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# Molecules in Motion: Chemical Reaction and Allied Dynamics in Solution and Elsewhere

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## Abstract

After my acceptance of the kind invitation from Todd Martínez and Mark Johnson, Co-Editors of this journal, to write this article, I had to decide just how to actually do this, given the existence of a fairly personal and extended autobiographical account of recent vintage detailing my youth, education, and assorted experiences and activities at the University of Colorado, Boulder, and later also at Ecole Normale Supérieure in Paris (1). In the end, I settled on a differently styled recounting of the adventures with my students, postdocs, collaborators, and colleagues in trying to unravel, comprehend, describe, and occasionally even predict the manifestations and consequences of the myriad assortment of molecular dances that contribute to and govern the rates and mechanisms of chemical reactions in solution (and elsewhere). The result follows.

## TRANSLATIONAL, ROTATIONAL, AND SOLVATION DYNAMICS IN SOLUTION

This is basically where it all began for me. Beyond their fundamental interest, these three types of dynamics (translational, rotational, and solvation) can be important for chemical reactions in assorted regimes, although admittedly this is perhaps not always so obvious: Translation is relevant for diffusion-controlled and -influenced reactions, water rotation is important for proton transfers (PTs), for example, and solvation dynamics can have a significant effect on any reaction involving the redistribution or rearrangement of charges. I give only brief commentaries on our work at the University of Colorado, Boulder, on these types of dynamics in the 1970s and 1980s and end with more recent aspects carried out at Ecole Normale Supérieure (ENS).

In the 1970s, it was thought by not a few that macroscopic continuum hydrodynamics—as reflected in, e.g., Stokes’ friction laws for translation and rotation, the Stokes-Einstein equation for translational diffusion, and the Debye-Stokes-Einstein relation for rotational or reorientational diffusion—could actually apply in detail, and even quantitatively, at a molecular level. I myself have used (and continue to use) continuum hydrodynamic and dielectric models to provide concepts, perspectives, and guides for experiment. Clearly, I like such models greatly, but I just could not accept going this far. Together with Mike Weinberg and Ray Kapral (2–4), we addressed the issue with what we called a microscopic boundary layer approach, combining a molecular collisional picture for the immediate solvent neighborhood of a rotating or translating solute molecule with a hydrodynamic description of the remaining, outer solvent. We showed that for both rotational and translational friction (and thus for diffusion), the molecular aspects were indeed dominant. Although hydrodynamic influences could also enter, they only became the dominant story when the solute was far larger than the solvent molecules. We also found that the supposed agreement of assorted simulations and experiments with the hydrodynamic view disappeared upon suitable scrutiny.

### Solvation Dynamics

This flavor of dynamics came into its own in the early 1980s with the advent of picosecond time-dependent fluorescence (TDF) experiments (e.g., 5) examining the dynamic Stokes shift reflecting a solvent’s equilibration to a changed charge distribution of a solute within it. Here at last was an experimental probe telling us about an important solvent timescale! We and others were ineluctably drawn to this area by, for example, the possible connection to reactivity in solution. But first, one would like to have some kind of theoretical model to interpret the TDF experiments. What determined the measured times, and how should they be interpreted?

Among the earliest theoretical approaches to TDF in this period were those of Biman Bagchi, David Oxtoby, and Graham Fleming (6) and ourselves with postdoc Gert van der Zwan (7). We were all indebted to early Russian workers who had introduced a dynamic dielectric continuum perspective for the solvent. Our own effort had several extra wrinkles, including the introduction of the solvent’s inertia. This was familiar to workers in dielectric relaxation and had been used by Peter Wolynes and coworkers (8) for electron transfer. The inertia inclusion also allowed us to cast the solvation dynamics in the form of a generalized Langevin equation (GLE), which was just what was needed for the Grote-Hynes theory (GHT) for reactions, as discussed below.

Molecular-level insight into TDF and solvation dynamics began with the key molecular dynamics (MD) simulation work of Mark Maroncelli and Fleming (9) on model atomic solutes in water. Postdoc Emily Carter and I carried out a related MD study (10) on dipolar solutes and identified certain difficulties with the popular linear response mantra for the problem. We also pointed out the unexpected and important dominance of short-time inertial solvent dynamics for

nonhydrogen-bonded liquids, but in hydrogen-bonded liquids such as water, solvation dynamics due to librational motions will rapidly overtake such an inertial contribution.

## Water Reorientation and the Jump Model

The final entry in this section concerns a type of problem that has always held great appeal for me: re-examination of a long-established viewpoint and developing a new perspective for it. In this case, it was the traditional Debye picture of water reorientation as rotational diffusive motion involving very small angular steps (11). With ENS junior colleague Damien Laage leading the way, we could show that the reorientation mechanism was quite different, consisting of sudden, large-amplitude jumps (12, 13).

In fact, this reorientation can itself be viewed as a chemical reaction, in which a water OH group exchanges an initial hydrogen-bond partner for another final partner, with a transition state (TS) characterized by a bifurcated hydrogen bond involving both partners. This exchange reaction perspective highlights the importance of water reorientation for restructuring the water hydrogen-bonding network. It also allowed Laage, Guillaume Stirnemann, Fabio Sterpone, and I to create analytic treatments of the jump time and its free energy barrier dependence on excluded volume effects for hydrophobic and hydrophilic solutes (14, 15) and hydrogen-bond strength impacts (15–17) for the latter solvent type. With the inclusion of the usually minor contribution of the reorientation of an intact hydrogen-bonded molecular pair, our analytic extended jump model successfully accounted for a wide variety of water reorientation dynamics as probed by nuclear magnetic resonance and linear and multidimensional spectroscopies, as well as simulations, and for a considerable span of environments: pure water, water surfaces, and aqueous solutions involving ions, amino acids, and proteins, as well as general hydrophobic, hydrophilic, and amphiphilic solutes. Most of this has already been extensively reviewed in recent years (18–21), so I now simply pass to my next major topic.

## VIBRATIONAL ENERGY TRANSFER

### Vibrational Energy Transfer for Molecular Iodine

It was Ken Eisenthal and coworkers' seminal paper (22) on iodine recombination in 1974 that convinced me it was time to work on chemical reactions in solution. Eisenthal and his colleagues photoexcited  $I_2$  in liquid  $CCl_4$  to dissociate the molecule and then monitored the molecular  $I_2$  absorption reappearance. An observed timescale of  $\sim 100$  ps was tentatively associated with diffusive relative motion, prior to actual recombination, of photodissociated I atoms. In the early 1980s, graduate student David Nesbitt and I thought that a different interpretation was more likely for several reasons, including the small probability of the formation of solvent-separated atoms required for such diffusive motion and the inefficient vibrational energy transfer we had found in earlier trajectory studies (23, 24).

We first argued that, owing to Franck-Condon factors,  $I_2$  would have to become nestled back into its potential's very lowest part in order to be experimentally detected (25). Because vibrational relaxation was necessary for  $I_2$  to do this, we employed trajectory calculations on  $I_2$ - $CCl_4$  vibration to translation (VT) energy transfer to show that this relaxation was a slow process, even slower than 100 ps!

I pause in this tale to describe the prevailing community thinking at the time. It is no great distortion to say that the unobserved solvent was then regarded as being nearly omnipotent: Whatever was necessary for it to do, it could do it most rapidly and efficiently. Thus, the image

here was that the required vibrational relaxation of the amount involved for newly recombined and vibrationally very hot  $I_2$  ( $\sim 36$  kcal/mol) would be effected in a very few collisions; it would all be over in 1–2 ps. I well recall that the first time I presented our work, a distinguished physical chemist (who I am pleased to say subsequently became a very good friend) bellowed at me, in quite a high-decibel averral, that the nascent  $I_2$  vibrational energy would be rapidly taken away by the liquid’s “phonons,” and these were of course present with a very high density of states to boot. Our predicted slow vibrational relaxation was accordingly patent nonsense. Fortunately, I could counter by pointing out that the collisions taking away the energy would have to be quite local, and primarily binary, in nature and involve rapid motion, and could not at all be characterized by the long-wavelength delocalized phonons being invoked in the assault.

We left the  $I_2$  story at our finding that  $I_2$ ’s vibrational relaxation via VT transfer was too slow (we estimated a time of  $\sim 1$  ns) to account for the  $\sim 100$ -ps timescale in  $CCl_4$ . But lower in the  $I_2$  potential,  $I_2$  would come into near resonance with a  $CCl_4$  vibration; we predicted that the additional, associated vibration-vibration transfer route would speed up the relaxation into the required timeframe. Our basic picture was later confirmed by Charles Harris and colleagues (26) and others, although it was refined and enriched in assorted ways (e.g., by the involvement of several electronic states). I think it fair to say that after this, few people automatically assumed that vibrational relaxation in solution was very slow.

### **Intramolecular Energy Flow in Highly Excited Molecules**

Our next foray focused on energy flow in isolated highly vibrationally excited molecules [intramolecular vibrational relaxation (IVR) or intramolecular energy redistribution/relaxation]. The driving force was of course the then current intense interest in the validity of RRKM theory for unimolecular reactions, which assumes that such energy flow is so rapid and extensive that it is irrelevant for the reaction rate. Our entry into this quintessential gas phase topic had several catalysts. One was my enthusiasm, derived from several (non-physical chemistry) papers, for nonlinear, or Chirikov, resonances; these seemed particularly appropriate to deal with the fundamentally anharmonic energy flow problem. (Our enthusiasm here was heavily, albeit transiently, damped when Paul Brumer gave me Chirikov’s massive technical report on the topic; I understood the first half of the first page, but that was it!) Another, and especially important, catalyst was the arrival of graduate student Ned Sibert and postdoc John Hutchinson, who wanted to work on such things. The final catalyst (I admit only partially sheepishly) was a certain desire to show (in the heavily gas phase-oriented Boulder community) that I could also contribute to gas phase things.

The early work of Sibert, Hutchinson, Bill Reinhardt, and I focused on the water molecule, for which Mark Child and coworkers (27) had shown the importance, at higher levels of vibrational excitation, of the (localized) local-mode description, as opposed to that of (delocalized) normal modes. We used the Chirikov nonlinear resonance perspective to provide a detailed analytical description of the dynamical flow (or lack thereof) between the local modes—the OH bonds—for a fairly realistic model for the water molecule in a classical mechanical description (28). Happily, the entire approach translated to quantum mechanics (29), in which we could characterize (30) two quantum energy flow routes when the two OH bonds are out of 1:1 resonance: direct dynamical quantum tunneling probability transfer between the water OH bonds, à la Rick Heller (31), and an indirect superexchange dynamic transfer path.

Sibert, Reinhardt, and I (32) then addressed the interpretation of the exciting experimental results of Michael Berry and colleagues (33) on the overtone spectrum of the isolated benzene molecule ( $C_6H_6$ ), probing up to the  $\nu_{CH} = 4-9$  CH vibrational levels. Among the striking features requiring elucidation were the  $\sim 100\text{-cm}^{-1}$  line width [full width at half maximum (FWHM)] at

$\nu_{\text{CH}} = 6$  and a subsequent narrowing for higher overtones. Was this  $\nu_{\text{CH}} = 6$  line width in fact indicative of rapid intramolecular energy flow? And if so, what was the mechanism for such an apparently very rapid flow? Predictions via simple density-of-states arguments clearly were inapplicable here: They would say that the line widths would increase with increasing overtone.

Numerous interesting prior efforts had largely envisioned that the coupling between the ring's CH bonds was at the core of the problem. We found a different mechanism, involving a 2:1 Fermi resonance coupling between the CH stretch and its wag (hindered bend). This kinetic coupling arises from the CH wag moment of inertia's dependence on the CH bond extension. This coupling is quite obvious in a curvilinear perspective, but is not at all transparent in the traditional rectilinear perspective [in fact, the often-cited, but evidently less often read, original 1931 Fermi paper on the 2:1 resonance in  $\text{CO}_2$  (34) adopted just this curvilinear perspective!]. The wag itself is then coupled to ring modes, as the wagging motion stretches/compresses CC bonds, and these modes are in turn coupled to other ring modes (e.g., other CC stretches, in-plane CCC bends). A corresponding spectral tier picture naturally emerged; for the  $\nu_{\text{CH}} = 6$  overtone state, this consisted of consecutive tiers of coupled vibrational states for  $\nu_{\text{CH}} = 6, 5, 4, \dots$ , with energy transferred to the rest of the molecule in the wag and assorted coupled ring mode states (although only the first three tiers were explicitly constructed).

Calculated stick spectra for this  $\nu_{\text{CH}} = 6$  state and others correctly predicted the essential experimental features for  $\text{C}_6\text{H}_6$  and several deuterated analogs. For example, the spectral narrowing from  $\nu_{\text{CH}} = 6$  to  $\nu_{\text{CH}} = 9$  arose from the reduced effective 2:1 stretch-wag coupling as the required Fermi resonance frequency match was lost with the decreasing anharmonic CH stretch frequency. A dynamical perspective constructed along the same lines gave comparable agreement with the experiment. This showed, for example, that the  $\sim 100\text{-cm}^{-1}$   $\nu_{\text{CH}} = 6$  line width could indeed be associated with a rapid probability decay out of this state. A highly appealing aspect was that the classical correspondence for the quantum vibrational state tiers was exactly that expected in a nonlinear resonance view (35). The character, mechanism, and timescale for decays of the highly excited overtones directly calculated via classical trajectories were all very well described in terms of a sequence of overlapping nonlinear resonances, and all qualitatively agreed with the quantum results.

Of course, the ultimate rationale for IVR study was to elucidate its role in chemical reaction rates. The overtone experiment of Rizzo, Hayden, and Crim (36) for the  $\nu = 6$  OH overtone-induced dissociation of hydrogen peroxide provided the opportunity to examine this. The tantalizing aspect of their measured  $86\text{-cm}^{-1}$  FWHM line width was that, if it were associated with the  $\text{H}_2\text{O}_2$  dissociation, the associated  $\sim 0.05\text{-ps}$  timescale was far shorter than the estimated RRKM time of 5–50 ps. Turgay Uzer, Reinhardt, and I (37) undertook a classical trajectory study of this issue, exploiting nonlinear resonance ideas. The  $\nu = 6$  OH frequency was far off any sensible multiple of the much-lower frequency of the OO bond fated to rupture. An indirect flow path was thus indicated, and a likely participant here was the vicinal HOO wag, whose fundamental was in close 2:1 Fermi resonance with the OH overtone. But the HOO wag was not at all in close 1:1 resonance with the OO bond, although the wag and OO stretch were fairly strongly coupled. Still, there might be sufficient flow, and anharmonic reduction of the wag frequency with OO extension could come to the aid of the flow.

Our calculations showed some surprising results. Energy did flow from the OH stretch to the vicinal HOO wag, but then it hopped over the target OO bond and entered into a beating pattern with the OOH wag on the other side of the bond! This *pas de deux* continued, but not solely “*a deux*”: Energy gradually built up in the intervening OO bond, whose frequency was gradually lowering and whose amplitude was gradually increasing, until . . . suddenly enough energy flowed into the bond for its rupture! (To my regret, we never succeeded in capturing/understanding this

in a nonlinear resonance framework.) The dissociation timescale was  $\sim 6$  ps, within the RRKM range. Thus, we did not find fast nonstatistical reaction; the large FWHM of the  $v = 6$  overtone instead resulted from rotational structure. This was of course disappointing, but it did give a clear illustration of one reason why RRKM theory would often work: the lack of a sufficiently “perfect” resonance path to reaction and the ease of being deflected from that path to the target bond.

It seems to me that there is still much that we neither understand nor know how to simply describe for IVR and the role it plays in chemical dynamics. Wolynes, David Logan, and a few others have made important further progress here, often involving nonlinear resonance ideas; I wish that there were more.

## Vibrational Dynamics in Aqueous Solution

With our next vibrational effort, we took the plunge into water, a fairly adventurous step at the time. The Laubereau group’s (38) measured vibrational relaxation time was  $\sim 8$  ps for an excited  $v = 1$  OH stretch in an HOD molecule in liquid  $D_2O$ —a combination designed to avoid complications from resonant OH interactions both within the molecule and with the solvent molecules. Why was the relaxation so fast, and what was its mechanism?

The mechanism that postdoc Rossend Rey and I (39) found involved a 2:1 Fermi resonance between the OH stretch and the HOD bend as rate limiting for the OH excitation’s loss and production of the  $v = 2$  bend overtone; this overtone then relaxed through the  $v = 1$  bend overtone and on to the ground state. But the 2:1 stretch-bend resonance condition was certainly not perfectly satisfied, as there was a mismatch of  $\sim 500\text{ cm}^{-1}$  to be surmounted. However, analysis of the frequency spectrum of the relevant force time correlation function indicated strength at this frequency owing to the liquid  $D_2O$  librations (i.e., hindered rotations), implicating these librations as acceptors for the energy mismatch. At the end of the day, the calculated time of the rate-limiting step was 7.5 ps. Although this was in good agreement with the Laubereau group’s result, the careful reader of our paper will see that in fact I had hoped for a completely different mechanism (40)! But a consoling thought was that we had found a nontrivial route for the decay dependent on the molecular features of the relaxing molecule and its surrounding solvent. Subsequent experimental and theoretical (by Jim Skinner) work showed that, in fact, the relaxation time should be noticeably shorter but that our basic mechanism was nonetheless sound (41). But the wheel of fortune kept turning, as discussed momentarily below.

But before we see just how the wheel turned, I briefly mention some other, not often discussed, vibrational relaxation aspects that can be quite important. The real origin of our efforts on these was our  $Cl^- + CH_3Cl \rightarrow CH_3Cl + Cl^-$   $S_N2$  reaction in water studies (Cl isotopes are clearly required to see this in real life); these studies are discussed in some detail below; here I only mention two vibrationally relevant aspects. The first is that the key force exerted by the water solvent in the reaction barrier crossing resulted not from a fixed charge perspective, but rather from the changing charge redistribution, or charge shift, between the attacking and leaving  $Cl^-$  anions (42). The second is that, whereas the rates of vibrational activation and deactivation of the reactant and product methyl chloride molecules do not influence the reaction rate constant, these processes clearly are important aspects of the overall molecular reaction mechanism (43) [a similar statement applies to a simulated  $A + BC$  atom transfer reaction (44)]. For the first aspect, a similar charge shift force should be important whenever a polar or charged molecule can be significantly polarized over the component localized valence bond states necessary for its charge description (45). This is the case for  $I_2^-$  (46), for example, and postdoc Brad Gertner, colleagues Ilan Benjamin and Paul Barbara, and I found that this force was quite important in accelerating vibrational relaxation in a polar solvent (47). [This feature can also be important for solvation dynamics, as we

demonstrated with Laage, Ward Thompson, and then ENS colleague Mireille Blanchard-Desce (48).] For the second aspect, as an important illustration of a general phenomenon, we could show that the dipolar  $\text{CH}_3\text{Cl}$  molecule's Coulombic interaction with the water solvent molecules was decisive for its vibrational relaxation (49); such interactions had typically been considered important only in exerting a mild long-range influence on molecular reorientations.

## Work and Power Route to Molecular Detail

The study of HOD in liquid  $\text{D}_2\text{O}$  discussed above had an unsatisfactory aspect for us: to wit, the use of a force time correlation frequency spectrum to assign the responsibility of energy transfer to certain solvent motions (here,  $\text{D}_2\text{O}$  librations taking up the OH stretch–HOD bend overtone mismatch). Certainly this (and numerous other such inferences; e.g., 49) was plausible, but it was not a direct demonstration. The necessary tool had in fact been provided in an  $\text{S}_{\text{N}}2$  reaction study with Kent Wilson (43, 49): a power (time rate of change of energy) and work (time-integrated power) formulation for energy transfer.

Rey and I, together with postdoc Francesca Ingrosso and colleague Thomas Elsaesser, finally applied this formulation (50, 51) to try to understand the impressive experimental results of Elsaesser, Erik Nibbering, and their colleagues (52) on the very rapid, few-hundred-femtosecond, excited HOH bend relaxation in liquid water (and the even faster relaxation of its librations): no isotopes this time! Our most surprising result was that the dominant excited water bend energy flow was not, as one might expect, to the surrounding waters; it was instead intramolecular to that same molecule's rotation, especially for the lowest moment of inertia axis (i.e., highest librational frequency). This flow resulted from—what else?—a 2:1 Fermi resonance, this time a bend-rotation centrifugal coupling. The remaining flow from the bend-excited water was to its first hydration shell neighbors, primarily to the librational motion of those water molecules that were hydrogen bonded to the excited water's hydrogen atoms. We could also trace in detail the flow from the now rotationally excited central  $\text{H}_2\text{O}$  to its hydration shell neighbors and beyond, and the entire relaxation process could be well described by simple kinetic equations. Later explicit examination of a rotationally excited water's energy transfer in liquid  $\text{H}_2\text{O}$  also revealed the energy flow path in a correspondingly molecularly detailed manner (53). All this was of course quite satisfying, but there was a less pleasing corollary. These results also revealed (50) that we had—blush!—unfortunately selected the wrong rotation axis to assess (and so discard) centrifugal effects in our work on HOD in  $\text{D}_2\text{O}$  (39), and the intramolecular bend to rotation route should be important there too (50), a feature independently established by Schwarzer, Schroeder, and colleagues (54).

Over the years, other vibrational issues in water solution (55–60)—involving ENS graduate student Jean Boisson and postdocs Peggy Bruehl, Steve Klippenstein, Klaus Moller, Bruno Nigro, Sai Ramesh, Suyong Re, and Thompson—have also fascinated us, but spatial boundary conditions now push us on to our major topic.

## CHEMICAL REACTIONS IN SOLUTION

### The Stable States Picture and Grote-Hynes Theory

Beyond our  $\text{I}_2$  efforts, our early reaction work in the 1970s was largely concerned with diffusion-influenced or -controlled reactions and caging effects—all with graduate student Scott Northrup. Although we still consider these quite valuable contributions, their most central role, in a sense, was an important preparation and source of insight for our first real foray into general activated reactions per se in two 1980 papers.

The first of these was with Northrup on what we called the stable states picture (SSP) for reactions (61). Its simple idea was based on a chemical perspective. Transition state theory (TST)—and various current simulation methods informed by it—focused all attention on a reaction dividing surface at the TS, usually a barrier top in free energy. But reactions actually involve the transition between stable reactants and stable products, which live at and near the bottom of free energy wells, usually far from the TS. Species immediately before and after the TS dividing surface are not at all like these chemical concepts, and it seemed highly artificial to call them reactants and products, respectively; indeed, trajectories involving them can rapidly recross the surface. Although passage through a TS surface is of course necessary for successful reaction, it made more physical sense to us to define surfaces located away from the TS. A very simple example would be an energy dividing surface well below a radical recombination reaction’s dissociation limit, such that energy stabilization below that surface to form the reaction product was much more likely than redissociation to separate radicals. As a computational prescription, however, this SSP perspective was not so useful for high-barrier reactions, as the stable species would be well below the TS or barrier top and rarely react, for example. But it is a successful and important computational method—where others fail—for low-barrier reactions, such as water jump dynamics (12, 13, 62). In any event, this SSP perspective let us derive expressions, involving absorbing surface boundary conditions, that allowed clear flux time correlation function definitions of rate constants. For example, a forward rate constant could be so defined involving the time correlation of the initial flux out of a stable reactant region with the later flux into a stable product region.

Several such rate constant formulae were implemented and further developed for various reaction types in a partner SSP article with graduate student Rick Grote (63). Far and away, the most well-known result has come to be called the GHT rate constant. I always consider this as an example, among others, of our research topics motivated by a “dog in the night-time” effect, from the Sherlock Holmes story “Silver Blaze” in which a curious (and revealing) incident is that a dog did nothing in the night-time. This allusion is explained by considering that the well-known Kramers’ theory (64) predicted that the reaction rate would continuously decrease, and ultimately vanish, as the environment’s friction or viscosity increased. But certainly there are many reactions not stopped in solids! Our thinking’s essence can be exposed by first considering Wigner’s (65) key insight that (at least classically) the dynamical condition for TST to be correct was that there be no TS surface recrossing. Our reflection about a reaction system’s passage over a TS barrier top strongly suggested that the role of any opposing environmental forces in inducing such recrossing should be essentially limited to the very short timescales and space scales in the barrier neighborhood, before stabilization in product or reactant wells was guaranteed. We related this key timescale to the inverse barrier frequency, which itself is proportional to the magnitude of the barrier’s curvature, so that the timescale can be very short if the barrier has any significant height. Thus, slow solvent molecule motions responsible for strong impedance of a solute motion on long timescales and large space scales should often be completely irrelevant for a solution rate constant.

All this was handled by analyzing an SSP flux time correlation function rate constant expression, with the underlying dynamics described not by the Langevin equation used by Kramers, but by the GLE. The latter contained a non-Markovian time-dependent friction term, rather than the Langevin equation’s friction constant description; the former was able to capture the aspects of the short timescales and space scales, described above, that we thought to be key. The result was that the rate constant was given by its TST value times a transmission coefficient  $\kappa$ . GHT furnished a self-consistent equation for  $\kappa$ , depending both on the barrier frequency and on the (Laplace) frequency component of the time-dependent friction, which is the time correlation function of the fluctuating forces of the solvent exerted on the solute’s reaction coordinate. This component is the so-called frequency-dependent friction.

GHT's path was not an easy one. First, it was claimed in several quarters to be incorrect, until the considerable successes recounted below emerged. Then, various claims were made—often based on a solvent described as an infinite set of harmonic oscillators, linearly coupled to the reaction system—to the effect that GHT was simply and only a multidimensional form of variational TST. We strongly disagreed with this view, on several grounds; I discuss only one here. We ourselves had pointed out early on that for such simplified models, GHT was equivalent to TST (7, 66). But representing a solvent in interaction with a reacting solute as an extensive collection of harmonic oscillators is hardly physically accurate; most intermolecular interactions are obviously seriously anharmonic. A simple illustration of just one of the many difficulties of such oscillator pictures can be given from our work on atom transfer  $A + BC$  reactions in rare-gas solvents (44). The physics of the solvent's influence is that of independent binary collisions with the rare-gas atoms; these are rapid and short lived, and the associated time-dependent friction is approximately Gaussian in time. Certainly we believe in the Fourier integral theorem, and this friction has a mathematical spectral representation in terms of a collection of harmonic oscillators with a Gaussian distribution of frequencies. But there are no such physical oscillators responsible for the binary collisional friction! Rather than belabor such points here, I simply refer the interested reader to recent developments on the general basic issue (67, 68) and instead discuss what we ourselves focused on: testing the theory and applying it to learn important things about assorted reaction types.

GHT testing via MD computer simulations began in earnest collaboration with Wilson and his students for reasonably realistic models of several activated reaction types: the  $A + BC$  reaction in rare-gas solvents mentioned above and the  $Cl^- + CH_3Cl$   $S_N2$  nucleophilic substitution reaction in liquid water (42, 69, 70). The first notable result was that the theory agreed with the MD results, to within the latter's error bars. The same happy result ensued for many further reaction class simulations, of ours and others, including electron transfer (71–73); ion pair interconversion (74) [with Giovanni Ciccotti and Kapral, also partners with Carter and I, on the blue moon ensemble method for reactions (71, 75, 76)];  $S_N1$  dissociation (77); PT (78, 79); and, as a more complex recent entry, enzyme reactions (79, 80). In fact, the only realistic MD simulation results in which GHT definitely fails, of which we are aware, are for cationic hydration shell exchange kinetics, in which the theory's assumptions fail miserably: The recrossing dynamics is governed by events far from the barrier top (81, 82). Finally, there was also experimental support for the theory (e.g., 83–88); in particular, the theoretical/experimental work of Bagchi and Oxtoby (83) and Fleming (89) was especially important in putting GHT on the map.

The second aspect of note with regard to the simulation/theoretical results is that the MD and GHT transmission coefficients were typically not very far from the TST value of 1, with values such as 0.5–0.8 being common. In certain perspectives (e.g., age, salary, number of noses), a factor of two has considerable significance. But my interpretation was, and is, that these results show that TST is in fact an excellent rate constant theory for reactions with notable barriers and that GHT shows why this is so; it is difficult for the solvent (or other environments) to induce much recrossing on the very short timescale of the inverse barrier frequency. The opposite conclusion about TST's validity would be given by Kramers' theory, in which the transmission coefficient can be quite low (e.g., 90).

The third aspect to relate is that we could use the theory to explore all kinds of chemical reactions in an analytical, model perspective, the kind of thing I am wont to call “real theory” and certainly enjoy the most. These involved a number of different efforts spread over a decade or so of postdocs Dominic Ali, Hyung Kim, Sangyoub Lee, Gilles Peslherbe, Barton Smith, van der Zwan, Tony Zawadzki, and Dom Zichi; graduate students Grote and Jeff Mathis; and collaborators Sally Chapman, Teresa Fonseca, and Branka Ladanyi. These included studies of atom

transfers (91–93) (quantum PTs are discussed below);  $S_N1$  reactions (94, 95; Reference 96 deals with a change from the classic perspective for the solvent role in  $S_N1$  dissociations);  $S_N2$  reactions (69, 94, 97); assorted isomerizations (98), including dipolar (7, 66) and polymeric (99); electron transfers in solution (100, 101) and at electrodes (72) (in which the electrode’s electron-hole pair dynamics is a key friction source); reactions in electrolyte solutions (102); excited state twisted intramolecular charge transfer (90, 103); and (with ENS graduate student Laage and colleague Irene Burghardt) radical anion dissociation (104). In those efforts involving charge transfer of some sort, our solvation dynamics work described above was vital in characterizing the solvent’s influence.

Many aspects of these assorted analytical/modeling works pleased me inordinately, especially because they often provided quite new, and even unexpected, insights on the solvent’s role in chemical reactions, all well beyond the TST image of solely setting the equilibrium barrier height. I cannot forbear discussing at least one of these here.

The MD simulation results (42) on the  $\text{Cl}^- + \text{CH}_3\text{Cl}$   $S_N2$  reaction could be understood in considerable detail (69) with the analytic results developed within the framework of GHT—which we had gathered under the rubric of nonequilibrium solvation effects to distinguish them from the influence of equilibrium solvation included in TST. In particular, the frozen solvent or nonadiabatic solvation analytic description provided an excellent account. The passage through the  $S_N2$  TS surface is so rapid that the water molecules have no time to move, so their configurations are fixed during this passage. Recrossing arises, for example, because the surrounding water molecules’ hydrogen-bonding pattern is inappropriate to accommodate the negative charge on the emerging chloride ion. In effect, this type of situation leads to an extra barrier for the reaction not apparent in TST; it also shows that the influence of a nonequilibrium solvation’s reaction rate need not involve any dynamics, and the frictional effect can arise from purely stationary configurations!

## Proton Transfer Reactions

For all the above reactions, the nuclear motion was regarded as classical. This is of course utterly untenable for the fundamental and central reaction class of PT reactions. A capsule history of our extensive efforts here now follows. Our PT work started in earnest in the 1980s with the arrival of postdoc Daniel Borgis, with important contributions from postdocs Lee and Jesus Timoneda. Its important computational phase began with postdoc Koji Ando in the 1990s. It then added an excited electronic state wing in this century with postdoc Giovanni Granucci and French colleagues Philippe Millié and Thu-Hua Tran-Thi and in addition delved further into analytic/simulation developments with postdocs Thompson and (quite extensively with) Phil Kiefer. But even this listing is far from complete, as PTs have figured in a central way in many of the reactions to be discussed in the final subsection. We have reviewed a number of aspects of our work not so very long ago (105), so I only highlight a few features here.

From the beginning, we focused—with some important assistance from early work by Russian workers such as Kuznetsov and Dogonadze—on the analytic, dynamic perspective, treatment of the PT rate constant, both for the tunneling (nonadiabatic) regime and for the quantized over the barrier motion (adiabatic) regime (with the latter replacing the standard view of classical motion over the barrier). We especially emphasized the key role of the quantization of the proton’s nuclear motion, the reaction coordinate’s identification as the solvent rather than the proton, the electronic structure aspects of the reaction, and finally the crucial role in the tunneling regime of the hydrogen-bond coordinate (e.g., the A-B separation in an acid-base PT reaction  $\text{AH} + \text{B} \rightarrow \text{A}^- + \text{HB}^+$ ).

Many features of the early analytic theory work (106–109) were borne out in detailed Monte Carlo studies of the HCl and HF acid dissociations in water (110–112). The HCl investigation was

a particular joy; here was a reaction every chemist had “seen” but of course not really seen; how did it actually occur? We could show for the first time in solution the key change—via water molecule rotation (remember I told you earlier it could be important for reaction!)—in the hydrogen-bonding coordination number for a proton acceptor (and donor) necessary for successful PT in solution; this was the microscopic identification of the solvent coordinate. (Some history of this can be found in Reference 113.) For both the HCl and HF problems, we could also explicitly support the Mulliken charge transfer picture for PT (114), involving electron transfer from the base’s nonbonding orbital into the acid’s antibonding orbital. On a different fundamental issue—the origin of the dramatically enhanced acidity of excited electronic state photoacids—we showed (115, 116) that the origin was charge transfer in the excited state base, and not in the acid, its traditionally identified source (e.g., 117). Later analytic work produced a variety of important results, including the interpretation, for both tunneling and adiabatic reactions, of kinetic isotope effects, which were often treacherously misleading and thus misinterpreted (118–120), and the demonstration (121) of how something like the often-used Marcus equation connecting reaction kinetics and thermodynamics can apply to PT, even though that equation was never actually derived for PT.

I am sometimes a bit bemused that it is now taken for granted that PT is always quantum (although mistakenly thought that it is always tunneling). I recall that after our first few years of work and important results in the field, I would explain the new picture to assorted colleagues. They would listen politely, and at the end would say, “well, that’s all very interesting young man (sic!), but the standard version of isotope effects works quite well for us, so why do we need you?” Although it is sad to report that flawed descriptions and equations continue to appear, things have clearly and considerably progressed!

## Conical Intersection Dynamics

By the beginning of the twenty-first century, conical intersections (CIs) had definitely emerged from a specialty concern of a few chemical physicists to critically important rapid and efficient transition routes from excited to ground electronic states in photochemical and photobiological reactions. Accordingly, much impressive theoretical and computational work had been, and was being done, in the field. But I thought that there was an important lacuna in all this activity: the lack of a theoretical model basis for describing/comprehending such CI dynamics in solution and in proteins, obviously important reaction venues that were being studied computationally and experimentally.

With strong encouragement from ENS colleague Monique Martin, ENS colleague Burghardt and I constructed and analyzed a simplified model of the *cis* to *trans* isomerization of a protonated Schiff base (PSB) to try to capture key aspects for CI dynamics in solution (122, 123). PSBs involved intramolecular charge transfers both in the electronic transition to the excited state and in the CI passage to the ground state, so that there should be strong coupling to a polar solvent. It also bore an appealing cachet as a model for the retinal isomerization in rhodopsin associated with vision. The basic model had a lot in common with much of our other analytic modeling work (e.g., 90): (a) an electronic structure described by two valence bond states—with the attractive feature of being an extension of the two-electron, two-orbital model constructed years before by my Boulder colleague Josef Michl and his coworkers (124)—and (b) a few-coordinate description—here of the PSB torsion for the isomerization per se, an intramolecular bond length alteration coordinate to deal with the single-double bond switching involved, and a solvent coordinate, with the coordinate allowing for nonequilibrium solvation aspects related to the Franck-Condon electronic transition, the isomerization, and the passage through the CI. Further key modeling aspects were informed

by prior PSB work of Mike Robb and Massimo Olivucci (125–127), Todd Martínez (128, 129), and their coworkers. The major results of our analysis for the ground and excited state free energy surfaces and inertial motion on them were insights on the important role that the solvent could play. For example, the solvent coordinate generated an entire seam of CIs (whereas there was just a single CI in the corresponding gas phase model), and in some circumstances, the CI would actually disappear such that this seam could not be reached without solvent motion.

ENS graduate student Joao Malhado, former ENS postdoc Riccardo Spezia, and I (130) then included a more realistic dissipative dynamics allowing both important energy transfers via coordinate GLEs and Tully surface hopping for the nonadiabatic CI dynamics. Modeled acetonitrile and water solvents displayed differing rates and quantum yields of the photochemical isomerization producing the ground state product. Key for the quantum yield difference, for example, was the slower acetonitrile solvent's excited-to-ground state transitions occurring prior to reaching the CI seam. Spurred on by Martínez (131), Malhado and I (132) later re-examined the solvent effects in terms of the topological perspective of sloped versus peaked CIs, a distinction often regarded as decisive for photochemical reactivity (133–135). This study in fact supported our original interpretation, while certainly enriching it in topographical detail. Importantly, the essential role of the solvent coordinate found in the sloped versus peaked perspective provided an instructive contrast with the rather common focus on the PSB internal coordinates, with the solvent relegated (at most) to solely a parametric role.

Almost all of us (myself included) have tended to be riveted by the idea that CIs live solely in the world of excited electronic state photoreactions. But in fact CIs can have a striking impact on ground electronic state reactions (see, e.g., 48), an area that seems to me much underexplored.

## Atmospheric, Interstellar, Biological, and Renewable Energy Reactions

I place in this section, under this rather broad banner, a number of our (often quantum chemical type) calculation/simulation efforts on reactions whose study was driven not only by their fundamental interest, but also by their relevance to the greater world around us.

The numerous and wide-ranging talent in the atmospheric sciences surrounding me in Boulder was a natural catalyst for us to get involved in reaction issues for the stratospheric Antarctic ozone hole. The key issue had to do with the molecular-level mechanism of the heterogeneous  $\text{HCl} + \text{ClONO}_2 \rightarrow \text{Cl}_2 + \text{HNO}_3$  reaction of hydrochloric acid with chlorine nitrate that Susan Solomon (136) had proposed as the culprit for ultimately producing ozone-destroying chlorine. With (now) postdoc Gertner, we proposed a way for HCl—our old friend from our solution PT work (110, 111)—to acid dissociate at the surfaces of polar stratospheric cloud ice particles (137, 138). As for the net  $\text{Cl}_2$ -producing reaction itself, one suggestion was that it occurred in two steps, the first being the hydrolysis of chlorine nitrate,  $\text{ClONO}_2 + \text{H}_2\text{O} \rightarrow \text{HOCl} + \text{HNO}_3$ , followed by  $\text{HCl} + \text{HOCl} \rightarrow \text{H}_2\text{O} + \text{Cl}_2$ . Postdoc Roberto Bianco and I found the hydrolysis on a model of ice to be quite facile, courtesy of a proton relay chain (PRC) that assisted both water's nucleophilic attack on  $\text{ClONO}_2$ 's (electropositive) Cl atom and the stabilization of the  $\text{NO}_3^-$  leaving group (139). But later evidence suggested that the single-step mechanism cited above was in fact more likely, and indeed, our examination of the  $\text{HCl} + \text{ClONO}_2$  reaction on modeled ice showed this reaction to also be facile, with once again crucial PRC assistance (140). (As discussed below, this was not to be our last encounter with PRCs.)

Some subsequent thought suggested that the Antarctic stratospheric aerosols serving as the heterogeneous reaction site might not be ice aerosols after all but instead be sulfate aerosols—supercooled, concentrated aqueous sulfuric acid solutions (136). To study reactions on, and do a reasonable modeling of, these clearly nasty things, we needed to know what the ionic composition

was in their surface region. The composition was known in the bulk fairly well, but we thought it very unlikely that it would be the same in the less polar (in some sense) surface region. Despite some interesting results on sulfuric acid dissociation (141), we never really answered this question to my satisfaction. But—by an extremely circuitous route that I do not detail here—it led us to develop with postdoc Akihiro Morita a theoretical treatment of the sum frequency generation surface-sensitive vibrational spectrum of the water surface (142), a satisfying effort, but one that left me with uneasy reservations concerning any facile interpretations of such nonlinear spectra.

We did, however, pursue the acid dissociation at an aqueous interface for a different atmospherically relevant acid, nitric acid ( $\text{HNO}_3$ ), whose importance for ozone issues in the upper troposphere was pointed out to us by our Boulder colleague Maggie Tolbert. Bianco, graduate student Shuzhi Wang, and I attacked the issue of  $\text{HNO}_3$ 's acid dissociation versus the depth at a cold liquid water interface in assorted ways (143, 144). The upshot was the  $\text{HNO}_3$  did not dissociate atop the surface (in agreement with the experiments and calculations of Geri Richmond's group); it did dissociate when located a few layers down, but in between it did or did not, depending on specific orientations and local environments. Why this delicate state of affairs? It reflects what was to me a surprising fact for nitric and other classic strong acids. Certainly, I would not put my finger into a beaker of aqueous  $\text{HNO}_3$ , but the free energy change for its acid dissociation is only negative by a couple of kilocalories per mole!

As a result of our work on heterogeneous atmospheric reactions, I was invited to a French meeting on ice, where I first heard about ice (icy grain) particles in the interstellar medium (ISM). In response to my question asking what was the most important open heterogeneous reaction issue for the ISM, the answer was in the form of a question: Was there amino acid formation? The overriding interest here came from one of many theories about the prebiotic origin of life: Could the origin of amino acids on Earth have been their synthesis in the ISM and subsequent transport to Earth? This view at least had partial support by the well-known Murchison meteorite evidence. With postdoc Denise Koch, ex-postdoc Peslherbe, and CNRS researcher Celine Toubin, we showed via electronic structure calculations that the penultimate step for making (from molecules known to exist in the ISM) the simplest amino acid glycine ( $\text{NH}_2\text{CH}_2\text{COOH}$ ) on a modeled ice surface was viable even at the ISM's very low temperatures (145). This reaction's facility in generating the product aminoacetonitrile ( $\text{H}_2\text{NCH}_2\text{CN}$ )—only a hydrolysis step away from glycine—arose from (here it was again!) a PRC. Thus, in the net addition of the hydrocyanic acid isomer HNC to methane imine  $\text{CH}_2\text{NH}$ , the PRC allowed an HNC acid dissociation to lead both to the nucleophilic attack of the resulting  $\text{NC}^-$  anion on the methylene C atom and to the required protonation of the NH group. In fact, I have come to view PRCs as the chemical reactivity analog of 2:1 Fermi resonances in vibrational energy transfer; they are everywhere! It is pleasant to record that, shortly thereafter, the first radio telescope ISM detection of aminoacetonitrile was announced; this was no proof of course that our mechanism was correct, but it was certainly a solace after a long and arduous effort with frequent confusion and misadventure along the way.

Our MD studies of several enzyme reactions with Inaki Tunon and Vicente Moliner and their students are mentioned in passing above. The idea to do a different “bio” problem, this time concerning DNA, was planted years ago when I was an assistant professor. My then Boulder biophysical colleague Bill Bauer was interested in drug intercalation (insertion) into DNA. He pointed out to me that the equilibrium separation of the pairs of DNA base pairs (i.e., the intercalation site) was small compared to the size of most drugs. This meant that an opening of the pairs must occur for intercalation to succeed. This could be either—for me, the boring option—an equilibrium phenomenon in which the drug would sit just outside the DNA and simply wait until an equilibrium fluctuation allowed it to enter or—in my view, the more exciting scenario—a dynamic phenomenon in which the drug would force its way in, coupled to the DNA dynamics along

the way. After an approximately three-decade hiatus, we finally examined the intercalation of the anticancer drug daunomycin into DNA with postdoc Arnab Mukherjee and colleagues Bagchi, Richard Lavery, and Krystyna Zakrzewska (146, 147). We could see some of the key DNA, water solvent, and drug motions necessary for the intercalation in a scenario that suggested the aggressive rather than the passive role for the drug. Calculating the rate constant and determining the role of such motions therein remain tasks for the future.

Our final chemical reaction topics deal with our recent activity in the past few years on reactions of importance for renewable energy. As with most departments, this is a big deal in Boulder, where most efforts are on the more photophysical side of these problems (e.g., multiple exciton formation). As critical as those aspects are, our own interests have focused instead on the equally critical chemical side of these energy arenas. Our efforts on CO<sub>2</sub> reduction with Boulder colleague Charles Musgrave and his students are still ongoing (148), so we confine our discussion to our other energy research wing. In our first endeavor in this business, postdoc Bianco, ex-Los Alamos and now Colorado resident Jeff Hay, and I undertook a quantum chemical investigation of the mechanism of water oxidation  $2\text{H}_2\text{O} \rightarrow \text{O}_2 + 4\text{H}^+ + 4\text{e}^-$  by Tom Meyer's famous blue dimer biruthenium (Ru) transition metal complex, a very successful homogeneous catalyst for this daunting and most difficult part of water splitting (149, 150). The quantum complex's ligands were modeled in a reasonable fashion, and the complex was surrounded by a number of quantum waters and large number of classical waters. We picked up the story at the already-understood stage at which the catalyst was in its active form, in which each of the two Ru moieties had already been oxidized up to the nominal +5 oxidation state.

We found, and in fact had anticipated (149), that the first, and apparently rate-limiting, step in the process involved yet again—you guessed it—a PRC, this time via two water molecules bridging via hydrogen bonds the two oxygen atoms separately attached to the two Ru moieties, each located at an end of the complex. There is a nucleophilic attack by the oxygen atom of the first H<sub>2</sub>O on one O (let us call it the left-hand-side O) to form an O–O bond; this is coupled to a PT from that water molecule to the second H<sub>2</sub>O in the chain, which in turn transfers a proton to the other, right-hand-side O. This double PT is synergetically coupled to a negative-charge flow through the complex's  $\mu$ -oxo bridge; this flow originates from the nucleophilic attack and ultimately places negative charge on the right-hand-side O, aiding in its acceptance of the proton in the final PT. A surprise was that the reaction free energy barrier largely arose from the surrounding water solvent, which suggested that the catalysis would be even more effective in a partially hydrophobic environment.

This last subsection shows, I think, only a tiny glimpse of the incredibly rich panoply of real-world problems involving fundamental molecular issues to which theoretical physical chemistry has a chance to contribute. Surely the future here is bright.

## DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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