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Transition states from empirical force fields

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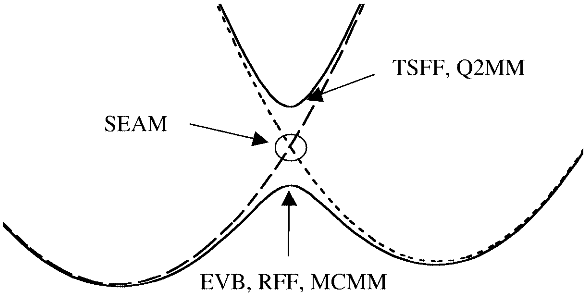
Abstract. This is an overview of the use of empirical force fields in the study of reaction mechanisms. Empirical-valence-bond-type methods (including reactive force field and multiconfigurational molecular mechanics) produce full reaction surfaces by mixing, in the simplest case, known force fields describing reactants and products. The SEAM method instead locates approximate transition structures by energy minimization along the intersection of the component force fields. The transition-state force-field approach (including Q2MM) designs a new force field mimicking the transition structure as an energy minimum. The scope and applicability of the various methods are compared.



Empirical force fields

Keywords: Molecular mechanics – Transition states – Empirical force fields

1 Introduction

Molecular modeling based on empirical force fields is today a mature field with applications in many areas of chemistry. The primary uses of force fields are to predict equilibrium structures, to perform conformational sampling, and for molecular dynamics. With well-chosen parameters, it is possible to determine distortion energies and barriers to conformational change, for example, bond rotation barriers, with good accuracy. Using current modeling software with graphical user interfaces, these tasks no longer require expertise in computational methods, but can be used as black-box techniques. Basic modeling is also entering the curriculum in more and more chemical educational institutions, even at undergraduate levels.

Molecular mechanics started out as a method for determining structures and conformational energies of simple organic molecules in vacuo. In this overview, the term "molecular mechanics" will be used interchangeably with "empirical force fields". Owing to its success in this area, the methodology has been augmented to allow application in other areas of chemistry, for example, calculations of heat of formation data to allow comparison of different molecules [1] and application to metal complexes [2, 3]. Empirical force fields are also widely used for simulations in condensed phases [4], because they allow sampling of a large number of configurations. Some of these methods may be considered mature, and are available in contemporary software, but applications beyond the area of simple organics require some experience to evaluate and validate the results.

The use of molecular mechanics for describing transition states (TSs)/structures is not yet a black-box technique. A transition structure is the geometry of a first-order saddle point on a potential-energy surface (PES). A TS is the hypersurface in phase-space dividing reactant and product, commonly taken to be an ensemble of molecules with the geometry of a transition structure at a given temperature. Often the two concepts are used interchangeably without a clear distinction. Since molecular mechanics relies on explicit bonding information, TSs may be divided into two groups: conformational changes (bond rotations and atom inversions) and chemical reactions (bond breaking/formation). The first type poses no new fundamental problems for molecular mechanics methods, beside those inherent in the force-field parame-

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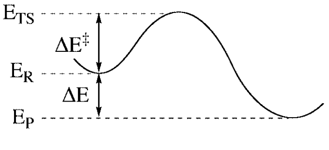
terization and geometry optimization algorithm. Barriers to conformational changes are frequently included as source data in deriving empirical force fields [5], and one of the first uses of molecular mechanics was the classic investigation by Westheimer [6] of steric effects on rotation barriers in substituted biphenyls. Several program packages have options for locating conformational TSs, but validation of the results is even more important than for standard force-field applications. A proper description of rotation and inversion barriers generally requires a careful parameterization of the force field.

The second type of reaction, namely bond breaking and formation, is beyond the scope of standard force-field modeling. The focus of the current overview is on specialized techniques for using force fields to describe chemical reactivity.

2 Background for TS modeling

The lowest-order model for describing chemical reactivity is TS theory (TST) [7], where the reaction rate depends only on the activation energy, defined as the difference in energy between reactant(s) and the TS. The rate constant is obtained from the Eyring equation, which is closely related to the empirical Arrhenius expression (Fig. 1). The rate should properly be obtained from a free-energy difference, including contributions from translation, rotation, vibration and solvation, calculated for both the reactant(s) and the TS. In part owing to the problems in computing these contributions, they are sometimes assumed to be similar in the reactant and the TS, and consequently neglected, in particular when only relative barriers are considered (e.g., in selectivity predictions). However, determination of absolute barriers will in most cases require an explicit consideration of all contributions to the free energy.

For more accurate calculations, it may be necessary to go beyond TST and determine the activation free energy by variational TST (VTST) [8] or constrained molecular dynamics simulations. Such calculations require a PES which is valid not only at the stationary points, but also at low-energy points along the reaction path. This is particularly important when the reaction rate is influenced by tunneling (e.g., hydrogen transfers).



$$r = -\frac{\partial[\text{reactant}]}{\partial t} = k[\text{reactant}]$$

$$k = Ae^{-E_a/RT} \quad \text{Arrhenius}$$

$$k = \kappa\frac{k_B T}{h}e^{-\Delta G^{\ddagger}/RT} \quad \text{Eyring}$$

Fig. 1. Energy profile for a unimolecular chemical reaction

If the objective is to compare relative rates of closely related systems, several simplifications are possible. Often there are several reactant states (conformations) which are in rapid equilibrium. If the equilibration is substantially faster than reaction, Curtin–Hammett [9] conditions apply, and the product ratio, y, is determined solely by the relative energies of the competing TSs. This is illustrated for the case of two competing TSs in Fig. 2, but is easily extended by summation over all TSs leading to the same product.

For relative reactivity it is thus not necessary to describe the reactants or the products, only the TSs. For sufficiently similar TSs it may be valid to ignore the solvent and vibration contributions, and calculate the product ratio directly from the potential energies (Eq. 1).

$$y \approx \frac{\sum_i^A \exp\left(-E_i^{\ddagger}/RT\right)}{\sum_j^B \exp\left(-E_j^{\ddagger}/RT\right)} \tag{1}$$

3 PES methods

Already in 1929, London showed that the PES for the reaction of H with H_2 can be modeled by mixing the wave functions for the symmetric ground states [10], and the concept was expanded by Eyring and Polanyi in the valence bond (VB) method [11]. In general terms, many systems can be modeled by two diabatic ground states interacting by a mixing term. The adiabatic states can be determined by solving a 2 × 2 secular matrix, as illustrated in Fig. 3, where the solution (the lowest root) can be obtained analytically (Eq. 2). E is the adiabatic reaction PES, E_1 and E_2 are the diabatic energies for the two ground states, and E_{12} is a term describing the mixing between the two diabatic states. In quantum mechanical terms the interaction E_{12} is the matrix element of the Hamilton operator with the two

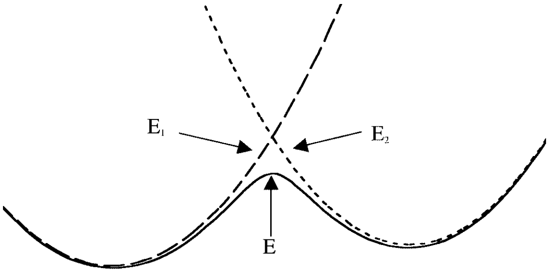
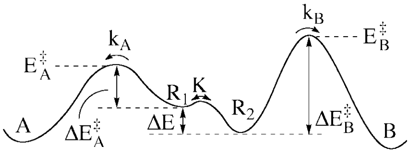


Fig. 3. An adiabatic potential-energy surface (*PES*), E, constructed from two diabatic states, E_1 and E_2



$$y = \frac{[A]}{[B]} \approx \frac{d[A]}{d[B]} = \frac{k_A[R_1]}{k_B[R_2]} = \frac{k_A K}{k_B} = \frac{e^{-\Delta G_A^{\ddagger}/RT}e^{-\Delta G/RT}}{e^{-\Delta G_B^{\ddagger}/RT}} = \frac{e^{-G_A^{\ddagger}/RT}}{e^{-G_B^{\ddagger}/RT}}$$

Fig. 2. Relative energies of competing transition states (*TSs*)

diabatic wave functions. The PES in Fig. 3 is calculated with a constant E_{12}, but in general the term will depend on the position on the PES. Extension of the concept to more than two interacting states is straightforward.

$$\begin{vmatrix} E_1 - E & E_{12} \\ E_{12} & E_2 - E \end{vmatrix} = 0 \quad \Rightarrow$$

$$E = \frac{\left((E_1 + E_2) - \sqrt{(E_1 - E_2)^2 + 4E_{12}^2}\right)}{2} \qquad (2)$$

In the absence of a mixing term ($E_{12} = 0$), Eq. (2) simplifies to Eq. (3), with a cusp at the intersection. This is also the case when the difference between the two ground-state energies becomes large enough so that the E_{12} term can be neglected.

$$E_{12} = 0 \;\Rightarrow\; E = (E_1 + E_2 - |E_1 - E_2|)/2 = \min(E_1, E_2) \qquad (3)$$

Equation (2) is general and is also used in electronic structure theory in the form of configuration interaction. In 1980, Warshel [12] suggested that the ground states in Eq. (2) could be represented by empirical force fields, giving the basis for the empirical VB (EVB) method. Over the years, the term EVB has taken on additional meanings and now indicates a procedure including continuum solvation and restricted molecular dynamics calculations, primarily geared for comparing reaction mechanisms in enzymes and in solvent [13]. A recent investigation of a phosphatase required inclusion of 14 VB states in the EVB calculation [14]. Kim et al. [15] recently proposed the term multiconfigurational molecular mechanics (MCMM) as a general term for obtaining a PES by mixing empirical force fields. Rappé et al. [16] have used a similar approach in the reactive force-field (RFF) method. There has been a recent debate about the correct nomenclature for these methods [17]. Throughout this overview, we have adopted the recently proposed label MCMM for the underlying method first proposed by Warshel [12], to differentiate it from actual applications of the EVB program.

To illustrate the use of Eq. (2), we will look in more detail at a simple organic reaction: addition of a nucleophile to an aldehyde (Fig. 4). In the reactant force field (E_1) the interaction between the nucleophile and the aldehyde is described by van der Waals and electrostatic interactions, whereas in the product (E_2) the interaction is described by a bond-energy term. There is also a smaller but significant difference in the description of the C=O bond, which becomes a C–O$^-$ bond in the product. For each geometry, there are two different bond lists and consequently two different energies. The reactant minimum is a van der Waals complex between the nucleophile and the aldehyde, which is a minimum on the E_1 PES, but not on the E_2 PES. For a geometry close to the reactant minimum, the product force field gives a high E_2 energy since the C–Nu bond is very long. The $(E_1 - E_2)^2$ term will thus swamp the E_{12} term, simplifying Eq. (2) to Eq. (3), and make E almost equal to E_1 close to the reactant geometry. Likewise, for a geometry near the product minimum, the E_2 surface will be low in energy, whereas the E_1 surface is high in energy owing to a strong van der Waals repulsion, giving $E \approx E_2$.

For all geometries in the vicinity of the TS, the E_1 and E_2 energies are similar. The $(E_1 - E_2)$ term can thus be neglected in Eq. (2) and the square root evaluates to $2E_{12}$, making the energy E lower than E_1 ($\approx E_2$) by exactly E_{12} at the point of intersection. The difference between E and $\min(E_1, E_2)$ disappears smoothly as $|E_1 - E_2|$ increases away from the TS. Note also that the difference between E and either of the diabatic energies E_1 and E_2 stays exactly E_{12} along the entire intersection of the reactant and product surfaces, and the saddle point on E consequently corresponds to a minimum along the intersection. We will return to this point later.

There are certain requirements for the combination procedure in Fig. 4 to give a realistic energy surface E. The first is that the relative energy of the reactant and product is correctly reproduced by the force field, which is not generally the case. Most empirical force fields are not parameterized to reproduce heats of formation, just relative energies for the same atom connectivity (i.e. conformational energies) [18]. The zero-energy level

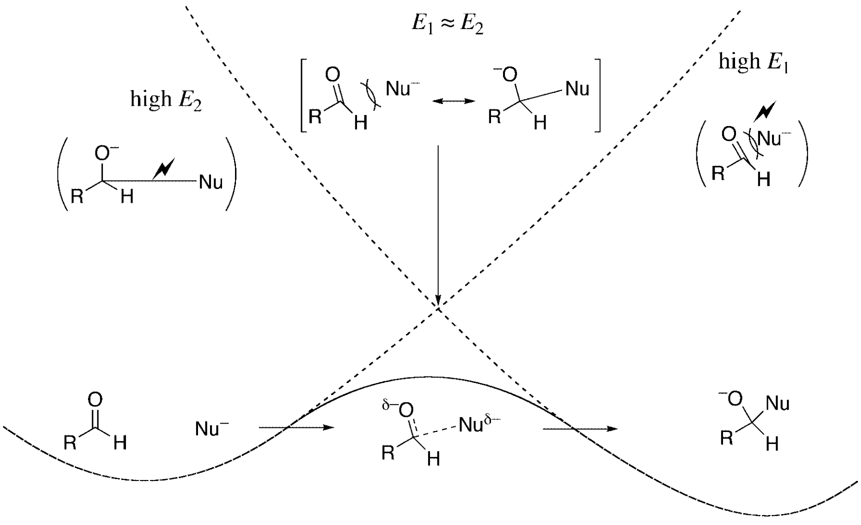


Fig. 4. Example of reaction evaluated by mixing two force fields

usually corresponds to a strain-free structure, whereas the reaction energy difference in Fig. 4 also requires correct bond dissociation energies. In practice, one of the reactant/product force fields can be corrected by a constant term to reproduce the relative energy of the two minima, determined from some other source (experiment or quantum chemical calculations) [13].

The second requirement is that the force field must be valid over a wide range of geometrical distortions, much wider than for standard molecular mechanics calculations aimed at equilibrium structures. In particular, the force field must give a reasonable description of the distortion energy for reaching the TS geometry, and a bit beyond. In our example, this means that the forming C–Nu bond must be correctly described more than 0.5 Å from the equilibrium distance. This is beyond the validity range for simple harmonic bond stretch potentials used in many force fields, and also for most higher-order polynomial expansions [19]. Some specialized polynomial expansions allowing large distortions have recently been developed [20], but among the functional forms in common use, only the Morse potential [21] gives a sufficiently accurate description of the bond breaking occurring at large distances.

It is also clear from Fig. 4 that the van der Waals repulsion must be reasonably accurate at short interatomic distances, invalidating the use of a simple Lennard-Jones potential, which is known to be much too repulsive at short distances [22, 23]. An alternative form using a lower power than 12 for the repulsive part of the potential, or using an exponential function, is required to give a more realistic energy. The MM2/MM3 form with an exponential function for describing the repulsion has been found to yield good results [23]. Furthermore, the angle-bending potential must also allow large distortions from equilibrium values, although in many cases a simple harmonic or cubic polynomial expansion appears sufficiently accurate. Finally, if the force field employs cross terms, like stretch/bend, it must be ensured that they behave reasonably when long bond lengths are present.

Once the force fields are properly set up, the mixing term E_{12} must be selected. The simplest possibility is to use a constant value, chosen to reproduce a suitable reference activation energy; however, most users of MCMM methods attempt to control the shape of the PES by allowing E_{12} to be a function of the reaction coordinate. With the EVB method, Åqvist and Warshel [13] and Hwang et al. [24] have employed an exponential function of the length of a forming or breaking bond. In a more recent use of force-field mixing methods for evaluating tunneling contributions to reaction rates, Kim et al. [15] have used a complex interpolation function to ensure a fit of E, $\partial E/\partial x$, and $\partial^2 E/\partial x^2$ to the results from quantum chemical calculations at several points along the minimum energy path.

The MCMM PES can be used in the same way as any other continuous PES for locating minima and saddle points, following reaction paths (e.g. by intrinsic reaction coordinate methods), or for more advanced ways of determining free energies of activation (e.g., VTST). The EVB method includes a model potential to drive molecular dynamics simulations over the barrier (Fig. 5). The model potential is constructed as a weighted average of the two contributing force fields (Eq. 4). The resulting PES displays a minimum-energy structure which progresses smoothly from the reactant to the product geometry as λ increases, and λ can consequently be used as the incremented variable in a free-energy perturbation calculation. Energies for all geometries on the model surface are projected onto the true EVB PES before sampling (Fig. 5). For a value of λ close to (but usually not exactly equal to) 0.5, the intersection of the reactant/product force fields will correspond to a minimum on the model PES, ensuring sufficient sampling close to the TS.

$$E = (1 - \lambda)E_1 + \lambda E_2 \quad \text{EVB model potential} \qquad (4)$$

In most applications of the MCMM method so far, substantial parameterization has been required. Rappé et al. [16] have listed the requirements (vide supra) for a generally applicable force field that can be applied to arbitrary chemical reactions with little or no parameterization, building on the earlier universal force field (UFF) [25]. The concept has been tested on some model reactions, but a completely general method is not yet available. As with the UFF method itself, a method employing general parameters may suffer from reduced accuracy compared to methods that have been specifically parameterized to solve a particular problem [26], but the ability to get approximate TSs for systems of arbitrary size without extensive method development would be a decisive advantage.

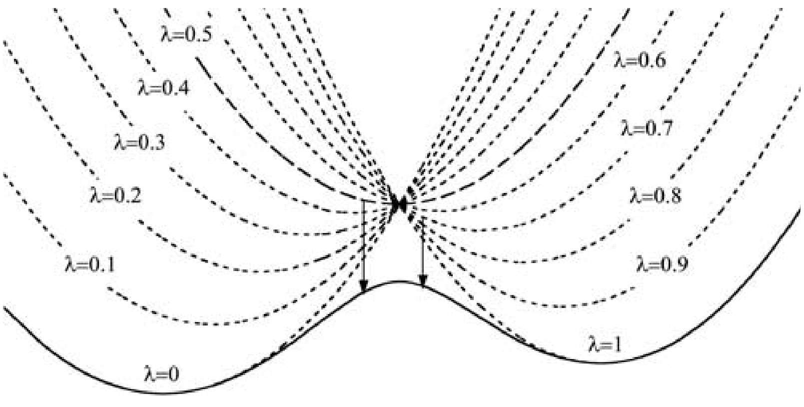


Fig. 5. Energies for all geometries on the model surface are projected onto the true empirical valence bond PES before sampling

Direct TS methods

For all methods employing a continuous PES the TS is a first-order saddle point, and locating such points on a multidimensional PES is substantially more complex and less reliable than locating energy minima. A plethora of methods for finding TSs are available [19, 27], but none are guaranteed to converge to the desired stationary point, and many need accurate information about the energy curvature in addition to a good starting guess of the TS geometry. This makes automation difficult, in particular for conformational search methods or for configurational sampling of the TS in molecular dynamics methods. There is thus a distinct need for methods that are robust enough for converging to an approximate transition structure from a poor starting geometry, thereby automating the problem of locating TSs. One solution to this problem is given by the EVB model potential (Fig. 5). With a correctly chosen λ, energy minimization on the model PES leads to a saddle point on the EVB PES. However, if the objective is only to get a transition structure, and not to drive a molecular dynamics simulation over the barrier, then the model potential has the drawback that the optimum λ is unknown a priori, and may well vary with the steric requirements in the vicinity of the reaction center.

A more direct method is to locate the minimum on the intersection of the two ground-state diabatic energy surfaces and take this to be an approximate TS, the so-called SEAM method [28]. As already indicated, this geometry will correspond to a saddle point on the "true" PES if the coupling element E_{12} is constant. Furthermore, relative energies of isomeric TSs (Fig. 2) can be obtained by comparing relative intersection energies within this approximation, as seen from Eq. (2). Some of the requirements for a successful application of the SEAM method are the same as for the MCMM method, namely that the force field should be corrected to yield the appropriate reaction energy, and that it has a reasonably accurate description of distorted geometries, in particular, long bond lengths and short van der Waals interactions.

The main advantage of the SEAM method is that the geometry optimization problem is significantly simpler. The problem of locating a minimum on the intersection of the reactant and product energy functions can be formulated either as a minimization of a penalty function or as an optimization of a Lagrange function [28]. The penalty approach has the advantage that all methods for forcing convergence to a minimum can be directly applied, but locating the exact minimum on the intersection can only be done by a series of minimizations with increasingly larger penalty constants. The Lagrange method formally involves optimization to a first-order saddle point, but in contrast to the situation for continuous PES methods, the direction along which the function should be maximized is given implicitly by the gradients of the two energy functions. In practice this means that the optimization is just as stable as a regular minimization. Furthermore, in the Lagrange technique the minimum on the intersection is located in a single optimization. Convergence to a SEAM TS can thus be done from very poor starting geometries, including the reactant and product structures. This allows automated conformational samplings, by utilizing established methods for sampling minima (e.g., stochastic or Monte Carlo methods [29]). An added feature, which is also available for the EVB and MCMM methods, is that an approximate Hessian (second derivative of the energy with respect to the atomic coordinates) can be calculated and used as an inexpensive starting point for refining the TS with electronic structure methods.

Transition-structure-specific force fields

An alternative method for modeling transition structures builds on a concept similar to the EVB model potential, where any point on the PES can be modeled as a minimum on a suitable modified force field. In particular, it is possible to construct a force field where the transition structure is obtained by minimization on a model PES [30], a "TS force field" (TSFF). In a way, this type of force field can be seen as the high-energy root to Eq. (2), $\max(E_1, E_2)$ in the absence of a mixing term. The "reference" or "ideal" bond lengths and angles in the modified force field correspond to the lengths and angles found in the transition structure, and the reactants and products are consequently not considered. It is obvious that this type of force field can only be applied to relative reactivities, as depicted in Fig. 2. Furthermore, the transition structures being compared must be very similar. A good case for this methodology is the prediction of stereoselectivities, where all TSs are diastereomers [31].

A successful modeling of a transition structure as a minimum on the PES has different requirements from the methods based on ground-state force fields. The most important is that a complete set of new parameters must be determined for all atoms involved in the reaction center. It is generally assumed that the "nonreactive" part of the TS (the part that is the same in all ground-state force fields in an MCMM treatment) can be taken from the reference force field. However, new parameters must be determined for all bonds which change bond orders during the reaction, as well as for all angles, torsions, and cross terms including these bonds as a component. In the published examples; this has required determination of up to a few hundred parameters, which is a major computational task and one that is not easily automated. The advantage is that the reparameterization moves the reference state to the geometry being investigated, thereby lifting the requirement that the force field should be able to describe severely distorted geometries. Nevertheless, in some cases the mathematical form of the individual energy terms (stretch, bend, torsion, etc.) used for the reference ground state may be inappropriate for describing the energy surface near the TS. The relative energy of the reactant and product structures and the mixing term E_{12} have no meaning for a TSFF, only the relative energies between TSs can be described

Early derivations of TSFFs were plagued by the lack of accurate transition structure data for the parameterization, and many parameters were consequently

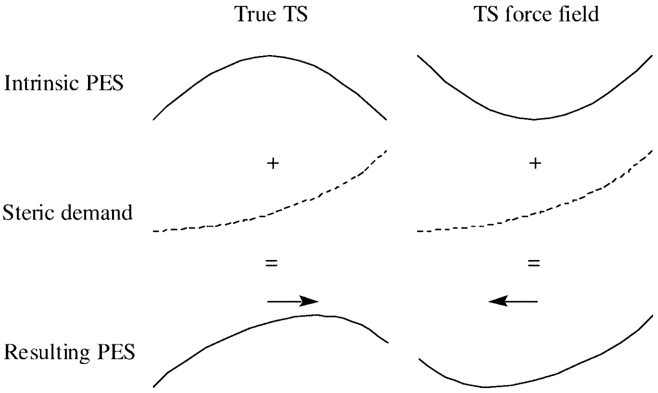


Fig. 6. The effect of steric requirements on the PES for a TS and a TS force field, respectively

assigned values more or less ad hoc. Indeed, early critique of the methodology was partly based on the fact that the number of parameters exceeded the number of data points [32], possibly resulting in severe overfitting. However, more recent work has been based on high-level quantum chemical calculations for small model systems, in which case the number of data points significantly exceeds the number of fitting parameters, although some redundancy is present in the data. In particular the recent Q2MM method relies solely on quantum mechanical data, ensuring that calculation of selectivities can be regarded as genuine predictions, and not fitting [31]. In Q2MM, the shape of the PES is adjusted to fit results from quantum mechanical normal mode analysis, except along the reaction coordinate, where a strong positive curvature is imposed [33]. Distortions perpendicular to the reaction coordinate are thus represented by the force field within the usual accuracy, allowing a determination of relative TS energies.

A distinct advantage of the TSFF method compared to the other methods described here is the ease with which it can be implemented in common molecular mechanics packages once the parameters have been derived, since only conventional procedures and energy functions are required. A few TSFFs are in fact included in MM2* within the commercial MacroModel package [34].

A main disadvantage of TSFFs compared to the EVB/MCMM and SEAM approaches, is the erroneous response of the TS to interactions that change the energetics along the reaction coordinate. This effect is illustrated in Fig. 6, and can be exemplified using the chemical reaction in Fig. 4. If the "intrinsic PES" has been determined for acetaldehyde, changing the substrate to pivalaldehyde (changing *R* from methyl to *t*-butyl) will add a steric energy that increases as the nucleophile approaches, resulting in the profiles at the bottom of Fig. 6. For this change, the true TS will become "later" when the steric component is added, whereas a TSFF will respond to the bulk by elongating the reacting bond, giving an "earlier" TS [35]. This effect could, in principle, be overcome by a dynamic update of the parameters in response to strain along the reaction coordinate, but such a correction would require substantial methods development, and would suffer from a lack of automation. In practice, the error is minimized by imposing a strong positive curvature along the reaction coordinate, in effect freezing it to the value for the reference reaction [33]. In the cases investigated so far, the energy error resulting from the incorrect distortion has been found to be fairly constant within a reaction and therefore cancels out when comparing energies of diastereomeric TSs [31].

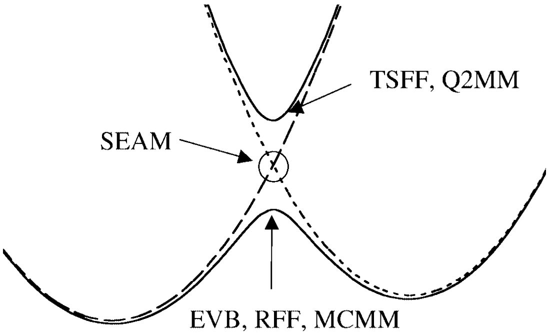


Fig. 7. Summary of force field methods used to model transition structures on PESs. See text for details

Summary

The difference in methods for modeling TSs for bond-breaking reactions by force-field-based methods is illustrated in Fig. 7. None of the methods are currently applicable as black-box techniques. In the EVB [13], RFF [16], or MCMM [15] group of methods, the entire reaction surface is described by employing force fields as diabatic states and using mixing terms to model an energy surface. A simpler technique based on the same underlying theory, SEAM, neglects the interaction term, which allows the efficient location of approximate TSs as minima on the intersection between diabatic surfaces [28]. In an alternative approach, it is possible to create a TSFF that treats the transition structure as a minimum [30], for example, in the recent Q2MM method [33]. Each technique has advantages and disadvantages. Q2MM (or more generally, TSFF) can be implemented as a rapid tool in standard molecular mechanics software, but is only applicable for a comparison of very similar TSs, and requires substantial development of parameters for each reaction to be studied. SEAM represents a fast way to find approximate transition structures with a low investment in parameterization, but requires specialized software. The EVB method and its analogs require a parameterization of the mixing term and can give an accurate description of the entire energy surface of the reaction, but require substantial development effort using specialized software, and tools for finding TSs and evaluating minimum energy paths.

References

1. (a) Allinger NL (1977) J Am Chem Soc 99: 8127; (b) Allinger NL, Yuh YH, Lii JH (1989) J Am Chem Soc 111: 8551; (c) Allinger NL, Chen K, Lii JH (1996) J Comput Chem 17: 642

2. Rappé AK, Casewit CJ (1997) Molecular mechanics across chemistry. University Science Books, Sausalito, Calif
3. Comba P, Hambley TW (2001) Molecular modeling of inorganic compounds. Wiley-VCH, Weinheim
4. (a) Allen MP, Tildesley DJ (1987) Computer simulation of liquids. Clarendon, Boston; (b) Frenkel D, Smit B (eds) Understanding molecular simulation: From algorithms to applications. Academic, Boston
5. Ewig CS, Berry R, Dinur U, Hill J-R, Hwang M-J, Li H, Liang C, Maple J, Peng Z, Stockfisch TP, Thacher TS, Yan L, Ni X, Hagler AT (2001) J Comput Chem 22: 1782
6. Westheimer FH (1947) J Chem Phys 15: 252
7. Eyring H (1934) J Chem Phys 3: 107
8. Gordon MS, Truhlar DG (1990) Science 249: 491
9. Maskill H (1985) The physical basis of organic chemistry. Oxford University Press, Oxford
10. London F (1929) Z Elektrochem 35: 551
11. Eyring H, Polanyi M (1930) Naturwissenschaften 18: 914
12. Warshel A (1980) J Am Chem Soc 102: 6218
13. (a) Åqvist J, Warshel A (1993) Chem Rev 93: 2523; (b) Warshel A (1991) Computer modeling of chemical reactions in enzymes and solutions. Wiley, New York
14. Kolmodin K, Hansson T, Danielsson J, Åqvist J (1999) ACS Symp Ser 721: 370
15. Kim Y, Corchado JC, Villa J, Xing J, Truhlar DG (2000) J Chem Phys 112: 2718
16. Rappé AK, Pietsch MA, Wiser DC, Hart JR, Bormann LM, Skiff WM (1997) Mol Eng 7: 385
17. (a) Florian J (2002) J Phys Chem A 106: 5046; (b) Truhlar DG (2002) J Phys Chem A 106: 5048
18. Burkert U, Allinger NL (1982) Molecular mechanics, ACS monograph 177. American Chemical Society, Washington, DC
19. Jensen F (1999) Introduction to computational chemistry. Wiley, Chichester
20. Dinur U, Hagler AT (1994) J Comput Chem 15: 919
21. Morse PM (1929) Phys Rev 34: 57
22. (a) Halgren TA (1992) J Am Chem Soc 114: 7827; (b) Hart JR, Rappé AK (1992) J Chem Phys 97: 1109
23. Lii JH, Allinger NL (1989) J Am Chem Soc 111: 8576
24. Hwang J-K, King G, Creighton S, Warshel A (1988) J Am Chem Soc 110: 5297
25. (a) Rappé AK, Casewit CJ, Colwell KS, Goddard WA III, Skiff WM (1992) J Am Chem Soc 114: 10024; (b) Casewit CJ, Colwell KS, Rappé AK (1992) J Am Chem Soc 114: 10035; (c) Casewit CJ, Colwell KS, Rappé AK (1992) J Am Chem Soc 114: 10046
26. Gundertofte K, Liljefors T, Norrby P-O, Pettersson I (1996) J Comput Chem 17: 429
27. Jensen F (1998) In: Schleyer PvR, Allinger NL, Clark T, Gasteiger J, Kollman PA, Schaefer HF III, Schreiner PR (eds) The encyclopedia of computational chemistry. Wiley, Chichester, p 3114
28. (a) Jensen F (1992) J Am Chem Soc 114: 1596; (b) Jensen F (1994) J Comput Chem 15: 1199
29. Chang G, Guida WC, Still WC (1989) J Am Chem Soc 111: 4379
30. Eksterowicz JE, Houk KN (1993) Chem Rev 93: 2439
31. (a) Norrby P-O, Rasmussen T, Haller J, Strassner T, Houk KN (1999) J Am Chem Soc 121: 10186; (b) Norrby P-O, Brandt P, Rein T (1999) J Org Chem 64: 5845
32. (a) Sherrod MJ, Menger FM (1989) J Am Chem Soc 111: 2611; (b) Menger FM, Sherrod MJ (1990) J Am Chem Soc 112: 8071
33. Norrby P-O (2000) J Mol Struct (THEOCHEM) 506: 9
34. (a) Mohamadi F, Richards NGJ, Guida WC, Liskamp R, Lipton M, Caufield C, Chang G, Hendrickson T, Still WC (1990) J Comput Chem 11: 440
    (b) http://www.schrodinger.com
35. Hammond GS (1955) J Am Chem Soc 77: 334