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# Perspective:  Bimolecular chemical reaction dynamics in liquids

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**Abstract**

Bimolecular reactions in the gas phase exhibit rich and varied dynamical behaviour, but whether a profound knowledge of the mechanisms of isolated reactive collisions can usefully inform our understanding of reactions in liquid solutions remains an open question. The fluctuating environment in a liquid may significantly alter the motions of the reacting particles and the flow of energy into the reaction products after a transition state has been crossed. Recent experimental and computational studies of exothermic reactions of CN radicals with organic molecules indicate that many features of the gas-phase dynamics are retained in solution. However, observed differences may also provide information on the ways in which a solvent modifies fundamental chemical mechanisms. This perspective examines progress in the use of time-resolved infra-red spectroscopy to study reaction dynamics in liquids, discusses how existing theories can guide the interpretation of experimental data, and suggests future challenges for this field of research.

## 1. Introduction

The molecules participating in a bimolecular chemical reaction in a liquid experience very different interactions with their surroundings than for a comparable reaction in the gas phase.[1] In a liquid solution, the reacting species are subjected to frequent collisions with solvent molecules and continuously interact with the solvent bath through intermolecular forces. If the solute-solvent collisions can be considered as individual events, they occur at intervals as short as a few hundred femtoseconds.[2, 3] The surrounding solvent modifies the energy landscape over which the chemical reaction occurs, and can also influence the reaction rate dynamically, for example by affecting the geometries of approach of reactants and hindering the separation of products.[4] In the gas phase, reaction products may form with distributions of energy in their vibrational, rotational and translational modes that are non-thermal. Asymptotic measurements of such distributions for separated products (often on nanosecond or longer timescales) provide detailed information on the motions of the participating atoms during the reaction. In contrast, the normal energy fluctuations of solvent and solute particles control the rates of relaxation of internally excited molecules in a liquid,[5] and redistribute energy on ultrafast (femtosecond to picosecond) timescales. This energy redistribution might even occur over the course of the reaction so that the products are born in thermal equilibrium with their surroundings. When comparing reactivity in gases and liquids, such considerations raise an important question: what value does the understanding of gas phase chemical reaction dynamics, developed over several decades of increasingly sophisticated experimentation and computer simulation,[6, 7] have in guiding our understanding of the dynamics of reactions in liquids? This article presents arguments based on recent experimental and computational studies that, in many cases, the gas-phase picture is an excellent starting point for interpreting the fundamental mechanisms of reactions in solution. Moreover, differences in the observed behaviour in gas and liquid phases can provide quantitative information on the ways in which the solvent modifies the energetics and dynamics of a chemical reaction. In addressing these questions, this article focuses on chemical reactions involving neutral radicals in organic solvents. However, many of the ideas presented should extend to ionic reactions and to other important solvents such as water.

## 2. Bimolecular Reaction Dynamics in Gases and Liquids

### 2.1 Overview

Experimental techniques based on molecular beam scattering combined with mass-spectrometric, laser spectroscopic and velocity imaging methods have exposed the fundamental mechanisms of isolated, gas-phase bimolecular chemical reactions in exquisite detail.[6-8] These reactions are initiated by a collision (or near collision, as in the case of electron-transfer driven mechanisms), and have been studied under conditions in which no further collisions are experienced so that asymptotic product properties relate directly to the forces experienced along the reaction coordinate. Scattering calculations on high-level *ab initio* potential energy surfaces (PESs) are able to replicate the experimental observations, identify quantum and classical contributions to the reaction cross sections, and provide microscopic insights that go far beyond what can be deduced from experiment alone.[9]

For a gas-phase reaction studied under "single-collision" conditions, measurement of quantum-state and kinetic energy resolved differential cross sections for one product species, combined with principles of conservation of momentum and energy, gives an essentially complete picture of the reactive scattering at a selected collision energy. Methods based on velocity map imaging (VMI)[10, 11] can deliver this degree of experimental sophistication,[8] and examination of the changes in the dynamics with collision energy of reactants is yet more insightful. Theoretical developments have kept pace with experimental studies, with computation and fitting of accurate PESs from first principles now well-established for polyatomic reagents such as methane.[12] Advances in time-dependent or time-independent quantum scattering and classical trajectory calculations, and incorporation of non-adiabatic dynamics, such as those occurring at conical intersections, allow direct comparisons of theoretical outputs with cutting-edge experimental data. These ideas developed for gas-phase reactions are also being profitably applied to inelastic and reactive scattering from the surfaces of liquids and self-assembled monolayers, for which additional pathways such as trapping and subsequent desorption can be examined.[13-16] However, the bulk liquid phase introduces numerous dynamical complexities that do not have parallels in a low pressure gas or a gas-surface interface.[17, 18]

Exploration of bimolecular chemical reaction dynamics in liquids is still relatively rare, with most prior dynamical studies focusing on photoexcitation, and the subsequent dynamics of relaxation, dissociation and recombination.[2, 19] Perhaps the notion that solvent collisions will destroy useful dynamical information on very short timescales discouraged further investigation, but a pioneering study by Hochstrasser and coworkers provided first hints that dynamical signatures might be usefully observed for reactions in liquids.[20] The exothermic reaction of CN radicals with $CDCl_3$ was examined by ultraviolet photolysis of a solution of ICN radicals in deuterated chloroform. Transient infra-red

absorption spectroscopy revealed a short-lived feature, assigned to vibrationally excited DCN, which relaxed to its ground vibrational level on a timescale of ~250 ps. Approximately 20% of the DCN was deduced to be produced with a quantum of C-D stretch excitation, whereas measurements for CN + CHCl$_3$ failed to observe vibrationally excited HCN. In the gas phase, similar reactions produce HCN or DCN products with population inversions relative to the ground vibrational level.[21-24] These comparisons suggested that the solvent either modifies the location of the transition state, moving it later along the reaction coordinate so the new H-CN or D-CN bond is not formed significantly elongated beyond its equilibrium geometry, or that a frictional effect of the solvent quenches vibrational excitation of nascent products on the timescale of the reaction.[4, 20] The production (or otherwise) of vibrationally excited reaction products in solution is a key theme of this article. As will be discussed in section 4, more recent studies of exothermic CN-radical reactions have now exposed a very detailed picture of the reaction dynamics in a range of solvents.[25-28]

Crim and coworkers recognized the importance of the early experiments from Hochstrasser's laboratory and combined transient ultraviolet and infra-red absorption spectroscopy methods in their extensive studies of reactions of CN radicals and of Cl atoms with various organic solutes.[29-32] This work highlighted the importance of recombination processes that compete with reactive loss of radical species in determining the overall kinetics (analysed using models based on Smoluchowski theory[33]), as well as the significant role of radical-solvent complexes in determining the subsequent reaction dynamics. Similar binary complexes have received attention from spectroscopists interested in weak intermolecular interactions and structures of pre-reactive complexes that are believed to influence reactive scattering in the gas phase.[34-44] Chateauneuf had earlier presented arguments for the ubiquity of Cl-solvent complexes in photochemical reactions of Cl atoms with organic molecules in chlorinated solvents,[45-47] and time-resolved spectroscopic studies characterized both these complexes and geminate recombination to higher energy isomeric forms (such as *iso*-Br-BrCHBr from bromoform, in which a C-Br bond is replaced by a Br-Br bond) upon photolysis of halogenated solvents and solutes.[48-69] These isomeric forms can show enhanced reactivity,[53, 70, 71] and it is now apparent that they and the solvent complexes are also observed in pulsed radiolysis experiments using high energy electrons in liquids such as CCl$_4$.[68]

Photo-initiation of reaction, combined with transient absorption spectroscopy of intermediates and products using ultrafast laser pulses, offers significant improvements in time resolution over studies initiated by alternative techniques such as pulsed radiolysis. These ultrafast laser "pump and probe" methods are likely to lead to reassessment of mechanisms of radical reactions in solution, particularly on sub-nanosecond timescales. The discussion of studies of chemical reaction dynamics

that follows therefore focuses on ultrafast laser experiments in which reaction is started by UV laser photolysis of a stable precursor, and the products are monitored in absorption following well-defined time delays that can be below 1 ps. Both time-resolved electronic and vibrational spectroscopy provide important insights, and are respectively carried out with broadband UV/visible and mid infra-red laser pulses. As will be shown, the dynamics of reactions in liquids are proving amenable to detailed investigation through a combination of such experimental methods and accurate computer simulations.[27, 72, 73] For example, Riedle and coworkers examined the nucleophilic attack of a methanol molecule at a carbo-cation to form an ether, a process chosen to illustrate a mechanism of importance in substitution reactions.[74] UV photodissociation of a precursor such as benzhydryl chloride generated a benzhydryl cation $Ar_2CH^+$ (Ar = phenyl or substituted phenyl) which was observed by ultrafast transient electronic absorption spectroscopy. With the aid of molecular dynamics calculations, this study distinguished the dynamics of planarization and solvation of the carbo-cation from the subsequent methanol addition step.

Although comparison of data from ultrafast transient absorption spectroscopy and computer simulation is an effective approach to understand reactions in solution, still richer rewards may be available. In particular, comparative studies of the dynamics of related reactions in the gas phase and in solution should allow quantitative and profound deductions to be drawn about how a solvent affects fundamental reaction mechanisms. Examples of recent progress and new dynamical insights deriving from this strategy are presented in section 4. However, it is first useful to identify aspects of the reaction dynamics that might be peculiar to, or modified by the liquid environment.


**2.2 Dynamical behaviour specific to reactions in solution**

Various processes that are not of concern in gas-phase experiments at low pressures become both significant and very fast in a liquid, and some are illustrated schematically in figure 1. The figure uses ICN photolysis in a chlorinated organic solvent as an example, and the timescales for many of the processes shown, and the factors determining branching between competing pathways, have been revealed by molecular dynamics simulations by Benjamin and coworkers.[75, 76] These simulations also show that such behaviour can extend to within one solvent layer from the liquid surface.[77]

As was noted in the Introduction, "collisions" between a solute and the solvent molecules occur on timescales of a few hundred fs, and the solute is embedded in a medium that may be polar as well as anisotropic on the microscopic scale. Rapid relaxation to thermal equilibrium is therefore expected, with inhibition of free translational and rotational motions and quenching of excess energy in these

degrees of freedom within a few collisions with the solvent. However, coupling of *vibrational* modes of a solute to the solvent bath may be weaker, particularly for high-frequency modes (such as C–H stretches).[19] This presents an opportunity to monitor vibrational excitation and relaxation dynamics of solutes either by optically driving a population out of thermal equilibrium, or as a result of exothermic chemical reactions. If vibrationally hot reaction products can persist in solution over timescales of picoseconds to nanoseconds, assumptions of local thermal equilibrium may be called into question in the chemistry of exothermic processes.[78, 79]
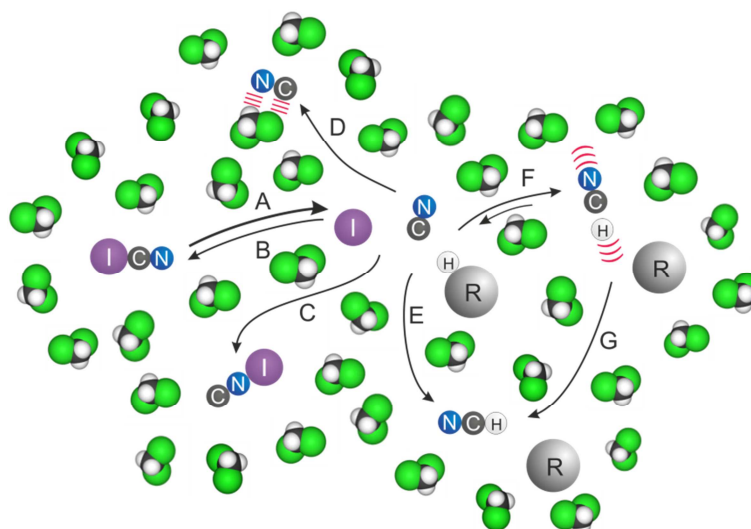


**Figure 1:** Dynamical behaviour relevant to the discussion of photo-initiated reactions in liquids, illustrated by ICN photolysis in a solution containing an organic species RH. R denotes an organic radical. A: photodissociation of ICN and thermalization of the photofragments by interaction with the solvent. B & C: geminate recombination to ICN and INC respectively. D: complexation of a CN radical with a solvent molecule. E: reaction to form thermalized HCN. F: reaction to form vibrationally excited HCN (which may be reversible if the solvent prevents separation of products). G: relaxation of internally excited HCN by coupling to the solvent bath. In each step, the solvent cage surrounding the reacting species may be the original one in which reactants / products form, or may differ because of intermediate diffusion.

If a reaction is initiated by photo-excitation and dissociation of a precursor compound, a photolytically generated reactive intermediate faces many choices in solution. It may simply geminately recombine with its co-fragment, either within the initial cage of solvent molecules in which the two photoproducts were formed, or after some diffusive excursion outside this solvent cage. These recombinations can lead to the parent precursor compound in its ground or excited

electronic states, or indeed to isomers of the parent molecule. If the reactive intermediate survives recombination, it may instead bind to a solvent molecule and form a stabilized complex (perhaps following thermal relaxation of any initially excited degrees of freedom), or react with the solvent or a co-solute. Reaction may be prompt and occur with solvent or solute molecules in the immediate vicinity of the newly formed intermediate, or may occur after diffusion into the bulk liquid.

As the reactive intermediate (perhaps now present as a complex with a solvent molecule) and a co-reactant approach, collisions with the solvent may activate them sufficiently to surmount any energy barrier to reaction. However, solvent collisions can also steer the reagents away from their optimum stereochemistry for reaction, and might inhibit the separation of products, leading to re-crossing of the energy barrier back towards the reactants' side.[17, 18] The presence of the solvent will also influence the overall energetics of the reaction, perhaps stabilizing the transition state relative to the reactants or vice versa and so influencing the activation barrier height and the reaction rate.[2] The timescale in which a shell of solvent molecules adapts to changes in the reagents as they progress along the reaction coordinate must be compared to the time taken for the transition region to be crossed if solvent effects are to be understood.[4] Entropic effects of solvent restructuring must also be considered alongside the energetic changes associated with a reaction coordinate on a PES, so a free-energy description is more appropriate. For computational studies of reactions in solution, the concept of a potential of mean force (PMF)[17, 18] is valuable and will be modified from the gas-phase PES by the interaction with the solvent. The newly formed reaction products are unlikely to be born into an equilibrated solvation environment, not least because there will be a co-product in close proximity within a solvent cage. As the solvent molecules and solute reorient, local intermolecular interactions will change so spectral diffusion might be evident in vibrational (infra-red) bands as the local environment of the products evolves towards equilibrium.

Reactions in solution offer many experimental parameters amenable to variation to explore their effects on reactivity. Bulk liquid properties of temperature, viscosity and dielectric constant, as well as externally selected conditions such as applied pressure, influence the rates and mechanisms of reactions, and solvent-solute interactions in hydrogen-bonded and non-hydrogen bonding solvents differ. The physical structure and intermolecular interactions of the solvent affect diffusion rates and solvent reorganization timescales. The spectrum of frequencies of vibrational modes of the solvent influences energy transfer from internally hot solute molecules, and can be controlled to some extent by selecting hydrogenated or deuterated isotopologues of the solvent. Studying the same reaction in a variety of solvents can therefore be very instructive, although the possibility of competing and unwanted reactions with the solvent must be considered. Unintended reaction

pathways can open up for UV photo-initiated processes in certain solvents: for example, some chlorinated solvents are known to react rapidly with photoexcited states of aromatic solutes,[80] and to undergo photo-isomerization to less energetically stable forms that may exhibit different chemical reactivity.[53, 68, 70, 71] Only a small part of this rich parameter space has so far been covered in experimental studies of the dynamics of reactions in liquids of the type discussed here, leaving abundant opportunities for future investigation.

This article concentrates on exothermic reactions of neutral radicals in organic solvents, either with the solvent as one of the reagents, or with introduction of an additional reactive solute. In a polar environment in a liquid, charge-separated states may be preferentially stabilized to a degree that ionic reaction pathways need to be considered. Examples might include proton-coupled electron transfer mechanisms in place of neutral H-atom exchange reactions,[81, 82] or the onset of an $S_N1$ pathway for nucleophilic substitution. However, these ionic reactions lie outside the scope of the current perspective. Before turning attention to specific reaction systems, an overview is provided of theoretical methods that are essential for the interpretation of experimental studies.

## 3. Theoretical Considerations

### 3.1 Solvent effects on reaction rates

If a chemical reaction follows a pathway that involves a potential energy barrier somewhere along the reaction coordinate, the solvent may reduce or enhance the barrier height relative to the energies of the reactants.[17] The transition state for the reaction, which is likely to be located at the top of the energy barrier, can be stabilized or destabilized by this static influence of the solvent, resulting respectively in an increase or decrease in the rate of the reaction if this rate is not limited by the timescale for diffusion of the reactants. However, it is now well recognized that the solvent can also affect rates of reaction dynamically, through collisions during passage from reactants to products. The Langevin equation (LE) provides a description of the dynamics of reacting particles subjected to a frictional force imposed by the solvent $F_{fr} = -\gamma v$ (with $\gamma$ denoting a friction coefficient and $v$ being the instantaneous microscopic speed of the particles), and a stochastic force $F(t)$ associated with the solvent collisions, which has a time-average $\langle F(t) \rangle = 0$.[17, 18] Kramers theory considers an activated reaction with a barrier height greater than $k_BT$ in which solvent forces act instantaneously, giving a solvent friction described by $\gamma$.[3, 83] Collisions with the solvent provide a means of activation of reactants to surmount the energy barrier, but can also hinder the evolution of reactants to products. The Kramers theory model identifies causes of deviations from conventional

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Transition State Theory (TST), the most significant for the current discussion being that solvent collisions induce re-crossings of the transition state from the products' side to the reactants' side, reducing the overall rate of reaction. Free motion across the reaction barrier, as envisaged in TST, becomes a diffusive motion along the reaction pathway in the vicinity of the barrier when solvent friction is significant. For lower solvent friction, the effect of solvent induced barrier re-crossing becomes small and the Kramers theory prediction of the reaction rate coefficient tends towards the value expected from TST (although there are also consequences associated with the rate of activation of the reagents and slow cooling of products in the very low friction regime that can again reduce reaction rate coefficients from the TST value).

The constant friction assumed in the LE and in Kramers theory provides a poor description of many chemical reactions of small molecules in which the passage through the transition state region is fast compared to solvent relaxation times. The solvent can be pictured as frozen in its configuration at the instant before reaction initiates, and equilibrium is not maintained in all degrees of freedom over the course of the reaction. In this *"non-adiabatic"* limit, the reaction may pass over an energy barrier that is not the same as that for the fully solvated and equilibrated transition state. These considerations have been addressed by developing reaction rate theory based on the Generalized Langevin Equation (GLE). In Grote-Hynes theory,[84, 85] the time-dependent solvent friction is described by a "memory kernel" that accounts for the evolution of the reaction and its surrounding solvent. In the limit of slow barrier crossing (an *"adiabatic"* regime with time for solvent re-organization), Grote-Hynes theory reduces to the Kramers theory description of instantaneous readjustment of the solvent. However, in general Grote-Hynes theory predicts reaction rates slower than Kramers theory and so necessarily lower than those from TST. Experimental studies are now testing the validity of Kramers theory,[86-88] and Grote-Hynes theory is finding applications in, for example, computational studies of enzyme-catalysed reaction rates.[89]

## 3.2  Molecular Dynamics simulation of reactions in liquids

Molecular Dynamics (MD) simulations allow estimates of the effects of solvent friction to be computed because the Fluctuation-Dissipation theorem provides a connection between the microscopic friction coefficient $\gamma$ and the correlation function for the forces exerted by the solvent on the reacting species.[4] Furthermore, MD simulations that include an accurate treatment of the energetics along the reaction path are desirable because they can provide a quantitative visualization of the combined dynamics of the reactants and surrounding solvent. Computing

reactive trajectories embedded in an explicitly simulated solvent composed of individual molecules, when combined with analysis of experimental measurements, provides many insights of the type discussed in Section 4.[27, 72, 73]

If a reaction is to be embedded in a solvent in a realistic computer simulation, a computationally efficient representation is required of the potential energy function and of the coupling of the reaction with the explicit solvent molecules. Glowacki and Harvey accomplished this objective by using an Empirical Valence Bond (EVB) fit to high level *ab initio* calculations of molecular energies at a range of nuclear geometries.[27, 72, 73] They combined this EVB model with an MD simulation for all the remaining solute and solvent degrees of freedom, and implemented this approach within the CHARMM suite of programs.[90] This combined EVB and MD strategy also finds many applications in wider dynamical problems such as simulation of enzyme catalysed reactions.[91] However, in these contexts, it is typically used for analysis of free energy profiles in the adiabatic regime, rather than non-equilibrium dynamics of the sort discussed in this article, which are intermediate between adiabatic and non-adiabatic regimes. Computer simulations of chemical reactions can be highly inefficient because steric, solvent and energetic factors lead to many non-reactive trajectories. A new class of accelerated molecular dynamics methods was therefore implemented to improve the efficiency and ensure propagation of sufficient numbers of reactive trajectories to provide meaningful dynamical insight in the post transition state region.[92-94] As will be discussed in Section 3.3, coupling between the solvent modes and vibrational degrees of freedom of the reacting molecules must be treated accurately if vibrational relaxation timescales (pertinent to the discussion in section 4) are to be correctly computed. A calculation of the spectrum of the solvent from the MD simulation is one method to test the suitability of the force fields employed.


### 3.3 Vibrational relaxation of products of exothermic reactions

The experimental measurements discussed in section 4 raise questions about the coupling of solvent to the reaction coordinate that go beyond those considered within formalisms such as Kramers or Grote-Hynes theories. These experiments focus on exothermic reactions with barriers that are known to be low from gas-phase studies and *ab initio* electronic structure calculations. Figure 2 shows the type of energy profile considered here. The reactions release $\geq 100$ kJ mol$^{-1}$ of energy, but the chemical dynamics and solvent couplings will determine how this excess energy is channelled into the various degrees of freedom of the reaction products and how quickly it is dissipated to the solvent bath. One limiting case might be imagined in which the coupling of the

solvent to the reaction coordinate and orthogonal modes of the separating products is so strong that dissipation occurs on timescales comparable to, or faster than the passage from the transition state to products. Alternatively, for weak coupling, nascent motions of the reaction products might survive with lifetimes significantly longer than the timescale for reaction, or even for diffusive separation of the post-reaction species. These limits could be described using an alternative interpretation of the concept of solvent friction, in which it represents the strength of dissipative coupling of vibrational and hindered translational and rotational motions of the products to the solvent bath. The motion of interest in the discussion that follows will be vibrational, but instances are known from photodissociation studies of persistence of rotation within a solvent cage,[95, 96] and high-speed photofragments may penetrate one or more solvent shells before equilibrating their translational motion with the surrounding liquid.[75, 76]
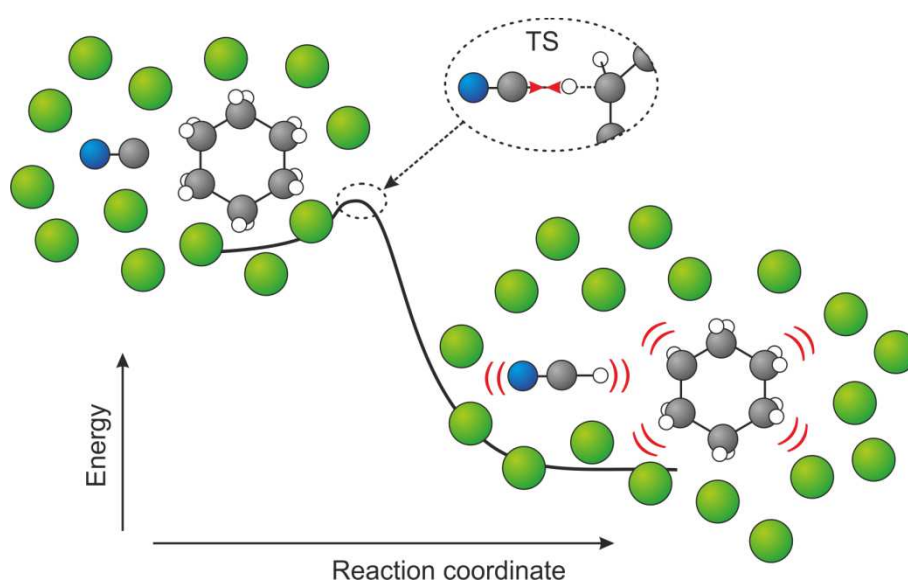


**Figure 2:** Schematic diagram of an exothermic reaction (in this case CN + c-$C_6H_{12}$ → HCN + c-$C_6H_{11}$) in solution, with the solvent molecules represented as green circles. The solid black line is the potential energy profile along the reaction coordinate, and the inset shows an early transition state (TS) with a the new C-H bond extended beyond its equilibrium length, giving a restoring force shown by red arrows. In the absence of solute-solvent interactions, this force will give rise to vibrationally excited HCN, indicated by (( )). The radical co-product may also be internally excited. However, coupling to the solvent bath during or after the reaction will damp this excess vibrational energy of both products, with the timescale depending on the strength of the coupling.

Landau-Teller (LT) theory (and refinements thereof) provides a method to compute rates of vibrational relaxation in solution. Time-dependent perturbations caused by the solvent induce

population transfer between energy levels of the solute.[19] LT calculations require a Fourier transform of the time-correlation function for the forces exerted by the solvent on the vibrational coordinate,[18] or equivalently a Langevin-type frequency-dependent solvent friction. For a harmonic oscillator, the rate of transition from vibrational level *v* to *v*-1 scales linearly with *v*. For high frequency vibrational modes, the time-dependent force experienced by the vibrating molecule must have an appreciable Fourier component at the frequency of the molecular vibration for efficient vibrational energy transfer to the solvent. That is, (nearly) resonant coupling promotes the relaxation, and simulation of vibrational relaxation therefore requires very accurate force fields for the solvent modes and for their coupling to the solute. If the vibrational mode energy is less than $k_B$T the rate of vibrational relaxation becomes comparable to the rate of the reverse vibrational excitation process. Within the context of the exothermic reactions discussed in Section 4, such considerations of vibrational couplings to the solvent bath will be of greatest significance in the post-TS region of the reaction pathway. Figure 2 illustrates schematically the reaction path for an exothermic reaction in solution. As the reaction products emerge from the transition state, they may acquire vibrational excitation from the dynamics induced by the PMF governing the reaction, but will also develop couplings to the solvent modes as the new chemical bonds form. Whether the couplings switch on and exert a damping effect on timescales competitive with the passage of the reactants through the transition state region, or whether they can be treated as a separate, post-reaction phenomenon remains to be established, but is likely to depend on the exact nature of the solvent and the reacting species. As will be discussed in section 4, the solvent caging of co-products of a reaction can also affect the vibrational relaxation if one or other forms vibrationally hot.[73]

Section 4 highlights some of the key outcomes of recent experimental and computational studies of exothermic CN radical reactions in solution. The HCN (or DCN) is formed with substantial vibrational excitation – to a much greater degree than was appreciated from the early results of Hochstrasser and coworkers[20] – but this vibrational excitation is lower than for products of comparable reactions in the gas phase.[21-24, 97] Perhaps the picture most appropriate for the reactions considered here is therefore analogous to the non-adiabatic picture resulting from Grote-Hynes theory: the solvent cannot adjust to an equilibrated configuration on the timescale of the chemical reaction dynamics, so gas-phase like dynamics may persist into the condensed phase, but with some damping of vibrational excitation because of solvent coupling (a post-transition state "friction"). The extent to which these gas-phase dynamics are replicated in solution offers a means to study the dynamical role the solvent plays in modifying the reaction, above and beyond its influence on the (free) energy landscape over which reaction occurs.

## 4. CN Radical Reactions: A Case Study of Reaction Dynamics in Solution

### 4.1 Prior studies of CN radicals in solution

CN radical reactions are chosen here as an illustrative example because they exhibit many dynamical features that can be observed experimentally. Ultraviolet photolysis of ICN is a prompt and convenient source of CN radicals, and Benjamin and Wilson proposed experimental study of the photodissociation dynamics of this compound in solution as a way to probe the effects of solvent on chemical dynamics.[98] Zewail and coworkers,[99] Keiding and coworkers,[100] and Bradforth and coworkers[95, 96, 101] subsequently performed a range of transient UV-visible absorption measurements on the CN photoproducts in various solvents, including water. These experiments, and complementary molecular dynamics simulations,[75-77] exposed a rich vein of dynamical behaviour. Examples included ballistic versus diffusive cage escape, and an abrupt change in the liquid structure around rotating CN radicals that causes sudden breakdown of linear response for the rotational relaxation.[96] Hochstrasser's early studies of the reactive loss of CN radicals,[20] and later investigations by Crowther *et al*.[29, 30] also provide very important foundations for the dynamical studies discussed here.

Absorption anisotropy experiments by Bradforth demonstrated that the CN radicals from 255 or 224-nm photolysis of ICN in methanol, ethanol, water or chloroform initially possess substantial rotational angular momentum. A strong torque associated with passage through a conical intersection during the I−C bond breakage generates this rotational excitation.[95] Even in solution, the CN-radical rotation can take a few picoseconds to equilibrate, although relaxation in chloroform is faster than for the other solvents, perhaps as a consequence of collisions with heavier solvent molecules. Crowther *et al*. followed the ps − ns time evolution of the CN ($B^2\Sigma^+$-$X^2\Sigma^+$) electronic transition in solution in dichloromethane in the presence of a variety of organic solutes, in parallel with transient IR spectroscopy of the newly forming HCN reaction products. To account for observed differences in timescales for removal of CN and production of HCN, [29, 30] they suggested that the CN complexes to dichloromethane in linear and bridged conformers that have different reactivities with the organic solutes. The structures of these complexes are illustrated in figure 3. The more weakly complexed linear form was argued to be responsible for most of the HCN production, whereas the more strongly bound bridged complex reacted slowly with the solvent to form ClCN. These measurements underline the benefits of monitoring both reactant and product species to unravel some of the complexities of liquid phase reactions.
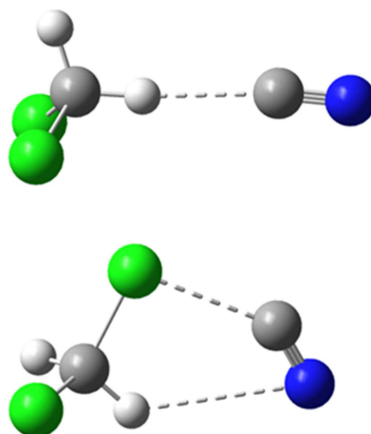
**Figure 3:** Structures of the linear and bridged complexes of a CN radical with a dichloromethane molecule, as calculated with DFT at the B3LYP/6-31+G* level.

### 4.2 Time-resolved IR spectroscopy of CN reactions in organic solvents

Profound investigation of reaction mechanisms in solution is possible with transient IR spectroscopy. In the work of Crowther *et al*., the time constant ($\tau = 313 \pm 93$ ps) for the rise of the IR absorption signal for HCN from reaction of CN radicals with pentane was comparable to the earlier observations ($\tau = 194 \pm 20$ ps) by Hochstrasser for CN radical reaction with $CHCl_3$ (which also served as the solvent).[20] The latter study reported that ~20% of the DCN from CN reactions in $CDCl_3$ was vibrationally excited, whereas the HCN from the CN + $CHCl_3$ reaction was all born in its vibrational ground state. The substantial product vibrational excitation observed in gas-phase experiments appeared to be quenched (almost) completely in solution, and the authors proposed that the solvent shifted the transition state for H/D-atom abstraction later along the reaction coordinate than for isolated reactions, with solvent induced energy dissipation in the transition region removing residual vibrational excitation. A decrease in the reaction rate in solution was attributed to geometric constraints that reduce the CN radical reaction probability. This perspective seems to be consistent with the aforementioned argument for reactions mediated by solvent complexes, although these complexes will also modify the height of the energy barrier to reaction.

However, significant new insights about the reaction mechanism were obtained when Greaves *et al*. applied broadband transient IR absorption spectroscopy methods that could observe simultaneously both the C-H stretching fundamental ($v_3 = 1 \leftarrow 0$) band of HCN at 3263 cm$^{-1}$ (in dichloromethane solution) and the vibrational hot-band at 3160 cm$^{-1}$ corresponding to the ($v_3 = 2 \leftarrow 1$) absorption.[25] Representative spectra are shown in figure 4 for the reaction of CN radicals (from ICN photolysis) in

a 1.0 M solution of cyclohexane in $CH_2Cl_2$. For the CN + c-$C_6H_{12}$ $\rightarrow$ HCN + c-$C_6H_{11}$ reaction which dominates, $\Delta_r H$ = -100 kJ mol$^{-1}$. Similar behaviour was observed for other solutes, and for solvents such as $CD_2Cl_2$ and $CDCl_3$. Integration of the band intensities at each time-delay between ICN photolysis and IR probing of the sample gives time-dependent absorption signals of the type plotted in figure 5. These integrated band intensities depend on population *differences* between the vibrational levels connected by an IR transition. From data such as those presented in figure 5, it is clear that the majority of the HCN produced by the CN + cyclohexane reaction initially forms with one quantum of C−H stretching excitation. Moreover, the spectroscopic data provide evidence that the HCN is excited in its bending vibrational mode as well. A kinetic fit to the data set indicates that the time-constant of ~140 ps for rise of the HCN fundamental absorption band is determined by the vibrational relaxation rate of the internally hot HCN, not by the rate of reaction, and measurement of the vibrational relaxation rate in separate IR-pump and IR-probe experiments verified this deduction. No evidence was observed for vibrational excitation in the C−N stretching mode despite sufficient energy being available.[28] The reaction dynamics therefore not only produce vibrationally hot HCN within a solvent bath, but the dynamics are also mode specific, with the CN moiety acting as a spectator to the reaction.
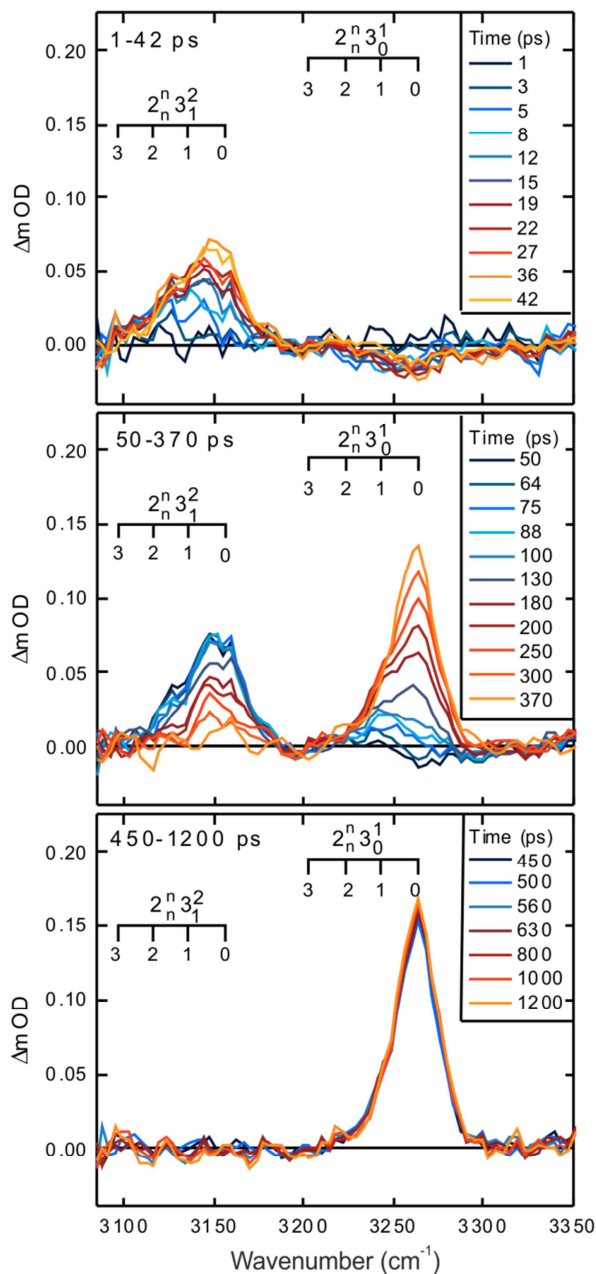
**Figure 4:** Time-resolved IR absorption spectra for HCN formed from reaction of CN radicals with cyclohexane in solution in $CH_2Cl_2$. The spectra are for the C-H stretching region and the insets show the time delays between initiation of reaction and detection of products for each spectrum. Combs above the bands provide assignments, with the main digit specifying the vibrational mode (1 = C–N stretch, 2 = bend and 3 = C–H stretch) and the sub- and superscripts denoting the number of quanta of vibration in the lower and upper levels connected by the IR transition. Possible values of $n$ (the number of quanta of bending excitation) are indicated by numbers below the combs.
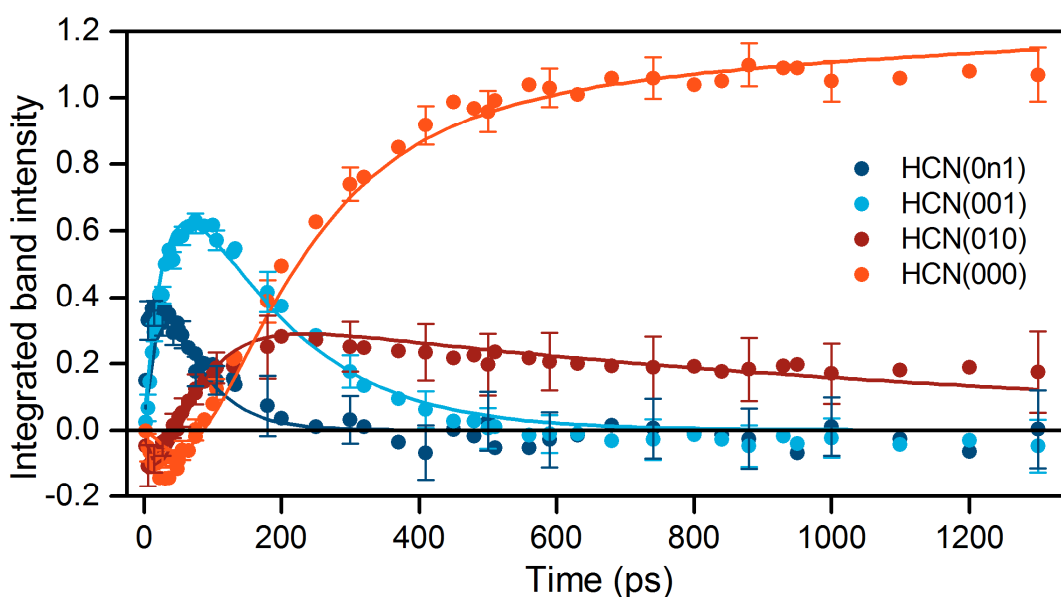
**Figure 5:** Time dependence of the intensities of the bands observed in the IR spectrum shown in figure 4. The notation ($v_1,v_2,v_3$) indicates the number of quanta of C–N stretching ($v_1$), bending ($v_2$) and C-H stretching ($v_3$) vibrational modes of the HCN giving rise to each spectral feature.

This remarkable outcome illustrates that the dynamics of the CN + cyclohexane reaction (and other H-atom abstractions by CN radicals) in solution are very similar to those for the gas phase at low pressures. However, the solution phase experiments did not reveal any production of HCN with $v_3$ = 2 although these internally hotter products have been reported in recent chemiluminescence studies of the same reaction in the gas phase.[97]

Other fates can befall the CN radical, including geminate recombination with the Iodine atom co-photofragment.[75, 99, 100] The broadband IR detection is also very informative here because the transient bleach of the ICN mode at 2176 cm$^{-1}$ (the C–N stretching vibration) caused by ICN photolysis can be observed simultaneously with growth of an INC band at 2065 cm$^{-1}$ and of the C–N stretching mode of HCN. Example data in figure 6 show the latter two features. Partial decline of the ICN bleach indicates that geminate recombination accounts for no more than 20% of the CN radical losses over times longer than 1 ps (the limiting time resolution of the experiment). Although the growth of the INC band might suggest a more significant branching to this unusual isomer, the transition dipole moment for this species is estimated to be ~120 times greater than for the stretching mode in ICN,[102] so INC is deduced to be a minor recombination channel. This deduction is

consistent with the molecular dynamics simulations of Benjamin, who discussed factors that might control the branching between ICN and INC isomers.[75]
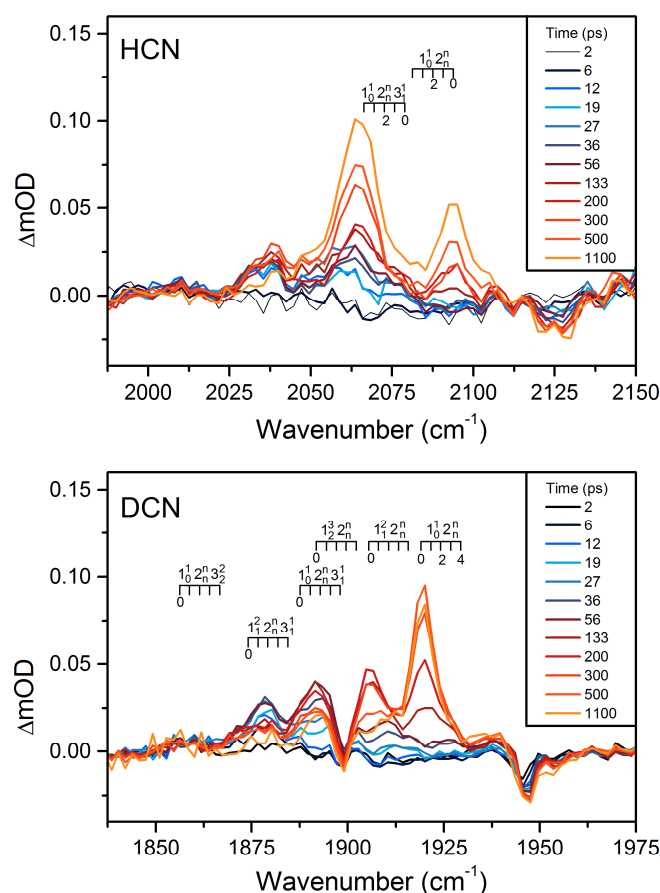


**Figure 6:** Time-dependent IR spectra obtained in the C−N stretching region of HCN (upper panel) and DCN (lower panel) following reaction of CN radicals with cyclohexane in solution in a chlorinated solvent. The INC feature derives from geminate recombination of CN radicals with I atoms. Combs indicate expected wavenumbers for absorption on vibrational bands associated with the C−N stretch ($v_1$), bend ($v_2$) and (nominally) C-H / C-D stretch ($v_3$) for both vibrational ground state and vibrationally excited molecules. See the caption to figure 4 for further explanation of the notation.

The lower panel of figure 6 shows an example of DCN formation from reaction of CN radicals with $d_{12}$-cyclohexane in CHCl$_3$, with observation in the C−N stretching region. The early-time absorption at wavenumbers around 1880 cm$^{-1}$ is assigned to DCN that is vibrationally excited in both the C−N and C-D bonds.[28] Evolution of the spectrum towards higher wavenumber with time is consistent with relaxation to lower vibrational levels. At times greater than 500 ps, the absorption is restricted to the fundamental band because thermalization is complete. Channelling of reaction exothermicity

into both stretching vibrations may be a consequence of these two modes of DCN involving significant motions of all three atoms, whereas the corresponding modes of HCN are more localized in the individual C-H and C$-$N bonds.  At early times, population inversion with respect to the ground vibrational level is close to complete in the new-born products.

When the co-reagent was switched from cyclohexane to tetrahydrofuran (THF), a series of measurements for THF concentrations from 12.3 M (*i.e.*, neat) to 0.5 M in $CD_2Cl_2$ or $CDCl_3$ demonstrated that the rise time of the HCN $v_1 = 1 \leftarrow 0$ fundamental band was now controlled by the bimolecular reaction rate instead of the vibrational relaxation time constant.[27]  The THF interacts more strongly with the HCN than does cyclohexane, and has a C-H stretching vibrational mode that is close to resonant with the HCN C-H ($v_3$) stretch.  As a consequence, the time-constant for HCN($v_3 = 1$) vibrational relaxation in solutions containing THF is $\tau_{1\to0}$~7 ps (as verified by ultrafast IR pump and IR probe experiments), whereas $\tau_{1\to0}$ ~140 ps for HCN in solutions of cyclohexane and a chlorinated solvent.  The dynamics of the bimolecular reaction of CN with THF and with cyclohexane otherwise appear to be very similar, with initial production of vibrationally hot HCN, but the post-reaction coupling of the newly formed and internally excited HCN to the solvent bath is considerably stronger when THF is present.

Beyond the gas-phase-like dynamics of the CN radical reactions in solution, the experiments revealed a number of further processes.  Two timescales for formation of INC of 10 – 20 ps and >500 ps indicated that the I + CN radical recombination can occur both within (or after a short excursion from) the initial solvent cage (<40% of the total INC) and after diffusion into the bulk solvent (>60%).[28]  However, as noted above, this recombination and the competing ICN re-formation are minor channels for CN radical loss.  The removal of CN radicals is controlled by rates of chemical reactions with organic solutes and the solvent molecules.

The solvent cage around the reaction products has another, more surprising role to play.  This unexpected behaviour emerged from analysis of the outcomes of computer simulations for the CN + cyclohexane reaction in dichloromethane, as shown in Figure 7, together with experimental data for early times from initiation (t < 25 ps).[73]  The reaction products, HCN and cyclohexyl radicals, form within a surrounding shell of solvent molecules that confines them in close proximity for ~20 ps until diffusion separates the product pair.  During this confinement, the weak coupling of the HCN to the solvent bath does not effectively quench the C$-$H stretching vibrational excitation of the HCN. However, the cyclohexyl radical is a much better sink for this HCN internal excitation than individual solvent molecules because of its larger density of vibrational states, and because the frequencies of its C-H stretching modes are closer to resonance.  Consequently, the initial flow of energy from the

internally hot HCN is to the geminate cyclohexyl radical, and thence to the solvent. This efficient quenching channel switches off after ~25 ps because of diffusive separation of the reaction product pairs, but indicates that the vibrational excitation of the HCN products could be still higher than the initial experimental analysis indicated. Two regimes therefore govern the relaxation of the HCN: at short times, in the "wake" of the reaction this relaxation mediated by the co-product radical is efficient, but at longer times when the HCN is surrounded only by solvent molecules and some small fraction of cyclohexane, the relaxation slows down significantly. This behaviour is not observed for the reaction of CN with THF because the coupling to nearby THF molecules is already strong enough to ensure vibrational relaxation within a few ps. The above discussion overlooks the Iodine atom co-product of the ICN photodissociation, which will also be in close proximity to the reaction products. However, other than geminate recombination with the CN radicals, the combination of simulation and experiment suggests that the Iodine atom does not play a significant further role. This spectator behaviour occurs because an I atom has no internal degrees of freedom (other than high energy electronic excitations) with which it might interact with the hot reaction products.
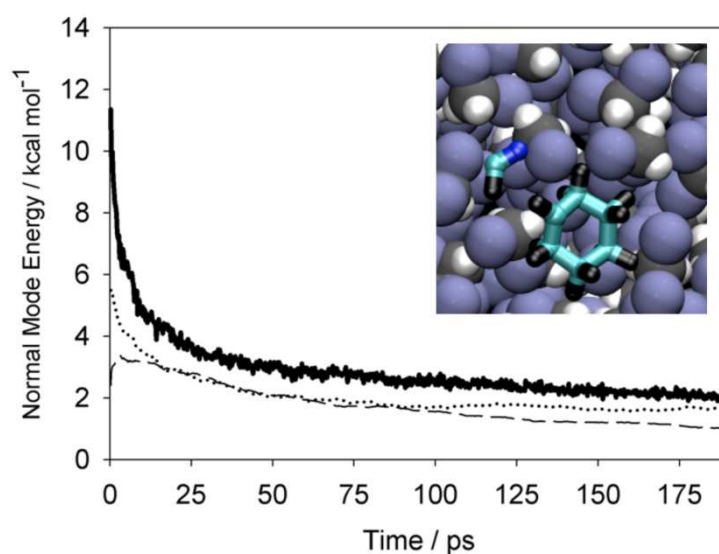


Figure 7: Time-dependence of the average energies in the three normal modes of HCN following formation by reaction of CN with cyclohexane in dichloromethane: ---- $v_1$ (C–N stretch); ····· $v_2$ (bend); and —— $v_3$ (C–H stretch). The mode energies were computed from the simulations of Glowacki and Harvey described in the main text, and are the average of 250 reactive trajectories. The inset shows a snapshot of the caged reaction products responsible for the fast decay of the C–H stretching mode energy at early times. The figure is adapted from references [72, 73].

The nature of the reactive form of the CN radicals probably differs in solution from the isolated radicals involved in gas-phase reactions. Crowther *et al*. proposed that CN will complex with dichloromethane solvent molecules in bridged and linear forms (see figure 3) which exhibit different reactivities towards organic solutes.[29, 30] The transient IR absorption experiments of Greaves *et al*. in the C−N stretching region revealed a weak feature to lower wavenumber than the INC and HCN fundamental bands, and the central wavenumber of 2037 cm$^{-1}$ and rise time (15 ps in neat $CH_2Cl_2$) led to assignment of this band to a CN-solvent complex.[25, 27, 28] The CN radical consumption kinetics can also be followed by broadband transient UV-vis spectroscopy, making use of the $B^2\Sigma^+ - X^2\Sigma^+$ electronic transition which is known from gas-phase spectroscopic studies to have an origin at 388 nm. In solution, this band appears at similar wavelengths. Current work in the Bristol group exploits both IR and UV-visible transient absorption of CN-radical spectral features. This combination of measurements is proving essential in ongoing efforts to unravel the dynamics of reactions of CN radicals with methanol. However, dynamical studies of chemical reactions in polar and hydrogen bonding solvents such as alcohols and water are still at an early stage.

## 5. Conclusions and Outlook

### 5.1 Deductions from CN radical reaction studies in solution

The experimental and computational results for CN radical reactions provide evidence that the solvent neither significantly changes reaction barrier heights, nor does it shift the location of the transition state later along the reaction coordinate. Because the dynamics correspond to the low friction regime of the Kramers or Grote-Hynes theories of reactivity, in which solvent collisions do not significantly impair motion along the reaction coordinate and across the transition state, the rates are similar to those for gas-phase CN radical reactions. Once the reaction commences, passage through the transition state is faster than, or comparable to, solvent collision times. A picture of non-adiabatic solvation applies to these reactions in which the solvent relaxation time exceeds the reaction time, and the dynamics of passage along the reaction coordinate are therefore strongly reminiscent of those for isolated events in the gas phase. However, the degree of vibrational excitation of the products from liquid-phase reactions is lower, which is not thought to be a consequence of Kramers-type friction associated with re-crossing of the transition state. Instead, we need to consider a different type of friction acting after the transition state and corresponding to coupling of the vibrational modes of the newly forming products with those of the nearby solvent molecules. The solvent also plays further important roles, for example through caging of reactants

and products, stabilization of pre- and post-reaction complexes, and imposition of steric constraints on reaction. All of these effects, in addition to the coupling of solvent modes to product motions, and the relaxation of internally hot nascent products, depend on the nature of the chosen solvent.

The CN-radical reactions provide important paradigms for liquid phase reaction dynamics because product vibrational excitation and subsequent coupling to the solvent bath can be studied with vibrational mode specificity through transient IR absorption. Moreover, the strength of coupling to the solvent can be "tuned" by choice of solvent, and comparison between experimental results and MD simulations provides critical tests of the quality of standard force-fields used in the computer models (in particular, in regions away from the minimum energy path). The reaction kinetics can be conveniently followed both for loss of CN (by UV-visible absorption) and production of HCN (by IR absorption). This class of reactions therefore presents new opportunities to study other effects in the liquid environment. For example, reaction dynamics in hydrogen-bonded solvents can be explored, and, towards this goal, the Bristol group has recently conducted detailed experimental studies of CN radical reactions with methanol. Whether such experiments can be extended to reactions in water remains to be established, but is an important objective. The energy disposal into the radical co-product may also be amenable to study by transient IR spectroscopy to give a more complete picture of the reaction mechanism, and work is currently in progress to test this idea using acetone as a co-reagent. Competition between direct abstraction pathways and addition / elimination (or simply addition followed by adduct stabilization) may also be accessible to investigation using IR or UV absorption features detected with broadband transient spectroscopy methods.

## 5.2 Towards a broader picture

Section 4 concentrated on CN radical reactions with organic compounds, but did not address the generality of the outcomes of the experimental and computational studies of these reactions in solution. Complementary studies have been undertaken of exothermic reactions of Cl atoms and of F atoms with organic solutes in solvents such as acetonitrile or dichloromethane. Most Cl-atom reactions with hydrocarbons are only mildly exothermic,[103] but the H-atom abstraction pathway from 2,3-dimethylbut-2-ene releases sufficient energy for HCl(v=1) to be an accessible product. The reaction in solution can be usefully contrasted with the Cl + propene reaction in the gas phase, because both form a resonance-stabilized allylic radical following H-atom transfer. These reactions of Cl atoms with alkenes have a competing pathway of addition to the C=C bond, followed by adduct

stabilization (in a collisional environment) or HCl elimination if the adduct retains sufficient energy to dissociate. Nevertheless, vibrationally excited HCl products associated with direct H-atom abstraction were observed by transient IR absorption spectroscopy in a variety of chlorinated solvents (CCl$_4$, CHCl$_3$ and CH$_2$Cl$_2$). However, the measured branching to HCl(v=1) was lower than was reported for the gas-phase analogue, suggesting a role for solvent coupling in the post-transition-state region.[104] The Cl atoms were produced by UV photolysis of a solvent such as CCl$_4$, and rapidly form complexes followed by recombination to the parent CCl$_4$ or an isomeric form (*iso*-Cl-ClCCl$_2$). Comparison with gas-phase dynamics therefore requires careful consideration of the exact nature of the reactive chlorine-containing species. The roles of these intermediates on reactions with unsaturated organic solutes have also recently been explored.[68]

F-atom reactions with various organic molecules are highly exothermic, and are known to favour production of vibrationally excited HF (or DF) products in the gas phase or from direct reactions at hydrocarbon liquid surfaces.[105, 106] Recent experimental and computational studies of analogous reactions in solution by the Bristol group reveal a wealth of fascinating dynamics in solvents such as acetonitrile, but the outcomes are beyond the scope of the current article.

This perspective has not discussed the dynamics of reactions in clusters, although these are often argued to provide a bridge between the gas and liquid phases. Photo-induced dynamics in clusters have much to offer in understanding the influence of solvation, for example through systematic and controlled stepwise addition of solvent molecules to a photochemically active "solute" molecule,[107] or study of solvent-mediated processes.[108] However, differences between the cluster and bulk liquid environment should be considered when drawing conclusions about reactions in liquids. For example, the cluster environment is typically very cold (a few K) whereas liquid phase experiments are mostly conducted at room temperature, and the clustered molecules are not structurally fluxional to the same degree as in a liquid.

In Section 2.2, various parameters of the solvent were identified that can be varied to explore their influence on chemical reaction mechanisms. These parameters include viscosity, dielectric constant, temperature, applied pressure, and the physical structure and intermolecular interactions prevalent in the solvent. Very little of this parameter space has so far been systematically explored: the Bristol group is making inroads with studies of reactions in a variety of solvents that so far include chloroform, tetrachloromethane, dichloromethane, acetonitrile, and tetrahydrofuran, with (as yet unpublished) work with methanol and acetone. However, all these studies have so far been limited to ambient external conditions of temperature and pressure, and extension to aqueous solutions is a priority.

**5.3 Future challenges**

Progress with study of the liquid-phase dynamics of bimolecular reactions of the type outlined in this article suggests various new directions for future research. Lifetimes of 10s – 100s of picoseconds for vibrationally excited molecules in solution in weakly interacting solvents might open up the tantalizing prospect of study of vibrationally mediated – or controlled – chemistry in solution. Crim and coworkers[109, 110] and Zare and coworkers[111-113] showed how vibrational excitation modifies the dynamics and pathways of gas-phase bimolecular reactions. However, extending these ideas to liquid solutions presents many difficulties, such as ensuring that the vibrational energy remains in the mode of interest despite dissipative influences of intramolecular vibrational energy redistribution and vibrational energy transfer to the solvent. A further complication will be to observe the reactions mediated by vibrational excitation against other background reactive signals.

Reactions involving ions are of considerable significance not only for chemistry in aqueous solution, and for reactions in living organisms, but also because they feature in textbook organic reactions such as nucleophilic substitutions ($S_N1$ and $S_N2$ mechanisms). The dynamics of these substitution reactions have been extensively studied in the gas phase and in small clusters,[114-116] but with the recent exception of the photoinitiated benzhydryl cation reaction measurements reported by Riedle and coworkers,[74] initiating and observing these processes on ultrafast timescales in liquid solutions remains an unresolved challenge.

Many of the ideas presented in this article are also applicable to photodissociation or photo-induced ring-opening dynamics which may generate internally excited products. The pathways for these processes take place on excited electronic states as well as the ground state, and the mechanisms commonly involve non-adiabatic dynamics mediated by conical intersections. Again, the strategy of detailed comparison between gas and liquid phase dynamics offers abundant opportunities to study the ways in which a solvent modifies fundamental chemical mechanisms.[117] However, measurements need to be made with sub-picosecond time resolution to observe some of the very fast excited state dynamics.

The mechanistic deductions presented in this Perspective are drawn from experiments and complementary theory that examine chemical reactions in liquids with time resolution as short as a few hundred femtoseconds. This time resolution is necessary to compete with dissipation of energy from nascent reaction products to the solvent bath. Consequently, transient absorption measurements on such timescales can reveal significantly more about the fundamental mechanisms of reactions in solution than have earlier studies of the kinetics of reactions over nanosecond to

microsecond time intervals.  However, the question remains whether experiments on still shorter timescales might reveal even greater insights.  For photo-induced unimolecular processes, such as photodissociation or isomerization, advantages of time resolution in the 10s of femtosecond regime have already been demonstrated,[101] and very fast interactions with the solvent can be observed.  For bimolecular reactions, the case is not so clear because the limiting factor becomes the time delay between production of a reactive atom or radical and its subsequent collision (with appropriate stereochemistry) with a co-reactant molecule.  Capturing information on bimolecular reactive events as they happen, and observing the onset of coupling to the solvent bath from the reactive transition state onwards, or the restructuring of the solvent molecules around the transition state, may therefore continue to elude us.

**References**

1.      F. F. Crim, Faraday Discuss **157**, 9-26 (2012).
2.      C. G. Elles and F. F. Crim, Annu Rev Phys Chem **57** (1), 273-302 (2006).
3.      J. T. Hynes, Annu Rev Phys Chem **36**, 573-597 (1985).
4.      G. A. Voth and R. M. Hochstrasser, J. Phys. Chem. **100** (31), 13034-13049 (1996).
5.      D. Chandler, *Introduction to Modern Statistical Mechanics*. (Oxford University Press, New York, 1987).

6.      R. D. Levine, *Molecular Reaction Dynamics*. (Cambridge University Press, Cambridge, 2005).

7.      M. Brouard and C. Vallance, *Tutorials in Molecular Reaction Dynamics*. (Royal Society of Chemistry, Cambridge, 2010).

8.      S. J. Greaves, R. A. Rose and A. J. Orr-Ewing, Phys. Chem. Chem. Phys. **12** (32), 9129-9143 (2010).

9.      S. C. Althorpe and D. C. Clary, Annu Rev Phys Chem **54**, 493-529 (2003).

10.     D. W. Chandler and P. L. Houston, J. Chem. Phys. **87** (2), 1445-1447 (1987).

11.     A. T. J. B. Eppink and D. H. Parker, Rev Sci Instrum **68** (9), 3477-3484 (1997).

12.     G. Czakó and J. M. Bowman, Science **334** (6054), 343-346 (2011).

13.     W. A. Alexander, J. M. Zhang, V. J. Murray, G. M. Nathanson and T. K. Minton, Faraday Discuss **157**, 355-374 (2012).

14.     B. G. Perkins and D. J. Nesbitt, J. Phys. Chem. A **114** (3), 1398-1410 (2010).

15.     C. Waring, P. A. J. Bagot, M. L. Costen and K. G. McKendrick, J Phys Chem Lett **2** (1), 12-18 (2011).

16.     A. M. Zolot, P. J. Dagdigian and D. J. Nesbitt, J. Chem. Phys. **129** (19) (2008).

17.     N. Henriksen and F. Y. Hansen, *Theories of Molecular Reaction Dynamics*. (Oxford University Press, Oxford, 2008).

18.     A. Nitzan, *Chemical Dynamics in Condensed Phases*. (Oxford University Press, Oxford, 2006).

19.     J. C. Owrutsky, D. Raftery and R. M. Hochstrasser, Annu Rev Phys Chem **45**, 519-555 (1994).

20.     D. Raftery, E. Gooding, A. Romanovsky and R. M. Hochstrasser, J. Chem. Phys. **101** (10), 8572-8579 (1994).

21.     L. R. Copeland, F. Mohammad, M. Zahedi, D. H. Volman and W. M. Jackson, J. Chem. Phys. **96** (8), 5817-5826 (1992).

22.     V. R. Morris, F. Mohammad, L. Valdry and W. M. Jackson, Chem. Phys. Lett. **220** (6), 448-454 (1994).

23.     G. A. Bethardy, F. J. Northrup and R. G. Macdonald, J. Chem. Phys. **102** (20), 7966-7982 (1995).

24.     G. A. Bethardy, F. J. Northrup and R. G. Macdonald, J. Chem. Phys. **105** (11), 4533-4549 (1996).

25.     S. J. Greaves, R. A. Rose, T. A. A. Oliver, D. R. Glowacki, M. N. R. Ashfold, J. N. Harvey, I. P. Clark, G. M. Greetham, A. W. Parker, M. Towrie and A. J. Orr-Ewing, Science **331** (6023), 1423-1426 (2011).

26.     A. J. Orr-Ewing, D. R. Glowacki, S. J. Greaves and R. A. Rose, J. Phys. Chem. Lett. **2** (10), 1139-1144 (2011).

27.     R. A. Rose, S. J. Greaves, F. Abou-Chahine, D. R. Glowacki, T. A. A. Oliver, M. N. R. Ashfold, I. P. Clark, G. M. Greetham, M. Towrie and A. J. Orr-Ewing, Phys. Chem. Chem. Phys. **14** (30), 10424-10437 (2012).

28.     R. A. Rose, S. J. Greaves, T. A. A. Oliver, I. P. Clark, G. M. Greetham, A. W. Parker, M. Towrie and A. J. Orr-Ewing, J. Chem. Phys. **134** (24) (2011).

29.     A. C. Crowther, S. L. Carrier, T. J. Preston and F. F. Crim, J. Phys. Chem. A **112** (47), 12081-12089 (2008).

30.     A. C. Crowther, S. L. Carrier, T. J. Preston and F. F. Crim, J. Phys. Chem. A **113** (16), 3758-3764 (2009).

31.     L. Sheps, A. C. Crowther, S. L. Carrier and F. F. Crim, J. Phys. Chem. A **110** (9), 3087-3092 (2006).

32.     L. Sheps, A. C. Crowther, C. G. Elles and F. F. Crim, J. Phys. Chem. A **109** (19), 4296-4302 (2005).

33.     M. Tachiya, Radiation Phys. Chem. **21** (1-2), 167-175 (1983).

34.     Y. L. Chen and M. C. Heaven, J. Chem. Phys. **109** (13), 5171-5174 (1998).

35.     Y. L. Chen and M. C. Heaven, J. Chem. Phys. **109** (7), 2808-2813 (1998).

36.     Y. L. Chen and M. C. Heaven, J. Chem. Phys. **112** (17), 7416-7424 (2000).

37.     S. Fei and M. C. Heaven, J. Chem. Phys. **98** (1), 753-756 (1993).
38.     J. Han, M. C. Heaven and U. Schnupf, J. Chem. Phys. **128** (22) (2008).
39.     J. D. Han, M. C. Heaven, U. Schnupf and M. H. Alexander, J. Chem. Phys. **128** (10) (2008).
40.     A. L. Kaledin and M. C. Heaven, Chem. Phys. Lett. **347** (1-3), 199-204 (2001).
41.     Y. M. Lin and M. C. Heaven, J. Chem. Phys. **94** (8), 5765-5768 (1991).
42.     J. M. Beames, B. A. O'Donnell, M. Ting, M. I. Lester and T. A. Stephenson, J. Chem. Phys. **134** (18) (2011).
43.     B. A. O'Donnell, J. M. Beames and M. I. Lester, J. Chem. Phys. **136** (23) (2012).
44.     B. A. O'Donnell, J. M. Beames and M. I. Lester, J. Chem. Phys. **136** (23) (2012).
45.     J. Chateauneuf, J. Org. Chem. **64**, 1054 - 1055 (1999).
46.     J. E. Chateauneuf, Chem. Phys. Lett. **164** (6), 577-580 (1989).
47.     J. E. Chateauneuf, J. Am. Chem. Soc. **112** (1), 442-444 (1990).
48.     W. M. Kwok, C. S. Ma, A. W. Parker, D. Phillips, M. Towrie, P. Matousek and D. L. Phillips, J. Chem. Phys. **113** (17), 7471-7478 (2000).
49.     W. M. Kwok, C. S. Ma, A. W. Parker, D. Phillips, M. Towrie, P. Matousek and D. L. Phillips, J. Phys. Chem. A **107** (15), 2624-2628 (2003).
50.     W. M. Kwok, C. S. Ma, A. W. Parker, D. Phillips, M. Towrie, P. Matousek, X. M. Zheng and D. L. Phillips, J. Chem. Phys. **114** (17), 7536-7543 (2001).
51.     W. M. Kwok, C. S. Ma, D. Phillips, A. W. Parker, M. Towrie, P. Matousek and D. L. Phillips, Chem. Phys. Lett. **341** (3-4), 292-298 (2001).
52.     W. M. Kwok and D. L. Phillips, Chem. Phys. Lett. **235** (3-4), 260-267 (1995).
53.     Y. L. Li, D. M. Chen, D. Q. Wang and D. L. Phillips, J. Org. Chem. **67** (12), 4228-4235 (2002).
54.     Y. L. Li and D. L. Phillips, Chem. Phys. Lett. **349** (3-4), 291-298 (2001).
55.     Y. L. Li, D. Wang and D. L. Phillips, J. Chem. Phys. **117** (17), 7931-7941 (2002).
56.     X. M. Zheng, C. W. Lee, Y. L. Li, W. H. Fang and D. L. Phillips, J. Chem. Phys. **114** (19), 8347-8356 (2001).
57.     X. M. Zheng and D. L. Phillips, J. Chem. Phys. **113** (8), 3194-3203 (2000).
58.     X. M. Zheng and D. L. Phillips, J. Chem. Phys. **104** (29), 6880-6886 (2000).
59.     P. Z. El-Khoury, L. George, A. Kalume, S. A. Reid, B. S. Ault and A. N. Tarnovsky, J. Chem. Phys. **132** (12) (2010).
60.     P. Z. El-Khoury, W. M. Kwok, X. G. Guan, C. S. Ma, D. L. Phillips and A. N. Tarnovsky, Chemphyschem **10** (11), 1895-1900 (2009).
61.     P. Z. El-Khoury, M. Olivucci and A. N. Tarnovsky, Chem. Phys. Lett. **462** (4-6), 192-195 (2008).
62.     S. K. Pal, A. S. Mereshchenko, E. V. Butaeva, P. Z. El-Khoury and A. N. Tarnovsky, J Chem Phys **138** (12) (2013).
63.     S. K. Pal, A. S. Mereshchenko, P. Z. El-Khoury and A. N. Tarnovsky, Chem. Phys. Lett. **507** (1-3), 69-73 (2011).
64.     A. N. Tarnovsky, I. Pascher and T. Pascher, J. Phys. Chem. A **111** (46), 11814-11817 (2007).
65.     S. K. Pal, A. S. Mereshchenko, E. V. Butaeva, P. Z. El-Khoury and A. N. Tarnovsky, J. Chem. Phys. **138** (12), 124501-124519 (2013).
66.     T. J. Preston, M. Dutta, B. J. Esselman, A. Kalume, L. George, R. J. McMahon, S. A. Reid and F. F. Crim, J. Chem. Phys. **135** (11), 114503-114510 (2011).
67.     T. J. Preston, M. A. Shaloski and F. F. Crim, J. Phys. Chem. A **117** (14), 2899-2907 (2013).
68.     F. Abou-Cahine, T. J. Preston, G. T. Dunning, A. J. Orr–Ewing, G. M. Greetham, I. P. Clark, M. Towrie and S. A. Reid, J. Phys. Chem. A (2013).
69.     S. L. Carrier, T. J. Preston, M. Dutta, A. C. Crowther and F. F. Crim, J. Phys. Chem. A **114** (3), 1548-1555 (2010).
70.     P. Z. El-Khoury, W. M. Kwok, X. Guan, C. Ma, D. L. Phillips and A. N. Tarnovsky, Chem.Phys.Chem. **10** (11), 1895-1900 (2009).
71.     A. N. Tarnovsky, I. Pascher and T. Pascher, J. Phys. Chem. A **111** (46), 11814-11817 (2007).

72. D. R. Glowacki, A. J. Orr-Ewing and J. N. Harvey, J. Chem. Phys. **134** (21), 214508-214511 (2011).

73. D. R. Glowacki, R. A. Rose, S. J. Greaves, A. J. Orr-Ewing and J. N. Harvey, Nature Chem. **3** (11), 850-855 (2011).

74. B. P. Fingerhut, C. F. Sailer, J. Ammer, E. Riedle and R. de Vivie-Riedle, J. Phys. Chem. A **116** (46), 11064-11074 (2012).

75. I. Benjamin, J. Chem. Phys. **103** (7), 2459-2471 (1995).

76. N. Winter, I. Chorny, J. Vieceli and I. Benjamin, J Chem Phys **119** (4), 2127-2143 (2003).

77. J. Vieceli, I. Chorny and I. Benjamin, J Chem Phys **115** (10), 4819-4828 (2001).

78. D. R. Glowacki, R. Lightfoot and J. N. Harvey, Mol. Phys. **111** (5), 631-640 (2013).

79. D. R. Glowacki, C. H. Liang, S. P. Marsden, J. N. Harvey and M. J. Pilling, J. Am. Chem. Soc. **132** (39), 13621-13623 (2010).

80. K. Iwata and H. Takahashi, J. Mol. Struct. **598** (1), 97-102 (2001).

81. S. Hammes-Schiffer and A. A. Stuchebrukhov, Chem. Rev. **110** (12), 6939-6960 (2010).

82. D. R. Weinberg, C. J. Gagliardi, J. F. Hull, C. F. Murphy, C. A. Kent, B. C. Westlake, A. Paul, D. H. Ess, D. G. McCafferty and T. J. Meyer, Chem Rev **112** (7), 4016-4093 (2012).

83. H. A. Kramers, Physica **7**, 284-304 (1940).

84. R. F. Grote and J. T. Hynes, J. Chem. Phys. **73** (6), 2715-2732 (1980).

85. R. F. Grote and J. T. Hynes, J. Chem. Phys. **75** (5), 2191-2198 (1981).

86. J. M. Anna, C. R. Baiz, M. R. Ross, R. McCanne and K. J. Kubarych, Int. Rev. Phys. Chem. **31** (3), 367-419 (2012).

87. J. M. Anna and K. J. Kubarych, J. Chem. Phys. **133** (17) (2010).

88. H. S. Chung and W. A. Eaton, Nature **502** (7473), 685-+ (2013).

89. N. Kanaan, S. Ferrer, S. Marti, M. Garcia-Viloca, A. Kohen and V. Moliner, J. Am. Chem. Soc. **133** (17), 6692-6702 (2011).

90. B. R. Brooks, C. L. Brooks, A. D. Mackerell, L. Nilsson, R. J. Petrella, B. Roux, Y. Won, G. Archontis, C. Bartels, S. Boresch, A. Caflisch, L. Caves, Q. Cui, A. R. Dinner, M. Feig, S. Fischer, J. Gao, M. Hodoscek, W. Im, K. Kuczera, T. Lazaridis, J. Ma, V. Ovchinnikov, E. Paci, R. W. Pastor, C. B. Post, J. Z. Pu, M. Schaefer, B. Tidor, R. M. Venable, H. L. Woodcock, X. Wu, W. Yang, D. M. York and M. Karplus, J. Comput. Chem. **30** (10), 1545-1614 (2009).

91. S. C. L. Kamerlin and A. Warshel, Comput. Mol. Sci. **1** (1), 30-45 (2011).

92. D. R. Glowacki, E. Paci and D. V. Shalashilin, J. Phys. Chem. B **113** (52), 16603-16611 (2009).

93. D. R. Glowacki, E. Paci and D. V. Shalashilin, J. Chem. Theory Comput. **7** (5), 1244-1252 (2011).

94. D. V. Shalashilin, G. S. Beddard, E. Paci and D. R. Glowacki, J. Chem. Phys. **137** (16) (2012).

95. A. C. Moskun and S. E. Bradforth, J. Chem. Phys. **119** (8), 4500-4515 (2003).

96. A. C. Moskun, A. E. Jailaubekov, S. E. Bradforth, G. H. Tao and R. M. Stratt, Science **311** (5769), 1907-1911 (2006).

97. J. Few, D.Phil. Thesis, University of Oxford, 2013.

98. I. Benjamin and K. R. Wilson, J. Chem. Phys. **90** (8), 4176-4197 (1989).

99. C. Z. Wan, M. Gupta and A. H. Zewail, Chemical Physics Letters **256** (3), 279-287 (1996).

100. J. Larsen, D. Madsen, J. A. Poulsen, T. D. Poulsen, S. R. Keiding and J. Thogersen, J. Chem. Phys. **116** (18), 7997-8005 (2002).

101. C. A. Rivera, N. Winter, R. V. Harper, I. Benjamin and S. E. Bradforth, Phys. Chem. Chem. Phys. **13** (18), 8269-8283 (2011).

102. U. Samuni, S. Kahana, R. Fraenkel, Y. Haas, D. Danovich and S. Shaik, Chem. Phys. Lett. **225** (4-6), 391-397 (1994).

103. C. Murray and A. J. Orr-Ewing, Int. Rev. Phys. Chem. **23** (3), 435-482 (2004).

104. F. Abou-Chahine, S. J. Greaves, G. T. Dunning, A. J. Orr-Ewing, G. M. Greetham, I. P. Clark and M. Towrie, Chem. Sci. **4** (1), 226-237 (2013).

105. J. J. Lin, J. G. Zhou, W. C. Shiu and K. P. Liu, Science **300** (5621), 966-969 (2003).

106.     M. A. Wickramaaratchi, D. W. Setser, H. Hildebrandt, B. Korbitzer and H. Heydtmann, Chem Phys **94** (1-2), 109-129 (1985).
107.     M. A. Thompson, J. P. Martin, J. P. Darr, W. C. Lineberger and R. Parson, J Chem Phys **129** (22) (2008).
108.     L. Sheps, E. M. Miller, S. Horvath, M. A. Thompson, R. Parson, A. B. McCoy and W. C. Lineberger, Science **328** (5975), 220-224 (2010).
109.     R. B. Metz, J. D. Thoemke, J. M. Pfeiffer and F. F. Crim, J. Chem. Phys. **99** (3), 1744-1751 (1993).
110.     J. D. Thoemke, J. M. Pfeiffer, R. B. Metz and F. F. Crim, J. Phys. Chem. **99** (37), 13748-13754 (1995).
111.     M. J. Bronikowski, W. R. Simpson, B. Girard and R. N. Zare, J. Chem. Phys. **95** (11), 8647-8648 (1991).
112.     M. J. Bronikowski, W. R. Simpson and R. N. Zare, J. Phys. Chem. **97** (10), 2194-2203 (1993).
113.     W. R. Simpson, T. P. Rakitzis, S. A. Kandel, A. J. Orr-Ewing and R. N. Zare, J. Chem. Phys. **103** (17), 7313-7335 (1995).
114.     X. Chen, C. K. Regan, S. L. Craig, E. H. Krenske, K. N. Houk, W. L. Jorgensen and J. I. Brauman, J. Am. Chem. Soc. **131** (44), 16162-16170 (2009).
115.     G. Vayner, K. N. Houk, W. L. Jorgensen and J. I. Brauman, J. Am. Chem. Soc. **126** (29), 9054-9058 (2004).
116.     R. Otto, J. Brox, S. Trippel, M. Stei, T. Best and R. Wester, Nature Chem. **4** (7), 534-538 (2012).
117.     S. J. Harris, D. Murdock, Y. Y. Zhang, T. A. A. Oliver, M. P. Grubb, A. J. Orr-Ewing, G. M. Greetham, I. P. Clark, M. Towrie, S. E. Bradforth and M. N. R. Ashfold, Phys. Chem. Chem. Phys. **15** (18), 6567-6582 (2013).