound **6b** is calculated to be 5.8 kcal/mol compared to the experimental value of 0.4 kcal/mol for **6c**. The experimental reaction energy for structures **7–11c** are in the range 0.6–1.6 kcal/mol are given in Table VI. We have chosen to add a factor to the calculated steric energies for systems **6–11b** such that their exothermicity matches the experimental value. Systems labeled **a** are, of course, thermoneutral.

Structural data for the MM2 reactant and TS of structures labels **b** are shown in Table V. The difference in C–H distance for the breaking/forming bonds at the TS is very small, on the order of 0.003 Å, and only the average value has been listed. The overall geometries vary little between structures, and the experimental variation of the migrating distance is only partly reproduced. This could either be due to crystal packing forces, or more

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Table VI. Relative Activation Energies for the Double Hydrogen Transfer in Substrates **6–11**[a]

	ΔE(MM2)		ΔE(exp)	ΔE_0(exp)
structure	**a**	**b**	**c**	**c**
7	0.00	0.00	0.00	–1.52
6	–0.08	+0.29	–2.72	–0.48
8	–2.28	–3.38	–5.07	–1.58
9	–1.26	–1.36	–6.85	–0.68
10	–2.55	–2.65	–8.19	–0.41
11	–2.55	–3.09	–8.67	–1.28

[a] ΔE(MM2)'s are relative activation energies (kcal/mol) as calculated by the present MM2 model, and ΔE(exp)'s are experimental values.[22] ΔE_0(exp) is the exothermicity of the reaction.

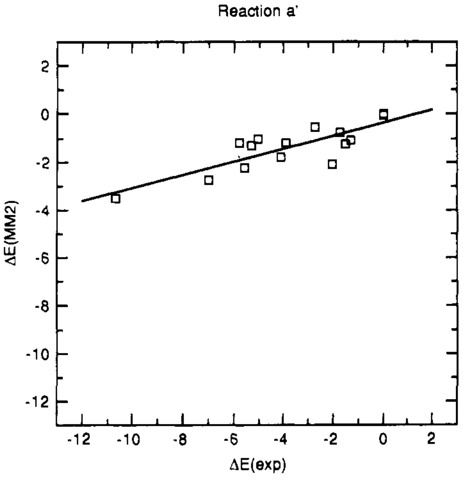

Figure 3. Calculated relative activation energies versus experimental values (kcal/mol) for the lactonization of hydroxy acids with reaction **a′** being rate determining.

likely, to inherent limitations of the MM2 method. Table VI shows relative activation energies for the double hydrogen transfer. In all cases the predicted changes are too small, and even the trend is only marginally reproduced; e.g., **8** is too stable and **6b** is calculated to be destabilized. However, the calculations also cast light on certain features; e.g., the faster reaction of **11** over **10** is almost certainly due to the larger exothermicity of the former reaction since the difference in activation energy is calculated to be zero for structure **a** but correctly reproduced for **b**. For calculated changes as small as these, the difference in exothermicity, which is not taken into consideration by usual transition-state modeling, makes a significant contribution.

The question of reaction exothermicity becomes more aggravating in the modeling of the acid-catalyzed lactonization of hydroxy acids. It is experimentally difficult to determine the reaction energy of a single kinetic step such as the attack of an alcohol group on a protonated acid. The overall reaction is slightly exothermic, the MM2 value for compound **12** is –0.1 kcal/mol, and reaction energies for the proton transfers can be estimated from known pK_a values for acids, alcohols, and ethers.[42] The first step in Scheme IV is thus endothermic by ≈9 kcal/mol, the last exothermic by a similar amount, and the third step exothermic by ≈2 kcal/mol. The sum of the two remaining energies must thus be approximately zero, and both steps are probably close to thermoneutrality. In the absence of any better data, a constant factor has been added to all the calculated steric energies such that reaction **12a** is exothermic by 5 kcal/mol and **12b** endothermic by the same amount. Test calculations showed that relative activation energies are insensitive to the exact value used; e.g., setting both reactions to be thermoneutral gave changes less than 0.01 kcal/mol.

Reaction **a** can be modeled in two different fashions depending on whether the O–H bond of the alcohol group breaks in the same kinetic step as the C–O bond is formed, or this occurs subsequently. Calculations for both models have been performed; the reaction where the C–O bond is formed at the same time as the O–H is broken is labeled **a′**, while the other where the alcohol hydrogen remain on the oxygen during the reaction is labeled **a″**. A technical

Table VII. Relative Activation Energies for the Lactonization in Substrates **12–26**[a]

		ΔE(MM2)		
structure	ΔE(exp)	**a′**	**a″**	**b**
12	0.00	0.00	0.00	0.00
13	0.00	–0.05	–0.77	–0.02
23	–1.31	–1.11	–1.54	–1.28
24	–1.53	–1.25	–4.28	–1.93
15	–1.73	–0.75	–1.78	–1.14
14	–2.03	–2.08	–1.94	–2.32
17	–2.72	–0.53	–2.08	–1.71
18	–3.93	–1.20	–1.47	–2.17
19	–4.12	–1.81	–3.79	–3.56
25	–5.02	–1.02	–3.45	–6.24
20	–5.29	–1.31	–0.37	–3.51
21	–5.54	–2.24	–2.94	–3.82
22	–5.75	–1.17	–1.38	–3.15
16	–6.98	–2.74	–2.88	–4.56
26	–10.68	–3.52	–5.38	–10.20

[a] ΔE(exp)'s are experimental relative activation energies (kcal/mol) calculated from relative rates,[44] and ΔE(MM2)'s are values calculated by the present MM2 model assuming either reaction **a** or **b** is rate determining.

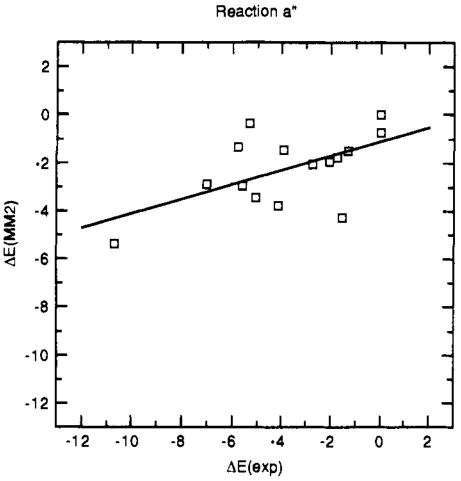

Figure 4. Calculated relative activation energies versus experimental values (kcal/mol) for the lactonization of hydroxy acids with reaction **a″** being rate determining.

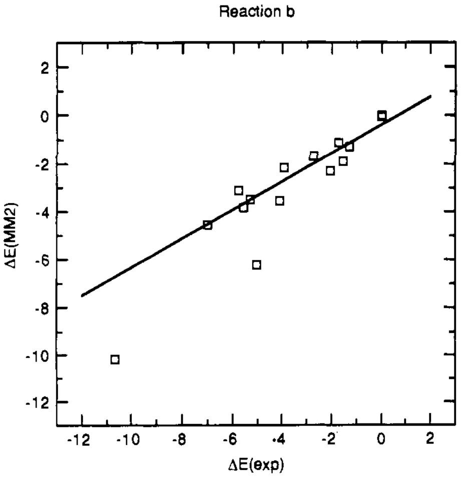

Figure 5. Calculated relative activation energies versus experimental values (kcal/mol) for the lactonization of hydroxy acids with reaction **b** being rate determining.

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(42) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley-Interscience: New York, 1972.

detail is that the latter reaction had to be modeled without lone pairs on the oxygens as MM2 does not allow pentacoordinated atoms. Calculations where lone pairs were omitted for reaction **a**′ showed that this only gave very minor changes.

Relative activation energies[43] calculated for the reactions **a**′, **a**″, and **b** together with experimental values[44] are shown in Table VII, and corresponding scatter plots are given in Figures 3–5. The MM2 values for reaction **a**′ shows a slight correlation with the experimental data, with calculated effects in general being too small. The least-squares line has a correlation coefficient of 0.82 with a slope of 0.27. Allowing the alcohol hydrogen to remain on the oxygen during the reaction (reaction **a**″), deteriorates the correlation (Figure 4, correlation coefficient = 0.58, slope = 0.30).

As mentioned above, it is generally assumed that it is the breakdown of the tetrahedral intermediate that is rate determining,[24] and indeed relative activation energies for reaction **b** show a quite respectable correlation with the experimental values, Figure 5. It is immediately clear that the two aromatic compounds fall significantly below the least-squares line, which is not unreasonable since the phenols presumably are stronger solvated than the alcohols. As the calculations do not take solvent effects into consideration, the calculated (relative) activation energies will be too low. When these two points are neglected in the fitting procedure, the least-squares line shown in Figure 5 is found with a correlation coefficient of 0.94 and a slope of 0.59. Including all points gives a slightly lower correlation coefficient of 0.92.

Conclusion

The present approach represents an alternative way of modeling chemical reactions by force field methods which in its basic premise is more sound than existing models. Activation energies are calculated as the difference between the reactant and a structure which fulfills the requirement of a TS in being an energy maximum in one, and only one, direction, although the energy functional has discontinuous derivatives at the TS. The advantage over other methods where activation energies are calculated as the difference between the reactant and a TS model, treated as a minimum on the PES, is that only information regarding the two minima, reactant and product, is required. If these two structures have been parameterized in the given force field no extra data are necessary, and assumptions regarding parameters for partly formed bonds at the TS can be avoided. The disadvantage is that energy functionals, especially those describing bond stretch, should be reasonably accurate over a wider range of geometries than is normally encountered in force field calculations. Of course, the accuracy of TS modeling is also limited by how well the reactant and product are represented by the force field.

Which of the above approaches is most useful in predicting/rationalizing trends in reactivity must depend on comparisons with accurate ab initio calculations and experimental data. In this paper a few typical test cases have been examined and the calculated force field TS's are structurally close to those obtained by ab initio methods. The major differences are in the bond lengths of the forming/breaking bonds, a discrepancy that is readily understood in terms of the expression used for the bond stretch energy in MM2. However, even quite subtle details like the chair/boat TS's for the Cope rearrangement are reproduced closely. The prediction of trends in reactivity for closely related methods do also in general compare favorably with experimental data, as inferred from the (limited) number of reactions studied here. One remarkable feature of the calculations is the small variation between the transition structures in each series. Whether this is a consequence of the similarity of the compounds, or merely an artifact of the method or the employed force field, will have to await more elaborate calculations.

The present paper shows that the theoretical model appears useful and that reasonable results can be obtained almost without any modifications of existing force fields. The necessity of choosing a proper value of c in the stretch energy is clearly not a desirable feature, but improvements of the method will require more accurate functional forms of at least some of the energy terms. We hope to report such investigations later and also to make program modifications generally available.

Many of the arguments regarding the pros and cons of transition state modeling have originated from the "spatiotemporal" hypothesis advocated by Menger.[45] The basic idea is that reaction rate is proportional to the time atoms spend within a "critical" distance of each other, with each reaction type having its own critical distance. Initially the critical distance for a given reaction was taken to be rather large (~3 Å), and it was at least implied that shorter distances even in the reactant would cause a faster reaction. Dorigo and Houk countered this by their investigation of the acid-catalyzed lactonization of hydroxy acids where they showed that no such correlation exists.[2] Later Sherrod and Menger have shown by semiempirical calculations that the main part of the activation energy is not due to breaking/forming of bonds but rather is invested in achieving a geometric configuration where the reaction takes place with a small extra energy cost.[46] This corresponds to a shorter "critical" distance (~2 Å), and the view that the main part of the activation energy is due to structural changes required to reach the TS geometry is similar to that expressed by Dorigo and Houk.[2] Of course, systems with short interatomic distances in the reactant will often also be the ones which easiest can distort to the TS. The present method calculates exactly the energy required to distort the geometry to that of the TS without allowing any electronic stabilization to take place. For closely related reactions where the electronic stabilization can be expected to be roughly constant, the spatiotemporal hypothesis should work well, especially if the concept of a "critical" distance is taken to imply that the "electronic" part of the activation barrier rises (strongly) with distance.[47]

Registry No. 1, 74497-75-9; **2**, 74459-93-1; **3**, 74561-15-2; **4**, 6225-73-6; **5**, 62082-53-5; **6b**, 138513-44-7; **7b**, 138433-98-4; **8b**, 138433-99-5; **9b**, 138434-00-1; **10b**, 138434-01-2; **11b**, 138513-45-8; **12**, 138434-02-3; **13**, 66808-01-3; **14**, 74513-22-7; **15**, 41977-15-5; **16**, 33913-58-5; **17**, 38347-82-9; **18**, 33649-27-3; **19**, 41991-24-6; **20**, 38347-88-5; **21**, 38347-90-9; **22**, 33649-30-8; **23**, 591-81-1; **24**, 13532-37-1; **25**, 495-78-3; **26**, 3812-97-3; 1,5-hexadiene, 592-42-7; ethylene, 74-85-1; butadiene, 106-99-0.

Supplementary Material Available: Listing of additional MM2 parameters used in this paper and full geometrical details of the structures in Figures 1 and 2 (5 pages). Ordering information is given on any current masthead page.

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(43) Activation energies are calculated relative to the protonated acids since MM2 predicts quite varying protonation energies for the acids.

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(47) From an ab initio point of view, it is not possible to uniquely divide the activation energy up into "structural" and "electronic" contributions. In electronic structure calculations the reaction occurs via a reaction coordinate which usually is defined in terms of a steepest decent path from the TS to the reactant/product. The reaction coordinate can be written as a linear combination of (all) internal coordinates where the coefficients vary along the reaction path. The equivalent of the spatiotemporal hypothesis in this picture is thus that the particular internal coordinate(s) chosen by the observer to represent the essentials of a reaction only enter the reaction coordinate with a large coefficient when close to the TS. The point where the coefficient rises above a certain value represents the "critical" distance for the given internal coordinate.