

## Reply to Comment on Molecular Mechanics for Chemical Reactions

Donald G. Truhlar

*Department of Chemistry and Supercomputer Institute,  
University of Minnesota, 207 Pleasant Street S.E.,  
Minneapolis, Minnesota 55455–0431*

*Received: November 28, 2001; In Final Form:  
February 22, 2002*

Florian<sup>1</sup> has submitted a Comment discussing our recent paper<sup>2</sup> on multiconfiguration molecular mechanics<sup>2,3</sup> (MCMM) and some related issues concerning other combined quantum mechanical/molecular mechanics (QM/MM) methods and methods for predicting potential energy surfaces (PESs) that are motivated by valence bond (VB) theory. The Editor has indicated that a published reply might be of interest, and so I have prepared these remarks. I will take up various points raised by Florian in approximately the order that he raises them.

Florian indicates that it is unfortunate when there is more than one name or acronym for two methodologies differing only in the fitting procedure for obtaining Hamiltonian matrix elements. I disagree. As an example from another field, it is very useful to have separate names for MNDO and AM1, which are both semiempirical molecular orbital (SEMO) methods<sup>4</sup> that differ only in the formalism for such matrix elements. Indeed, it is very fortunate that we have separate names for CNDO, INDO, and PRDDO as well, since simply calling all these methods SEMO would hide critical distinctions that can be conveyed concisely and clearly by simply calling each method by its own name. The use of appropriate and distinct names for methodologies based on significantly different fitting procedures enhances our ability to communicate clearly and does not detract from understandability, as Florian believes.

Florian implies that the approximate VB (AVB) methodology of Bala et al.<sup>5–7</sup> should be called EVB, which denotes an empirical VB method<sup>8–11</sup> introduced by Warshel and Weiss.<sup>8</sup> Florian himself calls EVB a trademark; trademarks are legally restricted to the use of the owner or developer, but it is not correct to treat EVB as a trademark, so it is legitimate to ask if AVB is essentially the same as EVB. Bala et al. state that “AVB is similar to the EVB approach but uses ab initio rather than empirical parametrization.”<sup>7</sup> Florian implies that methods that represent parts of the system by adding molecular mechanics potentials to Hamiltonian matrix elements and that share two other features of EVB should be called EVB, without commenting on the critical difference mentioned above that was singled out by Bala et al. In my opinion, it is reasonable that they used a new name for their method to distinguish its underlying assumptions from those employed in the method called EVB.

Florian, citing a 1980 paper,<sup>8</sup> states that Warshel coined the acronym EVB. This may be true, but the phrase “semiempirical valence bond” is older, and it appears in a review article as early as 1971.<sup>12</sup> The words “empirical” and “semiempirical” are often used interchangeably. It is potentially confusing to name a method with such broadly encompassing language, since one may be unclear whether the term is used with its everyday descriptive meaning or the term is used as a name of a specific method. It would be counterproductive to insist that all empirical

molecular orbital methods should simply be labeled EMO, but given the fact that “EVB” has now become associated with a specific empirical formalism, one should probably restrict the acronym EVB for methods that are essentially the same as the specific method that is widely associated with the name, i.e., the method of Warshel and Weiss.

Florian states that the MCMM acronym fails to convey the quantum character of the method. Actually, the “C” in MCMM denotes “configuration” in both the VB and MM sense as a bonding pattern (as in Rumer diagrams<sup>13</sup>) and also in the configuration interaction (CI) sense of quantum mechanics (as in valence bond configuration state functions,<sup>13,14</sup> which are many-electron wave functions). The prefix MC, denoting multiconfiguration, is widely used as a prefix for quantum mechanical methods, as in MCSCF.<sup>15,16</sup>

Florian states that the only conceptual difference between MCMM and EVB or AVB is that MCMM does not presently include solvent effects. He also states his opinion that “MCMM” should be replaced by “EVB” or “AVB”. I will comment on this suggestion in response to the Editor’s invitation to reply. My Comment consists of comparing the main elements of EVB and MCMM. According to Warshel,<sup>17</sup> his main contributions to the EVB method are

- the use of empirical VB theory to extend MM to chemical reactions,
- using mixed diabatic states so that the overlap integrals are eliminated,
- using a calibration on the energy of fragments for quantitative studies of large molecules (e.g., enzymes) and molecules in solutions,
- showing how to use EVB for transferring PESs between environments (e.g., aqueous solution to enzyme) by adding solvent effects to the diagonal Hamiltonian matrix elements.

To these I would add that in most EVB calculations, the off-diagonal elements are represented by simple functional forms (a constant or a single exponential function of a single coordinate) whose values or parameters are determined empirically by comparison to experimental kinetics data.

The central elements of MCMM are

- use of a multiconfiguration formalism<sup>8–12,18–40</sup> to extend MM to chemical reactions,
- use of the Taylor series formalism of Chang and Miller<sup>41–43</sup> to represent off-diagonal Hamiltonian matrix elements locally in terms of energies, gradients, and Hessians of the diagonal matrix elements and of the PES and thereby to obtain the required local approximations to the PES from electronic structure theory (not from experimental kinetics data, which does not yield this information),
- joining the local approximations together by Shepard interpolation.<sup>44,45</sup>

A critical practical element that we introduced for the last step is the use of internal valence coordinates to eliminate ambiguity in orienting the various local coordinate frames. The use of electronic structure theory rather than experimental kinetics data to determine the values of non-MM parameters in the theory is a significant conceptual difference from EVB in that the MCMM formalism allows one to attempt to refine all aspects of the PES, whereas experimental kinetics data mainly allows one to fix the free energy of activation or the barrier height but does not provide a good handle on other aspects of the PES. Thus the EVB method can lead to significant errors

on the entire potential energy surface except for three points, the reactant, transition state, and product that are fitted to the experimental effective barrier height and reaction energy.

It is well-known, for example from studies employing diatomics-in-molecules (DIM) theory, that approximating potential energy surfaces for chemical reactions in terms of fragment data can be quantitatively inaccurate due to the slow convergence of CI expansions and the resulting sensitivity of the results to truncating the configuration list at a small number of states or even only two states.<sup>24,29–40</sup> Sometimes more than two states are required even for a good zero-order description.<sup>32–40,46,47</sup> It is important to emphasize that the MCMM method does not rely on the completeness and resulting predictive quality of the reduced-state description as minimal-basis DIM theory does; the use of target-level adiabatic energies (and their partial derivatives) to fit off-diagonal elements in the region of partially broken bonds is the key new element in this regard.

Florian refers to the “excellent performance” and “excellent numerical results” of parametrized VB methods for predicting PESs, but he does not give any references for this claim, and it is worth noting that, away from the three fitted stationary points, PESs predicted by parametrized VB methods have not been extensively validated against either experiment or more accurate theory for systems with more than three atoms. The EVB method was developed as a way to predict a PES by using MM plus experimental kinetics data in one medium (e.g., aqueous solution) and then to adapt that PES to another medium (e.g., an enzyme). It is especially useful for modeling the participation of solvent or protein polarization in the reaction coordinate. At the same time it incorporates important physical approximations such as a truncation to two valence bond states, neglect of overlap, neglect of the effect of bond rearrangement on fragment matrix elements, and approximating the off-diagonal Hamiltonian matrix elements and the internal solute part of the diagonal ones as independent of environment. To date, MCMM has been presented as a method for fitting a gas-phase PES to electronic structure data. It does not introduce new physical approximations of its own but rather inherits the physical approximations of the implicit PES that it fits. In MCMM, all aspects of the implicit target PES (not just the barrier height) are fitted, and in principle, even though the formalism involves  $2 \times 2$  matrices, the fit converges to a precise interpolation of the target-level electronic structure data as the input grid becomes finer. Certainly, if solvent effects (environmental effects) were treated in a manner similar to EVB theory, MCMM would become more similar to EVB (and to some other theories<sup>48–53</sup>), but it is hard to imagine a way to do this such that they would not still be different in very significant ways.

Florian's Comment is directed in part to “the image of computational biochemistry”, but our papers<sup>2,3</sup> were not about biochemical applications, except for references where we gave extensive (but not exclusive) credit to biochemical EVB antecedents in the work of Warshel, Weiss, Åqvist, and others. Since semiempirical valence bond calculations have a long history in nonbiological chemical physics, it would be unfortunate if a tendency develops in some quarters of the biological community to recognize only the biochemical literature and to cast all history in this light, as in the Comment by Florian. In my opinion, progress in the biological computational sciences will continue to benefit in the future, as it has in the past, from an influx of new ideas from chemistry, physics, mathematics, and computer science, and it is important to recognize new aspects of computational advances that arise rather than

pigeonholing new advances from interdisciplinary subfields into oversimplified categories derived from a single biochemical perspective.

It is useful to comment on the relationship of EVB, AVB, and MCMM to other semiempirical VB methods. EVB, AVB, and MCMM use semiempirical MM for diagonal Hamiltonian matrix elements that may be associated with basis states that correspond to definite bonding structures, i.e., with VB basis states. (Orthogonal mixed valence bond basis states are implied in all three formalisms and have also been used in earlier work.<sup>30</sup>) AVB and MCMM use electronic structure theory to determine off-diagonal matrix elements, and this may be either *ab initio* or semiempirical (e.g., the semiempirical G2 or MCG2 methods<sup>54,55</sup> or DFT,<sup>56</sup> most versions of which have empirical elements). EVB, in contrast, is parametrized against experimental kinetics data. This distinction is reminiscent of a distinction emphasized by Johnston<sup>57</sup> many years ago between empirical theories of PESs where the empirical data comes from kinetics and empirical theories of PESs “with the empiricism outside the field of kinetics.” The history of semiempirical VB theories contains many methods that can be parametrized either way.

Ultimately one needs to look beyond labels to see the origin of ideas. In this respect I note that the intramolecular terms in molecular mechanics are the same kinds of terms that spectroscopists were calling valence force fields<sup>58</sup> already in the 1940s or earlier. The semiempirical use of valence force fields along with valence bond theory to model potential energy surfaces for chemical reactions of polyatomic species was pioneered by Raff,<sup>59</sup> who, however, presented the theory in a less general way than EVB has been presented. Other related methods that combine MM and VB elements are the MMVB method of Bernardi et al.<sup>60,61</sup> and MOVV/MM method of Mo and Gao.<sup>62,63</sup> It is also important to note that some methods, like these, actually use quantum mechanical valence bond formulas (or equivalent spin-only Heisenberg–Serber-type Hamiltonians) in detail, whereas other methods simply use the concept of configuration interaction with diagonal matrix elements corresponding to states with definite bonding character. It may be challenging to keep the names and details of all these methods from being confused, but it is important to do so because various strategies for combining MM, VB, and empirical parameters may be useful at different times, depending on the objective of the work, the size of the system, the information available, and so forth.

In all our published work to date<sup>2,3</sup> we have used MM3<sup>64</sup> functional forms for diagonal Hamiltonian matrix elements. However, that is not an essential part of the method; any MM potential function may be used.

**Acknowledgment.** I am pleased to thank Jiali Gao, Marshall Newton, and Arieh Warshel for informative discussions and communications on the subjects of this reply. My work on MCMM is supported in part by the U.S. Department of Energy.

## References and Notes

- (1) Florian, J. *J. Phys. Chem. A* **2002**, *106*, 5046.
- (2) Albu, T.; Corchado, J. C.; Truhlar, D. G. *J. Phys. Chem. A* **2001**, *105*, 8465.
- (3) Kim, Y.; Corchado, J. C.; Villà, J.; Xing, J.; Truhlar, D. G. *J. Chem. Phys.* **2000**, *112*, 2718.
- (4) Zerner, M. C. *Rev. Comput. Chem.* **1991**, *2*, 313.
- (5) Grochowski, P.; Bala, P.; Lesyng, B.; McCammon, J. A. *Int. J. Quantum Chem.* **1996**, *60*, 1143.
- (6) Bala, P.; Grochowski, P.; Lesyng, B.; McCammon, J. A. *J. Phys. Chem.* **1996**, *100*, 2535.

- (7) Bala, P.; Grochowski, P.; Nowinski, K.; Lesyng, B.; McCammon, J. A. *Biophys. J.* **2000**, *79*, 1253.
- (8) Warshel, A.; Weiss, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6218.
- (9) Warshel, A.; Russell, S.; Weiss, R. M. In *Biometric Chemistry and Transition State Analogues*; Green, B. S., Ashani, V., Chipman, D., Eds.; Elsevier: Amsterdam, 1982; p 267.
- (10) Warshel, A. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 444.
- (11) Warshel, A.; Russell, S. T.; Sussman, F. *Isr. J. Chem.* **1986**, *27*, 217.
- (12) Parr, C. A.; Truhlar, D. G. *J. Phys. Chem.* **1971**, *75*, 1844.
- (13) Eyring, H.; Walter, J.; Kimball, G. E. *Quantum Chemistry*; John Wiley & Sons: New York, 1944; Chapter 13.
- (14) Baybutt, P.; Bobrowicz, F. W.; Kahn, L. R.; Truhlar, D. G. *J. Chem. Phys.* **1978**, *68*, 4809.
- (15) Bauschlicher, C. W., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 5492.
- (16) Laidig, W. D.; Schaefer, H. F., III. *J. Chem. Phys.* **1981**, *74*, 3411.
- (17) Warshel, A. Personal communications, August 14 and October 30, 2001, included here with permission.
- (18) London, F. Z. *Elektrochem.* **1929**, *35*, 551.
- (19) Eyring, H.; Polanyi, M. *Naturwissenschaften* **1930**, *18*, 914.
- (20) Kimball, G. E.; Eyring, H. *J. Am. Chem. Soc.* **1932**, *54*, 3876.
- (21) Coulson, C. A.; Danielsson, U. *Ark. Fys.* **1954**, *8*, 239.
- (22) Sato, S. *Bull. Chem. Soc. Jpn.* **1955**, *28*, 450.
- (23) Yasumori, *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1110.
- (24) Ellison, F. O. *J. Am. Chem. Soc.* **1963**, *85*, 3540; *J. Chem. Phys.* **1964**, *41*, 2198.
- (25) Cashion, J. K.; Herschbach, D. R. *J. Chem. Phys.* **1964**, *40*, 2358, *41*, 2199.
- (26) Porter, R. N.; Karplus, M. *J. Chem. Phys.* **1964**, *40*, 1105.
- (27) Warshel, A.; Bromberg, A. *J. Chem. Phys.* **1970**, *52*, 1262.
- (28) Blais, N. C.; Truhlar, D. G. *J. Chem. Phys.* **1973**, *58*, 1090.
- (29) Tully, J. C. *J. Chem. Phys.* **1973**, *58*, 1396.
- (30) Numrich, R. W.; Truhlar, D. G. *J. Phys. Chem.* **1975**, *79*, 2745.
- (31) Truhlar, D. G.; Wyatt, R. E. *Adv. Chem. Phys.* **1977**, *36*, 141.
- (32) Kuntz, P. J. In *Atom-Molecule Collision Theory*; Bernstein, R. B., Ed.; Plenum: New York, 1979; p 79.
- (33) Kendrick, J.; Kuntz, P. J. *J. Chem. Phys.* **1979**, *70*, 736.
- (34) Faist, M. B.; Muckerman, J. T. *J. Chem. Phys.* **1979**, *71*, 225.
- (35) Zeiri, Y.; Shapiro, M. *J. Chem. Phys.* **1981**, *75*, 1170.
- (36) Schreiber, J. L.; Kuntz, P. J. *J. Chem. Phys.* **1982**, *76*, 1872.
- (37) Truhlar, D. G.; Duff, D. W.; Blais, N. C.; Tully, J. C.; Garrett, B. C. *J. Chem. Phys.* **1982**, *77*, 764.
- (38) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1129.
- (39) Shaik, S. S. In *New Theoretical Concepts for Understanding Organic Reactions*; Bertrán, J., Csizmadia, I. G., Eds.; Kluwer: Dordrecht, The Netherlands, 1989; p 165.
- (40) Salikhov, A.; Fischer, H. *Theor. Chem. Acc.* **1997**, *96*, 114.
- (41) Chang, Y.-T.; Miller, W. H. *J. Phys. Chem.* **1990**, *94*, 5884.
- (42) Chang, Y.-T.; Minichino, C.; Miller, W. H. *J. Chem. Phys.* **1992**, *96*, 4341.
- (43) Minichino, C.; Voth, G. A. *J. Phys. Chem. B* **1997**, *101*, 4544.
- (44) Ischtwan, J.; Collins, M. A. *J. Chem. Phys.* **1994**, *100*, 8080.
- (45) Nguyen, K. A.; Rossi, I.; Truhlar, D. G. *J. Chem. Phys.* **1995**, *103*, 5522.
- (46) Syrkin, Y. K.; Dyatkina, M. E.; Zhukhovitskii, A. A. *Usp. Khim.* **1941**, *10*, 121.
- (47) Gao, J.; Mo, Y. In *Theoretical Methods in Condensed Phase Chemistry*; Schwartz, S. D., Ed.; Kluwer: Dordrecht, 2000; p 247.
- (48) Levich, V. G.; Dogonadze, R. R. *Dokl. Akad. Nauk SSR, Ser. Fiz. Khim.* **1959**, *124*, 123.
- (49) Marcus, R. A. *Electrochim. Acta* **1968**, *13*, 995.
- (50) Shaik, S. S. *J. Am. Chem. Soc.* **1984**, *106*, 1227.
- (51) Kim, H. J.; Hynes, J. T. *J. Am. Chem. Soc.* **1992**, *114*, 10858.
- (52) Basilevsky, M. V.; Chudinov, G. E.; Napolov, D. V.; Timofeeva, L. M. *Chem. Phys.* **1993**, *173*, 345.
- (53) Bianco, R.; Hynes, J. T. *J. Chem. Phys.* **1995**, *102*, 7864.
- (54) Curtiss, L.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7721.
- (55) Fast, P. L.; Sánchez, M. L.; Corchado, J. C.; Truhlar, D. G. *J. Chem. Phys.* **1999**, *110*, 11679.
- (56) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974.
- (57) Johnston, H. S. *Gas-Phase Reaction Rate Theory*; Ronald Press: New York, 1996; p 209.
- (58) Wilson, E. B., Jr.; Decius, J. C.; Cross, P. C. *Molecular Vibrations*; McGraw-Hill: New York, 1955.
- (59) Raff, L. M. *J. Chem. Phys.* **1974**, *60*, 2222.
- (60) Bernardi, F.; Olivucci, M.; Robb, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 1606.
- (61) Bearpark, M. J.; Robb, M. A.; Bernardi, F.; Olivucci, M. *Chem. Phys. Lett.* **1994**, *217*, 513.
- (62) Mo, Y.; Gao, J. *J. Phys. Chem. A* **2000**, *104*, 3012.
- (63) Mo, Y.; Gao, J. *J. Comput. Chem.* **2000**, *21*, 1468.
- (64) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.