Theor Chem Acc (2006) 116: 253–261
DOI 10.1007/s00214-005-0071-3

REGULAR ARTICLE

Avital Shurki

Valence bond – rebirth of the phoenix or relic from the stone age

Received: 4 April 2005 / Accepted: 7 September 2005 / Published online: 21 February 2006

Abstract The valence bond (VB) method has enjoyed its prime time during the early stages in the field of quantum chemistry. After the advent of molecular orbital methods VB lost its popularity but continued to be improved and refined by a small community of scientists who appreciated its power of revealing insight into the origins of chemical reactivity. This review summarizes the developments of the VB theory in the past few decades by focusing on two major areas of research: studies of the reactivity of small chemical systems and discovering the origins of enzyme catalysis. In both cases the unique capabilities of VB that facilitated discoveries of new concepts in an elegant and seemingly effortless way are discussed. It is suggested that owing to the success of these discoveries VB methodology is once again steadily gaining momentum. It is believed that VB concepts will play a major role in the future of theoretical chemistry.

Keywords Valence bond · Valence bond diagrams · Reactivity studies · Empirical valence bond · Quantum mechanics molecular mechanics

1 Introduction

The understanding of structure, bonding and reactivity is one of the corner stones of chemistry. Theoretical description aimed at that goal involves two major approaches: valence bond (VB) and molecular orbital (MO) theories. The VB theory was first formulated in 1927 by Heitler and London [1,2], to describe the bond in the hydrogen molecule as a spin-pair. Later, London formulated the quantum mechanical (QM) description of nonionic bonds, based on the work of Lewis [2]. Rumer extended London's ideas to many electron systems by introducing the Rumer diagrams [3]. Following these concepts Pauling promoted VB to a unified theory of chemical bonding [4].

MO theory was formulated around the same time. Important developments were Hückel's treatment of the π-electrons in conjugated hydrocarbons [5–7], followed by Dewar's applications [8] and Roothaan's algebraic (LCAO type) framework of computational self-consistent field (SCF) methodology [9] which enabled the implementation of the theory. Later the Walsh diagrams [10], frontier orbital rules [11,12] and the Woodward–Hoffman rules [13,14] together provided a general approach to structure and reactivity.

The Valence bond (VB) and Molecular orbital (MO) approaches differ significantly; VB places electrons in orbitals, which are mainly localized on atomic centers, while in the MO theory the electrons are delocalized over the whole molecule. Therefore while VB describes the chemical bond and delocalization as a result of resonance between configurations, MO considers the chemical bond a result of delocalization of electrons in multi-center orbitals. Despite the different representations when taken to the exact limit, both theories are equivalent [15].

The relative popularity of these two theoretical approaches has changed greatly over the years. The VB theory, sometimes referred to as the more simplified and pictorial resonance theory, has dominated chemical thinking during the 1940s and early 1950s [2–4]. Beginning in the early 1960s the MO theory became the popular method while the VB theory fell out of fashion. The reasons for the changes in preferences of the chemical community, as discussed in a recent "Conversation" paper, are far from obvious [16–18]. It was the outcome of a combination of several factors relevant to that time. One factor for example was the success of the MO theory to explain chemical phenomena (such as

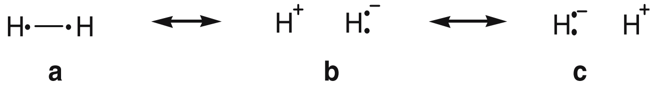
---

Electronic Supplementary Material Supplementary Material is available for the article at http://dx.doi.org/10.1007/s00214-005-0071-3 and is accessible for authorized users.

Affiliated with the David R. Bloom Center for Pharmacy at the Hebrew University.

A. Shurki
Department of Medicinal Chemistry and Natural Products,
School of Pharmacy, The Lise Meitner-Minerva Center
for Computational Quantum Chemistry,
The Hebrew University of Jerusalem,
Jerusalem 91120, Israel
E-mail: avital@md.huji.ac.il
Tel.:+972-2-6758696
Fax:+972-2-6757076

aromaticity vs. antiaromaticity) in a clear and simple manner [11–14], while people at that time mistakenly thought that VB theory fails to explain the same phenomena [19,20]. Another factor was the relative ease and efficiency of SCF–MO calculations compared to the computationally demanding nonorthogonal VB.



Scheme 1 presents graphically the VB structures of H_2 where 1a is the covalent (Heitler–London, HL) structure and 1b and 1c are the ionic structures. These are well known and widely used pictorial abstractions describing the electronic configurations used in VB to obtain the electronic structure. As such VB is closer to the chemist's way of thinking. Thus, despite the computational dominance of the MO theory, the language and underlying view of the chemical bond remained in the spirit of VB ideas. Hence, frequently used Lewis's electron–dot diagrams, the octet rule, hybrid orbital and resonance are simultaneously presented alongside MOs and MO energy level diagrams.

Moreover, the VB theory, which emphasizes electron bond pairs, has the ability to describe fundamental aspects of chemical reactivity such as the origin of barrier formation in chemical reactions and the mechanism of transition state (TS) formation. This ability is based on the behavior and mixing patterns of the VB configurations upon geometric distortion. The essence of the model dates back to the description of Evans and Polanyi [21] who studied three center type reactions of the form:

$$A - B + C \to A + B - C \tag{1}$$

They followed the energy variation of the initial and final states represented as bond eigenfunctions along the reaction coordinate and showed that the two states intersect (Fig. 1). Their explanation for the behavior of the two curves (E_i and E_f, respectively) involved partitioning of the system's interactions to bonding interactions and repulsion interactions. Thus, for example, in the above system they suggested that the energy of the initial wave function, which is an eigenfunction of the A–B bond, is expected to be raised as the A–B distance increases along the reaction path due to A–B bond breaking and as C approaches A–B due to B, C repulsion (presented as the curve E_i in Fig. 1). Similarly, it was suggested that the energy of the final wave function decreases as the reaction proceeds along the B–C attraction curve and due to the loss of repulsion energy as the A–B distance increases (presented as the curve E_f in Fig. 1). As a result of mixing between the two states at the intersection point two new states were suggested to have formed (dashed lines in the figure) and their energies were defined as $E_\mathrm{c} \pm E_\mathrm{if}$ where E_c is the energy value at the crossing point and E_if is defined as the perturbation energy between the initial and final state (Fig. 1). The TS was proposed to have the configuration for which E_c has its minimum value. Based on this diagram they concluded that the driving force for the reaction is the formation of the new bond, which lowers the activation energy [21].

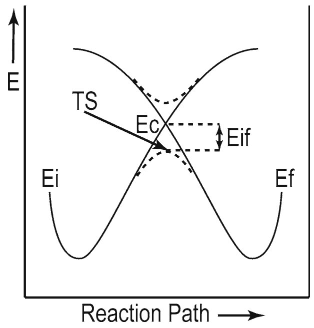


Fig. 1 A valence bond based model for activation energy and transition state formation as suggested by Evans and Polanyi [21]

Later similar VB models were developed and used by others in spite of the fact that VB was no longer the leading method in the computational field, and continuous progress and applications of the model were carried on side by side in several different areas of chemistry. The advantages of the VB theory were recognized not only in studies of chemical reactivity but also in other areas of chemistry such as chemical dynamics that also appreciated the insights of the VB theory and utilized VB based potential energy surfaces (e.g., [22, 23]). This paper, however, wishes to concentrate on chemical reactivity and to review some of the developments in this field while emphasizing the advantages of using VB ideas and methodology. It will bring together two major fields: small sized systems and large biological systems where both methodology and applications will be described. It will be shown that VB and its barrier formation concept established the basis for many studies dealing with reactivity problems in chemistry.

2 Small sized systems

This section describes briefly developments of the ab initio VB methodology, summarizes the VB diagram model as a thinking tool for chemical reactivity, and presents a few applications highlighting the benefits of that model.

2.1 Method development

Parallel to the MO theory several different ab initio methods based on the VB concept have been developed over the years. As in the MO theory, here too, the methods differ from each other by the amount of electron correlation which is considered in the calculations. The precise representation of a VB wave function is a linear combination of all the possible VB configurations in the system as depicted in Eq. (2)

$$\Psi_\mathrm{VB} = \sum_i c_i \Phi_i \tag{2}$$

The difference between the various configurations, Φ_i, is a different distribution of the electrons among the atoms. Hence, for example, the VB wave function of the simplest H_2 system is a linear combination of the three different VB configurations: the covalent (HL) configuration and the two ionic configurations. Over the years several distinct classes of methods have been developed: methods that express the wave function by a single VB electronic configuration and methods that follow the traditional VB picture.

The first class of methods is based on the Coulson and Fischer proposal that the role of the ionic structures can be established by delocalization of the orbitals [24] (see supplementary material for a detailed explanation). Following these ideas two major methodologies were developed: Goddard's generalized valence bond (GVB) scheme [25–27] and the spin-coupled (SC) scheme developed by Gerratt and his coworkers [15,28]. Both the GVB and the SCVB wave functions have the form of a single covalent VB electronic configuration with orbitals that are allowed to delocalize. The result is a compact wave function that incorporates implicitly the ionic structures (for more details see supplementary material).

The basic GVB wave function is the covalent configuration where the electrons are paired as in the most important Lewis structure – namely, the perfect pairing form [25–27]. Additionally, the orbitals of each pair are required to be orthogonal to all the other orbital pairs of the system. The result is a wave function with the advantages of an MO wave function in terms of computational complexity but providing a significant part of the nondynamical correlation energy of the singlet-coupled pairs of electrons. Consequently, GVB gives a correct description of homolytic dissociation, predicting for example positive bond energy for F_2, a molecule which is not bonded at the Hartree-Fock level [29]. Improvement of the method involves its augmentation with further configuration interaction (CI) [30].

The SC method is similar to the GVB method in its approach to utilize a single configuration wave function: however, both the orthogonality and the perfect pairing restrictions are removed [15,28]. Therefore, systems like aromatic compounds, which have more than one important covalent structure and where resonance is significant, get a better description when calculated with the SC method. Spin-coupled VB (SCVB) further improves the SC wave function by using the one-configuration calculation as a starting point for a CI calculation [15,28].

A different class involves methods that utilize MO based wave functions which are transformed to the VB space. Such methods include the half-determinant method of Hiberty et al. [31] and methods which are based on a CASSCF wave function [32–38].

The last class involves the valence bond self-consistent field (VBSCF) [39] and the breathing orbitals valence bond (BOVB) methods [29,40]. While losing the advantage of compactness of the wave function obtained in the first class of methods these methods can provide explicitly the covalent and ionic contributions to the wave function, their dissociation curves and a quantitative measure of the ionic–covalent resonance energies. The VBSCF wave function developed by van Lenthe and coworkers [39] consists of all the system's VB configurations (ionic and covalent) described by a common set of orbitals. The orbitals as well as the coefficients of the different configurations are optimized simultaneously, leading to a SCF type wave function. Thus, the method is a multi-configuration SCF method with an advantage of utilizing chemically interpretable configurations. The VBSCF approach was developed based on both the spin free formulation that uses symmetry group methods [41–45] and as a typical multi-configuration spin wave function [46,47].

An alternative possibility, developed by Hiberty [29,40], removes the average field restriction, and allows a unique set of orbitals for each VB structure. In this manner, each orbital can fluctuate in size and shape and adjust to the local charge of the VB structure as well as to the mixing with other structures. These optimized orbitals which differ from one structure to another can be viewed as instantaneously following the charge fluctuation by the rearrangement in size and shape; hence the name "breathing orbital" valence bond [40]. The BOVB wave function brings in some dynamic correlation, which follows the electronic fluctuations during the bonding, and is therefore a highly accurate method. Calculation of the bond energy of F_2 using BOVB for example yielded 36.2 kcal/mol in good agreement with the experimental results (38.2 kcal/mol) while CASSCF accounted for less than half of the bonding energy [48].

2.2 VB reactivity diagrams, concept development and application

In 1981 Shaik and coworkers [20,49–54] developed a unified model of chemical reactivity by expanding MO and MO-CI wave functions into more localized components, all the way to the classical VB structures. The model involves two generic diagrams: the VB state correlation diagram (VBSCD) and the VB configuration-mixing diagram (VBCMD). VBSCD is a modern version of the Evans–Polanyi diagram; it describes barrier formation as a result of avoided crossing between two state-curves: the reactants and the products, where each state can be a mixture of a few VB configurations. VBCMD on the other hand considers the contribution of each VB configuration separately and can, therefore, describe also stepwise reactions. In both cases mixing is avoided and new states are obtained (bold lines in Fig. 2): one defining the ground state and others (one in VBSCD or more in VBCMD) describing the system's excited states.

Using the VBSCD, Shaik and coworkers formulated an expression for the reaction barrier $\Delta E^{\ddagger}$. A simplified version is given here as a function of three parameters: G, the vertical gap between the reactant state and the product state at the reactant's geometry; f, the fraction of this gap that gives the height of E_c (the energy where the two states cross); and B, the energy gained by means of mixing of the two states (see also Fig. 2).

$$\Delta E^{\ddagger} = E_c - B = \mathrm{fG} - \mathrm{B} \tag{3}$$

Furthermore, the unique property of the VB wave functions, i.e. the ability to be translated to meaningful chemical formulas, was utilized to assign chemical meaning to these key parameters of the diagram. Thus, G was shown to be a function of the vertical charge transfer energy in reactions where the formal oxidation state changes and otherwise a function of the vertical singlet–triplet excitation energy. The quantity f measures the curvature of the diabatic curves, and was shown to depend on several intrinsic properties of the system such as the reaction free energy and the amount of delocalization, in the excited states of the diagram. Finally, B, the resonance integral between the two states, was shown to incorporate symmetry characteristics of the wave functions. This in turn facilitated the understanding and assessment of factors that control the barrier and therefore allowed to make predictions on different reactivity patterns.

The examples chosen here to represent the concept do not involve a chemical reaction but deal with intrinsic properties of molecules such as their structure, stability as well as spectroscopic aspects in order to emphasize the generality of the model to any reactivity scheme. The VBSCD model applied to the π-system of benzene using the two Kekulé structures along the b_{2u} π-localizing coordinate is typified by a vertical gap which is proportional to about three singlet–triplet excitation energies (ΔE_{ST}) of a π-bond (see Fig. 3). Since the ΔE_{ST} of a single π-bond amounts to about 100 kcal/mol the model predicts a very large vertical gap leading to a barrier along this coordinate (plain bold line in Fig. 3). More specifically, the VBSCD model predicts a dual nature of the π-system of benzene – possessing an energetic preference to be localized and at the same time held symmetric by the σ-frame and strongly stabilized by resonance energy [55, 56]. One could find this distortive tendency of benzene's π-electrons somewhat controversial considering the stability of benzene. Yet, as exemplified below, the two phenomena do not contradict and the same model is used both to estimate benzene's aromaticity and to explain some of its spectroscopic behavior.

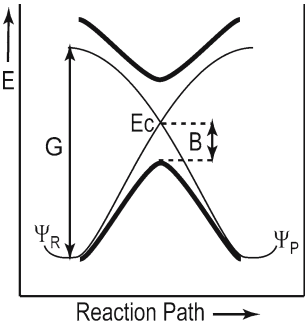


Fig. 2 A generic state correlation diagram (SCD) diagram showing some of the significant factors (G is the gap and B the resonance energy) controlling the barrier

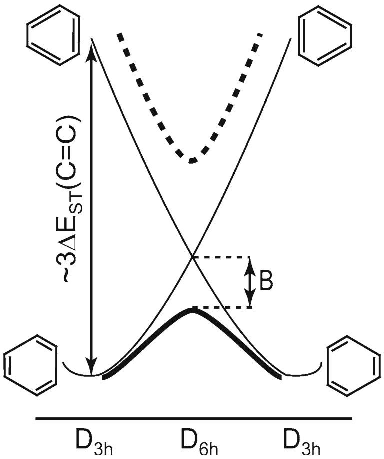


Fig. 3 An avoided crossing diagram between the two Kekulé structures of benzene. The curves represent the energy of the π-electrons alone. The bold plain line represents the ground state distortive behavior of the π-electrons, whereas the dashed bold line shows their attractive behavior in the B_{2u} excited state

The aromaticity of benzene is one of the most widely recognized concepts of organic chemistry and various theoretical studies aimed at estimating its actual value were carried out throughout the years [33,56–62]. The origin of the resonance term comes from VB theory and thus, it is just natural to use VB concepts for that purpose. Several studies used VB ideas while utilizing MO approaches for the actual calculations [57–61]. These calculations often over estimated the value of aromaticity, partially due to the method of choice (MO instead of VB) which is less suitable and thus leads to less accurate results. Here we will discuss three studies, two of which utilized the VBSCF methodology [56,62] and one that used the VB model derived from CASSCF [33]. However, the interested reader is referred to comprehensive reviews of benzene to get a better picture [56,63–66].

The experimental estimates of aromaticity are based on measurements of the stabilization energy relative to either a reference with isolated double bonds (regarded between 36–42 kcal/mol for benzene) or a hypothetical cyclo-diene reference with an open-chain type π-bond conjugation (21 kcal/mol for benzene) [63,67,68]. Following the first scheme and calculating the sum of the vertical resonance energy at the D_{6h} symmetry (B in Fig. 3) and the distortion energy of one Kekulé structure leads to a value of 44.48 kcal/mol using VBSCF [62] and 40.8 kcal/mol using the VB model derived from CASSCF [33]. Both these methods overestimate the standard experimental data of the homodesmotic reaction being 36 kcal/mol but are in good agreement with the 42.65 kcal/mol homodesmotic stabilization energy obtained using butadiene with the C–C single bond rotated by 90° as a reference molecule [68]. Following the second scheme and thus a different thermodynamic cycle that again considers the vertical resonance energy as part of the calculation, Shaik et al. [56] estimated benzene's aromaticity (referred to as Dewar's resonance energy) to be 20.4 kcal/mol at the VBSCF level in good agreement with the experimental value 21. Thus it is seen that VB despite its prediction of a distortive behavior for the π-electrons can reproduce experimental estimates of aromaticity with very good agreement.

Moreover, the distortive tendency of benzene's π-electrons explains using the VBCMD model several experimental phenomena that otherwise could not be explained. Thus, for example, the Kekulé b_{2u} vibration frequency undergoes an upward shift of $\sim 257\,\mathrm{cm}^{-1}$ upon excitation from the ground to the first $^1B_{2u}$ excited state of benzene [69]. This frequency exaltation is rationalized by considering the distortive tendency of the π-system of benzene in the ground state and the attractive behavior of the twin-excited state (plain and dashed bold lines in Fig. 3, respectively). The σ-attractive potential on the other hand is not expected to differ significantly between the ground and first excited state. Thus, the overall potential of the first excited state which is a sum of two attractive curves (the σ and the π) is anticipated to be more attractive than the overall potential of the ground state leading to the selective b_{2u} frequency exaltation [69–71].

Another example is the significant bond alternation observed in several cyclohexatriene motifs, which were synthesized in recent years. The structure of these compounds is rationalized by the small distortive propensity of the σ-electrons in these systems which combined with the π distortive tendency produces compounds with significant bond alternation [72]. Furthermore, the model was shown to successfully predict the structure of the twin-excited states of these alternant compounds.

Finally, both the VBCMD and VBSCD models comprise many more features and the reader is referred to more comprehensive reviews [20,50–54].

3 Biological systems

Biological systems are characterized by a large number of degrees of freedom, thus increasing the complexity of the problem. As a result a multitude of computational methods are used for studying these systems. This section describes the development of methods that apply the VB diagrams to study the reactivity of large systems and presents some applications.

3.1 Empirical valence bond: concept, method and application

A different direction in the development of the initial ideas of Evans and Polanyi was their ingenious application to large biological systems. Most of the chemical reactions in biological systems occur either in solution or in protein molecules. The surroundings (solvent/protein) affect such reactions in a variety of important ways and often determine the relative free energies or stabilities of the reactant, TS, and product molecules. Thus, prerequisites for a successful study of such reactions are reliable methods that consider the environment in the calculation. One of the major problems with incorporating the environment in the calculation is the vast number of degrees of freedom. Warshel and Bromberg combined an empirical force field with VB wave function to study the reactivity of a medium size molecule [73]. Another interesting reactivity problem solved in a similar manner was introduced by Raff et al. [74]. This utilization of the (semi)empirical VB solved the problem of the system's size but incorporation of the environment still remained unsolved. Soon after, seeking a way to introduce the solvent effect Warshel developed the VB reactivity diagrams together with ideas of combining QM with molecular mechanical (MM) approaches [75] to establish the empirical valence bond (EVB) method for calculations of reactions in solutions and in enzymes [76–79].

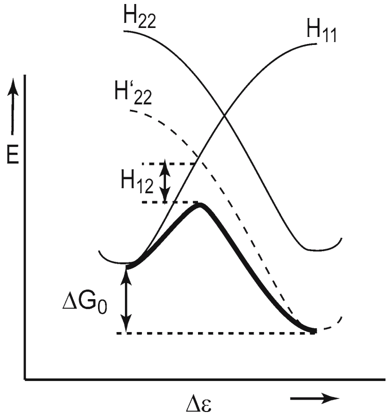


Fig. 4 A generic empirical valence bond (EVB) potential energy profile presented along $\Delta\varepsilon$. The *plain* and *dashed* lines correspond to the energy of the diabatic states before and after calibration, respectively. The *bold line* refers to the ground state energy profile

The basic idea of the VB treatment is to obtain the ground state potential in terms of the mixing between relevant diabatic states, Φ_i, where each state represents a specific bonding and charge configuration. Thus, the resulting diagonal elements of the VB Hamiltonian, $\langle \Phi_i | H | \Phi_i \rangle = H_{ii}^{\mathrm{QM}}$, possess a clear chemical meaning – the energy of the relevant chemical structures. The EVB method exploits this chemical character of the diagonal matrix elements H_{ii}^{QM} and approximates them by MM force fields. For each diabatic state, coupling between the reacting species and their macromolecular or solution environment is considered by evaluating the "classical" interaction between the environment and the reacting atoms. These interactions are added separately to the respective diagonal elements of the Hamiltonian and result in $H_{ii} = \varepsilon_i$, the potential energy of the ith state (plain curves in Fig. 4). These states are then mixed by an off diagonal element to give the ground state.

The EVB was developed as a tool for studying reactions in biological systems: thus, the emphasis is on having a reliable description of the potential energy curves. Furthermore, due to the difficulty in obtaining accurate potential surfaces in such complex systems, the method was designed to focus on the difference between the reactions in different environments (e.g., in enzyme and in solution). Therefore, the reaction in one of the environments (e.g., solution) is chosen as a reference reaction whose potential energy surface is fitted to the experimental data. Namely, a chemical meaning is assigned to different properties of the curves, which are then calibrated to reproduce the corresponding experimental values (or ab initio values when experimental data are not available) of that reference reaction (e.g., solution reaction). Therefore, the difference between the minima of the two diabatic states at infinite separation of the reacting species should

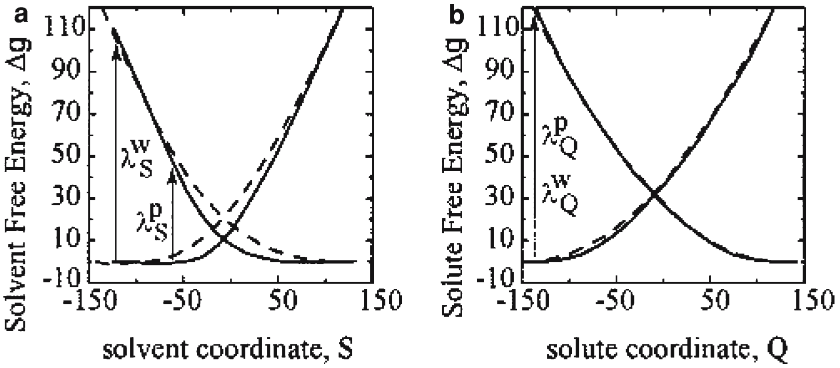


Fig. 5 Valence bond (VB) diagrams of the diabatic curves along the solvent (**a**) and solute (**b**) coordinates. *Plain* and *dashed* lines correspond to the reaction in protein and water, respectively. λ_Q and λ_S represent the solvent and solute reorganization energy, respectively. (Figure reproduced from [103])

be the reaction energy ΔG_0, and the diagonal elements are calibrated accordingly[1] (dash H'_{22} curve in Fig. 4). Moreover, the off diagonal element of the Hamiltonian, H_{ij}, is calibrated by the neglect of overlap between the different diabatic states while the ground state energy is required to reproduce the observed activation barrier for the reference reaction (e.g., solution reaction). These parameters are then used to describe the same reaction in the environment of interest (e.g., the protein environment). Since the calibration process ensures the correct experimental relative energetics of the reactants TS and products for the reference reaction (e.g., the solution reaction), it also prevents unrealistic results for the reaction studied (e.g. the reaction in the protein environment).

Finally, the EVB free energy is evaluated by driving the system from reactants to products by changing gradually the relative contributions of the diabatic states and by using a combination of the free energy perturbation [80,81] with umbrella sampling [82–84]. Additionally, the reaction coordinate $\Delta\varepsilon$ is defined as the energy gap between the two diabatic states [77] (see Fig. 4). This definition, which is unique to VB schemes, accounts for all the degrees of freedom in the system (solute plus solvent) since the energies of the diagonal elements incorporate their contribution. This, in turn, leads to a consistent description of the reaction coordinate. Moreover the correction for the nonequilibrium solvation effect which arises in the potential of mean force simulations when only the solvent coordinate is considered, is not required in the EVB type of simulations since the coordinate considers both the solvent and the solute [85,86][2].

The EVB method focuses on the difference between the reactions in enzyme and in solution, providing an effective way of studying catalysis. The method was applied to a wide range of problems and the reader is referred to the literature for a broader view [78,79,86–99]. Here, two examples were chosen to demonstrate the abilities of the EVB in studies of reactivity. The first relates to the fundamental question – what is the root cause of catalysis in general, whereas the second relates to a specific biological problem.

The steric effect is regarded as a major factor in enzyme catalysis. In particular, it has been proposed that enzymes push their substrate towards their TS configurations, also called near attack configurations, and thus catalyze their reactions [100–102]. The importance of this effect was examined using EVB for the S_N2 reaction of haloalkane dehalogenase [103]. The overall barrier was first reproduced, calculating the reaction both in water and in the enzyme. Several strategies manipulating the energy profiles were then employed to quantify the steric effect. For example, the electrostatic part of the interactions between the substrate and the environment was eliminated. The resulting new profiles were compared to the original ones leading to the conclusion that the electrostatic, rather than the steric, effects play a major role in catalysis. Additionally, the definition of the reaction coordinate as the energy difference between the diabatic states allows the characterization of the reaction coordinates of the reacting fragment and the environment separately [84]. This feature was utilized to calculate the Marcus reorganization energy, which is a natural component in the EVB scheme [104], independently for the environment and the substrate (Fig. 5a and b, respectively). It was shown that the main difference in the reorganization energy originates in the environment coordinate. It was therefore concluded that most of the catalytic effect results from environmental preorganization [103]. Related studies of the catalytic effect of the Claisen rearrangement of chorismate to prephenate in chorimate mutase result in similar conclusions [105].

The second example emphasizes the ability of the EVB as a predictive method. p21-ras proteins (Ras hereafter) act as switches of pathways regulating cell growth and differentiation cycling between their active GTP-bound and inactive GDP-bound forms, whereas GAP proteins accelerate the GTP hydrolysis (GTPase) reaction in Ras. Mutations of Gln-61 in Ras reduce the sensitivity to GAP and are found in a large number of human tumors. Thus, understanding the

---

[1] It is noted that since the emphasis is on the accuracy and not on the concept in this case, once the ground state energy is calculated this parameter is further refined if necessary to reproduce the corresponding experimental values of the reference reaction

[2] Note that the nonequilibrium solvation calculated with the EVB are properties of the underlying adiabatic surface and thus are independent of the specific assumed dibatic surfaces

role of this catalytic glutamine is of great importance. EVB calculations of the proton transfer between Glu61 and a water molecule in solution and in Ras predicted a higher barrier in the enzyme. This indicated that Gln61 is unlikely to serve as the general base (GB) in the intrinsic reaction of Ras [106]. Later experiments combined with theory have shown a linear relationship between the GTP hydrolysis rate and the $\mathrm{pK_a}$ of GTP [107,108]. The VB diagram analysis of these results suggested that GTP serves as a GB. Recent EVB calculations verified that GTP acts as a GB by calculating this mechanism and reproducing the experimental reaction rate [109]. Furthermore, the role of Gln61 was examined by mutating it in the calculation to its nonpolar variant and to several real mutations. It was argued that Gln 61 does not operate either in a direct chemical way or by direct electrostatic stabilization of the TS, but does rather by an allosteric effect [109, 110].

3.2 Other methods

The advantages of the EVB method were appreciated by several researchers, who tried to further improve it by treating its weaknesses. It was realized that the reliability of the EVB surfaces depends on its calibration and in particular on the estimation of the off diagonal elements, H_{ij}. Thus, Chang and Miller have shown how to choose the values of these exchange potentials H_{ij}, so that the EVB potential reproduces the TS geometry, energy and force constant matrix from an independent ab initio calculation [111,112]. Other attempts to use ab initio rather than the empirical parameterization of the off diagonal matrix element resulted in with the approximate valence bond method of McCammon and coworkers [113]. Extended EVB [95,96] and multistate EVB [93,94] utilizing several VB forms and ab initio based parameterization were also developed to model proton transport in water. All these methods may agree with high level ab initio data for the reactants, TS and products geometry, energy and frequencies, but they do not necessarily provide a good description of the global potential energy surface. Recently, Truhlar and coworkers presented the multi-configuration molecular mechanics (MCMM) which fits the off diagonal matrix element using the Chang-Miller formula [111,112] at a sequence of points and then utilizes the Shepard interpolation [114] to obtain the other points along the PES [115,116].

Other related methods that combine VB and MM elements are the MMVB method of Bernardi et al. [117,118] that couples the MM force field to a VB Heisenberg Hamiltonian parameterized from ab initio CASSCF calculations. Here the parameters are the Coulomb, Q_{ij}, and the exchange, K_{ij}, integrals, which are calculated analytically in the MMVB method. Parameterization is currently available only to the sp^2 and sp^3 carbon atoms, which limit the treatment to these centers only. Another method is the MOVB/MM method of Mo and Gao [119,120]. This method constructs localized wave functions representing diabatic states from an original MO wave function. CI calculations then lead to the adiabatic PES.

Finally, Shaik and Wu et al. have developed two distinct VB based methods for large systems. The first is the VBDFTs which is a Hückel type semiempirical VB method parameterized to reproduce DFT energies and applicable to conjugated systems[121–124]. The second method, recently developed, is a VB method that incorporates a polarizable continuum model [125], and thus enables calculations of the ab initio VB with the inclusion of solvent effects [126].

4 Perspective

For the last five decades the VB methodology has been overshadowed by the wide acceptance of MO methods. VB has been mistakenly disparaged as a somewhat primitive and simplified theory that fails explaining certain phenomena in chemistry. Nevertheless, despite VB's low recognition, developments in VB continue to emerge throughout the years owing to a small number of researchers who appreciate the unique capabilities inherent to VB. Consequently, VB was developed both as a thinking tool and as a quantitative method in different fields of chemistry. The VB wave function provides chemical insight, which is different from that obtained from the MO wave function and has an advantage when considering reactivity aspects of chemistry. As such VB is complementary to the MO theory and it is our belief that the future of theoretical chemistry involves coexistence of the two methods. With the increasing number of both QM and QM/MM methods applied to problems in chemistry there seems to be a renewed interest in the virtues of VB. Many researchers are realizing now how effective the VB theory is in the description of chemical reactions and are learning to appreciate its intuitive concepts. In other words, similar to organic chemistry where nuclear magnetic resonance, mass spectra and elemental analysis are all standard methods used to characterize molecules – where each highlights different aspects and yet all are considered as basic expertise, we hope that VB will slowly become a method of common knowledge, which in parallel with MO will serve as a standard method to solve problems in theoretical chemistry.

Furthermore, reactivity studies highlight the advantages of VB over MO. Thus, it is just natural that a substantial share of the progress of the VB ideas involved the development of tools aimed at understanding and quantifying reactivity. Distinct aspects were emphasized and developed in different fields. The VBSCD and the VBCMD paradigms, developed on small chemical systems, view the reaction barrier as a result of electronic reorganization. The EVB, developed to treat biological systems, views catalysis which is the difference in the solution and protein reaction barriers as a result of environmental reorganization. The VBSCD, VBCMD and the EVB concepts have been developed independently. Nevertheless, we believe that these methods have now reached a level of maturity, which enable them to contribute to each other. An instructive example of how the VBCMD and VBSCD concepts developed originally on small chemical systems have been employed to the $\mathrm{F_1}$-ATPase is a recent study of Strajbl and coworkers [127]. F_1-ATPase is the catalytic component of ATP synthase that couples rotation and major structural changes with a chemical process. This study utilized the VBSCD ideas together with thermodynamic cycles and linear response approximation to define the energetics of the whole process including evaluation of the rotation energy [127].

Hence, we anticipate that the future of theoretical chemistry will involve more such methods and applications that combine ideas from the two disciplines. Calculations of biological systems utilized VB ideas since the conception of this field and were never biased towards MO. We feel that coupling VB methods with MM and its application to studies of enzyme catalysis are exactly the right kind of problems where VB can excel and thus spark its revival.

Acknowledgements I would like to thank my two great teachers Prof. Sason Shaik and Prof. Arieh Warshel, who introduced me to the realm of the VB theory. I am also thankful to Prof. Philippe C. Hiberty, Prof. Wei Wu and Dr. David Danovich for illuminating discussions and fruitful collaborations. For financial support I thank the Alex Grass Center for Drug Design and Synthesis of Novel Therapeutics and The Hebrew University Internal Fund.

References

1. Heitler W, London F (1927) Z Phys 44:455
2. London F (1928) Z Phys 46:455
3. Rumer G (1932) Göttinger Nach :337
4. Pauling L (1939) The nature of the chemical bond. Cornell University Press, Ithaca, New York
5. Huckel E (1930) Z Phys 60:423
6. Huckel E (1931) Z Phys 72:310
7. Huckel E (1934) Trans Faraday Soc 30:40
8. Dewar MJS (1952) J Am Chem Soc 74:3341
9. Roothaan CCJ (1951) Rev Mod Phys 23:69
10. Walsh AD (1953) J Chem Soc:2260
11. Fukui K, Yonezawa T, Shingu H (1952) J Chem Phys 20:722
12. Fukui K (1982) Science 218:747
13. Woodward RB, Hoffmann R (1969) Angew Chem Int Ed Engl 8:781
14. Hoffmann R, Woodward RB (1968) Acc Chem Res 1:17
15. Cooper DL, Gerratt J, Raimondi M (1991) Chem Rev 91:929
16. Hoffmann R, Shaik S, Hiberty PC (2003) Acc Chem Res 36:750
17. Roberts JD (2004) Acc Chem Res 37:417
18. Streitwieser A (2004) Acc Chem Res 37:419
19. Shaik S, Hiberty PC (2003) Helv Chim Acta 86:1063
20. Shaik S, Hiberty PC (2004) Rev Comput Chem 20:1
21. Evans MG, Polanyi M (1938) Trans Faraday Soc 34:11
22. Truhlar DG, Wyatt RE (1977) Adv Chem Phys 36:141
23. Murrell JN, Carter S, Farantos SC, Huxley P, Varandas AJC (1984) Molecular potential energy functions. Wiley, New York
24. Coulson CA, Fischer I (1949) Phil Mag 40:386
25. Bobrowicz FW, Goddard WA III (1977) In: Schaefer HF III (ed) Methods of electronic structure theory, Vol 3. Plenum Press, New York, p 79
26. Hunt WJ, Hays PJ, Goddard WA, III (1972) J Chem Phys 57:738
27. Goddard WA III, Harding LB (1978) Annu Rev Phys Chem 29:363
28. Cooper DL, Gerratt J, Raimondi M (1988) Int Rev Phys Chem 7:59
29. Hiberty PC, Flament JP, Noizet E (1992) Chem Phys Lett 189:259
30. Carter EA, Goddard WA, III (1988) J Chem Phys 88:3132
31. Hiberty PC, Leforestier C (1978) J Am Chem Soc 100:2012
32. Bernardi F, Olivucci M, McDouall JJW, Robb MA (1988) J Chem Phys 89:6365
33. Bernardi F, Celani P, Olivucci M, Robb MA, Suzzi-Valli G (1995) J Am Chem Soc 117:10531
34. Blancafort L, Celani P, Bearpark MJ, Robb MA (2003) Theor Chem Acc 110:92
35. Thorsteinsson T, Cooper DL, Gerrat J, Karadakov PB, Raimondi M (1996) Theor Chim Acta (Berl) 93:343
36. Cooper DL, Thorsteinsson T, Gerratt J (1997) Int J Quant Chem 65:439
37. Hirao H, Nakano H, Nakayama K (1997) J Chem Phys 107:9966
38. Nakano H, Sorakubo K, Nakayama K, Hirao H (2002) In: Cooper DL (ed) Valence bond theory, Elsevier, Amsterdam, p 55
39. van Lenthe JH, Balint-Kurti GG (1983) J Chem Phys 78:5699
40. Hiberty PC, Humbel S, Byrman CP, van Lenthe JH (1994) J Chem Phys 101:5969
41. Matsen FA (1964) Adv Quantum Chem 1:60
42. McWeeny R (1988) Int J Quantum Chem XXXIV:23
43. Wu W, Mo Y, Zhang Q (1993) J Mol Struct (THEOCHEM) 283:227
44. Song L, Wu W, Mo Y, Zhang Q (2003) XMVB-0.1 – An ab initio non-orthogonal valence bond program, Xiamen University, Xiamen – China
45. Song LC, Mo YR, Zhang QN, Wu W (2005) J comput Chem 26:514
46. Verbeek J, van Lenthe JH, Pulay P (1991) Mol Phys 73:1159
47. Verbeek J, Langenberg JH, Byrman CP, Dijkstra F, van Lenthe JH (1998) TURTLE: an ab-initio VB/VBSCF program, (now implemented in Gamess)
48. Hiberty PC, Shaik S (2002) Theor Chem Acc 108:255
49. Shaik SS (1981) J Am Chem Soc 103:3692
50. Pross A, Shaik SS (1983) Acc Chem Res 16:363
51. Shaik SS (1989) In: Bertran J, Csizmadia GI (eds) In: New theoretical concepts for understanding organic reactions NATO ASISeries, Vol C267. Kluwer, Dordrecht, Holland
52. Shaik SS, Hiberty PC (1991) In: Maksic ZB (ed) Theoretical concepts for chemical bonding, Vol 4. Springer, Berlin Heidelberg New York, p 324
53. Shaik S, Hiberty PC (1995) Adv quantum chem 26:99
54. Shaik S, Shurki A (1999) Angew Chem Int Ed Engl 38:587
55. Hiberty PC, Danovich D, Shurki A, Shaik S (1995) J Am Chem Soc 117:7760
56. Shaik S, Shurki A, Danovich D, Hiberty PC (2001) Chem Rev 101:1501
57. Kollmar H (1979) J Am Chem Soc 101:4832
58. Hess BJ, Schaad L (1983) J Am Chem Soc 105:7500
59. Shaik SS, Hiberty PC, Lefour JM, Ohanessian G (1987) J Am Chem Soc 109:363
60. Glendening ED, Faust R, Streitwieser A, Vollhardt KPC, Weinhold F (1993) J Am Chem Soc 115:10952
61. Behrens S, Koester AM, Jug K (1994) J Org Chem 59:2546
62. Mo Y, Wu W, Zhang Q (1994) J Phys Chem 98:10048
63. Minkin VI, Glukhovtsev MN, Simkin BY (1994) Aromaticity and antiaromaticity. Wiley, New York
64. Streitwieser AJ (1961) Molecular orbital theory for organic chemists. Wiley, New York
65. Badgor GM (1969) Aromatic character and aromaticity. Cambridge University Press, Cambridge, London
66. Garratt JP (1986) Aromaticity. Wiley, New York
67. Deniz AA, Peters KS, Snyder GJ (1999) Science 286:1119
68. George P, Trachtman M, Bock CW, Brett AM (1976) Tetrahedron 32:1357
69. Haas Y, Zilberg S (1995) J Am Chem Soc 117:5387
70. Shaik S, Zilberg S, Haas Y (1996) Acc Chem Res 29:211
71. Shaik S, Shurki A, Danovich D, Hiberty PC (1996) J Am Chem Soc 18:666
72. Shurki A, Shaik S (1997) Angew Chem Int Ed Engl 36:2205
73. Warshel A, Bromberg A (1970) J Chem Phys 52:1262
74. Raff LM, Stivers L, Proter RN, Thompson DL, Sims LB (1970) J Chem Phys 52:3449
75. Warshel A, Levitt M (1976) J Mol Biol 103:227
76. Warshel A, Weiss RM (1980) J Am Chem Soc 102:6218
77. Warshel A (1991) Computer modeling of chemical reactions in enzymes and solutions. Wiley, New York
78. Åqvist J, Warshel A (1993) Chem Rev 93:2523

79. Warshel A (2003) Annu Rev Bioph Biom 32:425
80. Zwanzig RW (1954) J Chem Phys 22:1420
81. Valleau JP, Torrie GM (1977) Modern theoretical chemistry. Plenum Press, New York
82. Hwang J-K, Warshel A (1987) J Am Chem Soc 109:715
83. Hwang J-K, King G, Creighton S, Warshel A (1988) J Am Chem Soc 110:5297
84. King G, Warshel A (1990) J Chem Phys 93:8682
85. Muller RP, Warshel A (1995) J Phys Chem 99:17516
86. Villa J, Warshel A (2001) J Phys Chem B 105:7887
87. Warshel A, Parson WW (2001) Q Rev Biophys 34:563
88. Shurki A, Warshel A (2003) Adv Prot Chem 66:249
89. Warshel A (2002) Acc Chem Res 35:385
90. Warshel A, Russell ST (1984) Q Rev Biophys 17:283
91. Åqvist J, Fothergill M (1996) J Biol Chem 271:10010
92. Luzhkov V, Åqvist J (1998) J Am Chem Soc 120:6131
93. Schmitt UW, Voth GA (1998) J Phys Chem B 102:5547
94. Schmitt UW, Voth GA (1999) J Chem Phys 111:9361
95. Vuilleumier R, Borgis D (1997) J Mol Struct 436–437:555
96. Vuilleumier R, Borgis D (1998) Chem Phys Let 284:71
97. Billeter SR, Webb SP, Agarwal PK, Iordanov T, Hammes-Schiffer S (2001) J Am Chem Soc 123:11262
98. Hammes-Schiffer S, Billeter SR (2001) Int Rev Phys Chem 20:591
99. Neria E, Karplus M (1997) Chem Phys Lett 267:23
100. Bruice TC (2002) Acc Chem Res 35:139
101. Bruice TC, Lightstone FC (1999) Acc Chem Res 32:127
102. Hur S, Bruice TC (2003) Proc Nat Acad Sci 100:12015
103. Shurki A, Štrajbl M, Villa J, Warshel A (2002) J Am Chem Soc 124:4097
104. Marcus RA (1964) Ann Rev Phys Chem 15:155
105. Štrajbl M, Shurki A, Kato M, Warshel A (2003) J Am Chem Soc 125:10228
106. Langen R, Schweins T, Warshel A (1992) Biochemistry 31:8691
107. Schweins T, Geyer M, Kalbitzer HR, Wittinghofer A, Warshel A (1996) Biochemistry 35:14225
108. Schweins T, Warshel A (1996) Biochemistry 35:14232
109. Shurki A, Warshel A (2004) Proteins 55:1
110. Glennon TM, Villa J, Warshel A (2000) Biochemistry 39:9641
111. Chang Y-T, Miller WH (1990) J Phys Chem 94:5884
112. Chang Y-T, Minichino C, Miller WH (1992) J Chem Phys 96:4341
113. Grochowski P, Lesyng B, Bala P, McCammon JA (1996) Int J Quant Chem 60:1143
114. Ischtwan J, Collins MA (1994) J Chem Phys 100:8080
115. Kim Y, Corchado JC, Villá J, Xing J, Truhlar DG (2000) J Chem Phys 112:2718
116. Albu TV, Corchado JC, Truhlar DG (2001) J Phys Chem A 105:8465
117. Bernardi F, Olivucci M, Robb MA (1992) J Am Chem Soc 114:1606
118. Garavelli M, Ruggeri F, Ogliaro F, Bearpark MJ, Bernardi F, Olivucci M, Robb MA (2003) J Comp Chem 24:1357
119. Mo YR, Gao JL (2000) J Phys Chem A 104:3012
120. Mo YR, Gao JL (2000) J Comput Chem 21:1458
121. Wu W, Zhong SJ, Shaik S (1998) Chemical Physics Letters 292:7
122. Wu W, Shaik S (1999) Chemical Physics Letters 301:37
123. Wu W, Danovich D, Shurki A, Shaik S (2000) J Phys Chem A 104:8744
124. Wu W, Luo Y, Song LC, Shaik S (2001) Phys Chem Chem Phys 3:5459
125. Tomasi J, Persico M (1994) Chem Rev 94:2027
126. Song LC, Wu W, Zhang QN, Shaik S (2004) J Phys Chem A 108:6017
127. Štrajbl M, Shurki A, Warshel A (2004) Proc Nat Acad Sci 100:14834