DOI: 10.1002/ijch.202000090

Stories of My Journeys Through Valence Bond Theory, DFT, MD and their Applications to Complex Objects

Sason Shaik*[a]

The paper is dedicated to my teachers, collaborators and pupils who taught me what I would have not learned had I been by myself.

Abstract: This Rosarium Philosophorum essay tells the story of the author's "conversion" to a theorist, and then the events which led him to stumble over valence bond (VB) theory, and his developments of "VB diagrams" as conceptual tools which enable one to describe all chemical reactions. The story continues to the adventure with the enzyme Cytochrome P450, and how this interest led eventually the author to treat the reactivity of this enzyme using VB diagrams. And finally, the essay describes the author's struggle with complexity through molecular dynamics of these enzymes. This is also a story of interactions between individuals who seek insight and wisdom and how they influence one another through friendships and teacher-disciples relations. This is the key wisdom one garners through scientific life.

Keywords: Valence Bond theory · Molecular Orbital Theory · Density Functional Theory · Molecular Dynamic Simulation · VBSCD · VBCMD · Cytochrome P450 · Metallo-Enzymes

1. Introduction

I was asked to contribute an essay to this *Rosarioum Philosophorum* on computational quantum chemistry (CQC). In such an essay, one is supposed to share with readers "wisdom" he/she acquired from his/her field of research along time. Since a personal wisdom is entangled with one's life, I decided to write this essay as a story. As someone who has had a long career (47 years) in the field of CQC, I thought to tell the readers how I became a computational quantum theorist despite my initiation, during the M.Sc. research, as an experimentalist. Along this journey, I "discovered" VB theory and developed its conceptual aspects to become a useful tool for chemists.

In the end of the VB story, I shall discuss how I got involved with the enzyme Cytochrome P450 and other metalloenzymes which are complex entities. And how lucky I was to get familiar with density functional theory (DFT) as a useful tool for exploring these complex objects, and formulate some new paradigms on their electronic structures and chemical reactivity. Subsequently, I shall share with the reader how did I find myself applying quantum mechanical/ molecular mechanical (QM/MM) calculations of enzymes, and later shifting to molecular dynamic (MD) simulations of these creatures, and struggling to harvest some wisdom out of complexity. My story is also a lesson on how CQC has become a major branch of chemistry; one that unites chemistry.

However, the story is chiefly about people and their wisdom which was bestowed on me – those scientists I met in my way, and students and postdocs who influenced me and taught me things I would have not endeavored to learn had I been all by myself.

2. How I became a Computational Chemist

2.1 My Initiation as an Experimental Chemist

During my childhood and teens in Israel, it was easy to purchase chemicals, either in pharmacies or in stores that sold chemicals and laboratory equipment. I got a hold of some metals (Zn, Cu, Na, K), acids (H_2SO_4, HCl, HNO_3), bases, salts (e.g., $KMnO_4$, $KClO_4$) red phosphorous, yellow sulfur… as well as test tubes, pipettes … My love of chemistry was initiated by experiments I performed with these chemicals. Mixing chemicals led to changes of colors, evolution of gases, and sometimes to explosions. For a kid and even a teenager these were great fun, great magic; *the magic of chemistry.*[1]

You could repeat the Cavendish experiment by adding some flakes of Zn to HCl, and produce the "inflammable air" (dihydrogen). Using a bent glass tube having a constricted end, caused a slow liberation of the gas and it could be safely

---

[a] *S. Shaik*
Institute of Chemistry, The Hebrew University of Jerusalem,
Edmond J. Safra Campus, Givat Ram, 91904 Jerusalem (Israel).
phone: +97226585909
fax: +9726584680
E-mail: sason.shaik@gmail.com
sason@yfaat.ch.huji.ac.il

lighted by a match and burn gently. I didn't know much chemistry in those days, so I experimented uninhibitedly with my chemicals and "discovered" dichlorine (Cl_2).[1a] One day I mixed HCl and $KMnO_4$, and all of a sudden the solution was full of stormy bubbles and some gas came out of the flask. Like my alchemists ancestors I stuck my nose into the flask to smell the gas. I chocked and experienced chest pains… I "discovered" Cl_2, which was discovered some time before me, first by the great chemist Carl Wilhelm Scheele (who used regularly to taste and smell his new chemicals), and then by Sir Humphrey Davy who recognized that the gas was an "element" and responsible for the formation of HCl. Indeed, I was spellbound by the magic of chemistry; too captivated by this magic and too ignorant to worry about cautionary measures!

During my teens, my "love affair" with chemistry shifted to photography.[1a] Developing photos has its own unique magic; you place a white sheet of paper (thick as a postcard) in a solution of a "developer" and lo and behold an image comes forth, initially very faint and then all of a sudden the latent image becomes an image which your camera captured a day ago. By then, I knew some chemistry to realize that the developer was a mixture of chemicals (e.g., hydroquinone, sodium carbonate, etc.), that oxidizes the silver bromide. The silver bromide was spread as an emulsion on the white sheet and the developer converted it to black metallic silver, thus creating the image focused by the camera lens on a celluloid "film" and projected in the darkroom unto the white sheet. To stop the process, you had to transfer the developed sheet into a "fixer" tray, which contained a solution of sodium sulfite. The fixer reduced the developer's traces and arrested the blackening of the sheet thus protecting it from further oxidation in air. This was a wonderful magic, and it was all chemistry; *the magic of chemistry*!

I guess, these two hobbies initiated me to become a chemist. I entered Bar-Ilan University and chose chemistry as my major. I completed my B.Sc. studies very successfully, and began my M.Sc. degree in 1972. Since I was initiated as an experimental chemist by fulling around with my hobbies, I naturally chose an experimental project (given by my M.Sc. advisor Michael Albeck) to synthesize complexes of unsaturated organic molecules with $TeCl_4$.

2.2 Schools of Quantum Chemistry in the 1970s

Along with my love for experimentation, I had a hobby which started blossoming during my B.Sc. studies, eversince I saw the images of atomic orbitals. I was fascinated how these little cartoons could explain the Periodic Table and the chemistry of the elements.[1a] But in those days (1968–1972) computational quantum chemistry was embryonic, and had two major schools. One was the Hoffmann school. Hoffmann wrote in the early 1960s an Extended-Hückel (HE) program,[2a] and used this method to calculate molecules and chemical reactions in organic and inorganic chemistry. In 1972 when I started my M.Sc. all chemists noticed the elegance of Roald's orbital theory, which culminated later in the 1981 Nobel Prize in chemistry (shared by Hoffmann and Fukui).

The second approach was the Pople school. John Pople and his coworkers wrote in the 1960s a series of programs named, CNDO (1&2) and INDO, which were all-electron methods, simplified by neglect of electron-electron repulsion integrals that included differential orbital overlap.[2b] These methods were more sophisticated than EH, and served as a stepping stone in a long march for achieving numerical accuracy, so-called *ab-intio* quantum chemistry. This process eventually produced the GAUSSIAN package of programs, which is now a daily tool in the hands of chemists.[3] This effort culminated in the 1998 Nobel Prize to John Pople (and Walter Kohn).

The difference between the schools was fundamental. Roald, who was a chemist with a background in art history, used quantum mechanics to produce insight; his tools were the pictorial cartoons – the orbitals – which became mental elements of understanding, and were used for predicting chemical trends. Pople, who was a mathematician, focused on methods that enabled calculating molecules, their properties and reactions with numerical accuracy, which could be compared to respective observables. Even though these schools rivaled with one another, they were/are complementary[4] and essential for the development of chemistry.

In the 1990s, density function theory (DFT) entered chemistry[5a] and formed the third school led by Walter Kohn. DFT provided chemistry with Kohn-Sham orbitals,[5b] which formed a bridge to the Hoffmann School.[5c] At the same time, DFT produced generally decent numerical results, and seemed to combine the best of the two former schools.

Sason Shaik is a Saerree K. and Louis P. Fiedler Professor Emeritus of Chemistry at the Hebrew University. His main interests are in bonding, chemical reactivity, metalloenzymes, and electric field effects in chemistry. Alongside a variety of computational tools, he uses valence bond theory as a conceptual frame, and has developed a number of new paradigms and concepts using this theory. His main recent awards are the Schrödinger Medal (WATOC 2007); the August-Wilhelm-von-Hofmann-Medal (the German Chemical Society, 2012); Membership in the International Academy of Quantum Molecular Science (2015); and The Gold Medal of the Israel Chemical Society (2017). He also writes essays on history, the chemical bond as the heartland of chemistry, science and friendship, chemistry as a central pillar of human culture, etc.

The fourth school was established by Linus Carl Pauling, and was based on Valence Bond theory (VBT),[6] which rivaled with the MO-based school. Pauling's contribution to the understanding of the chemical bond culminated in the 1954 Nobel in Chemistry. Nevertheless, the VBT school was almost abandoned as a CQC tool in the 1970s.

I shall come back to these latter schools later in this essay. Right now, let me turn back to the M.Sc. student (me) who had to make complexes of $TeCl_4$ with unsaturated organic molecules.

2.3 My Adventure as an Experimental Chemist and My "Rebirth" as a Theoretical Chemist

$TeCl_4$ turned out to be a very difficult reagent to work with. The minute I added any nucleophile or an organic molecule with π bonds, the reaction mixture turned black, and gave black deposits, which I could not purify by whichever means I tried, nor could I identify anything in the goo using spectroscopy. All my efforts to crystalize something from the black goo failed and gave some whitish sticky goo. All my spatulas were ruined, lost their shine and got coated with something gray. It was obvious to me that $TeCl_4$ reacted with my spatulas. I started using Teflon coated spatulas, but to no avail. My M.Sc. research turned to be a nightmare. My only joy was drawn from two courses, which were taught by Milon Sprecher,[1] one on Group Theory and the other on Molecular Orbital Theory à la Hoffmann and Dewar.[7] These courses nourished my initial captivation by orbitals, and my attraction to the elegance of the Hoffmann School.

In October 1973, when I was still struggling with black goo in my experiments, the Yom Kippur War erupted. Like many Israeli youngsters, I was recruited to my army unit for reserve. After some duties in the South of the Sinai desert, we were flown to *Fayid*, an airfield in Northern Sinai, approximately 23 km south of the city Ismailia. *Fayid* was captured by the Israeli army on October 20, 1973, and our unit established there a communication post that served different units in the area. Since the Egyptian army used to shoot missiles daily at the airfield, we ended hiding for hours in the massive shelters of the airplanes.

There in the huge concrete shelters I spent many quiet moments. Much like in dreams the meditative silence of the mind resolves troubling issues. Thus, one day amidst the quietness of the shelter, all of a sudden I had a perfect solution to my research misery.[1a,b] I understood the chemistry of $TeCl_4$ in terms of an orbital approach to its electronic structure. This molecule possesses a trigonal bipyramidal structure, with one missing ligand in the equatorial position, which is occupied by a lone pair orbital on Te. The molecule is hypervalent, and its highest occupied molecular orbital (HOMO) is antibonding with respect to the interactions of Te and Cl in the axial Te–Cl bonds.[8] Consequently, when placed in a solvent one of the axial Te···Cl linkages of $TeCl_4$ easily stretches, and leads to Cl_3Te^+–$Cl:^-$ as an ion pair structure.

As such, the Cl substituents on the Cl_3Te^+ moiety became highly electrophilic, and prone to attack by the electron-rich unsaturated systems or nucleophiles. If I used e.g. anthracene, this generated chlorinated anthracene and $TeCl_2$, which is unstable towards disproportionation to $TeCl_4 + Te$. Te is the black goo which was formed in all the reactions, and which reacted with my spatulas. Understanding the essence of the black goo also suggested a simple way to extract the chlorinated anthracene – sublimation!

As soon as my reserve duty in Fayid ended, I went back to the lab and within a month or so completed all the reactions, isolated all the chlorinated products, and found a way to identify tellurium compounds by mass-spectrometry, and some complexes of $TeCl_4$ and $TeCl_2$ with ether.[8,9] It was a great relief, but more so, **I suddenly witnessed first-hand the beauty of the orbital theory and its potential impact on chemistry**. A number of small cartoons, which came to my mind in a thought, led me to a clear understanding of my experiments and suggested new ones! This was another miracle – *the magic of insight.* I understood the power of theory – theory that not only generates numbers but also creates insights into chemistry. *I was determined to become such a theorist…*[1]

3. My Ph.D. As a Theorist in the University of Washington

I completed my M.Sc. Thesis with excellence, and this was the time to start searching for a Ph.D. advisor. MO theory registered in my mind as a magic tool for generating insight and predicting chemistry. My ability to use the tool seemed to be more rewarding than my schlemiel skills as an experimentalist. I decided to pursue my Ph.D. in theory in the US, for which I received a Fulbright Fellowship. Hoffmann was my first choice, and I wrote to him requesting if he would admit me as a PhD student. On March 4th, 1974, he responded in a detailed letter about the admission to graduate school in Cornell, and the fact that I may have already missed the registration deadline. He advised me "*not to put all [my] eggs in a single basket*".[10] I took this advice seriously and continued searching for other potential PhD advisers.

I had a few options, but was particulary attracted to the structural theory papers of Nicholas D. Epiotis (Nick) who used MO theory to predict nonbonded attractions e.g. in difluoro ethene, and a paper on regioselectivity of cycloaddition reactions.[11] I found his ideas to be novel and exciting. I was admitted to the University of Washington (UW) in Seattle, and was offered a teaching assistantship. A few months after the war ended, and after completing some more reserve time in the army, I left Israel on my way to the US for my Ph.D. under the supervision of Nick in UW.

My first project as a PhD student was to participate in the writing of a book, which attempted to demonstrate how MO theory could account for a variety of problems in structural chemistry.[12] This was a tremendous experience, because I was forced to read copiously and find problems that could eventually be included in the book that was published in 1977. From Nick himself I learned to question everything I read. He would often say to me while raising his clenched fist, "*you see these data in my palm? I now toss it in the air and it falls on my desk and creates a new order*"; a new order that follows a new theoretical idea. Reading his papers I also learned to appreciate how simple mathematical expressions could lead to powerful predictions (e.g.,[11c] the fact that $a^2+b^2>2ab$ when $a\neq b$, could be applied to head-to-head vs. head-to-tail dimerizations of olefins using MO perturbation theory).

Nick's approach to see all chemistry through the lens of MO theory made me recall and use what I learned during my time in Bar Ilan University. These were many elegant concepts, like the Hund's rules, crystal-field theory, Hückel rules, orbital-symmetry rules for chemical reactivity, Fukui's frontier molecular orbital theory, Hudson-Klopman's orbital vs. charge controlled reactivity, Salem's diagrams for photochemical reactions, and so on. I was fascinated by the emerging quantum chemical theory and made a habit to try and apply these concepts to any new chemical data I was mining from the literature. This was a paradise of free thought, for which I owe Nick a debt of gratitude.

I also took a few theory courses in UW. One on MO theory which was taught by Weston T. Borden, in which I learned about diradicals and disjoint orbitals, and another course in quantum mechanics which was taught by the late Martin Gouterman (one of Hoffmann's Ph.D. advisers). In Gouterman's course I learned about the spin-orbit coupling operator, which later in my Ph.D. and during my postdoc at Cornell, I used for deriving selection rules for triplet organic reactions (note that in 1979 on, I added my middle name (S), and eventually abandoned the habit).[13] I made a habit of applying theoretical ideas to every new thing which I learned in chemistry. I kept delving into the theory, developing my own simple models, and deriving all kinds of equations and expressions, which would later become helpful. MO theory was a dreamland for me.

This feeling was further intensified when Roald Hoffmann visited UW during January 10–20th 1976, and gave a series of lectures, in which he showed how fruitful MO theory was for understanding transition metal chemistry. He was cutting molecules into fragments, and from the fragments he made other molecules, and all these with the aid of small MO cartoons. This was magic! I could see that cutting and reassembling leads to new understanding – a LEGO principle.[1a]

One day Roald invited any wishing student to join him in the evening for a beer. I went. At some point, when the beer relaxed me sufficiently, I dared asking him a presumptuous question: "*what did [he] think would be the future of theoretical quantum chemistry*?" He answered me in his usual thoughtful way*; he thought that VB theory would make a comeback*! Considering the consensus among chemists on VB theory in those days, what Hoffmann was saying sounded to me strange, and I thought to myself "*does he not know that VB theory is passe*?" Not long later, I myself would stumble over VB theory and would fall in love terminally with its magic.

3.1 Stumbling on Valence Bond Theory

At some stage during my Ph.D. I started thinking seriously about chemical reactivity. As an MO-fan, I was facing a conceptual puzzle, which preoccupied me. MO theory could not reveal explicitly the origins of the barrier except for cases of forbidden reactions,[14] where the orbital crossing gave a pictorial origin for the barrier. So, I kept asking myself and my fellow Ph.D. students in the group (Ron Yates and Jim Larson), what were the origins of the barriers for other chemical reactions, like S_N2, a Diels Alder reaction, or H-abstraction? None of us found in canonical MO theory a clear answer to this question. This quest led me, in a tortuous path, to stumble over VB theory.

I started this quest by trying to understand the theory that my adviser, Epiotis, published in *Angewandte Chemie*,[15] in which he used fragment orbital (FO) configurations, to interpret cycloaddition reactions. I realized that Mulliken used these configurations in his charge transfer theory. At this stage I was not making yet any connection between this and VB theory (which I anyway did not know). I simply wanted to find out systematically what was the relationship of the canonical MO description of molecules and transition states, to the description by means of FO configurations.

I spent much time trying to decompose Slater determinants by replacing the canonical MOs by linear combinations of fragment orbitals (FOs) or just hybrid atomic orbitals (HAOs). At some point I started getting some interesting trends, which seemed to resurface in many examples I was testing. Some of the wave functions I was getting out of the MO-based Slater determinant looked like simple VB functions of a singlet-coupled electron-pair, like the one used by Heitler and London[16] to describe the covalent bond in H_2.

Since my mind was still echoing the admonition that VB theory was a failed theory, I considered my results with some concern. Nevertheless, Roald's prediction that "VB theory will come back" was reassuringly against this negative general view. I started looking for quantum chemistry textbooks that included VB theory. I found some, I read and took notes… Unfortunately, none of the books made a systematic bridge between MO and VB for anything beyond the H_2 molecule, and in most of them, the matrix elements between VB structures were cast in a pictorial manner, but whereas a picture is supposed to elucidate the complex mathematics, these ones seemed cryptically complex.

I thought that either my derivations were wrong, or that I indeed found *an MO-VB bridge that may generate a new way to describe transition states for chemical reactions*, and to answer my questions about the origins of barriers in chemical reactions (even for non-forbidden reactions, for which MO correlation diagrams could not ascribe the barrier to orbital crossing). Soon enough I was able to draw *VB correlation diagrams*, which exhibited crossing between VB structures. I was excited and showed the diagrams to Jim Larson my colleague in Nick's group, who caught the principle instantly and was drawing some diagrams for fun.

But the time came to write my PhD dissertation, and I had to stop playing with MOs, FOs and VB. I also realized that I knew much too little about VB theory, and its rivalry with MO theory, to continue this line of research. I needed to educate myself. This education occurred along the way, at Cornell and then at Ben-Gurion University (BGU) where I will be getting my first academic appointment.

4. Postdoc at Cornell: Crossing Through Mirrors

On November 28, 1977, Hoffmann offered me a postdoctoral fellowship, and I was excited. In the summer of 1978, I collected my notes, travelled to Cornell, and forgot all about VB theory for a while. Roald was away, and I took the time to educate myself on what his group was doing on transition metal (TM) chemistry (being very kindly assisted by Birgitte Schilling, then a PhD student in the group). I read a lot, but one paper by Elian and Hoffmann[17] attracted my attention because it reminded me of the magic Roald was performing on the blackboard during his Hyp Dauben Lectures in UW. In retrospect, this was the fundamental paper that led to what became to be known as the "the isolobal analogy".[18] Let me describe the isolobal analogy and its link to bonding in VB theory.[19]

4.1 The Isolobal Analogy

In their 1982 paper, Elian and Hoffmann (E&H) [17] were using MO descriptions of transition-metal (TM) hexa-carbonyl complexes, in order to derive the binding capabilities of TM $(CO)_n$ fragments with $n<6$. They started with a d^2sp^3 hybridized valence shell for the TM, and made six TM-CO bonds. Then by plucking off CO ligands, they showed that at each such vacant site there grew a hybrid orbital. Thus, as shown in Figure 1a, TML_5 (L = CO) had one such hybrid orbital, TML_4 two, TML_3 three… The binding capability of these hybrids depends on the d-electron count on the TM. For example, for $Mn(CO)_5$ where Mn possessed a d^7 configuration (and a filled $t_{2g}{}^6$ sub-shell), this hybrid is occupied by a single electron, and E&H could show that this was the driving force for the dimerization of these two radicals by forming a Mn–Mn σ bond, or for the formation of a Mn–H bond, and so on. The fragment $Fe(CO)_4$ had two singly occupied hybrids, while $Co(CO)_3$ had three such hybrids. As such, these fragments could form two and three bonds with appropriate ligands, such as H, Cl or CH_3.

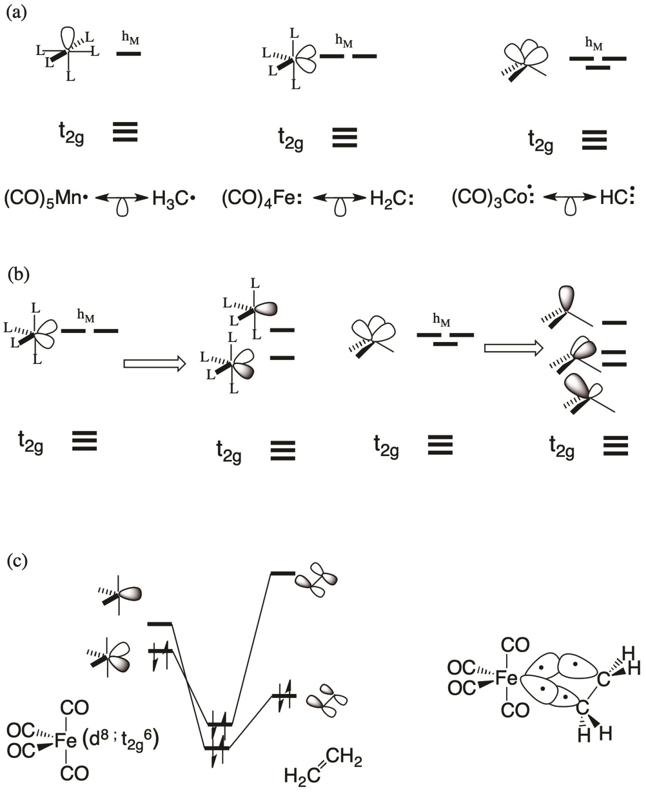

Figure 1. (a) Cutting ligands L (L = CO) from TML_6 generates hybrids at the vacant sites of the octahedron. TML_n (n = 5–3) fragments with d^7, d^8, and d^9 configurations are isolobal (symbolized by the lobe on the double headed arrow) to CH_3, CH_2, and CH fragments, respectively. (b) Symmetry adaptation of the hybrids. (c) Creating a new compound from $(CO)_4Fe$ and ethylene, using either the symmetry adapted hybrids (left) or electron-pairing cartoon (right). Adapted from Figures 4 and 5 in Ref. 19 with RSC permission. Copyright 2007.

All these MO transformations would later culminate in the *isolobal analogy*, which likens the transition metal fragments to organic fragments and vice versa. Thus, as shown in Figure 1a, $Mn(CO)_5$ was isolobal to CH_3, while $Fe(CO)_4$ to CH_2, and $Co(CO)_3$ to CH. The isolobal analogy meant that one could build *similarity bridges* between $Mn_2(CO)_{10}$ and C_2H_6, or $(OC)_5Mn–H$ and CH_3-H, $Fe_2(CO)_8$ and $H_2C{=}CH_2$, so on. Later in 1981 Hoffmann in fact entitled his Nobel lecture as "*Building Bridges Between Inorganic and Organic Chemistry.*"[18]

At some point in the E&H paper, the authors formed from the localized hybrids symmetry-adapted fragment orbitals, as shown in Figure 1b for $Fe(CO)_4$ and $Co(CO)_3$. By taking advantage of orbital symmetry match, they were able to construct new molecules with a variety of ligands. Figure 1c shows an example using the combination of $Fe(CO)_4$ with an olefin. It is seen that the symmetry adaptation of the hybrids facilitated the understanding, by showing that the two symmetry-adapted hybrids find match with the π and π* orbitals of the olefin and form thereby two bonds. On the right side, one can see the electron-pairing cartoon, which shows that the so formed complex has also a character of a metallacycle. The two cartoons showed complementary insight into the structure of the complex (the orientation of the olefin vis-à-vis the CO ligands) and the rotational barrier of the olefin ligand.[19]

This bond making process (cf. Figure 1c) looked precisely like the covalent bond making in the VB approach, and I realized that once you form fragments, you start getting localized orbitals from the delocalized MOs. In retrospect, the isolobal analogy has fascinated me, and moreover, it convinced me that my attempts to expand MO determinants into ones containing VB structures constituted a *bridge building between MO and VB wave functions.*

In mid-September 1978, Roald returned to Cornell from his sabbatical in Cambridge. We started having weekly group seminars, in which we either talked about what we were doing, or Roald would present extracts from his literature reading, like in Figure 1 above. He would usually take the new structures he collected and would analyze their orbital makeup. He would often apply the isolobal analogy in order to teach us. Figure 2 shows Roald lecturing on the isolobal analogy at Ben-Gurion University (BGU) to where I moved after my postdoc.

4.2 Chemical Reactions: Laying Bridges between MO and VB Theories

In the middle of my postdoc year, I have managed to educate myself sufficiently to know by then, that the hybridization (localized-MO (LMO)) model was part of VB and MO theories alike. It was initially developed for VB theory by Pauling and Slater in the 1930s,[6,20] Later, it was extended by Coulson[21] to explain the planarity of ethene, benzene etc., and further in time, the LMO model was formulated by Ruedenberg, Boys[22] and others for ab initio MO theory. It became clear to me that Hoffmann was shifting back and forth between MO and VB-like representations, and using advantages of both depending on the need.

Figure 2. Roald Hoffmann teaches organometallic chemistry at Ben-Gurion University, in 1981, shortly after his Nobel Prize. Courtesy of Roald Hoffmann.

My take-home lesson was that the art of bridges and analogies was evidently much more powerful and portable than the orthodoxy of staying in a single world of either MO or VB. I also realized that what I achieved during my Ph.D. in UW *was crossing the mirrors between the worlds of MO and VB and laying a natural and portable bridge between these worlds*, thus allowing eventually, a better understanding of chemical reactivity. This was the time to get back to this bridge…

I resumed my work in projecting the VB content of MO and MO-CI wave functions for simple chemical reactions. After a while, I finally found an automatic method to get the coefficients of these VB structures from the MO-based wave functions, and started looking how was the VB content of the wave function changing *along the reaction coordinate.*[23]

I considered model reactions of H-atom transfer, nucleophilic displacement, and nucleophilic additions to double bonds. I used Hückel and extended Hückel orbitals, as well as Hartree-Fock calculations with a minimal basis set, and including CI. To my excitement, there emerged a unified description of transition state (TS) formation and clear origins of the barrier in chemical reactions, as well as a handle for predicting barrier heights and their variation.[23a]

I proudly presented the model to my fellow postdocs and PhD students of the Hoffmann group, whenever they were willing to listen to me (what remained is one photo of me standing by a VB diagram drawn on the blackboard in the office I shared with Al Pinhas, Figure 3). I still remember that Eluvatingal D. Jemmis, a postdoc in the group, and Al Pinhas, a PhD student in Barry Carpenter's and Roald's groups, were very interested and supportive. Al Pinhas even helped with some ab initio calculations of simple reactions, which served me to map the MO and MO-CI wave functions to VB structures. The results of the MO-VB mapping showed uniformly the same VB diagram, which is based on correlation of VB structures which crossed and thereby *mimicked the exchange of bonding during the reaction, from reactant-bonding to product-bonding.* Crossing the mirrors between the

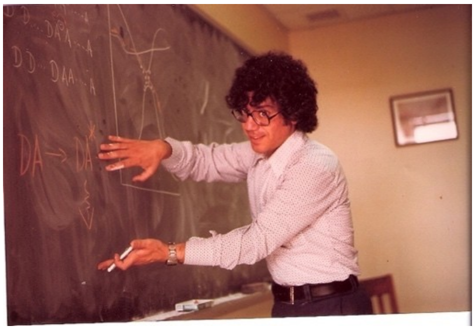

Figure 3. The author presenting a VB diagram during his postdoc at Cornell (1978). Invisible are Al Pinhas and Eluvantigal D. Jemmis.

worlds brought about a crystal clear insight, which was portable for the chemical community.

In view of this insight, I began to wonder why was VB theory considered as a failed theory, if not altogether a wrong one, while MO theory was the only kosher one. Let me therefor digress from my personalized story to say something about this more general issue.

4.3 The Background of MO-VB „“Wars“

I spent some time to read about the history of VB theory and its rivalry with MO theory.[24] The grassroots VB theory was formulated initially in 1916[25] when Lewis postulated that the *"quantum unit of chemical bonding" is an electron pair that glues the atoms of most known matter.*[26] In so doing he was brilliantly able to derive electronic structure cartoons that are used to this day and age. Lewis further distinguished between shared (covalent) and ionic bonds (and even one-electron bonds), and laid foundations for resonance theory and was even discussing geometry in terms looking like VSEPR.[26]

Eleven years later in 1927, the same idea was formulated in a new guise when the young Physicists Hietler and London (HL)[16] went to Zurich to work as postdocs with Schrödinger. In the summer of that year they came up with a quantum mechanical description of the shared bond in H_2, in terms of a resonance between two forms (Eq. 1):

$$\Psi(H_2) = 1s_a(1)1s_b(2) \Leftrightarrow 1s_b(1)1s_a(2) \qquad (1)$$

which exchange the two electrons, and form an electron pair by virtue of their coupling to a singlet spin-state. The wave function yielded a bond strength in reasonable comparison with the experimental D_e. In the winter of 1928, London generalized the properties of this shared bond (nonpolar bond).[16,27,28]

At the time when Heitler and London‘s work became public, Pauling was in Europe. He was excited and sent Lewis a letter telling him that his "shared“ bond (later to be called a "covalent“ bond) was verified by the new physical theory, called quantum mechanics. Pauling himself, as noted by his biographer Hager,[28b] immediately abandoned all the old mechanical descriptions of bonding in chemistry and started a major program on VB applications to structural chemistry. He and Slater masterminded the third birth of the theory in 1931, by extending the HL treatment to polyatomic molecules.[24] Even though they both contributed the seminal developments, Pauling's papers and his book,[6] published first in 1939 have been more influential as they communicated to chemists in their language in terms of resonance structures (which were similar to the mesomerism of Ingold). Resonance Theory appeared to describe many molecules and their properties in a manner akin to experiment.

MO theory was developed around the same time by Hund and Mulliken.[29] It was a brainchild of spectroscopy, and was not too chemical at the beginning. Later, the theory was extended by Lennard Jones and mostly by Hückel who applied it to organic molecules.[24] The two theories (VB and MO) became rivals within a short time.[30] The leading figures in this rivalry were Pauling and Mulliken, and it somehow became a "never ending rivalry" in generations to come.[31] At times this rivalry seemed to be personal and even bitter, so much so that in one of the reports, of the Löwdin Summer Schools, the writer of the report described the relationship between these two great scientists by the symbol: $<Mulliken|Pauling> = 0$.

Thus, for a while the tide was in favor of VB theory (VBT), because VBT was a chemical language, and because Pauling was very eloquent and persuasive. But this was temporary… The struggle between the Pauling camp and the Mulliken's growing camp started to shift in favor of MO theory by the late-1950s onwards, when successful semi-emprical methods started to be implemented and could be widely used. The Pauling-Mulliken rivalry had its share in the eventual branding of VB theory as a failed theory among the growing number of supporters of the MO approach.[24,31]

However, other factors combined to make this happen: the fast development of efficient molecular orbital (MO)-based software, the synthesis of aromatic and antiaromatic molecules (a dichotomy that seemed to have evaded VB theory), and the formulation of attractive qualitative concepts, like Walsh diagrams, Fukui's frontier molecular orbital theory, the Woodward-Hoffmann rules of conservation of orbital symmetry,[14] and the synthesis of molecules like ferrocene and the elegant interpretation of its unusual bonding by MO theory.[24,31] At the same time, VB theory stagnated conceptually, and its implementation into an efficient computer code proved to be less successful than that of MO theory. The theory ceased to guide chemists to new experiments, and it was cast aside and branded with mythical failures.[24]

While the death of VBT seemed final, it nevertheless remained the *Lingua Franca* in chemistry though the usage of Lewis structures, resonance structures, hybridization… It also remained effective in molecular dynamics.[32a] Additionally, a few groups kept the fire alive by developing VB software for general use. Some, like the generalized VB (GVB)[32b] code were even competitive with MO-based CI methods. Subsequent VB packages[32b-f] were developed in the 1980s and onwards, and slowly became efficient and robust.

Despite these developments, and even though Hiberty and I (and others) showed several times that none of the failures attributed to VB was real,[24] the theory is still regarded by chemists with skepticism. For example, despite of the fact that Pauling and Heitler published VB treatments of O_2 and showed that its ground state is a triplet spin state,[24] still many chemists insist that O_2 was/is described wrongly by VBT as a singlet ground state with a double O=O bond. This statement and similar ones exist to these days even in modern textbooks. This continuous brainwashing, which may be a byproduct of the old rivalry and poor teaching, still causes many chemists to believe that there is something wrong with VBT, even if at the same time it remains their natural language. After understanding this issue of split consciousness of many chemists about VBT,[33] it became clear to me already during my postdoc time that VBT is perfectly correct. Those who criticize VBT in fact do not know much about it. VBT and MOT are just two complementary representations of the chemical world.

After this digression, which I felt compelled to make, let me return to the main story.

5. Leaving the Paradise of the Hoffmann Group To Join Ben-Gurion University

In the midst of 1979 I got an offer from Ben-Gurion University (BGU) to join its ranks. Alas, I had to leave behind me the fun, inspiration and friendship I had experienced in Hoffmann's group. I started packing all my unfinished projects, among them were all the MO-VB projection data I developed, a draft of a paper I wrote on spin inversion in Diels Alder reactions,[34] and some outputs of calculations on electrostatic effects on molecules for which I was planning to derive selection rules, and which I ended doing much, much later.[35]

5.1 Piecing Up Energy Profiles from VB Building Blocks at BGU

Upon arrival to BGU, I had to overcome the expected cultural shock after having been away from Israel for five years. As soon as I felt sufficiently settled (this included meeting Sara, my wife to be), I returned to my preoccupation with MO-VB transformations and the understanding of the origins of the barrier in chemical reactions.

I reexamined the results I produced, while at Cornell, by computing simple reactions, one a model for an S_N2 reaction (Eq. 2a) and the other for radical exchange (Eq. 2b):

$$\mathrm{H:^{-} + H{-}H' \rightarrow H{-}H + :H'^{-}} \tag{2a}$$

$$\mathrm{H\cdot + H{-}H' \rightarrow H{-}H + \cdot H'} \tag{2b}$$

To recall, these reactions were calculated at the HF level with a minimal basis set (STO-3G), then augmented with CI, and subsequently with the double zeta 3–21G basis set and CI. For completeness, I used also EH calculations and then the simplest Hückel MOs.[23]

Irrespective of the wave function I used, and whether I employed for the VB projection, FOs or AOs, in all cases I did observe the same phenomenon: *the wave function of the reactants gradually diminished and was being replaced by another wavefunction, which was initially an excited state.* In the transition state (TS) the two wave function had equal weights, and then the excited configuration became the dominant one *en-route* to the products. Shifting to "larger" molecules, e.g., nucleophilic attack on a double bond of ethylene or formaldehyde, or radical attacks on these bonds, retrieved the same type of VB correlation and avoided crossing. This VB correlation and avoided crossing phenomena were topologically independent of the quality of the orbitals or the wave function level, and without exceptions, *this was characteristic of all reactions which exchange bonds.*

5.2 The Universal VB correlation *Diagram*

Already in the first manuscript on this topic,[23a] I realized that the root cause of this avoided crossing was the interchange of the two covalent structures (the Heitler-London (HL) structures) which describe the reactants and products. This interchange forms the spine of the VB diagrams, and hence, it was possible to draw a universal VB correlation diagram of the type shown in Figure 4.[24,36]

The identity of the excited states in the diagram could be easily recognized by looking at the covalent structures of the two ground states at their vertical excited states. These states are called "promoted states" and they are prepared for the requisite bond pairing to become ground states along the reaction coordinates; Ψ_{RP}* becomes Ψ_P while Ψ_{PR}* becomes Ψ_P^{-} in the reverse direction.

Thus, as shown in Figure 5a, for the nucleophilic reaction of the generic type in Eq. 2a, the promoted state Ψ_{RP}^{*} is the charge-transfer state of the reactants. Here an electron is transferred from $\mathrm{H:^{-}}$ to the H–H' molecule, and as symbolized by the arched lines, the single electrons on the two moieties are paired to a singlet state and constitute a bond-pair that correlates along the reaction coordinate to the product ground state, $\mathrm{H{-}H + :H'^{-}}$. On the other hand, for the simple H-atom abstraction reaction in Eq. 2b, no charge is being shifted between the atoms, and as such the promoted state Ψ_{RP}^{*}

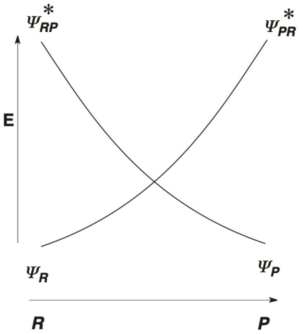

Figure 4. A universal VB correlation diagram, using the covalent structures for a single step reaction $R \rightarrow P$. All other states or VB structures are omitted for clarity. The diagram is anchored in four states: two ground states of reactants and products (Ψ_R and Ψ_P), and two unique excited states (Ψ_{RP}^{*} and Ψ_{PR}^{*}). In these excited states the double subscript (*RP* or *PR*) indicates first the ground state origins, and second the ground state to which it correlates. The unique excited states are vertical states having the same geometries as the ground states below them.

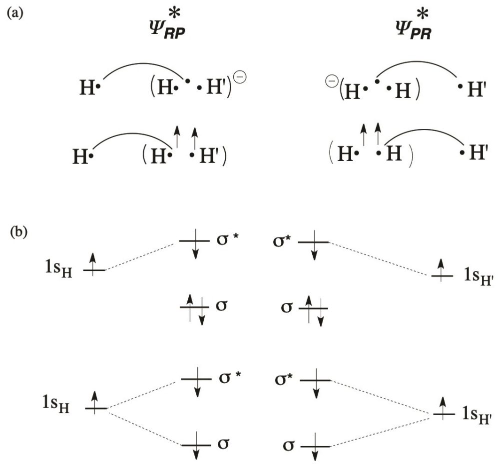

Figure 5. (a) AO representation of the Ψ_{RP}* and Ψ_{PR}* states for the reactions in Eq. 2a (upper drawing) and 2b (lower drawing). (b) FO representations of the Ψ_{RP}* and Ψ_{PR}* states in Eq. 2a (upper drawing) and 2b (lower drawing). Note that in each representation in (a) and (b) the Ψ_{PR}* states are mirror images of the corresponding Ψ_{RP}* states. The long lines in the excited states between AOs (in (a)), and dashed lines between FOs (in (b)), indicate the electron spin-pairing which will become bonds between the reactants.

involves unpairing of the reactants H–H' bond to a triplet pair, while re-pairing the electron of the middle $H^\bullet$ across the long linkage to the $H^\bullet$ on the left hand side.

Similarly, Figure 5b shows the FO representations of the Ψ_{RP}^* and Ψ_{PR}^* states. Thus, for the nucleophilic attack reaction (Eq. 2a), Ψ_{RP}^* involves a transfer of one electron from the filled 1 s orbital of $H:^-$ to the σ* orbital of H–H', and as shown by the dashed line the single electrons on the two moieties are paired to a singlet state and will become the new H–H bond in the products. For the H-atom exchange reaction, the promoted states involve a triplet $\sigma \rightarrow \sigma^*$ excitation on the respective H–H' moiety, and singlet pairing of the single electron on $H^\bullet$ to the single electron both in σ and σ* orbitals (this double pairing localizes the σ and σ* FOs into a 1 s orbital on the H' atom of the H–H' molecule). Identical arguments apply to he reverse reaction.

It is worthwhile to use the two approaches because they give complementary information. Thus, the VB-HAO approach allows a systematic and elegant generation of the entire VB diagram from a basis set of VB structures.[24,36,37] On the other hand, the FO-VB enables the derivation of selection rules and reaction stereoselectivity or regioselectivity, by utilizing the symmetry/nodal properties of the FOs.[24,38,39] Together, the two representation are more powerful than each one separately. Nevertheless, since these two approaches were discussed amply in previous works,[24,36,37,38,39] for the sake of brevity I shall focus henceforth mostly the VB-HAO representation.

The representations of the promoted states for the simple reactions are helpful for tracing the universal VB correlation diagram for any general single step reaction. All one needs to know is the identity of the promoted states. One can see that in Eq. 2a, there is a change of the oxidation number of the reactants; $H:^-$ becomes $H^\bullet$, while the right-hand atom of the H–H' molecule changes from $^\bullet$H' to $:H'^-$. On the other hand, in Eq. 2b, the H atoms retain one electron. This carries over to more complex reactions as summarized in **Rule 1**:

Rule 1: Whenever the reacting moieties change their oxidation numbers, the promoted states in the VBSCD of a single step reaction will involve charge transfer (CT) states. On the other hand, if the reaction proceeds without changes in the oxidation numbers, the promoted states will involve triplet decoupling of each bond that breaks during the reaction. The odd electrons in Ψ_{RP}^* and Ψ_{PR}^* are then paired to singlet pairs across the respective reactants.

The application of **Rule 1** is straightforward. For example, in an S_N2 reaction $Y:^- + R{-}X \rightarrow Y{-}R + :X^-$ the oxidation numbers of X and Y change by one electron, and hence the promoted states Ψ_{RP}* and Ψ_{PR}* are CT states in which the anion transfers one electron to the R–X and Y–R bonds. This is generally so for any reaction between a nucleophile and an electrophile.[24,36,37] Another example, is a radical attack on a double bond $R^\bullet + H_2C{=}CH_2 \rightarrow R(H_2)C{-}CH_2^\bullet$. Since there are no changes in the oxidation numbers of the atoms, the Ψ_{RP}* and Ψ_{PR}* states involve triplet decoupling of the bonds to be broken,[39b] these are respectively the C=C π-bond and the σ R–C bond.

In multi-bond cases like the Diels-Alder reaction or the 2 +2 cycloaddition, there are no changes in the oxidation numbers of the carbon atoms, and in any direction we break and make multiple bonds. As such, the corresponding Ψ_{RP}* and Ψ_{PR}* states in the VB correlation diagrams involve *the sum of triplet excitations for all these bonds that undergo breakage* and recoupling all the electrons to singlet pairs across the intermolecular linkages,[24,36,37] as shown in Figure 6.

It is seen that in terms of the VB correlations, the two reactions are similar. But already here, at the covalent-only level, one can see that the promotion gaps, G_R, from the ground to the promoted states are different, and it is significantly smaller for the Diels-Alder reaction (173 vs. 206 kcal mol^{-1}). The reason for this is that when we pair anew the four π-electrons of the diene, we form a π bond in the middle C–C bond, and we distance the triplet electrons to the terminals of the diene. This makes the triplet excitation of the diene significantly smaller than for a single C=C moiety as in the 2+2 case. This trend already hints the reason why the Diels-Alder reaction is so much favoured over the 2+2 reaction.[24,36] But wait patiently for more factors later on. Nevertheless, the VB correlation diagram is already useful for predicting that the 2+2 dimerization reaction of $H_2Si{=}CH_2$ ($G_R = 116$ kcal mol^{-1}) or of $H_2Si{=}SiH_2$ ($G_R = 80$ kcal mol^{-1}) will be much faster even more than the Diels-Alder reaction. Indeed they are, as shown by Apeloig.[36,40]

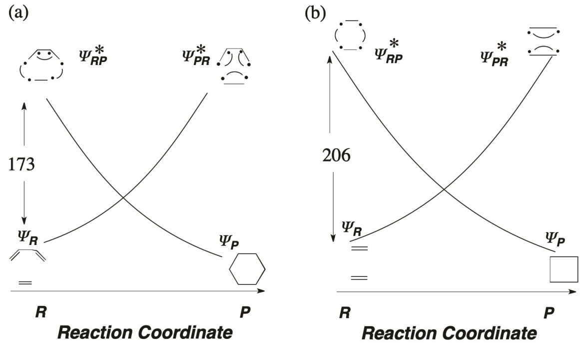

Figure 6. VB correlation diagrams for: (a) a Diels-Alder reaction, and (b) a 2+2 cycloaddition. The Ψ_{RP}* and Ψ_{PR}* states are depicted only in terms of hybrid AO (HAO) representation. The arched lines in Ψ_{RP}* and Ψ_{PR}* indicate singlet pairs of the respective electrons. For both cases we also indicate the size of the energy gap (in kcal mol^{-1}) between the ground to the respective promoted state at the reactants side. Adapted with RSC permission from Figures 17 and 18 in Ref. 36. Copyright 2014.

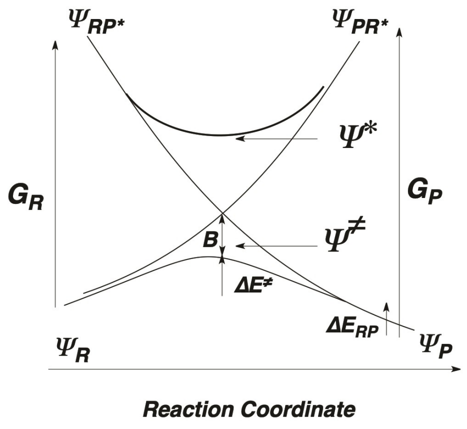

Figure 7. A universal VB state correlation diagram (VBSCD) along the reaction coordinate. The two state curves mix and avoid the crossing. The avoided crossing leads to a TS ($\Psi^{\neq}$) and a twin-excited state (Ψ*). *B* is the resonance energy of $\Psi^{\neq}$ due to the states' mixing, $\Delta E^{\neq}$ is the reaction barrier, G_R, G_P are the promotion energy gaps at the reactants and products sides, and ΔE_{RP} is the reaction energy (the thermodynamic driving force).

5.3 A VB State Correlation Diagram (VBSCD) as a Model for Barrier Formation

Let me turn now to discuss the conversion of the universal VB correlation diagram to a VB state correlation diagram (VBSCD). Turning back to Figure 4, we can see that it involves only the covalent structures while disregarding the ionic structures. Ionic structures are required to mix with the respective covalent structures and form thereby Lewis bonds, which involve mixtures of a covalent structures with two ionic structures, e. g., Eq. 3,

$$\Psi(\mathrm{H{-}H}) = a\Psi(\mathrm{H{-}H}) + b\Psi[(\mathrm{H}:{}^{-}\mathrm{H}^{+}) + (\mathrm{H}^{+}:\mathrm{H}^{-})];\quad a > b \tag{3}$$

where the Lewis bond (H–H) is described as a mixture of the covalent (H–H) structure and a combination of two ionic $[(\mathrm{H}{:}^{-}\mathrm{H}^{+})+(\mathrm{H}^{+}{:}\mathrm{H}^{-})]$ structures; with coefficients *a* and *b*, respectively:

As is clear from the relative coefficients size ($a>b$) in Eq. 3, the ionic VB structures are secondary structures, which complement the covalent structures and dress them to become Lewis states. However, for the promoted states (cf. Figure 4) this covalent-ionic mixing is zero[38] and the states retain their pure covalent forms. As such, the VB correlation diagram retains the form set by the covalent structures in Figure 4, with the exception that now the Lewis state curves constitute mixtures of covalent and ionic structures. Letting the two curves mix with one another generates the VBSCD.

Figure 7 is such a universal VBSCD, which involves the crossing of two Lewis state curves, which mix and avoid their crossing to generate a transition state ($\Psi^{\neq}$) and its twin excited state (Ψ*).[36] In so doing, the ground state curve acquires an energy barrier ($\Delta E^{\neq}$), which is lower than the crossing point by a quantity *B* which is *the resonance energy of the TS.* The quantities G_{R} and G_{P} are the corresponding promotion energies at the reactants and products sides, respectively. Finally, ΔE_{RP} is the thermodynamic driving force of the reaction. The twin states $\Psi^{\neq}$ and Ψ* play a key role in creating conical intersections which funnel excited molecules to the ground state products.[24,36]

The ground state profile in Figure 7 is a template for single-step reactions which involve bond exchange. **Rule 1** above enables us to identify the promoted states and instantly draw the diagram without computing anything. The VBSCD also outlines a general mechanism for activation. Thus, the reactants (Ψ_R) have specific bond pairing, and the only way to change this is to replace the reactants state by another one in which the reactants are "*prepared for bonding*" by having spin-paired odd electrons on the reaction centers that are going to be bonded in the product state (Ψ_P). Since at the geometry of the reactants the "prepared state" (Ψ_{RP}*) is an excited state of the reactants, this "*preparation for bonding*" occurs via the crossing and avoided crossing of the two state curves (cf. Figure 7). The same applies to the reverse reaction where now the products' state Ψ_{P} is being crossed by the corresponding prepared state (Ψ_{PR}*), along the reverse reaction coordinate.

The height of the crossing point in Figure 7 is determined by the promotion energy gaps (G_{R} and G_{P}) and the curvatures of the intersecting curve (f_{R} and f_{P}), which determine what fraction (f) of the promotion gaps enters under the crossing point. The simplest expression of the height of crossing point (ΔE_C) relative to the reactants in the ground state is given in Eq. 4a as a fraction (f) of the respective promotion gap:

$$\Delta E_C = fG_R \qquad (4a)$$

$$\Delta E^{\neq} = fG_R - B; \; < 1 \qquad (4b)$$

The corresponding barrier ($\Delta E^{\neq}$) expression is Eq. 4b, and it is given by the height of the crossing point (fG_R) minus the quantity B, which is the amount of avoided crossing (cf. Figure 7) and in chemical terminology, the resonance energy of the TS. An explicit equations which consider the quantities in both reactants and products sides (e. g., the reaction energy ΔE_{RP}, G_P, etc.) is presented later.

5.4 The First Paper and Its Reception

In the end of the process of piecing up the VBSCD, I concluded with some elation that what I discovered is a generalized mechanism of barrier formation and TS description, and that the resulting VBSCD (cf. Figure 7) forms a bridge from MO theory all the way to VB theory. As such, it was not an ad hoc curve-crossing model. *The diagram showed that energy profiles of chemical reactions could be pieced up systematically from VB building blocks, like in a game of LEGO.* By projecting the MO wave functions, I was able to find the VB building blocks of energy profiles, transition states and reaction intermediates, and was going to use these building blocks to reconstruct systematically the above "chemical reactivity objects" and conceptualize them. I decided therefore to finally write the paper, and since I was excited by the outcome of my labor I gave the paper the title, "*What happens to Molecules as They React*?…".[23a]

In mid 1980 I submitted the paper to JACS along with another paper that deals with the role of geometric distortions along the reactions coordinate, and asked the editor to consider the two for publication. This latter paper was instantly rejected and never published. I was convinced that the first paper would be accepted in flying colors. However, my little experience did not prepare me for the refereeing process. I got three referee reports. One rejected the paper because "*it did not have sufficient new results… and the 'chemical insight' gained by the author's circuitous path' is seriously flawed*". According to that referee, the charge transfer configuration was "*an artifact of the localized fragment configurations*", because "*electrons shift in pairs*". I would hear, time and again, this objection to a description of nucleophilic/electrophilic reactions as *single electron-shift processes.* The second report was not too bad, but it involved many comments. The third report was not too bad either, but the tone was somewhat harsh. The editor himself/herself was favorable but also had many comments, acting as a 4th referee, which I thought then be unusual (but later appreciated this).

It takes years to get used to the refereeing system, but at that time, this constituted an unpleasant reception for the young scientist that I was. In the end, the paper was accepted to JACS and appeared in 1981.[23a] Its attractive title drew hundreds of reprint requests.

6. Using the Simple Barrier Equation Based on the VBSCD

The simple barrier expression in Eq. 4b is rigorous. Thus, the term fG_R represents the height of the lowest-energy crossing point between the two state-curves in the VBSCD at the reactants end. Hence, fG_R constitutes the total reactants' distortion energies and Pauli repulsions that are required to destabilize the reactant state Ψ_R and bring it to resonance with the promoted state $\Psi_{RP}{}^*$ that correlates to the product, Ψ_P. In turn, the term B is the resonance-stabilization energy of the TS due to delocalization of the electrons in the bonds undergoing breakage and remaking.

The easily accessible term in Eq. 4b is the promotion gap G_R, which is the excitation energy from the reactant state to the promoted state, which can generally be related to a spectroscopic state. Thus, G_R can be easily evaluated from experimental quantities or from MO-based or DFT computations. For example, for an S_N2 reaction we need the vertical ionization of the nucleophile $X:^-$ and the electron affinity of the molecule A–Y.

Already in 1980, I derived some thermochemical expressions, and did simple semi-empirical VB calculations, which allowed me to estimate these quantities. This became handy, since in 1980, Pellerite and Brauman[41] published their seminal paper on gas phase identity reactions, in which they managed to quantify the barriers for a variety of $X:^-/CH_3{-}X$ systems. They found rather small barriers for the halides, and much higher barriers when the nucleophiles were OH^- or CH_3O^-.

The Pellerite-Brauman study posed an opportunity to test the VBSCD model and make specific predictions. I realized that the f factor in Eq. 4b is controlled by how steeply the charge transfer promoted-state, $X^{\bullet}/(CH_3X)^{\bullet -}$, correlates to the respective ground state along the reaction coordinate. This depends on the electronic structure of $(CH_3X)^{\bullet -}$; whenever the unpaired electron is localized mostly on the CH_3 group, this will lead to a strong $X^{\bullet}{-}^{\bullet}CH3$ coupling with the $X^{\bullet}$, and hence the charge transfer state will descend steeply towards the product, and generate thereby a small f value. And vice versa when the unpaired electron in $(CH_3X)^{\bullet -}$is delocalized on both moieties, the $X^{\bullet}{-}^{\bullet}CH_3$ coupling will be weak and the descent of the charge transfer state to products will be sluggish, thus resulting in a large f. For example, if the state curves can be approximated by parabolas the value of f will be 0.25, while straight lines give $f = 0.5$, etc.

Using simple semi-empirical VB calculations, I showed that for $X = $ halogen the $(CH_3X)^{\bullet -}$ radical-anion was localized on the CH_3 moiety, but for OH or MeO, the corresponding radical anion was quite delocalized over the two centers, and hence, $f_{\text{Halide}} < f_{\text{OH(OMe)}}$. The promotion energy gaps were also estimated using semiempirical VB calculations. Having the corresponding G_R gaps and f factors, it were possible to demonstrate that the larger f factor for $X = $ OH or OMe, leads to higher barrier compared with $X = $ halogen.

I wrote quickly a communication in which I treated a variety of identity S_N2 reactions. I submitted the work to JACS. Of the two referee reports, one was very positive. The second was negative and asserted: "*This papers is not publishable*", because "*the author has taken a model that gives nearly trivial results and has attached an unnecessarily complicated interpretation to them*". I was quite unhappy. I felt that while I was trying to do something new, general, and useful, my effort was being ridiculed and put down. In retrospect, this experience is not unique and it takes getting used to.

Nevertheless, since during 1980–1981 the number of JACS rejections was increasing, I was at a loss as to how to handle the situation. I needed advice. In the summer of 1981, I visited Cornell and Roald's group. At some point, I told Roald about my "publishing" experience. He asked me to sit down, went to his archives and came back with a pile of referee reports, which he placed on the desk in front of me. I read the reports, and I saw that "even" Hoffmann was not treated with silk gloves by referees. My share was not unique. I got a lesson to relax if I wanted to survive in science…

Roald then made two practical suggestions, one was to send the communication on identity S_N2 reactions to *Nouveau Journal de Chimie* (NJC) – "*they are more open minded*" he said. His second advice was to directly appeal to the Editor in Chief, which helped me bypass the JACS editors who were rejecting my papers. Following these suggestions, the communication was published in NJC in 1982[42] and the full paper on S_N2, which was coauthored with Addy Pross, was accepted in JACS.[43] Since then many papers were accepted by JACS and other journals, and it felt good to learn that these papers caused a renaissance in VB theory.[44] Roald's advice was very helpful!

Before shifting to describe my collaborations in BGU, let me demonstrate that the delocalization effect and its impact on f, which I used for S_N2 reactions, is physically meaningful. Figure 8 shows a plot of experimental free energies of activation for nucleophilic cleavage of an ester by a series of nucleophiles, X:$^-$, taken from a collaborative work with the groups of Erwin Buncel, his student Ik-Huan Um and the late Saul Wolfe.[45]

According to experiment, the rate-determining step here is the nucleophilic attack on the carbonyl group of the ester. This step can be analyzed by use of the VBSCD in Figure 7 and on **Rule 1**. Thus, the promoted state for reactions of nucleophiles with electrophiles is the vertical charge-transfer state. For the reaction in question, this meant that $G_R = I^*_{X:} - A^*_{Ester}$, where $I^*_{X:}$ and A^*_{Ester} are the vertical ionization potential and electron affinity of the nucleophile and ester, respectively, in the solvent used in the reaction. As such, the corresponding barrier is given by:

$$\Delta G^{\neq} = f[I^*{}_X : - A^*{}_{Ester}] - B \qquad (5)$$

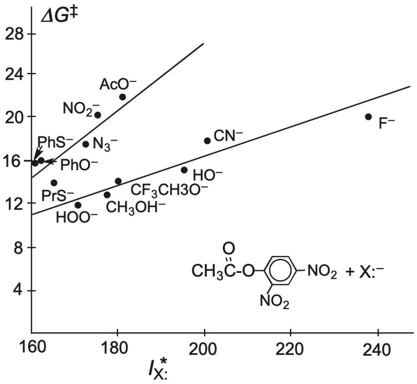

Figure 8. Experimental free energies of activations ($\Delta G^{\neq}$) plotted against the vertical ionization potentials ($I^*_{X:}$) in the reaction solvent, for a series of nucleophiles X:$^-$ activating the C=O in the ester shown in the figure (similar correlations existed for two other esters). Adapted with ACS permission from Figure 4 in Ref. 45. Copyright 1988.

Since the ester is common to the entire series, its electron affinity is a constant. If we assume that B is approximately a constant in the series, then equation 5 becomes simply equation 6:

$$\Delta G^{\neq} = f(I^*{}_X) - C \qquad C\text{-constant} \qquad (6)$$

Equation 6 predicts that a plot of $\Delta G^{\neq}$ vs. $I^*_{X:}$ will be a straight line with a slope equal to f. It is seen that the data set leads to two lines with different slopes (cf. Figure 8). The lower line involves those nucleophiles, which possess localized radicals (such as $F^{\bullet}$) in the charge-transfer state, and hence the respective f factor should be small as is indeed the slope of the respective line. On the other hand, the upper line involves nucleophiles which lead to highly delocalized radicals (such as $AcO^{\bullet}$), and hence having a larger f factor and a larger slope for the line. Clearly, therefore that the delocalization of the electrons of the bond-pairs in the promoted states is a factor which tempers the reactivity and must be reckoned with. This delocalization penalty effect is common to many other reactions.[46]

7. 1980–1983: VB Collaborations in BGU

My first office in BGU was Addy Pross's, who was on a sabbatical leave in Australia. Addy returned in the summer of 1980 and naturally came to his office where I was sitting. We started talking and he asked me about my research. I described to him my work on spin inversion, and then the VB model I just developed in the paper "*What happens to Molecules as They React*?…".[23] Addy seemed interested in the VB model and asked "*what can I do with it*"?, so I told him what I thought were the potential uses of the VB diagrams for discussing relative reactivity, stereochemistry, and reaction mechanisms. His eyes lit. He was excited…

Addy was (is) a renowned physical organic chemist and the VB model was specifically addressing the agenda of his field. I gave him the submitted draft of the submitted first paper,[23] and after a few days he came back to me and asked if I could translate all the FO-VB configurations to HAO-VB ones to facilitate the juggling between the two representations. I did so. After some time, he suggested that we collaborate on the S_N2 reactivity of benzyl derivatives. I of course agreed… As a prominent physical-organic chemist, Addy was naturally very familiar with the mechanistic issues in the field. This paper passed quite easily through the JACS referees, and ended up being published in 1981 back-to-back[47] with the theoretical paper on "*What happens to Molecules as They React*?…".[23]

The intellectual affinity between Addy and I forged an intense collaboration in the years 1980–1983. During this time we extended the art of piecing up energy profiles from VB building blocks to the major mechanisms in physical organic chemistry. Dealing with reaction mechanisms and with the physical organic chemical culture of substituent effects expanded the scope of the VB-diagram model. This required also expansion of the diagram and fitting it to mechanistic considerations.

7.1 Mechanistic Considerations with VB Diagrams

Let me refer to Figure 9 to describe this expansion of the model vis-à-vis Figure 7. For the sake of economy, I replace in Figure 9 the symbols Ψ_R and Ψ_P by *R* and *P*, and the promoted states by *R** and *P**. Figure 9a shows again the VBSCD with two state curves that are anchored in the ground states and promoted states of reactants and products, and which by mixing avoid the crossing and lead to a TS and a barrier for an elementary chemical step.

Besides the *R** and *P** states of the principal state-curves there exist many other excited states, so-called "intermediate states" (Ψ_{int}*), which can affect chemical reactivity. The corresponding diagrams that contain more state curves (or more structures) than just the two principal curves, are called by the name VB configuration mixing diagrams (VBCMD).[36,37] These intermediate states do not correlate to *R* ad *P*, and are drawn simply as horizontal curves in Figure 9b. In the simple situation, as in Figure 9b, the intermediate-state curves will lie above or close to the crossing point, and if symmetry allows it they will mix into the transition state (Ψ_{TS}) of the two principal curves and lower the energy of the TS, while endowing it with their characters.

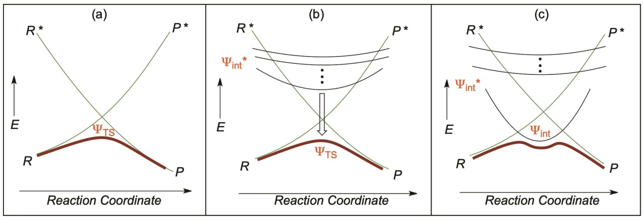

Figure 9. (a) Generic VBSCD with just the two principal curves of reactants and products. (b) VBCMD showing in addition to the principal curves a manifold of intermediate states (Ψ^*_{int}), which do not correlation to *R* or *P*, but may mix into the TS. (c) VBCMD where one of the intermediate states drops well below the two principal curves and defines an intermediate (Ψ_{int}) in a stepwise mechanism. Adapted from Figure 1 in Ref. 37 with RSC permission, copyright 2014.

Let us consider the examples of the Diels-Alder reaction vs. 2+2 dimerization of olefins (cf. Figure 6). One of these intermediates states is the charge-transfer (CT) state that involves a transfer of one electron from the HOMO of one molecule (e.g., the diene) to the LUMO of the other (the ethene). This state lies above the crossing point of Figure 9b, and it can potentially mix into the TS wave function and lower its energy. However, while this mixing is symmetry allowed for the Diels-Alder reaction (the HOMO and LUMO have the same symmetry), it is forbidden for the 2+2 dimerization (in which HOMO and LUMO do not share the same symmetry). Consequently, the TS for the latter reaction will distort from a D_{2h} symmetry, in order to enjoy some mixing with the CT state, and will proceed via a 1,4-diradical.

Figure 9c is an extreme VBCMD case where an intermediate state gets stabilized (by substitution, solvent, etc.)[24,36] and drops well below the crossing point of the principal state curves. Now, the intermediate-state curve and the two principal curves, undergo three-state mixing *leading to a stepwise mechanism with an intermediate between R and P.*

The intermediate-state curve can be the triple ionic structure $X:^- \; R^+ \; :Y^-$ in nucleophilic substitution of tertiary butyl/benzyl halides, thus defining the S_N1 or S_N2-intermediate mechanisms. It can be a carbocationic or carbanionic intermediate in elimination reactions of substituted ethane derivatives, thus defining the mechanistic crossovers from the single step E2 mechanism to the stepwise ones, E1 (via R^+ intermediate) and $E1_{CB}$ (via R^-).

For cycloaddition reactions, the CT intermediate state becomes very important in polar solvents and in the presence of an electric field (EF). When the EF is oriented along the dipole moment of the intermediate state, it leads to mechanistic crossover to a zwitterionic intermediate.[35,48] Just two diagram types, the VBSCD (Figure 9a) and VBCMD (Figures 9b,c), enable one to describe a wide scope of chemical reactivity features and mechanistic crossovers.

In 1983, the late Joe Bunnet, then the editor of Accounts of Chemical Research, invited Addy and me to write an account of the work on VB modeling of chemical reactivity, which we did.[49] After this paper, our interests diverted and the intense collaboration moderated. Eventually, Addy would dedicate his time to the origins of life problem, on which he published a wonderful book.[50]

7.2 Other VB Activities in BGU During 1980–1984

Along with reactivity, I started applying VB ideas to a variety of other problems. In 1981 I began addressing the relationship between organic conductors made from separate stacks of donor and acceptor molecules, and their isomeric charge transfer complexes made from alternating stacks of donors and acceptor.[51] I noted to myself then, that VB was a great theory for understanding conductivity. Regrettably, though, I applied these VB ideas to conductivity in only one more paper with Mike Whngbo from Roald's group.[52] My attention was quickly swept away to other topics.

I continued to develop the VBSCD model and to show its applicability to a variety of problems. In 1983 I addressed solvation, and showed how solvent effect could be predicted semi-quantitatively, using the VBSCD with non-equilibrium solvation in the promoted states. Based on this development, I was able to estimate S_N2 barriers successfully in many solvents. The paper was published in 1984 in JACS.[53] Together with the previous full papers on gas phase S_N2 reactivity[43] and on α- and β-carbon substituent effects,[54] I finally had in my hands a model that was making qualitative as well as semi-quantitative predictions. Quite a few years later (2006–2007), Wei Wu and his group, Philippe Hiberty and I applied this VBSCD(solvent) model for addressing the Menshutkin reaction, and a series of S_N2 reactions.[55]

Still in 1983, my friend and former classmate, Ronny Bar, from the BSc days in Bar Ilan, called me and asked if she could do again (after a short spell in 1980) research with me. Ronny was (is) a superb scholar, and I was fortunate that she wanted to do research, which she did not do for living, but out of her sheer curiosity for science. I offered her to engage in an idea which seemed a bit crazy, considering our education in organic chemistry. The idea was that *all the π-electronic components of delocalized systems like benzene and allylic species, were in fact transition states trapped by their σ-frames.*

This idea surfaced in 1982, in one of the Fridays in my favorite Coffee House in downtown Beer-Sheva, while sitting with my painter friend Oded Israeli. He was sketching by-passers and I let my mind wander aimlessly. Suddenly it struck me that if I would apply the VBSCD model only to the π-electrons, the delocalized π-electronic system would come out as a transition state with a sizable barrier, and hence in the real D_{6h} benzene molecule the delocalized π-electron system must be held in a uniform D_{6h} geometry by the σ-frame. Ronny Bar did the calculations using Extended Hückel, and showed that the π-electronic components of allylic species were transition states that had a propensity to distort to a localized state, and at the same time they exhibited rotational barriers.

We further considered the isoelectronic series of each π-electronic components (e.g., $XHX^{\bullet}$ or $X_3^{\bullet}$ ($X=H, CH_3, F, Cl, Li, Cu$, etc.) for π-allyl radical, X_6 species for π-benzene, etc.). We showed that using the promotion energy gap G in the corresponding VBSCD made it possible to predict whether the delocalized species will be a stable cluster or a transition state for an exchange reaction. Thus, for example, G for H_6 was many times larger than the same promotion gap for Li_6, and therefore H_6 is a very high-energy transition state for an exchange reaction, while Li_6 is a stable delocalized cluster. The same considerations apply to H_6 vs. Li_6. Generally, since the G quantity increased in proportion to the binding energy of the diatomic molecules, and since the π(CC)-bond is rather strong, the π-electronic components of the allylic species and of benzene fell among the unstable species. The paper was published in NJC in 1984, after having gone through 7 referees. Not that any of them was particularly negative, but there was a degree of disbelief in this idea. Nevertheless, the paper was finally published,[56] and would become a major theme in my future research.

7.3 Thinking About The Future

The two years 1983 and 1984 were quite eventful for me. I decided to take a sabbatical leave in the French laboratory established in Paris Sud (Orsay) by Lionel Salem. In the meantime, my daughter, Yifat Sela, was born and she had a heart-related problem, which made Sara and me highly concerned, until we saw her recovery. I completed a huge review on the VB model of reactivity, which I entitled "*The Collage of S_N2 Reactivity Patterns*" (eventually published in Progress in Physical Organic Chemistry in 1985[57]). While the focus was S_N2, the review gives a general scope of how to apply the VBSCD and VBCMD models to pattern data and to make new predictions.

Subsequently, the late Saul Wolfe visited Ben-Gurion University. He was doing *ab-initio* calculations of S_N2 reactions and wanted to meet "*this guy who calculated all the trends with a paper and pencil*" (in Saul's own words). Saul was an eminent chemist and I was glad he was interested in what I was doing. In our meeting he suggested that we write a book on S_N2 reactivity using the VB model and all the computational data his group in Kingston assembled. The enthusiasm of Saul was contagious and I drifted along. Too many commitment for a young scientist…

8. 1984–1991: VB in Orsay and in Kingston

As we prepared to go to France, I flew to Paris by myself, and the plan was that my family would join me after full recovery of our daughter Yifat from her surgery, and after she and Sara got their French VISAs. Luckily, the French administration was not too fast/eager to issue the VISAs, and Yifat had an extra month of recovery. We were also lucky since by the time Sara and Yifat were allowed to join me, I could already manage somehow with my newly acquired French language to know how to select the delicious foods which Paris could offer. If you spoke even a broken French, Parisians treated you with respect and helped you. In the meantime, I found an apartment and prepared it; it was in *Rue Massenet* adjacent to the place where the role of the French in the Suez war was planned. Finally, my family joined me in February 1984. This was a wonderful year in every respect.

8.1 Research in the Laboratoire de Chimie Théorique in Orsay

In Orsay I already had two friends from the Cornell days, Christian Minot (we overlapped at Cornell) and Odile Eisenstein (whom I met in 1980 during my visit to Cornell), but I did not know all the other members of this large and world-renowned laboratory that was established by Lionel Salem. In my first visit to the lab, Philippe Hiberty approached me and said he wanted to collaborate with me on the problem of π-electrons. It turned out he was one of the 7 referees who reviewed the NJC paper.[56] *He was simultaneously both intrigued by the whole idea as well as disbelieving it.*[31] I knew Hiberty's pioneering work on projection of MO-CI wave function to VB structures.[58] His work built an additional bridge from MO to VB, and we seemed to be very compatible with complementary knowledge; *two lone Samurais fighting the cause of an abandoned theory.* I was very happy to team with him.

Philippe invented all kinds of ways to probe the π-distortivity of conjugated molecules, which was predicted by applying the VBSCD to the π-electrons. There was a lot of resistance in the way of publishing these papers, but we somehow managed, initially in NJC, then in JOC and finally also in JACS.[59] Generally, these papers were met with interest mixed with disbelief… Eventually, vibrational spectroscopy of the ground state and the $^1B_{2u}$ excited state would provide a simple experimental evidence for the distortivity of the π-electrons of benzene.[60] This work on the root cause of π-delocalization started an intense collaboration between Hiberty and I (Figure 10), along with friendship that lasts to these very moments, as I am writing this essay.

During the same year in Orsay, I fervently continued developing the VBSCD and VBCMD models and applying them to more complex reactions, which were stepwise and involved mechanistic changes, such as nucleophilic-vinylic substitution.[61] Philippe, other members of the Orsay lab and I applied the VBCMD model to understand the stability of hypervalent radicals,[62a] and the stability of SiH_5^- *vs.* the very high energy of CH_5^-.[62b,c]

In the meantime, Saul Wolfe kept our mutual interests alive. He sent me to Orsay the results he and his collaborators found on relation of the barriers and corresponding deformation/distortion energy of the TSs in S_N2 reaction. He asked me if I could add to their manuscript the VB perspective. I did… The paper showed that in accord with the VBSCD model, the gas phase S_N2 barriers correlates with the deformation (distortion) energy of the CH_3X molecule in the TS.[63] The latter paper was one of the early papers to point out the role of the distortion energy in reactivity, and to relate it to the fG term (Eq. 4) in the VBSCD.

Figure 10. With Philippe Hiberty in a conference in Lagrasse. Curtesy of Philippe Hiberty.

The review on S_N2 was published in 1985,[57] and Jean-Jacques Perrier who already knew me, saw it and invited me for one month to Toulouse to give a mini-course on chemical reactivity. I went to Toulouse in January 1985 in the bitter cold winter when even Toulouse was snowed down. The warm friendship of the Toulouse group and my excitement to give a course on the VBSCD/VBCMD approach to reactivity compensated for the low temperatures outside. I also gave talks in the group of Jean-Paul Malrieu and engaed in an intense friendly debate with him. The model was acquiring gradually some popularity among chemists.

8.2 Quantitative VBSCD Calculations in Orsay

Early during the sabbatical, Hiberty and I decided to collaborate on the VBSCD model, and try to calculate these diagrams for real reactions. This collaboration extended well beyond the sabbatical year (1984–1985) and culminated in writing a book on VB theory, entitle: *A Chemist's Guide to Valence Bond Theory.*[24]

Generally, the French chemists were excited about ideas and I felt very welcome and comfortable in this atmosphere, which was in a way Talmudic and philosophical. I became a frequent traveler to France.

8.2.1 VBSCD Calculations

Luckily, Philippe found an old CI program which he put together with Jean-Michele Lefour and Jean-Pierre Flament from the Orsay group. Philippe loves putting together old things and repair them, e.g., his motorcycle … Importantly, this program could do for us VB calculations. We used it to construct the VBSCD model for S_N2 reactions, initially for H^-

$+CH_3–H \rightarrow H–CH_3+H^-$.[64a] Good few years later, we looked at another S_N2 reaction, $F^- + CH_3–F \rightarrow F–CH_3 + F^-$.[64b] These applications verified the qualitative considerations regarding the connection between the f factor (Eq. 4) and the delocalization of the radical anion in the charge transfer sate. Thus, for the hydride exchange the VB calculation led to $f=0.42$ while for the fluoride exchange $f=0.15$.

We also computed the VB diagram for the radical exchange reactions $X^\bullet + X–X \rightarrow X–X + {}^\bullet X$ (X = H, Li), for which we verified the nature of the promoted state as nascent from the triplet decoupling of the bond undergoing cleavage.[65] Even more importantly, we verified the VBSCD prediction that for both X = H and X=Li, there is the same type of avoided crossing. However, since the G value in the case of X = H is 8 times as large as that for X = Li, the avoided crossing led to a delocalized $H_3^\bullet$ transition state, whereas for X = Li the avoided crossing led to stable delocalized $Li_3^\bullet$ intermediate, as shown in Figure 11:

Figure 11 is not restricted to the two cases presented; it is rather a portrayal of the natural division of the periodic table to weak binders (many of the metals) which form stable delocalized species, and the strong binders for which the delocalized species were TSs of chemical reactions. The VBSCD projects this natural division in an easy and clear manner by mere inspection of the relative G values for the corresponding diatomic molecules.

Generally, the heights of the barriers or the depths of the energy wells followed the previous semi-empirical/qualitative estimates based on considerations of the VBSCD. Nevertheless, the quantitative VB calculations taught us quite a bit on effects that determine the f and B factors (Eq. 4b), and increased our confidence in the qualitative reasonings. Thus, we found that for the radical exchange reaction with X = Li, the f factor was rather small (0.13), while for X = H the f was significant (0.37),[65] and as already noted, for H^-/CH_4 f was large (0.44). Thus, both f and B in these systems varied in relation to the respective G values; *high G led to large f and B, and vice versa for low G values.* We also found that the TS resonance energies (B) for radical exchange reactions were proportional to the strength of the bonds undergoing activation (see later).

By comparison, in S_N2 reactions the f values were affected largely by delocalization in the promoted states (cf. Figure 8), and the corresponding B values changed in a very narrow range (since the two state curves in the VBSCD contained $X{:}^-\ CH_3^+\ {:}X^-$, as a common VB structure, which reduced the TS resonance[24,55b]). Understanding the root causes of all these trends enriched the qualitative theory and refined all future applications.[24,36,37,66]

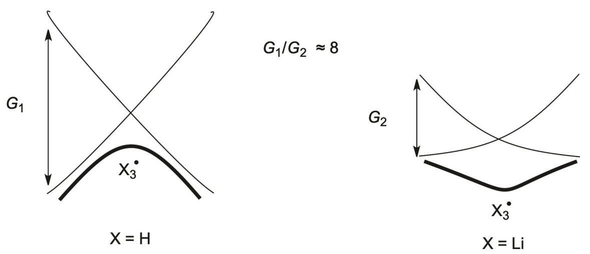

Figure 11. Comparison of the VBSCDs for H_3 vs. Li_3. Adapted with Wiley VCH permission from Figure 23 in Ref. 36, copyright 1999.

Philippe and I continue to collaborate to this day. Much of our current activity focuses on the chemical bond, which is the topic of the companion Rosarium essay.

8.3 1985: VB Activity in Kingston

By the end of 1984, when I was still in Orsay, Saul Wolfe called and suggested I come to visit Queen's University, and discuss the book with him and Berny Schlegel. I packed my suitcase and travelled to Kingston. During these discussions it became clear that I would have to take a leave of absence from BGU and spend about six months in Queens. After completing the sabbatical year in Paris my family and I went back to Israel for one month. Yifat, our daughter, was already chattering in French.

Soon enough we flew to Canada and arrived at Queens University in April 1985. Saul sent a huge limousine to pick us up. We were impressed with this and with his kind hospitality. We enrolled Yifat in a day care, and suddenly she would not speak to us but communicated with gestures. We were very concerned so we asked the teacher at Yifat's day care, if there was something wrong with Yifat. She told us that Yifat speaks English ceaselessly, and because she thinks we do not know English she does not speak to us…

Saul, Berny and I used to have periodic discussions on what kind of a book we should aim. Berny and I were coming from different schools in theoretical chemistry, and these discussions were essential for bridging the chasms, and establishing a mutual understanding and respect for each other's way in science. The book was initially planned to describe the VB modeling of S_N2 reactivity, based on the extensive computational data of Dave Mitchell (Saul's student), and the review I wrote for *Progress in Physical Organic Chemistry.*[57]

The idea of a small book was reasonable and attractive. However, in that phase in my life I was in the midst of developing the VB model and expanding its coverage, so that deep down, my creative urge was burning and pushing me towards a more general treatment of reactivity. It took me time to curb down my ambition for perfection and focus on S_N2 reactivity in the gas phase and in solution, though still generalizing. In late August 1985, Sara and Yifat flew back to Israel. I stayed one more month to complete my share in the book. It was decided that I would leave all the chapters in Saul's hands and he will finalize the book.

A few days later, Saul and I flew to Chicago to participate in the Physical Organic Chemistry Symposium of the ACS Meeting (where I presented my story of VBSCD treatment of S_N2), after which I flew back to Israel. The Israeli airport in those years was small and all the family members would wait outside for their passenger to come out. The first thing I saw when I came out was the face of my two years old daughter who was held up by Sara. Yifat saw me, and then like a flash she recognized me, and she started gasping with excitement (she did not yet speak Hebrew, and for her we did not know English). She clung to me for the next few days, as if not to let me off her sight so she will not lose me again. A week later I flew to France, and when I came back she ignored me for a few days – I was not reliable… This was a realization that my scientific work was tearing me away from my family. I had to learn the art of balance…

During the next six years, Saul coordinated the work on the book. He, Berny and I communicated by mail back and forth over the drafts of the book; this was not easy. But finally, Saul managed to condense the various chapters and to unify them into a coherent book. The book was published in 1992. When it came out the three authors were proud and hid a sigh of relief.[66] The book is not too poorly cited (667 cites).

9. 1986–1991: Returning to BGU

After my return to BGU, between 1986 and 1991, I resumed my activity in all fronts; teaching general chemistry and applied quantum chemistry, and working on organic conductors, establishing a group which synthesized new conductors, further developing of the VB ideas and applying VBT to new reactions, bonding, and the behavior of π-electrons.

In 1987 the department started the process of my promotion to a Full Professor, but the pace was sluggish. This changed when the textbook of Lowry and Richardson on mechanism and theory in organic chemistry[67a] came out and contained an extensive coverage of the VB work that Addy Pross and I did during 1981–1983. This made a deep impression on the Provost and the President of BGU and I was immediately promoted. Addy and I were very satisfied to see our efforts being included in a textbook. Later, another textbook by Carroll included an even more extensive coverage of the VB diagrams.[67b]

In 1986 I received a second invitation to teach a mini course on VB theory: this time from Sam McManus and Milton Harris from the University of Alabama, Huntsville. I had very interesting discussions in Huntsville… In 1987 I got the third invitation to come and give a series of lectures on the VB diagrams for modeling chemical reactivity, this time in Lund and Gothenburg in Sweden. The late Per Ahlberg and Lennart Eberson, and Jan Sandström, organized jointly this invitation. I gave these lectures only in 1989, just before the IUPAC meeting in Stockholm. I titled this mini-course as: "*The LEGO Way: Curve Crossing Diagrams as General Conceptual Models for Chemical Reactivity and Structure*". My family and I spent a few weeks in Lund and a period of two months in Gothenburg, living in a beautiful villa near the fountain with the awesome Carl Miles sculpture of Poseidon. The VB model was gaining some followers… Eberson and Bjorn Roos, from Lund, suggested a collaboration, which would take place but a decade later…

The benzene story was getting its share of attention too. In 1988 I went to Switzerland upon the invitation of the late Edgar Heilbronner and Jack Duntiz to give the *Kahlbaum Lecture* in Basel and two talks in the ETH Zurich. Edgar was interested in the π-electronic ideas we published, and already while I still was in Orsay, he wrote me on August 5, 1985, a letter, and in his special humor he let me know that he took our paper along with a few detective books to his vacation on the Swiss mountains. The ideas on the distortivity of the π-electrons of benzene were well accepted in Basel and ETH, even though they were still considered controversial. Edgar told me about his dialog with Binsch in the aromaticity symposium in Jerusalem (1971); Edgar asked what is an aromatic molecule, and Binsch replied "*Benzene is a perfect example*", to which Edgar responded: "*Name a second one*!"… End of discussion.

In 1991, Edgar would publish a lovely paper in *The Journal of Chemical Education*,[68] which was entitled "*Why is my molecule not symmetric*?" and this was the first positive reception of the idea. Edgar and I would publish together later on π-systems. Edgar impressed me by his engaging intellect and great wit and became a friend and in some ways my third important mentor in the years to come.

Names of others who supported the idea are Roald Hoffmann, Karl Jug, Lionel Goodmann, the late Yhuda Haas, Shmuel Zilberg, Fritz Schaefer, Gernot Frenking, Lionel Salem, Vladimir Minkin, Georg Holneicher, etc. The benzene story was publicly accepted when the late Paul Schleyer invited Philippe and I and my coworkers (Avital Shurki my Ph.D. student, and David Danovich, my permanent coworker) to write a review in Chemical Reviews.[69] In the introduction to the Issue (in Volume 101), Paul wrote: "*the review emphasizes the duality of the π-component of benzene … which characterizes all delocalized [organic] components [π-distortivity and apparent stability]. **The basis for the conclusion that the D_{6h} structure is due to the σ framework, now is widely accepted**…*"

10. 1988–1991: Derivations of Matrix Elements Between VB Structures

While still in Orsay I reached the conclusion that whereas I knew quite a bit about VB structures and their behavior along reaction coordinates, I had no good clues about the "matrix elements" that were responsible for the VB mixing.

VB theory without knowledge of matrix elements was merely a teeth-less resonance theory, because *it lacked selectivity* (any new resonance structure one could invoke was considered to stabilize the molecule). I recalled that Evans,[70] had treated the dimerization of ethylene and the Diels-Alder reactions, already in 1939. Using his empirical VB calculations he found that the mixing of the VB curves in the TS for the Diels-Alder reaction was larger than the same quantity in the dimerization of ethylene (which is correct; see discussion above). This led him to conclude/predict that the matrix element will increase in proportion to the number of π-electrons, which undergo delocalization in the TS. As such, this pioneering brilliant study missed the opportunity to formulate those reactivity rules, which were later derived by Woodward and Hoffmann through orbital symmetry.[71]

A related problem was that VB calculations of benzene and cyclobutadiene, which Pauling and Wheland were doing using only the covalent structures. These calculations led to the conclusion that the resonance energy of cyclobutadiene is larger than that of benzene; something which has been marked as a serious failure of VB theory.[24] As my Ph.D. student, Avital, showed in 2003, what made the $4n+2/4n$ difference were the di-ionic structures, which mixed efficiently with the covalent ones in benzene but not in cyclobutadiene.[72] This paper which also contains the derivation of selection rules for ring currents (diamagnetic and paramagnetic) has a meager number of citations (20), a fact that still amazes me, considering the huge activity in the topic of aromaticity.

10.1 Beyond Resonance Theory

I was determined to understand the mixing patterns in VB theory. However, unlike MO-based theory, where just two Slater Rules controlled the possible configuration mixing, in VB theory, all the VB structures maintained among them matrix elements, due to retention of overlap between the HAOs. Thus, while FO-VB had the benefit of orbital-symmetry insight into the mixing, the HAO-VB approach did not, and it is here where ionic structures are numerous and their impact on the energy was huge. I therefore decided to struggle with VB matrix elements, and thought to derive a Hückel type VB theory.

A few events accelerated the process. One was an invitation from the late Imre Csizmadia to participate as a speaker-teacher-tutor in the NATO school in Saint Feliu in 1988. I was supposed to teach a few hours and then to have a few tutoring sessions. Looking at the list of other teachers-speakers, I saw Don Truhlar, Bill Miller, the late Paul Schleyer, Berny Schlegel, Paul Mezey, Mike Robb, etc. It was clear to me that if I wanted to rise to the occasion; I had to develop something new.

I resumed my attempt to derive analytically all the energy expressions and the mixing patterns of VB structures. Since the matrix elements scaled by the overlap to the power of the number of differently occupied HAOs (AOs), it became possible to restrict the VB matrix elements to only two rules; **(a)** one for VB structures which differed in one HAO (AO) occupancy (e.g., the covalent-ionic mixing in Eq. 3), and (**b**) the second for VB structures which differed in two HAOs (AOs) occupancies (e.g., the two part of the HL structure, Eq. 1).

I ended up developing a Hückel/Extended Hückel type VB theory. Since VB theory deals with states, the semiempirical scheme included effectively also the electron-electron repulsion terms, and behaved properly with respect to the symmetry control of mixing between the structures. This was a lot of fun; once I figured out the systematic derivation of the matrix elements between VB structures and learned how to trim them, I found that the VB structure-set for a given problem mixes in Hückel or Möbius patterns, and I could therefore use simple Hückel MO programs to solve the state constitution. I derived the VB rules of aromaticity and antiaromaticity, including for odd electron systems, and had an immediate handle on excited states. This work was written as a Chapter in the *NATO ASI* series, which was published in 1989.[38] Even though this work is barely cited, it became eventually one of the foundations for the book written by Philippe and I, 19 years later.[24]

Matrix elements between VB-FO structures were much easier to derive and more portable, because these matrix elements provide information about symmetry and stereoselectivity. What got me initially motivated to focus on VB-FO matrix elements were the prospects of deriving selection rules for reactions, the need of understanding of the difference between allowed and forbidden cycloadditions in VBT (see the discussion of Evans' work[70] above), and deliberations on the relationship between electron transfer (ET) and polar reactions, which has become in the late 1980s a hot area in physical organic chemistry.

The late Lennart Eberson, a prominent physical-organic chemist, has written a monograph in 1987 in which he outlined the ET/Polar relationship using the VB diagram model.[73] In 1989 the IUPAC chemistry congress was held in Stockholm and one of the major topics was the ET/Polar dichotomy in organic reactions, and I was invited to talk about the dichotomy. This has diverted some of my attention to electron transfer theories and especially to the Marcus-Hush theory. Something that struck me was the outer-sphere model that was developed for distant electron transfer events in enzymes, was used by organic chemists to derive the reorganization energies of many organic ET reactions.

In organic ET reactions the reactants can come close together. As such, I used VBT to reason that there should be a strong mixing between the two intersecting state ET curves, and I was confident that usage of VB matrix elements would lead me to orbital selection rules for the ET/Polar dichotomy. I did so, using FO-VB, and found that ET and Polar reactions are controlled by different orbitals, and would have therefore distinct TS structures (e.g. in ET to one-electron bonds, the ET-TS would involve the donor from the frontside of the one-electron bond, while in substitution reactions the attack will be from the back side of the bond).[36]

During the meeting in Stockholm, Lennart and I decided to write a paper on this issue and to revise his reorganization energies that were derived assuming an outer-sphere mechanism. The paper, published in JACS in 1990,[74] derived orbital selection rules, and showed that the known experimental data matched an ET scenario wherein B (Eq. 4b) was significant, reaching 7 kcal/mol for dissociative ET of π-radical anions reacting with alkyl halides. In the same year, my postdoc J. K. Cho and I published a communication which showed that both the ET and the substitution TSs for the reaction of a nucleophile with ethane cation-radical, were strongly bonded.[75] The ET-TS was far from the outer-sphere model usually assumed to take place. For a few subsequent years, I wrote and gave talks in which I asked my physical organic colleagues: "*Why should a transition state give up its bonding and be outer-sphere*?". I do not think this idea was too popular among ET chemists who used the outer-sphere model unreservedly. Still, it was accepted by physical organic chemists (Eberson, Clark and later Schwarz, etc.)

Later during the years 1994–1998 (when I already moved to Jerusalem), my postdoc Sastry would investigate the reactions of ketyl radical anions with alkyl halides, and show that the ET and Polar processes follow different orbital selection rules that lead to different stereoselectivities and chemoselectivities and which could be predicted from the VB model of the ET/Polar dichotomy.

Sastry would further demonstrate that the ET-TS is strongly bonded, and that these transition states create entangled ET-Polar reactivity.[36,76] In this scenario the two processes share initially the same trajectory leading to a strongly bonded TS. From there onward the trajectory will bifurcate leading to ET and substitution products, *such that a single TS serves two mechanisms.* The entangled ET-Polar reactivity would later be verified by molecular dynamics simulation studies with Berny Schlegel and his coworkers.[77] Entangled mechanisms are expected in any mechanistic group, such as S_N1-S_N2, or E1-E1$_{CB}$-E2, which shares the same set of VB structures. I am sorry I never allocated the requisite time to deal with this generalization.

Another physical-organic chemist, whom I met in the IUPAC meeting, was Joe Dinnocenzo from Rochester, who was investigating reaction mechanisms of organic cation radicals. Joe was a student of Mel Goldstein in Cornell, and recognized me from the talk I gave in Mel's group while at Cornell. We became friendly during the meeting and spent our lunches and dinners together in a merry company, which included Christian Amatore and Ole Hammerich, having great laughs, drinking beer and paying exorbitant prices.

I decided to stop by Joe's poster, which was showing that nucleophilic cleavage reactions of cyclopropanic cation radicals proceeded with inversion of configuration at the site of attack on the $(R_3C^{\bullet}CR_3)^+$ bond. He showed in his poster that frontier orbital theory could not make a prediction because in odd-electron reactions, two different orbital interactions were equally important, the SOMO-LUMO and the SOMO-HOMO. Since I was thinking then in terms of orbital-selection rules for chemical reactions, I immediately presented him with a FO-VB analysis of the problem which showed that the LUMO of the radical cation determines the stereochemistry of nucleophilic attack. He was excited. We decided to collaborate and write a communication on the problem. I drafted a short paper, and Joe added all the experimental insights and even corrected some of my errors in theory. The paper was published in *the Journal of Organic Chemistry* in 1990.[39a] We used the FO-VB formalism which predicted the observed reaction stereochemistry. To date *this is the first and only paper that derives the stereochemical rules for odd electron reactions such as nucleophilic attacks on cation-radicals and the isoelectronic radical cleavage of σ-bonds.* Joe and I would publish a few more papers and would maintain a continuous communication on the application of VB theory to chemical reactivity.

11. 1992: Getting a Call from the Hebrew University

In 1991 we moved to our newly built house in Beer-Sheva, which shows that I had failed to predict my own future – the move to Jerusalem. The move was initiated when the late Mordecai Rabinovitz from the Hebrew University (HU), who was at the time the chairperson of the institute of chemistry, visited BGU for a colloquium. While conversing, Mordecai asked me if I would consider moving to HU. I said, "*Let me have some time to think about your initiative*".

In those days (1991) in Israel, moving between universities was rare. In fact, I was already having a flirt with the Weizmann Institute, but the President of the Institute vetoed "*taking away good people from the young university*". Another obstacle was the way we live in Israel; there are (still) not many apartments for rent and this meant that we had to sell our newly built house in Beer-Sheva and buy an apartment in Jerusalem. The price ratio was 1 : 2 and is now even higher. This meant a huge economic setback for us. Despite these obstacles I was encouraged by Sara, my brother, and by friends (Ronnie Bar, and Yitzhak Apeloig) to consider the move very seriously.

What helped the most to make a positive decision were: the tension in the department which created around me a very negative atmosphere, and Saddam Hussein who started sending missiles to Israel on January 15, 1991. My postdoc at the time, J.K. Cho, fled the country immediately; my research was left in shambles. I could not do anything anyway, because most of the time was spent sitting in shelters. My brother and his family were living with us, since their city (Ramat Gan) was badly hit by Sadam's missiles. I had some time to consider the situation in BGU vs. the prospects of moving to Jerusalem, and having a chance to rejuvenate my science and explore new directions.

After getting fed up with the situation, I called Rabinovitz and said, "*I do*". A week or so later, Rabinovitz called me, while I was in the shelter, and informed me that my case passed with flying colors and what I had to do now was to send him a "*shopping list*". This was so quick… I thought to myself that a university that could recruit so quickly must be a terrific place to move to. I knew that if I hedged too long, this might be my last chance to move in Israel.

A few months later I realized that I was simply fortunate; the new HU President, the late Yoram Ben-Porath was a dynamic person and was intent on rejuvenating the university, and as such made many critical decisions by himself bypassing the lengthy procedures in committees. After Rabinovitz discussed with him about my candidacy, Ben-Porath instantly called the referees proposed by Rabinovitz, and after these telephone conversations he gave the green light for my appointment. Ben-Porath and his family perished in a tragic car accident shortly afterwards.

By March 1991, I got a letter from HU, offering me a position as Full Professor at the Institute of Chemistry. This was followed by negotiations over the conditions of the move, with the new chairperson of the Institute, the late Eli Grushka, and the Dean, the late Michael Ottolenghi. Dean Ottolenghi was someone whose words were "engraved on a rock" and he stood firmly behind all his promises to me long after he stopped being a Dean. Eli Grushka and I became friends very quickly, and he made sure the Institute of chemistry treated me with generosity; I would be a member of the department of organic chemistry and of the Fritz-Haber Center of theoretical chemistry, would receive startup money to buy a good computing facility, I would be allowed to hire a computing specialist who would work with my group, as keeper of know-how, and so on. I was due to move on March 1st, 1992. The Chairman, Eli Grushka and the Dean, Ottolenghi, were exceptionally generous and allowed me to purchase the workstation (IBM/RISC 6000 model 550) early and use it while I was still in Ben Gurion University.

At about the same time, my colleague and friend Yitzhak Apeloig from the Technion, recommended to me his postdoc, David Danovich, who was an immigrant from Russia and had a PhD in quantum chemistry. He thought David would make a wonderful computing specialist. I interviewed David in Ben-Gurion University and could immediately see two features: He was highly skilled with computers as well as with use of quantum chemistry, and he was a very nice person, easy to get along with.

In January 1992, in the midst of snow storms all over Israel, the IBM workstation was brought to BGU. I invited David who immediately put the workstation to use, and within one day, Alexander Ioffe (another Russian immigrant working with me at the time) could start doing calculations – the new IBM workstation was fast and efficient. I started my service at HU on March 1st, 1992, and on August 12, 1992, my family joined me, and we moved to a University apartment near the campus in Givat Ram, known today as the Edmond J. Safra Campus.

The move to a new place was a chance for a change. Computational chemistry was then on the rise, and one could do descent computational studies of chemical reactivity and structure. Having the IBM/RISC 6000 (model 550) enabled these studies quite efficiently. On the other hand, VB calculations were carried out with TURTLE,[32e] and as the name hints, the calculations were slow, very slow (even though TURTLE was then the fastest VB program). It became very tempting to change course in my research, and abandon VB theory in favor of computational chemistry, especially DFT which opened the entire molecular world to computations, for reactions of Cytochrome P450 which I wanted to try because of the initial discovery of Two-states Reactivity (TSR) in its reactions. However, using the words of prophet Jeremiah (Jeremiah Ch. 20 verse 9) VB theory was "*in my heart as a burning fire shut up in my bones, … I weary myself to hold it in*", and I could not abandon it. In the next 26 years I would struggle to find a way to bring VB concepts into any area I ended up investigating, even for the complex reactions of Cytochrome P450.

11.1 1992–1995: Research in HU

Already during 1992, I had a small group at HU; Chandrasekhar Reddy a postdoc (former student of Jemmis), Alexander Ioffe who used to come once a week from Beer Sheva, and David Danovich who joined me in Jerusalem as a scientific programmer. Later in 1993 came the second postdoc, G. Narahary Sastry (another former student of Jemmis), and subsequently, Avital Shurki joined the group as a PhD student. She was followed by Pankaz Sharma, and Johnny Galbraith, and many others…

Danovich was initially the only one who could make the program TURTLE work, taught the postdocs and students to do VB calculations. Avital started to investigate with TURTLE the $H_3E–Cl$ ($E=C$, Si, Ge, Sn, Pb) bonds, in order to explore the nature pf these polar bonds. She was also engaged in VB calculations of benzene with an interest of supporting or refuting the prediction that its π-electronic component was distortive. Reddy and Sastry were doing cation- and anion-radical chemistries using the VB ideas developed in past years (see above).

In 1993, I resigned from BGU, we sold our house in Beer-Sheva and then bought a new apartment in Jerusalem; it was still on paper … Already in early 1993, the computational needs exceeded the capability of our new workstation. A new one came along on the market, the RISC 590 model, which was defined as a "supercomputer". I started raising the money to upgrade my one year old RISC 550 to the new model, and was generously helped by the late Ilan Chet, the Vice President for research and development, and Avinoam Ben-Shaul, the vice Dean for research in the faculty of science. While I managed to do so, I realized that securing state-of-the-art computing facilities at any given time is going to be a major problem for me in the future.

After a while I learnt about the possibility to establish a new center with endowment from the Minerva Foundation in Germany. I also understood, from Charlotte Goldfarb, the Head of Germany Desk at the research and development authority, that Minerva would favorably regard a multi-institutional center. I naturally contacted Yitzhak Apeloig and we decided to team and submit a proposal.

We needed however, to demonstrate support of the idea by a few prominent German scientists. Our natural choice was Helmut Schwarz; he and Yitzhak were good friends, and we knew each other quite well from the many conferences, and the many visits of Helmut to Israel and in particular to Jerusalem and the Technion. The second person was Lenz Cederbaum, whom I knew very well already from the Cornell days. Helmut suggested that I write to Sigrid Peyerimhoff, one of the most highly esteemed theoreticians in Germany, and the Vice President of the DFG (Germany's Reasearch Authority). So I did. Apeloig suggested the late Paul Schleyer who was then alternately at Erlangen and Athens. And finally, Helmut suggested that I write to or visit Joachim Sauer who had been a theoretician in East Germany and was now appointed to form a theory group in the revitalized Humboldt University. I was familiar with Joachim's work, as well as with the work of his spouse, Angela Merkel (now, the Chancellor of Germany) who did theoretical work on S_N2 reactivity and cited my own work, while still being in the East.

In June 1993 I visited Helmut Schwarz. This would be one of the many visits to Berlin and the establishment of long and very friendly relationships, with Helmut and his group members, and would lead to the establishment of the *Lise Meitner Minerva Center for Computational Chemistry*, with me as its Director and Yitzhak Apeloig as co-director, while Helmut was the chairman of the advisory committee. The Center existed for 20 years (1997-2017), and was steered by the three of us throughout that period. Figure 12 shows the three us in one of the many meetings of the Center.

The Lise Meitner Center makes a fascinating story by itself,[78] but I must skip it for the sake of telling the scientific story. The Schwarz group was conducting then research on C–H bond activation by small transition metal cationic species and accumulated quite a few puzzles.[79] One of these puzzles was the reactivity of FeO^+ in hydrogen abstraction. I had a talk with the group members, and learnt from the late Andreas Fiedler, the student who was doing his PhD on the topic, that he was running calculations with Wolfram Koch, and they were getting that the ground state of FeO^+ is $^6\Sigma$, but this state featured a high barrier for H–H activation. Andreas further added that all his attempts to understand the reactivity of this species with H_2 failed.

Figure 12. From right to left, Y. Apeloig, H. Schwaz and S. Shaik in 2005 (curtesy of the Sara Shaik, the photographer).

My subsequent visit to Berlin was in November 1993. I gave a mini-series of talks on the VB model of reactivity, and had a discussion with Helmut, and the group members who were involved in the FeO^+ research. November 20 and 21 were bitter cold days. I tried going out to see some more of Berlin, but the cold chased me back into my hotel room. So, I sat in there and drafted two documents: one of these was a draft of the paper on the reactivity FeO^+ with H_2.[80] In the first draft of the paper, I used VB theory to show that the electronic structure of FeO^+ was analogous to O_2, with a high-spin ground state and a low-spin excited state. I further suggested that much like in the case of O_2, where the more reactive state is the $^1\Delta_g$ state, in FeO^+ with the $^6\Sigma$ ground state, the reactive state is the lower spin quartet state analog of $^1\Delta_g$, which would cross the high spin state and mediate the process. Using VB ideas it was also possible to predict the structure of the transition state.

On the eve of November 21 (Sunday), the draft of the paper was finished, and I mentioned it to Helmut during the break in the concert of Maurizzio Pollini. On Monday, I presented the ideas to Helmut and his involved coworkers. This paper was finally submitted to JACS. This paper,[80] and others that followed[81] eventually ushered two-state reactivity (TSR) as a mechanism of bond activation. The TSR concept, essentially a brainchild of VB thinking, has started another long and intense collaboration with Helmut and his group, and became one of the major mechanisms in bioinorganic chemistry, and in the chemistry of metalloenzymes like Cytochrome P450 and nonheme enzymes.[79,81] Later on, the P450 adventure is discussed in some details.

12. 1995–1996: Sabbatical In Rochester – A Course in VB Theory

In August 1995 my family and I left Israel on our way for a sabbatical year in Rochester University, mainly to collaborate with Joe Dinnocenzo on cation radicals and teach a VB course in his department. Joe and I became very good friends. He likes fixing old things (cars, toasters, etc.), and in a way reminded me of Philippe. In 2008 I managed to bring them together to my 60th Birthday Symposium during the symposium of the Lise Meitner Center. They then started their own friendship and VB collaboration.

I have only vague memories of the atmosphere during the VB course in Rochester, and the only vivid reminder of the course is a set of hilarious cartoons designed by Joe. The first one showed that I was preaching VB theory at the exclusion of all other approaches. I do not wish to show this cartoon since it is against the cross cultural spirit I generally espouse.[31] I am showing instead another cartoon, which Joe designed after Lecture #4, in which I taught the audience the details of VB mixing. The cartoon (Figure 13) speaks for itself – I was teaching with enthusiasm, which Joe saw as zeal. Considering that most of the attendees were experimentalist physical organic chemists, I could have in retrospect given up the "art" of matrix elements. This course taught me to curb some of my desire to teach everything I know and achieved. Indeed the next invited VB courses (in Stockholm and then twice in Berlin) were delivered in a lighter format. The Rochester course and those that followed formed a basis for a book on VB theory, which Philippe and I would write and publish later in 2008.[24]

Other than the maddening weather in Rochester, this was a very productive year. During this time, Avital completed her VB study of benzene and the frequency of its b_{2u} mode. She showed that the π-electronic component experiences avoided crossing along this mode, and thereby generates the twin states, the ground state $^1A_{1g}$ and the excited $^1B_{2u}$ state, which correspond to the positive and negative combinations of the Kekulé structures, K_1+K_2 and K_1-K_2, respectively. Consequently, the π-component of the ground state behaved as distortive TS that is forced into a D_{6h} structure by the σ-frame. As such, the total force constant for the b_{2u} mode, $k(\sigma)+k(\pi)$, was small due to the negative k(π), this leading to a small vibrational frequency. On the other hand, the π-electronic component of the $^1B_{2u}$ excited state was attractive along the same b_{2u} mode so that the corresponding total force constant was high due to mutually reinforcing positive force constants k(π) and k(σ), thus resulting in a high vibrational frequency. This paper was published in JACS in 1996.[60a] It was followed by a short review for *Accounts of Chemical Research*, in which my coauthors and I demonstrated that this behavior of the b_{2u} mode and its frequency was general, and constituted a spectroscopic signature of the π-distortivity in the ground state, while being exalted in the excited state. [60b]

On July 7, 1996 I travelled back to Jerusalem to participate as a plenary speaker in the WATOC conference. It was a lot of excitement to see friends, my group members, and my new apartment that was being all too slowly constructed. In my

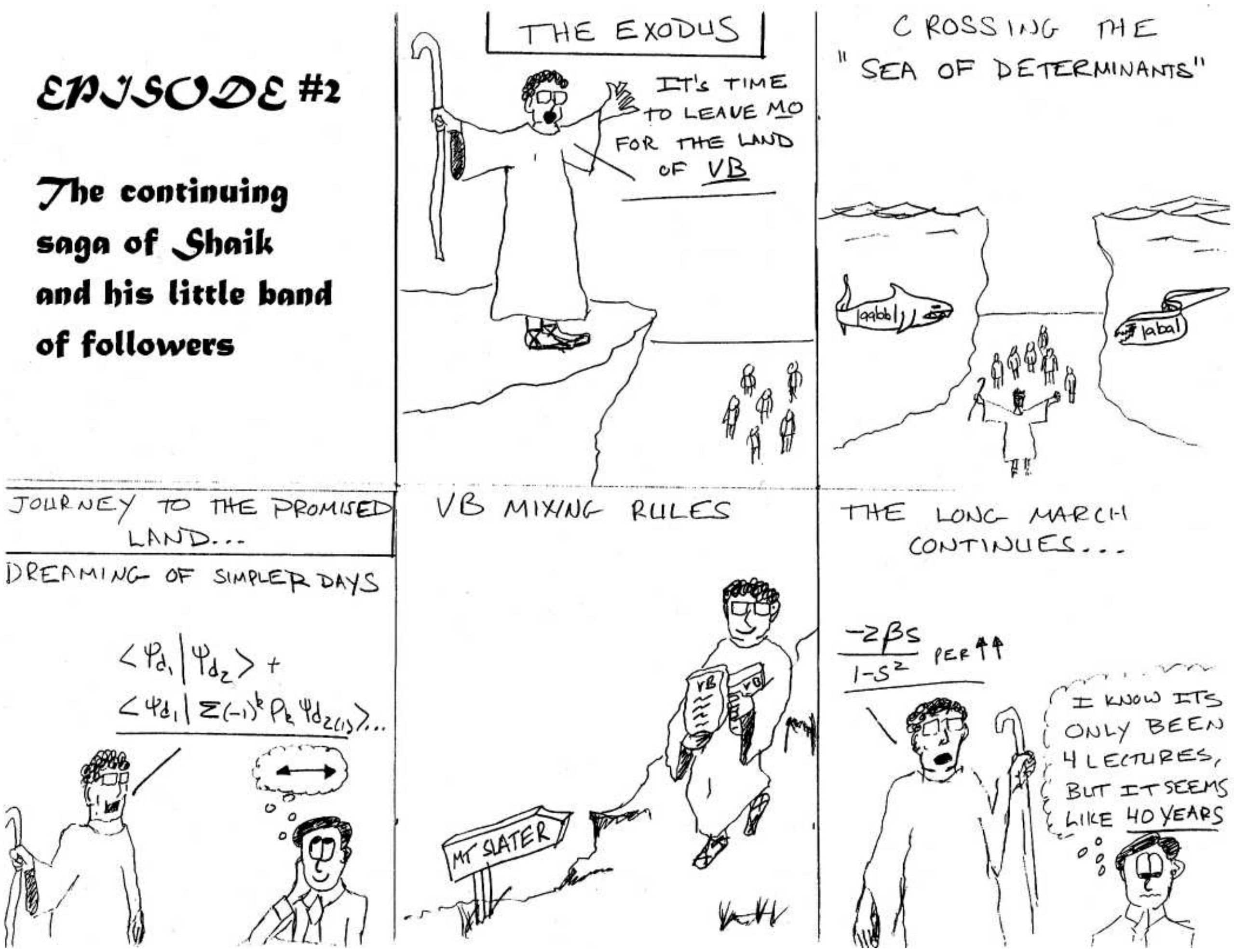

Figure 13. A cartoon prepared by J. P. Dinnocenzo (U. Rochester) to characterize the author's lecture on matrix elements between VB structures. Courtesy of J. P. Dinnocenzo.

lecture I talked about the new story of benzene. According to the notes in my diary it was well received. A year later Avital studied the tri-annelated benzene derivative made by Siegel,[82] and found it to exhibit strong bond alternation in the ground state. She demonstrated that in the 1st excited state, analogous to $^1B_{2u}$ in pristine benzene, the bond alternation virtually vanishes (presumably because the ground state resonance in the π-system was disrupted in the excited state and exposed the preference of the σ-frame for uniform C–C distances in the benzene skeleton). This paper was highlighted in *Chemistry and engineering News* (in Science and technology Concentrates in *C&E News*, November 3, 1997). The late Jeremy Burdett included in his 1997 book a whole chapter on the benzene story.[83] As I already told, in 2001 the late Paul Schleyer stated the acceptance of the idea that the D_{6h} symmetry of benzene was due to the σ-frame.

In 2011 Ulusoy and Nest[84] showed that scrambling the $^1A_{1g}$ and $^1B_{2u}$ states by laser pulses enables one to follow the dynamics of the single Kekulé structure to the ground state on a femto-second time scale. *Thus, the Kekulé structure can be dressed with physical reality*, by probing the vibrational frequency of the bond alternation mode, as well as by scrambling the states that are made from the two Kekulé structures and generating a single structure Kekulé, which could be followed. The same technique is in principle applicable to many other delocalized species, even to H_2^+, where it can show the behavior of the localized one-electron structures, e.g, $H^{\bullet}H^+$.

Lennart Eberson, Bjorn Roos, Dinoccenzo and I finally teamed on a paper that tested the predicted orbital-selection rules based on the FO-VB model on the regioselectivity of nucleophilic substitution of odd-nonalternant hydrocarbon radical cations.[85] Dinnocenzo and I formulated a VB model that could predict the structural patterns of σ-cation radicals (we never published the material). I had intensive discussions with Dinnocenzo on the possibility of TSR in cytochrome P450, based on the work he had done in collaboration with Jeffrey Jones on KIE determination for alkane hydroxylation by cytochrome P450. Later, these results will serve to show that KIE serves as a probe of the reactive spin state in P450.[86]

13. 1997–2020: Back to HU

After returning to HU from the sabbatical leave, I immediately travelled to Berlin and spent there two months of the Alexander von Humboldt senior researcher award. Helmut was extremely interested in P450 because of the similarity between its active species and FeO^+, and bacuase of experimental controversies in the field.[87] While in Berlin, I managed to reconstruct the electronic structure of the active species (Compound I) of P450, and to recover the two-state nature of the reagent, but these were degenerate ferromagnetic and antiferromagnetic states of three unpaired electrons, one residing on the porphyrin, the other two on the FeO moiety. I prepared a rough draft of a paper, and after many rounds, it was completed in 1997 in Jerusalem during the inauguration of *the Lise Meitner – Minerva Center for Computational Quantum Chemistry*, in July 1997.

The P450 paper (that was eventually published in *Chemistry A European Journal*[87]) and the establishment of the center would define a new phase in my scientific activity, which stretches from 1997 till 2017. The center enabled us to purchase a computing facility that was yearly updated and kept at a state-of-the art form till 2003, and subsequently was further supported by several yearly grants. We had money for guests, small grants to members, awards, conferences, etc. But above all, the sheer existence of the center has served as a seed to raise more money. I, for example, had from 1997 on several active grants, which gave me the means to expand my group and to do more extensive scientific work. Then there was DFT – a method that enabled calculations of "real' molecules.

The VB work has greatly benefited from the Center. First, there was David Danovich, who became a wonderful VB expert and kept the know-how (now for 29 years). Second, I did not need any more to apply for grants to carry out VB work. The work was supported by the Lise Meitner Center, which became a little VB haven for David, me, and all our future studies.

13.1 A Second Phase of Quantitative VB – This Time, in Jerusalem

In 1997–1999 my group has expanded to include a few excellent young scientists. The first was Wei Wu, from Xiamen in China. He wrote to me when I was still in Rochester about his wish to join my group and do research on VB theory. Wei had done a postdoctoral research with Roy McWeeny (who was then in Pisa). When I asked Roy his opinion, he wrote an enthusiastic letter about Wei and noted that he works 24/7. I decided to offer Wei a fellowship. He joined me in 1997.

Wei was (is) a wonderful programmer, and a former PhD student of the late Qianer Zhang, himself a student of Lu Jiaxi who was Pauling's student. Upon Lu's return to China, he preserved the VB culture (which at the time was slowly dying in the West). Wei Wu, a physicist by training, wrote a VB program as a PhD student with Zhang, and Zhang encouraged him to go for postdoctoral research in the West. Wei's presence in the group marked the second phase of quantitative VB theory.

In the same year, 1997, Johnny Galbraith a former Ph.D. student of Fritz Schaefer, joined my group with a specific intention to learn VB theory. With Wei, David, Avital and Johnny we had a critical mass to form a VB sub-group that investigated bonding and reactivity: Avital continued her work on benzene and bonding, Johnny was doing transition metal hydrides, π bond energies in double bonded molecules, and the Bergman cyclization, while David and Wei were looking at no-pair bonding of ${}^{n+1}M_n$ species, where M is a monovalent atom, like Li, Cu, etc.[88]

With Wei being around, we developed during those years a semiempirical VB method, with DFT input, so called VBDFT (s),[89] with which we investigated large polyenes in the ground and hidden excited state 2^1A_g,[89c] and showed for the first time that (a) polyenes longer than $C_{12}H_{14}$ had a major diradicaloid/polyradicaloid nature, and (b) much like in benzene, in polyenes too the force constant in the bond alternating vibrational mode was small in the ground state and larger in the 2^1A_g excited state. Wei and I also started marrying DFT and VB theories in a non-empirical VB-DFT method,[90] which later was further developed to a form where the dynamic correlation from DFT was added to the VB structures.[91]

Subsequently, we launched a "mother plan" for VB development for the years to come. This plan focused on the development of VB methods along the philosophy of Post Hartree-Fock theories, thus creating VBCI,[92a] VBPT2,[92b] and VBPCM.[92c] These methods along with the BOVB method, developed by Hiberty), provided a considerable arsenal for looking at a variety of problems and testing the qualitative models, VBSCD and VBCMD with inclusion of solvation.[93] I became a frequenct traveler to Xiamen where I collaborate with Wei's group and serve in the Advisory Board of the State-Key Laboratory in Xiamen.

Among the many collabirations with the Xiamen group, let me point out Peifeng Su, Junjing Gu and Binju Wang, with whom I have many papers. Junjing is a special case, he is a technical staff member with passion for science. We wrote together a few papers which showed the diradicaloid nature of polyenes and cross-conjugated polyenes.[89d,e]

Long collaborations leads in most cases to friendships: Wei and I (Figure 14) are still collaborating in 2020. Thus, along with Wei's former students, my former postdocs, and Philippe and his former students, and their students, the VB community has grown into a respectable group. The growth was stimulated by four VB Workshops in Paris (2012), Xiamen (2015), Aachen (2017) and Marseilles (2018), which have attracted general audience.[94]

Figure 14. Wei Wu and the author during the author's 1999 visit to Xiamen. Courtesy of Wei Wu.

14. 1998–2001: Kickstarting The Metallo-Enzyme Research

Luckily, DFT entered mainstream chemistry in those days. The method was quite efficient (and quickly growing to become very efficient) and enabled the calculations of large molecules like those in P450. Moreover, the method seemed to be decently reliable, which made it attractive for research on these metalloenzymes. These were new and exciting challenges…

The postdoc who brought DFT expertise to my group was Michael Filatov, who joined us after a postdoc period with the late Walter Thiel. Michael was (is) a DFT expert who did elegant methodology and applications. Soon enough, the group started running DFT calculations, which were essential for entering the field of metallo-enzymes and bioinorganic chemistry. The first such calculation was carried out by Nathan Harris, formerly a postdoc of Koop Lammertsma. Nathan came with a Fulbright Fellowship and was a superb computational chemist with immense patience and perseverance. I admitted also to the group a few undergraduate students, among them Shimrit Cohen who would later become my PhD student.

With Michael Filatov, Nathan Harris, Shimrit Cohen and François Ogliaro, we could start DFT calculations of P450 species. These calculations were painfully slow in 1998–1999, but nevertheless, the results enabled to treat pieces of the reaction mechanism of alkane hydroxylation by P450; we published these papers in 1998 and 1999 in *Angewandte Chemie*, and we laid thereby the foundations for TSR in P450.[95]

In 1999, I visited Berlin for the last portion of my Alexander von Humboldt Award. I also went for a seminar tour in Germany, France, London, Switzerland. I brought with me my usual set of talks and added one on P450. Of all the set, the P450 story was the star, and was selected with priority everywhere I lectured (including Germany, France, London, and Switzerland – where I were twice as a Trosieme-Cycle Lecturer).

In the same year, the WATOC conference was held in London. I gave a talk there on P450, which was well received by the audience. Theorists like when theory can be used to make order in such a complex system. After my talk, the late Walter Thiel, who was then still in Zürich, suggested we collaborate on this topic using the QM/MM method he was developing then. Walter and I had known each other for quite a few years, we got along extremely well and we seemed to complement one another. I of course agreed, but it took two years to consummate the collaboration.

In the meantime, the full P450 treatment with DFT had to wait until we acquired the software Jaguar, which was fast, and when François Ogliaro, a former PhD of Saillard and a postdoc of David Cooper, joined us (as a Marie Curie Fellow), and reinforced the P450 team (see Figure 15). Initially with guidance from Nathan and then independently, François under-

Figure 15. Part of the P450 group in 2001. From left to right are Shimrit Cohen, Francois Ogliaro, Joseph Kaneti, Sam de Visser, and David Danovich (photo taken by the author).

took, even if somewhat reluctantly at the beginning, the study of the full mechanism of alkane hydroxylation by P450. We started with methane as a model alkane, nevertheless what we found then is a still viable model for the TSR paradigm in P450 reactions in general. We showed that the quartet (ferromagnetic) and doublet (antiferromagnetic) states of the active oxo-iron species, so called Compound I (Cpd I) performed hydrogen abstraction, at almost equal energy barriers, leading to the formation of weakly coordinated alkyl radicals/hydroxo-iron species. Subsequently *the two spin-state surfaces bifurcated*: the quartet state process encountered an additional barrier for the formation of the ferric-alcohol complex, while the doublet state process was barrier free (see later Figure 16). This excellent work of François, which clarified many of the major puzzles and controversies in the field, was published in the year 2000 in JACS,[96] and introduced TSR as a new mechanistic paradigm in the P450 field.

In the year 2000, Sam de Visser, a former postdoc of Mike Robb, joined my group. After a sluggish start he soon became a highly productive postdoc. Furthermore, Sam was a very patient teacher and he took charge of educating many of the undergraduate students who were in the group. He and François got along well and started collaborating and producing together first-rate work and lots of it. Then Pankaz Sharma, a former Ph.D. student of Jemmis, joined the group, followed by Jose Kaneti, from Bulgaria, and Shimrit Cohen who has started her graduate research with me (Figure 15). The P450 team grew somewhat.

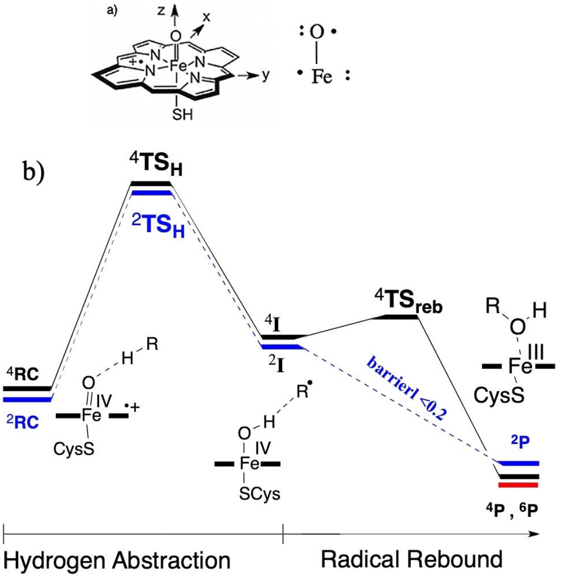

Figure 16. (a) A simplified model of Compound I (Cpd I) of P450, which has two closely lying spin states, doublet ($2S+1=2$) and quartet ($2S+1=4$). The porphyrin is in a radical-cationic state. The electron dot cartoon to the right of Cpd I provides a simplified electronic distribution of the $\pi^2\pi^{*1}$-electrons of FeO, using one of the resonance structures of the 3-electron bond in the xy plane. The other structure (skipped for simplicity) is a mirror image of the one shown. (b) Energy profile of alkane (R–H) hydroxylation. Roman numerals are oxidation states of Fe. The porphyrin is represented by the two bold bars flanking the Fe ion. As shown by the energy profile, the H-abstraction step has two states almost degenerate in energy. The radical formed by H-abstraction has no barrier for rebound to an alcohol on the doublet state, but the radical in the quartet manifold has a finite rebound barrier.

In the year 2000, François together with Michael, Nathan, Sam and Shimrit considered the effect of bulk polarity and amidic-type hydrogen bonding to the thiolate ligand of Cpd I, and found that the electronic structure including the Fe–S bond distance were undergoing large variations compared with the gas phase; it was then that we started calling Cpd I "*a chameleon species*" that adopts itself to the environment that accommodates it.[97a] We presented a VB model, which helped us conceptualize the variable nature of Cpd I. Then with a team effort led by François, we looked at a bigger model system and showed that Cpd I was behaving like a chameleon also for this larger model system, which contained the full cysteinate axial ligand. This larger model system helped us verify the role of strategic protein residues which are stabilized by H-bondiing the cysteine ligand as an anionic rather than a radical species. Subsequently, Sam, François and Pankaz, showed that this "chameleon" feature of Cpd I, which is controlled by H-bonds to the cysteine ligand, carries over to its reactivity-selectivity in C–H hydroxylation vs. double bond epoxidation of propene.[97b]

Later in 2002 when Devesh Kumar joined, he and Sam forged an efficient unit that studied many problems in P450. Devesh, a physicist and a former student of Roychoudhury, explored extensively the KIE patterns of TSR in alkane hydroxylation, and will establish what was noted in a preliminary study by Francois,[98] that KIE measurements probe the reactive spin state during TSR. This notion was strengthened significantly in 2007 by Yong Wang,[99] who has started his collaboration with me when he was still a Ph.D. student of Keli Han in the Dalian Institute of Molecular dynamics in China. This signature of TSR in P450 is now part of the normal science in bioinorganic chemistry.[86,99,100]

I would like to leap forward in time and describe the VB modeling of Cpd I reactivity, which took place since 2008. My goal in this section is not to repeat the TSR story, which was amply told between 2007 and 2010 in at least four review articles.[101] I wish rather to focus on the VB modeling of the H-abstraction reactivity of Cpd I, and to proceed with my adventure with complexity, which was motivated by one of the postdocs.

14.1 2008–2016: Modeling P450 Reactivity in H-Abstraction

Between the years 2000–2014 the group kept increasing. These were mostly postdocs who were interested in the enzyme Cytochrome P450 and analogous enzymes like horse radish peroxidase (HRP) and nitric oxide synthase (NOS), Heme oxygenase (HO) and chloroperoxidase (CPO), as well as in nonheme enzymes like TauD, etc. Some of these postdocs were Etienne Derat (a former student of Stephane Hmbel), Hajime Hirao (from the Fukui school), Yong Wang, Yohan Morreau, Maria-Angels Carvajal Barba (a former student of Santiago Alvarez), Hui Chen (a former student of Shuhau Li from Nanjing) and his spouse Wenzhen Lai, Usha Dandamudi (a former student of Jemmis), Deepa Janardanan (a former student of Raghavan B. Sunoj), Dhurairajan Senthilnathan, Chunsen Li (a former student of Wei Wu), Kyung Bin Cho (a former student of Per Siegbahn), Patric Schyman (from University of Stockholm), Petr Milko, Karina Hazan (from Israel), Binju Wang (a former student of Zexing Cao), Soumen Saha, Changwei Wei (a former student of Wei Wu), Rejeev Ramanan (a former student of Sunoj), Debasish Mandal, Dibyendu Mallick (a former student of Jemmis), Jing Huang (a former student of Wei Wu), Kshatresh Dubey, Saritha Banda, Zhanfeng Wang and Su Hao. I was also joined by new M.Sc. and Ph.D. students, Rina Meir, Elina Ploshnik, Sebastian Kozuch (a new immigrant from Argentina), Dan Fishelovich (jointly with Ruth Nussiniv and Chaim Wolfson from Tel Aviv University), and a visiting Ph.D. student Jinshuai Song (from Wei's group), and two visiting Fulbright awardees, Dina Sharon and Croix Laconsay (a former student of Johnny Galbraith) from the US.

Although not all worked on enzymes, many did. As such, the number of Cpd I reactions which the group studied increased, and I felt that the VB modeling of these reactions was becoming timely. Figure 16 shows the C–H hydroxylation by Cpd I, which involves initial H-abstraction followed by rebound of the radical $R^{\bullet}$ onto the hydroxo iron to form an alcohol. The Roman numerals are the oxidation states of the iron during the process.

There were issues which needed to be resolved before we start the VB modelling. The main issue was how to embed into the VBSCD and VBCMD the "oxidation state formalism". This formalism is based on the tacit assumption that the bonds to the metal are all ionic, while in fact, many of the bonds are actually covalent (e.g., the FeO bonds). It was important to conserve the oxidation state formalism since it enables to track the number of electrons in the d-orbitals of the transition metal along the reaction mechanisms we were looking at. Eventually, I managed to embed the oxidation state formalism into the VB diagram and this opened the road for VB modeling of P450 reactivity. During 2008–2014 we completed this modelling for the key oxidative reactions of Cpd I; H-abstraction from alkanes by Cpd I,[37,102] oxo transfer to dialkyl thioether[103] oxidation of aromatic molecules,[104] and olefin epoxidation.[37] These projects were conducted mostly by Chen, Wenzhen, Chunsen, and Usha.

Let me restrict myself to the H-abstraction reaction,[37,102] which could be treated by a single VBSCD and generalized to many seemingly unrelated reactions. This VBSCD is shown in Figure 17, which is identical to the generic VBSCD in Figure 7 with quantities that pertain to H-abstraction.

The $X^{\bullet}$ species on the left of Figure 17 represents radical abstractor, while $Y^{\bullet}$ on the right is the alkyl radical generated after H-abstraction. The diagram can handle P450, because the FeO moiety of Cpd I is analogous to the O_2 molecule, and possessing an unpaired electron on the oxo group of the FeO bond (cf. Figure 16a).[37,102b] Furthermore, since the two spin states of Cpd I have very similar barriers for H-abstraction (cf. Figure 16b), and since we are not treating the rebound step, we do not need to model the two states separately (we can use an averaged barriers).

As a first step, the unification of H-abstraction reactivity required abandoning the simple barrier equation (Eq. 4), and using one that considers explicitly the promotion gaps, and f factors for both reactant and product sides of the VB diagram, as well as the thermodynamic driving force in the VBSCD in

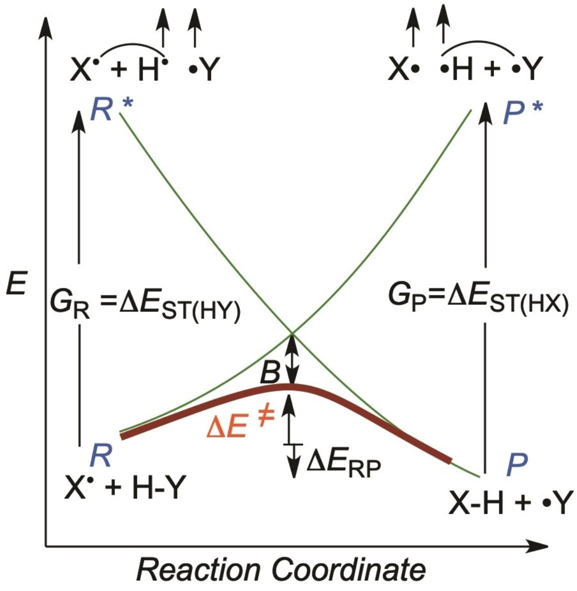

Figure 17. A general VBSCD for H-abstraction reactions. Adapted from Figure 2d in Ref 37 with RSC permission, copyright 2014.

Figure 17. Such an explicit expression for the barrier that treats the forward and reverse barriers on equal footing is given in equation 7:[37,102b]

$$\Delta E^{+} = f_0 G_0 + {}^{1}\!/_{2}\Delta E_{\mathrm{RP}} + {}^{1}\!/_{2}\Delta E_{\mathrm{RP}}{}^{2}/G_0 - B \quad (7a)$$

$$G_0 = {}^{1}\!/_{2}[G_{\mathrm{R}} + G_{\mathrm{P}}] \quad (7b)$$

$$f_0 = 0.5[f_{\mathrm{R}} + f_{\mathrm{P}}] \quad (7c)$$

$$B = {}^{1}\!/_{4}[BDE_{\mathrm{H-Y}} + BDE_{\mathrm{H-X}}] \quad (7d)$$

Here G_0 and f_0 are average factors for the two sides of the diagram, in Figure 17, while ΔE_{RP} is the thermodynamic driving force, and B is the resonance of the TS. The promotion gaps, G_{R} and G_{P}, involve singlet-triplet decoupling of the H–Y and X–H bonds. Each such singlet-triplet excitation can be approximated by twice the corresponding vertical bond energies (D), which are given by the sum of the corresponding bond dissociation energies (BDEs) and reorganization energies of radicals ($RE_{\mathrm{X}\bullet}$, $RE_{\mathrm{Y}\bullet}$). As such, the promotion gap at the reactants side (R) is given by Eq. 8a, as twice the sum ($BDE_{\mathrm{H\text{-}Y}} + RE_{\mathrm{Y}}{}^{\bullet}$). The expression for the promotion gap at the product side is analogous and is given in Eq. 8b

$$\Delta E_{\mathrm{ST(H-Y)}} \simeq 2D_{\mathrm{H-Y}} = 2(BDE_{\mathrm{H-Y}} + RE_{\mathrm{Y}\bullet}) \quad (8a)$$

$$\Delta E_{\mathrm{ST(H\text{-}X)}} \simeq 2D_{\mathrm{H\text{-}X}} = 2(BDE_{\mathrm{H-X}} + RE_{\mathrm{X}\bullet}) \quad (8a)$$

The term B in Eq. 7d is ${}^{1}\!/_{4}$ of the sum of the two BDEs of the exchanging bonds, while ΔE_{RP} is given as the difference of the corresponding BDEs of H–Y and H–X. The f terms are equal to ~0.3 according to semi-empirical VB (close to f values computed by VB for other H-abstraction reactions).[65,93d] The reorganization energy terms of the radicals. e.g., $RE_{\mathrm{X}}{}^{\bullet}$, are calculated by changing the geometry of the radical ($\mathrm{X}^{\bullet}$) to the one it has in the bonded molecule (H–X). This term involves the energy cost of changing the geometry of the radical and localizing its unpaired electron when it gets bonded. As such, one could estimate barriers using either empirical, or calculated BDEs of the bonds and REs of the respective $^{\bullet}$X and $^{\bullet}$Y radicals).[37,102b]

Let me just flash two plots in Figure 18 that reflect the performance of the VBSCD.

Figure 18a plots the VB predicted barriers against computed ones for 45 reactions, $\mathrm{Y}^{\bullet} + \mathrm{H{-}X} \rightarrow \mathrm{Y{-}H} + \mathrm{X}^{\bullet}$, which include identity (X = Y) and nonidentity (X ≠ Y) reactions of radicals ($\mathrm{X}^{\bullet}$, $\mathrm{Y}^{\bullet}$ = H, CH_3, SiH_3, Cl, F, CN, $NCCH_2$, HCC, $PhCH_2$, etc.), studied at the CCSD(T)/CBS-limit, as well as all the DFT barriers of H-abstraction by Cpd I of cytochrome P450. The correlation of the predicted barriers with the computed ones is reasonable considering the wide variety of reactions and the mixed quality of the calculations (the correlation coefficient is much better for the CCSD(T)/CBS data alone). The model equation (Eq. 7) of the VBSCD seems to capture the essence of the bond activation during a variety of H-abstraction reactions.[37,102b]

A major contribution to the barrier is the reorganization energy of the radical, $\mathrm{X}^{\bullet}$ ($RE_{\mathrm{X}}{}^{\bullet}$), from its relaxed geometry to the geometry it possesses in the H–X molecule. For identity reactions ($\mathrm{X}^{\bullet} + \mathrm{H{-}X} \rightarrow \mathrm{X\text{-}H} + {}^{\bullet}\mathrm{X}$), the radical reorganization energy is the key to understanding the barriers. Thus, using Eq. 8 and the expressions of the various quantities in terms of BDEs and $RE_{\mathrm{X}}{}^{\bullet}$, as well as $f = 0{,}3$, we find the following expression for the identity barrier:[102b]

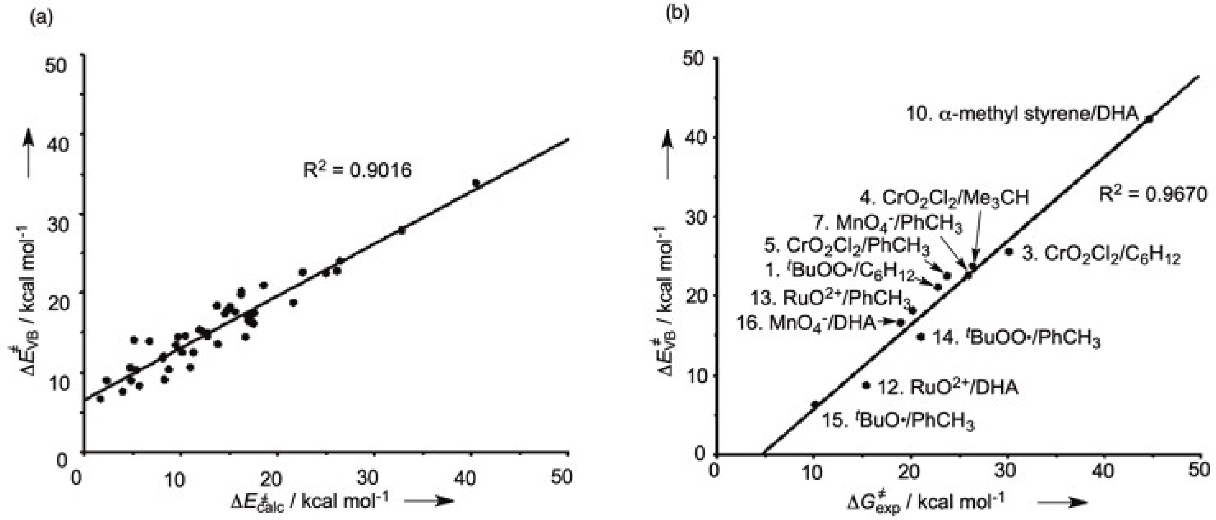

Figure 18. (a) A plot of VB calculated empirical barriers (using Eqs. 7 and 8) for 45 H-abstraction reaction vs. CCSD(T)/CBS and DFT calculated ones. (b) A plot of empirical VB barriers for a few H-abstraction reactions (indicated on the line) vs. corresponding experimental free energies of activation. Adapted from Figures 2b and 3b in Ref. 102b with permission of Wiley VCH, copyright 2012

$$\Delta E^{\neq} = 0.6(RE_{X\bullet}) + 0.1(BDE_{H-X}) \qquad (9)$$

It shows that the identity barrier is dominated the reorganization energy term for the radical $X^\bullet$. For example, comparing $X = HCC^\bullet$ to $NCCH_2^\bullet$, the identity barrier is larger for the latter even though the bond dissociation energy of HCC–H is huge compared with NCH_2–H (132.9 s. 95.7 $kcal\,mol^{-1}$). The reason is the much higher reorganization energy of the $NCCH_2^\bullet$ radical (10.7 vs. 0.1 $kcal\,mol^{-1}$), which is delocalized and planar in the relaxed form while being localized and pyramidal in the NCH_2–H molecule. $HCC^\bullet$ is localized and has no geometric reorganization upon bonding.[37,102b,105]

Figure 18b shows predicted VB barriers based on Eq. 7c plotted against experimental free energies of activation, for a variety of reactions including closed-shell H-abstractors like CrO_2Cl_2, MnO_4^-, and α-methylstyrene. It is evident that the VB model predicts well the experimental trends, and shows that all the closed shell abstractors have high barriers (compared e.g., with localized oxyl radicals). These high barriers originate in the reorganization energies that the closed-shell abstractor must invest in order to localize the radical on the site that forms the new Y–H bond.[37,102b,105]

We continued to do VB calculations and modelling and we still do (e.g., on electric field effects on structure and reactivity of molecules.[35,106] But it was this modelling of 45 reactions, which include simple H-abstractions, complex H-abstractions (e.g., by closed shell molecules), and very complex ones by Cpd I of P450, which convinced me that VB is an extremely useful theory. *Such a theory should be taught to students.*

Let me shift now to a recent story, in which I ended up dealing with much higher complexities using MD simulations of enzymes, followed by QM/MM calculations. Part of this adventure was due to the perseverance of my postdoc Kshatresh who joined the group in 2014, and who was intent on convincing me that MD simulations were essential and important.

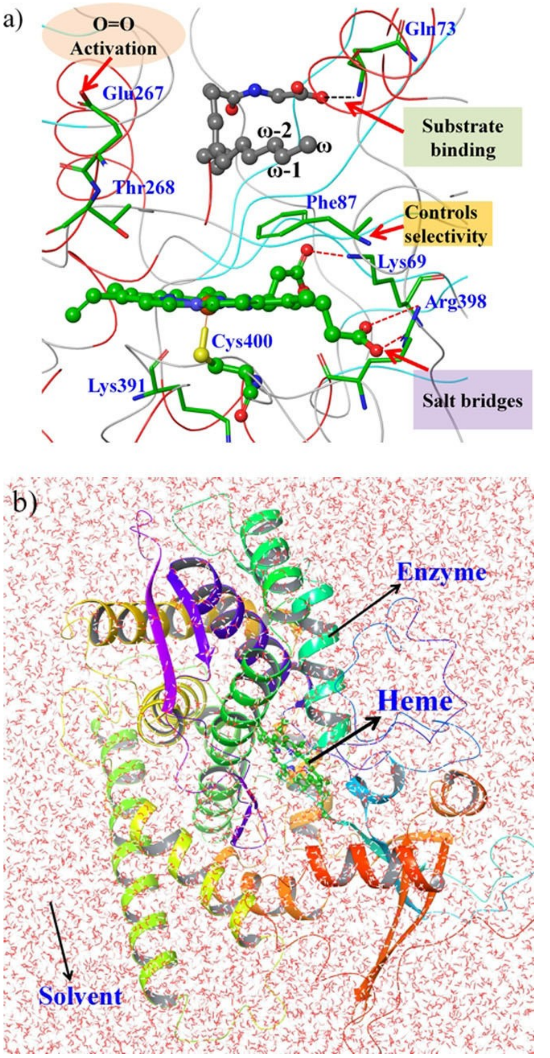

Figure 19. a) A cartoon of a P450 enzyme with strategic residues. The heme is the green object at the bottom of the drawing; b) A different view on the entire enzyme showing the little heme in the midst of many helices and pieces of protein, while the entire enzyme is bathing is tens of thousands of water molecules. Adapted from Figure 2 in Ref. 107 with ACS permission, copyright 2019.

15. Modelling Enzymes by Means of QM/MM Calculations

In the year 2001 Walter and I could finally consummate our collaboration. David Danovich, François Ogliaro and Shimrit Cohen traveled to Mülheim to learn from Thiel's group how to design and run QM/MM calculations. Enzymes are complex systems, as can be glanced from Figure 19. Therefore QM/MM is a multiscale method, it involves a QM subsystem, which is being cut from the rest of the protein, and is treated by DFT after mending the cuts by adding H atoms. The rest of the protein is treated by MM, and it interacts with the QM system by means of London and van Der Waals interactions. The MM point charges are embedded in the electronic Hamiltonian of the QM subsystem, so the later can be polarized and change its geometry according to the electrostatic field of the protein. From a theoretician who was accustomed to small up to moderately large molecules, like Cpd I, I suddenly found myself entering a world of complexity, where your target object had to undergo a series of pruning steps (almost looking experimental procedures), which prepared the final stage for calculations.

QM/MM is not a simple user-friendly method. One has to prepare the enzyme by adding all the missing hydrogens in the structures taken from the Protein Data Bank (PDB), then add a large number of water molecules (e.g., 20,000 molecules), and make sure this addition does not create hollow spaces. These steps of pruning the enzyme are done with the MD method in various steps. Finally, one runs a long MD equilibration trajectory (we reached 1,000 ns),[107] and then applies various methods to select best representative snapshots of the QM-MM system. Then one runs the QM/MM calculations and optimizations on these snapshots and gets e. g., an optimized structure of the enzymatic active species or a mechanism of its reaction and TSs along a reaction coordinate. The process is long and the quantity of chemical groups is baffling. Not every theoretician can handle the calculations sufficiently carefully. On the other hand, some are very good at this art, and I have been blessed with quite a few of those.

David, Francois and Shimrit learned to use the method by interacting with Walter Thiel's student Jan Schöneboom and his postdoc Natalie Reuter. It was decided to look first at Cpd I of the enzyme P450$_{CAM}$, which is a bacterial enzyme that hydroxylates camphor. To our satisfaction, the QM/MM results supported completely the conclusions of the model system that Cpd I behaves like a chameleon species and accommodates its electronic structure to the protein environment of the enzyme. Furthermore, Cpd I featured two closely lying spin states (separated by less than 1 kcal mol^{-1}), one is a doublet ($2S+1=2$), the other is a quartet ($2S+1=4$). The paper, which was published in JACS in 2002, was as far as we know the first QM/MM treatment of a complex metallo-enzymatic species.[108] In 2006, an experimental paper by Brian Hoffmann, John Dawson and coworkers would verify the results of these calculations, using the analogous enzyme chloroperoxidase (CPO).

Subsequently, the QM/MM investigations of Jan Schöneboom and Shimrit Cohen, recovered fully the TSR mechanism (cf. Figure 16) of camphor hydroxylation by P450cam.[109] This compatibility of a carefully chosen model system with a complete treatment of the species in its native protein environment was encouraging. So, in the next years we continued to use a blend of model calculations and QM/MM treatments. The collaboration between Walter's and my groups would continue with intensity till 2010. During this time duration we published two major Chemical Review Articles,[101b,d] and each one of these would include a section on applications of VB; to the electronic structure of Cpd I and the VBCMD for alkane hydroxylation.

15.1 MD Simulations of Enzymes

Let me proceed now to my adventure with complexity. My postdoc Kshatresh joined my group in 2014. In his background he is a physicist who did during his Ph.D. some courageous MD simulations, e. g., of the Dengue virus, which is one of the worst mosquito-borne human pathogens, and a relative of the Corona virus. He nevertheless, wanted to join my group because he liked the P450 work we were doing, and was ready to learn it. When he arrived I asked Usha and Binju who were then the team's experts on QM/MM, to tutor Kshatresh. He was quick to learn and started a few studies of P450 BM3 and P450$_{CAM}$, which are bacterial enzymes.

Kshatresh gave a few group seminars on P450 BM3, but initially tended to overemphasize the MD aspects in action; many groups vibrating and the entire enzyme is agitating like jelly. I was repeatedly asking him, "*but where is the chemistry*?" Even though such comments must be unpleasant, Kshatresh was not seemed to be offended. Rather, he went back to his calculations and produced the chemical talks I was asking to deliver.

He demonstrated how the entrance of the fatty-acid substrate to the "mouth" of the enzyme gates the enzyme by H-bonding interactions with residues that lined up the entrance channel, and consequently cause the closure of the channel by pulling together three major helices and a β sheet of the protein. In turn, at the bottom of the substrate's channel, the Phe 87 residue controlls the orientation of the fatty acid chain, which curls up due to its interaction with Phe 87 (cf. Figure 19a). As such, the chain exposes only its ω-1/ω−2/ ω-3 CH$_2$ groups, which are also the only ones which undergo oxidation. He further demonstrated that the Phe 87 also drives the enantioselectivity by preferring *R* hydroxylation. When he replaced Phe87 by the smaller residue Ala87, Kshatresh showed that the mutated enzyme leads to exclusive ω hydroxylation.[110] Thus, a coordinated movements of pieces of the protein were responsible for the regio- and enantio-selectivity of the fatty acid hydroxylation.[110] His understanding of both MD and QM/MM was helpful to other group members and led to many key publications on P450 enzymes.[111]

My first take on the P450 BM3 and P450$_{CAM}$ studies[110,111] was that I was witnessing the hands of evolution. Secondly, it became clear that a well conducted MD study can predict the selectivity outcome during the chemical reaction. Put together, all the studies,[110,111] led to a similar conclusion. *The protein was equipped with the right machinery, which got awakened when the substrate entered the active site of the enzyme.* MD is the tool that makes us aware of these trigger aspects of the nanomachine.

My enchantment with MD simulations increased dramatically, when Kshatresh and I investigated the catalytic cycles of the enzymes P450 BM3 and P450$_{CAM}$.[107,111f] The catalytic cycle involves a series of steps which are depicted in Figure 20. The cycle commences with the entrance of the substrate to the active site, and then proceeds in a series of steps which involve reduction of the enzyme, uptake of O$_2$, protonation, formation of Cpd I (cf. **VII** in Figure 20), substrate oxidation, departure of the oxidized molecule, and regeneration of the resting state.

By the time Kshatresh joined my group, Walter's and my groups have already calculated most of the individual steps in the cycle. Furthermore, my Ph.D. student Fishelovitch (jointly with Nussinov and Wolfson from Tel Aviv University), also an MD expert, has handled the MD simulations of three events in the cycle.[112] The entrance/exist of the substrate and oxidized substrate,[112a,c] and the formation of water aqueducts which enable water molecules to flow in and out of the enzyme and

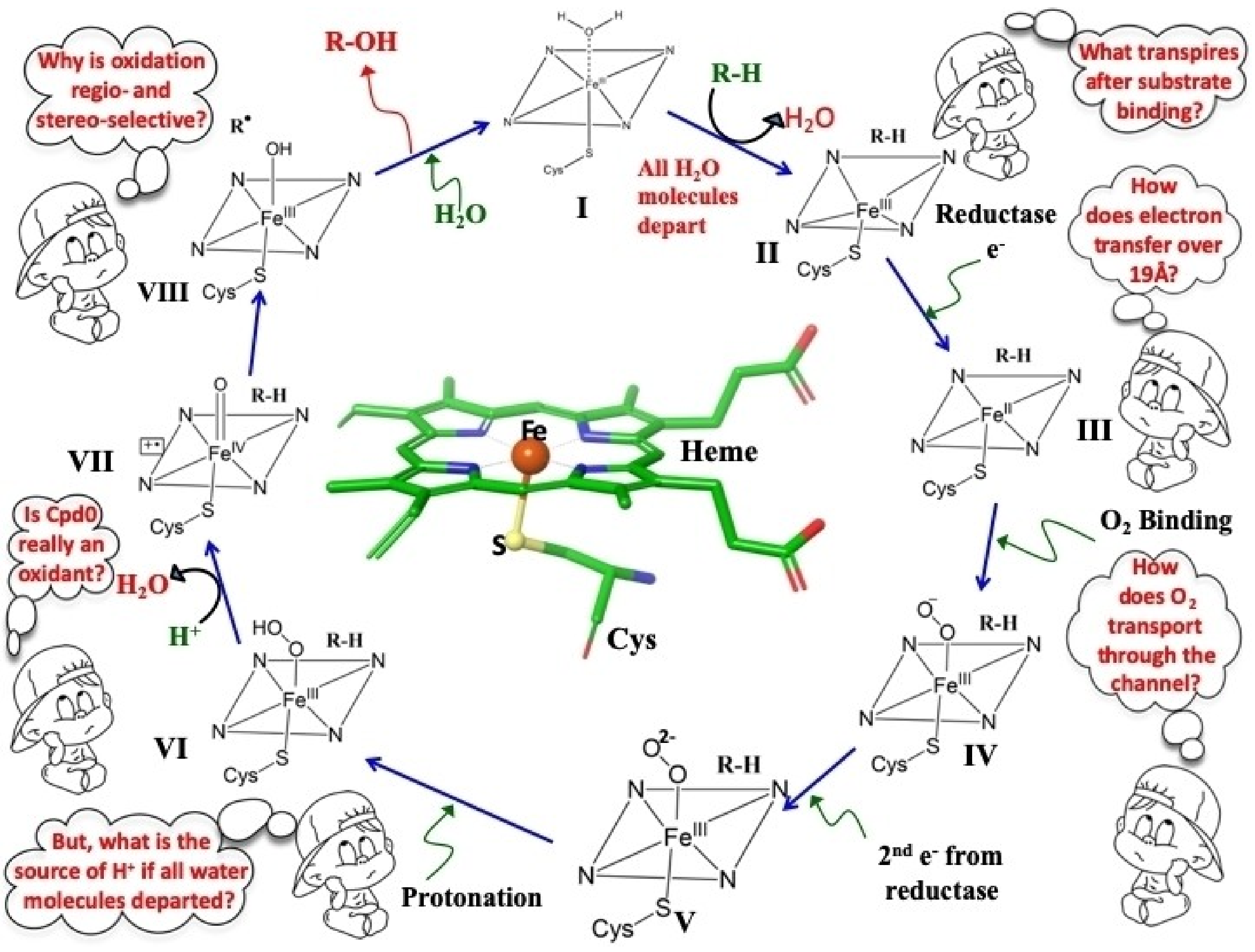

Figure 20. A typical catalytic cycle of P450 enzymes with the heme in the middle. The questions about each step that were answered in Ref. 107 and 111f. Reproduced with ACS permission from Figure 1 in Ref. 107. Copyright 2019.

enable hereby the protonation of the O_2 molecule during the generation of Cpd I.[112b]

The discovery of the water aqueducts,[112b] was exciting. Nevertheless, we still did not have a tight overview of this nanomachine. It was Kshatresh who put the story together and showed that all the steps have to be studied together and each should begin with a sufficiently long MD to capture the main movements of the key protein residues.[107] Otherwise one misses the mechanism by which this complex machinery operates. In the most recent study[111f] Kshatresh, his student Kalita, my postdoc Kisan and I answered the remaining questions: on the mechanism of O_2 diffusion and its binding to the iron, and on the mechanisms of protonation (**V→ VI→VII** in Figure 20).

May be it would not be surprising anymore if I told you that the same strategic residue (e.g. Phe 87 in P450 BM3 in Figure 19a) kicks up the substrate and thereby helps O_2 approach the heme iron. Furthermore, the recent MD simulations[111f] show that the few-decades old paradigm that the two protonation steps involve the same pair of acid-alcohol residues (e.g., Asp 252-Thr 252 in $P450_{CAM}$) has to be revised. Thus, after the first protonation, the anionic form of the acid points to the surface of the protein, wherein it enjoys stabilization by H-bonds, and as such, it cannot rotate back inside sufficiently quickly to perform a second protonation. What comes to the rescue is one of the propionate side chains of the porphyrin (cf. middle of Figure 20), which is gated open by the reductase, and can shuttle protons to complete the formation of Cpd I. So even those side chains have evolutionary role in P450 enzymes. What a wonderfully complex nanomachine and how essential is MD for deciphering these unusual events!

For me personally, as one who has spent his career making predictions and gaining insight from electronic structure calculations, this was also a humbling experience. Chemists can make almost any molecule they decide to make and quantum theorists can understand the molecule profoundly. But to predict how and which parts of a big enzyme would react in response to an interaction of a "foreign" molecule, requires insight into kinematics of many body objects, something that chemists have not yet mastered through their synthetic practices and their molecular calculations (but they will get to it…). And even if chemists would understand the mechanism perfectly well in retrospect, *still the creation of a poly-molecular machine that would duplicate the selectivity (regio- and enantio-selectivities) of enzymes and perform as "instructed by the maker", is not a fully developed general art in chemistry.* The intuitive understanding of many-body kinematics is going to be needed for a full control.

I was also wondering about quantum chemical theory. It is a beautiful tool for the mind, which uses objects like orbitals or VB structures to understand molecules, their bonds, and their reactions with other molecules. But still the mind falls short of predicting the above results for the enzymes. Theoreticians would have to master their understanding of kinematics through MD simulations. Artificial intelligence (machine learning) may be helpful for that in the future.

16. A Collage of VB Studies

This brings me back to VB theory which is the main theme of this Rosarium Philosophorum. I described a few of our VB studied and demonstrated how useful and predictive can VB theory (VBT) be for chemists. I did not touch however, main themes in our applications of this theory:

(a) Application of VBT to predict new bonding motifs; charge-shift electron pair bonding,[113] and bonding of triplet pairs, which exits in high-spin clusters of monovalent metallic atoms ($^{n+1}Li_n$, $^{n+1}Na_n$,…, $^{n+1}Cu_n$, $^{n+1}Ag_n$, $^{n+1}Au_n$) and can reach bonding energies, as much as or more than 20 kcal mol^{-1}/atom.[114]

(b) Understanding weak interactions using a VB approach, which were done in collaboration with Santiago Alvarez, Frank Neese and Yirong Mo (formerly from the Xiamen group).[115,116]

(c) Application of VBT for understanding and predicting the manners by which oriented-external electric fields (OEEFs), affect bonding, structure and reactivity[35,48,106,117]

Bonding and similar issues will be addressed in the companion Rosarium.

The field of OEEF constitutes these days as the main activity in the group, and I have been blessed with brilliant coworkers, Reajeev Ramanan, Debasish Mandal, David Danovich, Jyothish Joy and Thijs Stuyver,[35,106,117] who made seminal contributions to this area and broadened the VB insight. The future prospects of this field are exciting, and I have been fortunate to share[118] my excitement with a growing group of colleagues.

17. Conspectus

A Rosarium Philosophorum is supposed to summarize and share with readers "wisdom" one has acquired during his/her journey of seeking knowledge and insight. I selected to tell the readers of this Issue, about the manner by which my short career as an experimentalist (1972–1973) converted me to a theorist at a time when my scant knowledge of MO theory proved capable of solving the "mysteries" of my experimental research.

I continued with personal adventures during the Ph.D. and postdoctoral research, and recounted my "discovery" of VB theory, and the labor to develop its conceptual aspects to become a useful tool for chemists.

In the end, I discussed the journey that led me to Cytochrome P450 and other metalloenzymes which are complex systems. I was lucky to get familiar with density functional theory, as a useful tool for exploring these objects, and ended showing that all reactivity patterns of the enzyme could be comprehended using just two VB diagrams (VBSCD and VBCMD).

Then my journey shifted into multiscale QM/MM calculations, and later into MD simulations of these creatures. I described our struggles to create wisdom from complexity; some of which I managed to create… But I doubt any such wisdom can be easily transferrable to other enzymes, or be replicated by design into a complex nanomachine. *These creatures are unique, and each one tells itst own unique story.*

What is the next adventure? I am waiting with anticipation…

In summary, my story is a lesson on how computational quantum chemistry (CQC) has become a major branch of chemistry; one that unites chemistry. QCQ will become even more useful when its branches (VB, DFT, and MO) will be united by bridges, which will be part of the education system of every chemist.

At the same time, this story is chiefly about people and their wisdom which was bestowed on me – those teachers and scientists who I met in my way, and student and postdocs who influenced and taught me things I would have never endeavored to learn by my own initiative. *One's wisdom is the sum of the wisdoms he/she absorbs during these many human encounters. I am grateful to my teachers, colleagues, students and postdocs for their gifts to me.*

Acknowledgements

SS is supported by the Israel Science Foundation (ISF Grant 520/18). He thanks M. Michman for the TOC cartoon.

References

[1] a) S. Shaik, *J. Phys. Chem. A* **2008**, *112*, 12724–12736; b) A. W. Wilson, *Profile of Prof. Sason Shaik – recipient of the 2017 Gold Medal, The Israel Chemists and Chemical Engineer*, **2018**, *4*, 42–43.

[2] a) R. Hoffmann , *J. Chem. Phys.* **1963**, *39*, 1397–1412; b) J. A. Pople, D. L. Beveridge, *Approximate Mollecular Orbital Theory;* **1970**, McGraw-Hill, Inc., New York.

[3] W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*; **1986**, John Wiley, New York.

[4] For discussions and eventual consilience between computations (facts seeking) and understanding, see: R. Hoffmann, J. P. Malrieu, *Angew. Chem. Int. Ed.* **2020**, *59*, 12590–12610; 13156–13178; 13694–13710.

[5] a) P. Geerlings, F. De Proft, W. Langenaeker, *Density Functional Thoery: A Bridge Between Chemistry and Physics;* **1986**, Free University of Brussels University Press, Brussels, Belgium; b) W. Kohn, L. J. Sham, *Phys. Rev.* **1965**, *140*, A1133- A1138; c) For the orbital culture in DFT, see: G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. Van Gisbergen, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931–967.

[6] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press; 1939, Ithaca, New York, (3rd Edition, **1960**).

[7] M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, **1969**, McGraw-Hill, Inc., New York.

[8] M. Albeck, S. Shaik, *J. Chem. Soc. Perkin I* **1975**, 1223–1229.

[9] M. Albeck, S. Shaik, *J. Organomet. Chem.* **1975**, *91*, 307–313.

[10] Correspondence between Roald Hoffmann and Sason Shaik (March 4th, 1974). Courtesy of R. Hoffmann.

[11] a) N. D. Epiotis, *J. Am. Chem. Soc.* **1973**, *95*, 3087–3096; b) N. D. Epiotis, D. Bjorkquist, L. Bjorkquist, S. Sarkanen, *J. Am. Chem. Soc.* **1973**, *95*, 7558–7562; c) N. D. Epiotis, S. Sarkanen, D. Bjorkquist, L. Bjorkquist, R. Yates, *J. Am. Chem. Soc.* **1974**, *96*, 4075–4084.

[12] N. D. Epiotis, W. Cherry, S. Shaik, R. L. Yates, F. Bernardi, *Top. Curr. Chem.* **1977**, *70*, 1–250.

[13] a) S. S. Shaik, N. D. Epiotis, *J. Am. Chem. Soc.* **1978**, *100*, 18–29; b) S. S. Shaik, *J. Am. Chem. Soc.*,**1979**, *101*, 2736–2738; c) S. S. Shaik, *J. Am. Chem. Soc.* **1979**, *101*, 3184–3196.

[14] R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, **1971**. Verlag Chemie, Academic Press, GmbH, Weinheim, Germany.

[15] N. D. Epiotis, *Angew. Chem. Int. Ed.* **1974**, *13*, 751–780; *Angew. Chem.* **1974**, *86*, 825–855.

[16] W. Heitler, F. London, *Z. Phys.* **1927**, *44*, 455–472.

[17] M. Elian, R. Hoffmann, *Inorg. Chem.* **1975**, *14*, 1058–1076.

[18] R. Hoffmann, *Angew. Chem. Int. Ed.* **1982**, *21*, 711–724; *Angew. Chem.* **1982**, *94*, 725–739.

[19] S. Shaik, *New J. Chem.* **2007**, *31*, 2015–2028.

[20] J. C. Slater, *Phys. Rev.* **1931**, *37*, 481–489.

[21] a) C. A. Coulson, *Valence*, **1952**, Oxford University Press, London; b) See comments in: B. S. Park, In: *Pedagogy and the Practice of Science*, **2005**, D. Kaiser, Ed. MIT Press, Boston, pp 287–319 ("*In the Context of Padagogy: Teaching Strategy and Theory Change in Quantum Chemistry*").

[22] a) C. Edmiston, K. Ruedenberg, *Rev. Mod. Phys.* **1963**, *35*, 457–465; b) K. Ruedenberg, *J. Chem. Phys.* **1964**, *41*, 588–589; c) C. Edmiston, K. Ruedenberg, *J. Phys. Chem.* **1964**, *68*, 1628–1653; d) S. F. Boys in *Quantum Theory of Atoms, Molecules, and the Solid State* (Ed.: P.-O. Löwdin), Academic Press, New York, **1968**, p. 253.

[23] a) S. S. Shaik, *J. Am. Chem. Soc.* **1981**, *103*, 3692–3701; b) See the Supporting information document in a).

[24] S. Shaik, P. C. Hiberty, *A Chemist's Guide to Valence Bond Theory*, **2008**, Wiley, Hoboken, NJ ; a) Chapter 1; b) Chapter 5; c) Chapter 6; d) Chapter 3.

[25] G. N. Lewis, *J. Am. Chem. Soc.* **1916**, *38*, 762–785.

[26] S. Shaik, *J. Comput. Chem.* **2007**, *28*, 51–61.

[27] F. London, *Zeits. für Physik* **1928**, *46*, 455–477.

[28] a) For English translations, see: H. Hettema, *Quantum Chemistry Classic Scientific Papers;* World Scientific, Singapore, **2000**, pp. 140–155 (HL paper) and 156–174 [London's paper]; b) T. Hager, *Force of Nature: The Life of Linus Pauling*, **1995**; Simon and Schuster: New York, p. 63.

[29] a) R. S. Mullliken, *Phys. Rev.* **1929**, *33*, 730–747; b) F. Hund, *Zeits. für Physik*, **1928**, *51*, 759–795.

[30] S. G. Brush, *Stud. Hist. Phil. Sci.* **1999**, *30*, 21–79; S. G. Brush, *Stud. Hist. Phil. Sci.* **1999**, *30*, 263–302.

[31] R. Hoffmann, S. Shaik, P. C. Hiberty, *Acc. Chem. Res.* **2003**, *36*, 750–756.

[32] a) D. G. Truhlar, *J. Comput. Chem.* 2007, 28, 73–86; b) W. A. Goddard III, T. H. Dunning, Jr., W. J. Hunt, P. J. Hay, *Acc. Chem. Res.* **1973**, *6*, 368–376; c) D. L. Cooper, J. Gerratt, M. Raimondi, *Chem. Rev.* **1991**, *91*, 929–964; d) L. Song, Y. Mo, Q. Zhang, W. Wu, *J. Comput. Chem.* **2005**, *26*, 514–52; e) J. H. van Lenthe, F. Dijkstra, W. A. Havenith, in *Valence Bond Theory*, D. L., Ed. Elsevier, Amsterdam, **2002**, pp 79–116; f) W. Wu, P. Su, S. Shaik, P. C. Hiberty, *Chem. Rev.* **2011**, *111*, 7557–7593.

[33] R. Gershoni-Poranne, P. Chen, *Chem. Eur. J.* **2017**, *23*, 4659–4668.

[34] S. S. Shaik, N. D. Epiotis, *J. Am. Chem. Soc.* **1980**, *102*, 122–131.

[35] S. Shaik, D. Mandal, R. Ramanan, *Nat. Chem.* **2016**, *8*, 1091–1098.

[36] S. Shaik, A. Shurki, *Angew. Chem. Int. Ed.* **1999**, *38*, 586–625; *Angew. Chem.* **1999**, *111*, 616–657.

[37] U. Dandamudi, W. Z. Lai, C. Li, H. Chen, D. Danovich, S. Shaik, *Chem. Soc. Rev.* **2014**, *43*, 4968–4988.

[38] S. S. Shaik, "*A Qualitative Valence Bond Approach to Organic Reactions*" in "*New Theoretical Concepts for Understanding Organic Reactions*", NATO ASI Series C267, Eds. J. Bertran, G. I. Csizmadia, Kluwer Publ., Dordrecht, Holland, **1989**.

[39] a) S. S. Shaik, J. P. Dinnocenzo, *J. Org. Chem.* **1990**, *55*, 3434–3436; b) S. S. Shaik, E. Canadell, *J. Am. Chem. Soc.* **1990**, *112*, 1446–1452.

[40] Y. Apeloig in *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport); **1989**, Wiley, Chichester, chapter 2, pp. 57–227.

[41] M. J. Pellerite, J. I. Brauman, *J. Am. Chem. Soc.* **1980**, *102*, 5993–5999.

[42] S. S. Shaik, *Nouv. J. Chim.* **1982**, *6*, 159–161.

[43] S. S. Shaik, A. Pross, *J. Am. Chem. Soc.* **1982**, *104*, 2708–2719.

[44] R. Hoffmann, *Chem. Br.*, (*Valence Bond Theory*, March **1991**). Courtesy of R. Hoffmann.

[45] J. E. Buncel, S. S. Shaik, I.-H. Um, S. Wolfe, *J. Am. Chem. Soc.*, **1988**, *110* 1275–1279.

[46] a) W. Z. Lai, C. Li, H. Chen, S. Shaik, *Angew. Chem. Int. Ed.* **2012**, *51*, 5556–5578; *Angew. Chem.* **2012**, *124*, 5652–5676; b) T. Stuyver, F. De Proft, P. Geerlings, S. Shaik, *J. Am. Chem. Soc.* **2020**, *142*, 10102–10113.

[47] A. Pross, S. S. Shaik, *J. Am. Chem. Soc.* **1981**, *103*, 3702–3709.

[48] R. Meir, H. Chen, W. Lai, S. Shaik, *ChemPhysChem.* **2010**, *11*, 301–310.

[49] A. Pross, S. S. Shaik, *Acc. Chem. Res.* **1983**, *16*, 363–370.

[50] A. Pross, *What is Life?* **2012**, Oxford University Press, Oxford, UK.

[51] S. S. Shaik, *J. Am. Chem. Soc.* **1982**, *104*, 5328–5334.

[52] S. S. Shaik, M.-H. Whangbo, *Inorg. Chem.* **1986**, *25*, 1201–1209.

[53] S. S. Shaik, *J. Am. Chem. Soc.*, **1984**, *106*,1227–1232.

[54] S. S. Shaik, *J. Am. Chem. Soc.* **1983**, *105*, 4359–4367.

[55] a) P. Su, F. Ying, W. Wu, P. C. Hiberty, S. Shaik, *ChemPhysChem*, **2007**, *8*, 2603–2614; b) L. Song, W. Wu, P. C. Hiberty, S. Shaik, *Chem. Eur. J.* **2006**, *17, 7458–7466*.

[56] S. S. Shaik, R. Bar, *Nouv. J. Chim.* **1984**, *8*, 411–420.

[57] S. S. Shaik, *Prog. Phys. Org. Chem.* **1985**, *15*, 197–337.

[58] P. C. Hiberty, C. Leforestier, *J. Am. Chem. Soc.* **1978**, *100*, 2012–2017.

[59] a) S. S. Shaik, P. C. Hiberty, G. Ohanessian, J. M. Lefour, *Nouv. J. Chim.* **1985**, *9*, 385–388; b) P. C. Hiberty, S. S. Shaik, J. M. Lefour, G. Ohanessian, *J. Org. Chem.* **1985**, *50*, 4657–4659; c) S. S. Shaik, P. C. Hiberty, *J. Am. Chem. Soc.* **1985**, *107*, 3089–3095.

[60] a) S. Shaik, A. Shurki, D. Danovich, P. C. Hiberty, *J. Am. Chem. Soc.* **1996**, *118*, 666–671; b) S. Shaik, S. Zilberg, Y. Haas, *Acc. Chem. Res.* **1996**, *29*, 211–218.

[61] D. Cohen, R. Bar, S. S. Shaik, *J. Am. Chem. Soc.* **1986**, *108*, 231–240.

[62] a) A. Demolliens, O. Eisenstein, P. C. Hiberty, J. M. Lefour, G. Ohanessian, S. S. Shaik, F. Volatron, *J. Am. Chem. Soc.* **1989**, *111*, 5623–5631; b) G. Sini, P. C. Hiberty, S. S. Shaik, *J. Chem. Soc. Chem. Commun.* **1989**, 772–774; c) G. Sini, G. Ohanessian, P. C. Hiberty, S. S. Shaik, *J. Am. Chem. Soc.* **1990**, *112*, 1407–1413.

[63] D. J. Mitchell, H. B. Schlegel, S. S. Shaik, S. Wolfe, *Can. J. Chem.* **1985**, *63*, 1642–1649.

[64] a) G. Sini, S. S. Shaik, J. M. Lefour, G. Ohanessian, P. C. Hiberty, *J. Phys. Chem.* **1989**, *93*, 5661–5665; b) G. Sini, S. Shaik, P. C. Hiberty , *J. Chem. Soc. Perkin Trans. 2* **1992**, 1019–1025.

[65] P. Mâitre, P. C. Hiberty, G. Ohanessian, S. S. Shaik, *J. Phys. Chem.* **1990**, *94*, 4089–4093.

[66] S. S. Shaik, H. B. Schlegel, S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry. Application to the S_N2 Transition State*, **1992**, Wiley Interscience, NY.

[67] a) T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper & Row. Publ., New York. NY, **1987**, 3rd ed., pp. 218–222, 220, 354, 354–360, 381–382, 412, 604, 685; b) F. A. Carroll, *Perspectives on Structure and Mechanism in Organic Chemistry*, 2nd ed., John Wiley & Sons, Hoboken, New Jersey, **2010**, pp. 19, 27, 205, 238, 240, 276, 309, 365, 479, 500, 503, 513, 417, 533, 724.

[68] E. Heilbronner, *J. Chem. Educ.* **1989**, *66*, 471–478.

[69] S. Shaik, A. Shurki, D. Danovich, P. C. Hiberty, *Chem. Rev.* **2001**, *101*, 1501–1539.

[70] M. G. Evans, *Trans. Faraday Soc.* **1939**, *35*, 824–834.

[71] J. A. Berson, *Chemical Creativity: Ideas from the Work of Woodward*, Hückel, Meerwein, and Others, Wiley-VCH, New-York, **1999**.

[72] A. Shurki, P. C. Hiberty, F. Dijkstra, S. Shaik, *J. Phys. Org. Chem.* **2003**, *16*, 731–745.

[73] L. Eberson, *Electron Transfer Reactions in Organic Chemistry;* Springer-Verlag, Heidelberg, Germany, **1987**, pp. 8. 141–142, 192.

[74] L. Eberson, S. S. Shaik, *J. Am. Chem. Soc.* **1990**, *112*, 4484–4489.

[75] J. K. Cho, S. Shaik, *J. Am. Chem. Soc.* **1991**, *113*, 9890–9891.

[76] a) G. N. Sastry, D. Danovich, S. Shaik, *Angew. Chem. Int. Ed.* **1996**, *35*, 1098–1100; *Angew. Chem.* **1996**, *108*, 1208–1211; b) G. N. Sastry, S. Shaik, *J. Phys. Chem.* **1996**, *100*, 12241–12252.

[77] V. Bakken, D. Danovich, S. Shaik, H. B. Schlegel, *J. Am. Chem. Soc.* **2001**,*123*, 130–134.

[78] S. Shaik, M. Karni, D. Danovich, Y. Apeloig, *Isr. J. Chem.* **2015**, *55*, 1167–1176.

[79] S. Shaik, *Isr. J. Chem.* **2020**, *60*, 938–956.

[80] A. Fiedler, D. Schröder, S. Shaik, H. Schwarz, *J. Am. Chem. Soc.* **1994**, *116*, 10734–10741.

[81] a) S. Shaik, D. Danovich, A. Fiedler, D. Schröder, H. Schwarz, *Helv. Chim. Acta* **1995**, *78*, 1393–1407; b) D. Schröder, S. Shaik, H. Schwarz, *Acc. Chem. Res.* **2000**, *33*, 139–145; c) S. Shaik, H. Hirao, D. Kumar, *Acc. Chem. Res.* **2007**, *40*, 532–542.

[82] A. Shurki, S. Shaik, *Angew. Chem. Int. Ed.* **1997**, *36*, 2205–2208; *Angew. Chem.* **1997**, *109*, 2322–2324.

[83] J. K. Burdett, *Chemical Bonds. A Dialog*, John Wiley & Sons, Chichester, UK, **1997**, Ch. 12, pp. 113–120.

[84] I. S. Ulusoy, M. Nest, *J. Am. Chem. Soc.* **2011**, *133*, 20230–20236.

[85] L. Eberson, R. González-Luque, M. Merchán, F. Radner, B. O. Roos, S. Shaik, *J. Chem. Soc. Perkin Trans. 2*, **1997**, 463–472.

[86] C. Li, W. Wu, D. Kumar, S. Shaik, *J. Am. Chem. Soc.* **2006**, *128*, 394–395.

[87] S. Shaik, M. Filatov, D. Schröder, H. Schwarz, *Chem. Eur. J.* **1998**, *4*, 193–199.

[88] D. Danovich, W. Wu, S. Shaik, *J. Am. Chem. Soc.* **1999**, *121*, 3165–3174.

[89] a) W. Wu, S.-J. Zhong, S. Shaik, *Chem. Phys. Lett.* **1998**, *292*, 7–14; b) W. Wu, Y. Luo, L. Song, S. Shaik, *Phys. Chem. Chem. Phys.* **2001**, *3*, 5459–5465; c) W. Wu, D. Danovich, A. Shurki, S. Shaik, *J. Phys. Chem. A*, **2000**, *104*, 8744–8758; d) for additioal studies of polyenes, see: J. Gu, W. Wu, D. Danovich, R. Hoffmann, T. Yuta, S. Shaik, *J. Am. Chem. Soc.* **2017**, *139*, 9302–9316; e) J. Gu, W. Wu, T. Stuyver, D. Danovich, R. Hoffmann, Y. Tsuji, S. Shaik, *J. Am. Chem. Soc.* **2019**, *141*, 6030–6047.

[90] W. Wu, S. Shaik, *Chem. Phys. Lett.* **1999**, *301*, 37–42.

[91] F. Ying, P. Su, Z. Chen, S. Shaik, W. Wu, *J. Chem. Theory Comput.* **2012**, *8*, 1608–1615.

[92] a) W. Wu, L. Song, Z. Cao, Q. Zhang, S. Shaik, *J. Phys. Chem. A*, **2002**, *106*, 2721–2726; b) L. Song, W. Wu, Q. Zhang, S. Shaik, *J. Comput. Chem.* **2004**, *25*, 472–478; c) L. Song, W. Wu, Q. Zhang, S. Shaik, *J. Phys. Chem. A*, **2004**, *108*, 6017–6024.

[93] a) L. Song, W. Wu, P. C. Hiberty, D. Danovich, S. Shaik, *Chem. Eur. J.* **2003**, *9*, 4540–4547; b) S. Shaik, S. P. de Visser, W. Wu, L. Song, P. C. Hiberty, *J. Phys. Chem. A* **2002**, *106*, 5043–5045; c) L. Song, W. Wu, P. C. Hiberty, S. Shaik, *Chem. Eur. J.* **2006**, *12*, 7458–7466; d) P. Su, L. Song, W. Wu, P. C. Hiberty, S. Shaik , *J. Am. Chem. Soc.*, **2004**, *126*, 13539–13549.

[94] B. Braida, E. Derat, S. Humble, P. C. Hiberty, S. Shaik, *ChemPhysChem* **2012**, *13*, 4029–4030.

[95] a) M. Filatov, N. Harris, S. Shaik, *Angew. Chem. Int. Ed.* **1999**, *38*, 3510–3512; *Angew. Chem.* **1999**, *111*, 3730–3733; b) N. Harris, S. Cohen, M. Filatov, F. Ogliaro, S. Shaik, *Angew. Chem. Int. Ed.* **2000**, *39*, 2003–2007; *Angew. Chem.* **2000**, *112*, 2070–2074.

[96] F. Ogliaro, N. Harris, S. Cohen, M. Filatov, S. P. de Visser, S. Shaik, *J. Am. Chem. Soc.* **2000**, *122*, 8977–8989.

[97] a) F. Ogliaro, S. Cohen, S. P. de Visser, S. Shaik, *J. Am. Chem. Soc.* **2000**, *122*, 12892–12893; b) S. P. de Visser, F. Ogliaro, P. K. Sharma, S. Shaik, *Angew. Chem. Int. Ed.* **2002**, *41*, 1947–1951; *Angew. Chem.* **2002**, *114*, 2027–2031.

[98] F. Ogliaro, M. Filatov, S. Shaik, *Eur. J. Inorg. Chem.* **2000**, 2455–2458.

[99] Y. Wang, D. Kumar, C. Yang, K. Han, S. Shaik, *J. Phys. Chem. B* **2007**, *117*, 7700–7710.

[100] a) D. Kumar, S. P. de Visser, P. K. Sharma, S. Cohen, S. Shaik, *J. Am. Chem. Soc.* **2004**, *126*, 1907–1920; b) S. Shaik, H. Hirao, D. Kumar, *Acc. Chem. Res.* **2007**, *40*, 532–542.

[101] a) B. Meunier, S. P. de Visser, S. Shaik, *Chem. Rev.*, **2004**, *104*, 3947–3980; b) S. Shaik, D. Kumar, S. P. de Visser, A. Altun, W. Thiel, *Chem. Rev.* **2005**, *105*, 2279–2328; c) S. Shaik, H. Hirao,

D. Kumar, *Nat. Prod. Rep.* **2007**, *24*, 533–552; d) Shaik, S. Cohen, Y. Wang, H. Chen, D. Kumar, W. Thiel, *Chem. Rev.* **2010**, *110*, 949–1017.

[102] a) S. Shaik, D. Kumar, S. P. de Visser, *J. Am. Chem. Soc.* **2008**, *130*, 10128–10140; 130, 14016 (Correction); b) W. Z. Lai, C. Li, H. Chen, S. Shaik, *Angew. Chem. Int. Ed.* **2012**, *51*, 5556–5578; *Angew. Chem.* **2012**, *124*, 5652–5676.

[103] S. Shaik, Y. Wang, H. Chen, J. Song, R. Meir, *Faraday Discuss.* **2010**, *145*, 49–70.

[104] S. Shaik, P. Milko, P. Schyman, U. Dandamundi, H. Chen, *J. Chem. Theory Comput.* **2011**, *7*, 327–339.

[105] C. Li, D. Danovich, S. Shaik, *Chem. Sci.* **2012**, *3*, 1903–1918.

[106] S. Shaik, R. Ramanan, D. Danovich, D. Mandal, *Chem. Soc. Rev.* **2018**, *47*, 5125–5145.

[107] K. D. Dubey, S. Shaik, *Acc. Chem. Res.* **2019**, *52*, 389–399.

[108] J. C. Schöneboom, H. Lin, N. Reuter, W. Thiel, S. Cohen, F. Ogliaro, S. Shaik, *J. Am. Chem. Soc.* **2002**, *124*, 8142–8151.

[109] J. C. Schöneboom, S. Cohen, H. Lin, S. Shaik, W. Thiel, *J. Am. Chem. Soc.* **2004**, *126*, 4017–4034.

[110] K. D. Dubey, B. Wang, S. Shaik, *J. Am. Chem. Soc.* **2016**, *138*, 837–845.

[111] a) B. Wang, C. Li, K. D. Dubey, S. Shaik, *J. Am. Chem. Soc.* **2015**, *137*, 7379–7390; b) R. Ramanan, K. D. Dubey, B. Wang, D. Mandal, S. Shaik, *J. Am. Chem. Soc.* **2016**, *138*, 6786–6797; c) A. Li, B. Wang, A. Ilie, K. D. Dubey, G. Bange, I. V. Korendovych, S. Shaik, M. T. Reetz, *Nat. Commun.* **2017**, *8*, 14876–14883; d) K. D. Dubey, B. Wang, M. Vajpai, S. Shaik, *Chem. Sci.* **2017**, *8*, 5335–5344; e) K. D. Dubey, S. Shaik, *J. Am. Chem. Soc.* **2018**, *140*, 683–690; f) S. Kalita, S. Shaik, H. Kisan, K. D. Dubey, *ACS Catal.* **2020**, *10*, 9521–9532.

[112] a) D. Fishelovitch, C. Hazan, H. Hirao, H. J. Wolfson, R. Nussinov, S. Shaik, *J. Phys. Chem. B* **2007**, *111*, 13822–13832; b) D. Fishelovitch, S. Shaik, H. J. Wolfson, R. Nussinov, *J. Phys. Chem. B* **2010**, *114*, 5964–5970; c) D. Fishelovitch, S. Shaik, H. J. Wolfson, R. Nussinov, *J. Phys. Chem. B.* **2009**, *113*, 13018–13025.

[113] S. Shaik, D. Danovich, J. M. Galbraith, B. Braida, W. Wu, P. C. Hiberty, *Angew. Chem. Int. Ed.* **2020**, *59*, 984–1001.

[114] D. Danovich, S. Shaik, *Acc. Chem. Res.* **2014**, *47*, 417–426.

[115] D. Danovich, S. Shaik, F. Neese, J. Echeverria, G. Aullon, S. Alvarez, *J. Chem. Theory Comput.* **2013**, *9*, 1977–1991.

[116] C. Wang, D. Danovich, Y. Mo, S. Shaik *J. Chem. Theory Comput.* **2014**, *10*, 3726–3737.

[117] S. Shaik, D. Danovich, J. Joy, Z. Wang, T. Stuyver, *J. Am. Chem. Soc.* **2020**, *142*, 12551–12562.

[118] Out of many, see for example: a) A. C. Aragonès, H. L. Haworth, N. Darwish, S. Ciampi, J. J. Bloofield, G. G. Wallace, I. Diez-Perez, M. L. Coote, *Nature* **2016**, *531*, 88–9; b) A. A. Arabi, C. F. Matta, *Phys. Chem. Chem. Phys.* **2011**, *13*,13738–13748; c) C. Foroutan-Nejad, M. Novák, R. Marek, *J. Phys. Chem. C.* **2013**, *117*, 21509–21515; d) N. J. English, C. J. Waldron, *Phys. Chem. Chem. Phys.* **2015**, *17*, 12407–12440; e) B. Friedrich, *Scientia*, 2017, **115**, 26–32; f) C. Geng, J. Li, T. Weiske, M. Schlangen, S. Shaik, H. Schwarz, *J. Am. Chem. Soc.* **2017**, *139*, 1684–1689; g) C. Climent, J. Galego, F. J. Garcia-Vidal, J. Feist, *Angew. Chem. Int. Ed.* **2019**, **58**, 869.

Manuscript received: October 22, 2020
Revised manuscript received: November 24, 2020
Version of record online: ■■, ■■

ESSAYS