Gas-Phase Femtosecond Particle Spectroscopy: A Bottom-Up Approach to Nucleotide Dynamics

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Abstract
We summarize how gas-phase ultrafast charged-particle spectroscopy has been used to provide an understanding of the photophysics of DNA building blocks. We focus on adenine and discuss how, following UV excitation, specific interactions determine the fates of its excited states. The dynamics can be probed using a systematic bottom-up approach that provides control over these interactions and that allows ever-larger complexes to be studied. Starting from a chromophore in adenine, the excited state decay mechanisms of adenine and chemically substituted or clustered adenine are considered and then extended to adenosine mono-, di-, and trinucleotides. We show that the gas-phase approach can offer exquisite insight into the dynamics observed in aqueous solution, but we also highlight stark differences. An outlook is provided that discusses some of the most promising developments in this bottom-up approach.
1. INTRODUCTION

The study of excited state dynamics in complex molecular systems can generally be approached from two viewpoints. The top-down approach starts with studies on a complex system in its entirety and in its natural environment and then unpicks the details by performing specific experiments that probe particular processes. In contrast, the bottom-up approach initially considers the building blocks of the complex molecular system without the environment and then systematically probes how the dynamics of these species change with increased complexity. The limitation of the top-down approach is that the level of detailed insight attainable may be limited because the system in its entirety often has too many interactions for mechanisms to be unambiguously discerned and because the system often is theoretically intractable. This is not the case for the bottom-up approach, where the dynamics can be understood in great detail and specific interactions can be introduced to probe impacts on the dynamics in a systematic manner that is amenable to high-level theoretical study. However, a core limitation of the bottom-up approach lies in the question of the relevance of the building blocks in the complex molecular system in its natural environment. Therefore, there is a drive to build up toward the complex system, to probe how the increase in size and complexity alters the dynamics, and to determine how these dynamics compare to those observed in the natural environment. In this review, we discuss experimental methodologies for probing this evolution that are based on time-resolved charged-particle imaging. Specifically, we focus on the dynamics of adenine, both because it represents how the bottom-up approach can provide detailed insight into complex systems and because of the importance of understanding its excited state dynamics as a mechanism in DNA photoprotection.

As the carrier of genetic code, DNA is used in the development and function of all living organisms. Damage to its structure can lead to mutations, which can impair or destroy genetic function (1–4). Although there are many mechanisms by which damage can be induced, perhaps the most direct is photodamage, in which irradiation of DNA by solar UV light leads to enhanced chemical reactivity and, at higher photon energies, to fragmentation and radical formation (1–2). DNA strongly absorbs light in the UV range (λ < 300 nm) via π∗ ← π transitions on the nucleobases that constitute the core of the double helix. The four nucleobases, adenine (Ade), thymine (Thy), guanine (Gua), and cytosine (Cyt), are interwoven in hydrogen-bonded pairs of Ade-Thy and Gua-Cyt and stacked along the polymer, and each nucleobase is connected to the backbone through a deoxyribose group and a phosphate. From a bottom-up perspective, it is the nucleobases and the chromophores within them that have been the focus of intense study, providing unprecedented insight into their photochemistry and photophysics (1–2, 5–7). The use of advanced and differential experimental techniques has provided ever-greater detail and insight into the nucleobases’ excited state dynamics. This additional information is a key benchmark for high-level theoretical modeling (see References 8 and 9 and the references therein). Experimental techniques and theoretical modeling, combined, provide the basic ingredients for building a detailed understanding of excited state processes in larger complexes, as the same electronic states are present, but perturbed. By analogy to perturbation theory, we can view the chromophores and nucleobases as a zeroth-order picture and, by systematically increasing complexity, we can understand the effects of perturbations on these zeroth-order dynamics. These effects can be extensive, possibly including reordering of electronically excited states, changes in dynamics, or dramatic conformational changes. Going larger, a first-order perturbation could be the addition of sugar and phosphate to each nucleobase to form the respective nucleotides. Higher-order perturbations could include oligonucleotides, base stacking, base pairing, and solvation.

This review focuses on the use of ultrafast and differential gas-phase spectroscopy as a tool for building a bottom-up picture of dynamics in adenosine nucleotide polymers. It is not intended to
be an exhaustive review of the excited state dynamics of nucleotides and oligonucleotides. Several reviews provide details about aspects of what is covered herein (2, 6, 7, 10). Instead, this review aims to give an overview of recent progress in the application of ultrafast techniques in the gas phase toward attaining insight in ever-larger complexes. We focus on the most studied nucleobase, Ade, and before discussing Ade itself, we begin by considering the dynamics in a chromophore of Ade. Building up from there, we consider the perturbations of the dynamics when the sugar and phosphate are included and when several Ade bases are in an oligomer, and how the presence of solvent further perturbs the dynamics. Finally, we provide an outlook and consider the key avenues that will yield the next level of insight as one builds up to ever-larger complexes.

2. METHODOLOGIES: GAS-PHASE FEMTOSECOND PARTICLE SPECTROSCOPY

As our focus is on experimental methods, our discussion begins with a brief overview of the methodologies used to track the excited state dynamics of isolated molecules, which are summarized in Figure 1. These techniques are time-resolved ion yield spectroscopy, time-resolved velocity map ion imaging spectroscopy, and time-resolved photoelectron spectroscopy. For excellent reviews containing further details, the reader is referred to References 6, 7, and 10–12.

The production of gas-phase molecules can be achieved in many ways. The most common way is to seed the vapor of an analyte in an inert carrier (typically He or Ar) at high pressure and then to allow this high-pressure gas mixture to expand into a vacuum using either a piezoelectric or a solenoid-driven pulsed valve (13, 14), thus generating a molecular beam of the sample analyte. This is shown diagrammatically in Figure 1a, where heating of the sample can be used to increase its partial pressure. This method has been the workhorse of gas-phase spectroscopy, but its limitation

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**Figure 1**

Schematic overview of the experimental setup for time-resolved charged-particle imaging. Gas-phase species can, for example, be formed by: (a) a seeded molecular beam; (b) laser desorption (LD) or laser-induced acoustic desorption (LIAD); or (c) electrospray ionization coupled to a mass spectrometer (MS). These species interact at the center of a velocity map imaging arrangement shown in panel d, yielding cations (M⁺ or H⁺) or electrons (e⁻). The velocity map images acquired can be transformed into kinetic energy (KE) distributions, providing information about the temporal (Δt) and spectral evolution of excited state processes as well as angular information (θ), as shown in panel e. Abbreviations: CCD, charge-coupled device; TOF, time of flight; v, velocity.
is that molecular beams can only be generated using sufficiently volatile samples. Many large molecules are not volatile enough and thermally decompose prior to achieving a sufficient vapor pressure (6). Other methods have been developed to enable the production of such species and have been coupled to ultrafast spectroscopic methods. In Figure 1b, laser desorption (15–18) and laser-induced acoustic desorption (19, 20) are shown as examples; the former is a commonly applied method and the latter has undergone rapid recent development. Both methods use lasers to desorb analytes from a surface, which is a much more gentle method of producing the molecule in a vacuum and results in little fragmentation. In the mass spectrometry community, large biological complexes, including DNA complexes, have been successfully transferred to a vacuum. Perhaps the most successful method for producing gas-phase molecules is electrospray ionization (ESI) (21), the basic arrangement of which is shown in Figure 1c, and this method has also been coupled to ultrafast spectroscopic methods (22, 23). In ESI, the analyte is an ion in solution, which is pushed through a syringe. The tip of the needle is at a high potential relative to the entrance of the mass spectrometer. The ions in solution effectively close the circuit and are sampled by a transfer capillary into the vacuum, producing gas-phase ions. As the ions are charged, they can be manipulated and mass-selected before being spectroscopically investigated. Mass-selection is crucial when studying molecular size-dependent dynamics.

2.1. Time-Resolved Ion Yield Spectroscopy

The simplest gas-phase experiment that can be used to probe excited state dynamics in real time is time-resolved ion yield spectroscopy (TR-IYS). In TR-IYS, the molecular gaseous sample is intercepted by femtosecond laser pulses in the center of a time-of-flight (TOF) arrangement (24). A first femtosecond pump pulse is used to initiate an excited state process, and the excited state population is probed by ionization of the system with a second femtosecond probe pulse. The ionized parent, M+ in Figure 1d, can then be monitored by its TOF and its yield probed as a function of pump–probe time delay, Δt. Alternatively, TR-IYS can be used to probe the appearance of photofragments. Any ionizable photofragment can be distinguished by TOF and its yield monitored in a single experiment. However, the ionization energy of neutral fragments is typically much higher than the probe photon energy, so that specific schemes are required to probe specific products. An important example of this is the monitoring of H-atom photoproducts (25, 26). For this, a time-delayed femtosecond probe pulse is centered at 243.1 nm and utilizes [2 + 1] resonance enhanced multiphoton ionization, taking advantage of the two-photon 2s ← 1s transition that is allowed in the H atom. In general, the temporal resolution of the experiment is determined by the convoluted width of the pump and probe pulses.

2.2. Time-Resolved Velocity Map Ion Imaging

Although TR-IYS can provide much insight into the kinetics of processes, its integral nature limits the information that can be extracted from measurements. A major advancement in molecular dynamics was the advent of charged-particle imaging (27) and specifically velocity map ion imaging (VMI) (28). Both recover the recoil speed and angular distributions (i.e., the velocity vector, \( \mathbf{v} \)) of the ionized photofragments that are expanding on a Newton sphere (12, 29, 30). VMI utilizes a gridless TOF electrode arrangement that, under certain design criteria, results in the spatial focusing of \( \mathbf{v} \) onto a given point on a plane regardless of its initial spatial distribution. At this plane, a position-sensitive detector such as a pair of microchannel plates coupled with a phosphor screen allows a charge-coupled device to capture individual charged-particle impacts, as shown in Figure 1d. By gating the detector, the two-dimensional distribution of photofragment ions of
a particular mass-to-charge ratio, \( m/z \), can be detected, and this can be reconstructed to yield the initial three-dimensional distribution using a range of algorithms (30). In this review, we specifically focus on H\(^+\). In contrast to TR-IYS of H\(^+\) ions, the combination of pump–probe spectroscopy with VMI, i.e., time-resolved hydrogen ion imaging (TR-HII), enables one to extract both time and kinetic energy (KE) information, which is crucial in providing mechanistic insight regarding the origin of the photogenerated H atoms.

With reference to the appearance timescales of H atoms (e.g., following dissociation of some bond), at each pump–probe time delay, the one-dimensional total kinetic energy release (TKER) spectrum may be recovered from the measured two-dimensional distribution of H\(^+\) (probed at 243.1 nm) using an appropriate image reconstruction method (30–32) and transforming from velocity space to KE space \((|v| \propto KE^{1/2})\). The measured KE of the photofragments is then converted to TKER according to the equation \( TKER = KE \left( \frac{m_p}{m_p - m_i} \right) \),

where \( m_p \) and \( m_i \) are the masses of the parent molecule and fragment (in this case H atoms), respectively. Although the resolution of the H fragments into TKER space provides the most mechanistic insight, the angular emission of the H atoms is also dispersed, where the angle \( \theta \) is defined between the polarization axis of the light, \( \epsilon \), and the emission vector \( \mathbf{v} \), as shown in Figure 1e. This time-resolved angular distribution can provide additional, and often very important, information when interpreting the photodissociation process and the associated electronic states from which the dissociation takes place (12).

2.3. Time-Resolved Photoelectron Imaging

Time-resolved photoelectron imaging (TR-PEI) is an extension of time-resolved photoelectron spectroscopy (TR-PES) and uses the same VMI spectrometer as TR-HII, but instead of probing the H\(^+\) (or M\(^+\)), the polarity of the ion optics is reversed to monitor electrons, e\(^-\) (11, 34–36). The probe pulse detaches an electron from the photoexcited molecule, and the KE and angular distribution of this electron can be measured using the same methods as in ion imaging. The photoelectron angular distribution (PAD) has a different origin than in dissociation (37). It is determined by the interference between outgoing partial waves of the photoelectron. The initial phase and amplitude of the partial waves are governed by the molecular orbital from which the electron is detached (38–40). The quantitative analysis of the PAD of a large molecule is notoriously difficult (41); however, in TR-PEI, changes in the PAD’s anisotropy can be detected with great sensitivity. Such changes can be an indicator of changes in the electronic structure at the time the electron is removed and can thus provide insight into nonadiabatic transitions (42–44).

TR-PEI is often described as a universal probe because it can monitor the dynamics along the entire reaction coordinate, as ionization is always an allowed process (11). In principle, the initially excited state, any intermediate excited states, the ground state, and any products can be probed and distinguished by their characteristic electron kinetic energies (eKEs) and PADs. In practice, this is not trivial because the ionization potentials of neutrals are typically >7 eV, requiring femtosecond vacuum UV (VUV) radiation with high flux. Much recent progress has been made in generating tabletop VUV femtosecond light sources for TR-PEI applications (45–48). However, TR-PEI of anions provides an interesting alternative, as these have electron affinities typically <5 eV (49–52), which are compatible with radiation easily attainable through commercial laser sources [e.g., the fourth harmonic of Ti:Sapphire yields 6.2 eV (200 nm)]. Indeed, nucleotides in nature are deprotonated at the phosphate group and are therefore negatively charged.
Figure 2
The structures defining the bottom-up approach to understanding the excited state dynamics and photostability of adenosine nucleotides.

3. DYNAMICS OF ADENINE: FROM A CHROMOPHORE TO OLIGONUCLEOTIDES

3.1. Imidazole

We begin our discussion on the excited state dynamics of Ade and adenosine nucleotides by presenting experimental work carried out on imidazole (Im), one of the chromophore building blocks of Ade (Figure 2). This serves a dual purpose, both introducing some exemplar nonadiabatic relaxation mechanisms mediated by $^1\pi\pi^*$ and $^1\pi\sigma^*$ states that will feature in this review and also offering the opportunity for the reader to gauge the relative importance of some of these mechanisms with increasing molecular complexity.

The important role of $^1\pi\sigma^*$ states in the photostability of heteroaromatic biomolecules and their subunits was first recognized by Domcke, Sobolewski, and coworkers (53) and has since led to a plethora of gas-phase spectroscopic studies (5, 7). The $^1\pi\sigma^*$ states are dissociative along heteroatom hydride bonds ($X$–H, where $X$ is usually O or N) and can be accessed either directly, following excitation from the $S_0$ state through vibrational intensity borrowing (54, 55), or indirectly, following progression through a conical intersection (CI) (9, 56, 57) with the initially photoexcited optically bright $^1\pi\pi^*$ states (53). Once populated, the $^1\pi\sigma^*$ states can facilitate an effective route to internal conversion, repopulating $S_0$ via an appropriate $^1\pi\sigma^*$/S0 CI, or can lead to $X$–H bond fission. This is shown schematically for Im in Figure 3a, where the $^1\pi\pi^*$ $^1\pi\sigma^*$ CI occurs near the vertical Franck–Condon region (i.e., with minimal N–H bond extension).

Using TR-PES, Crespo-Otero et al. (58) demonstrated both how the excited state dynamics of Im depended on excitation wavelength and whether initial photoexcitation was to the lower-lying $^1\pi\pi^*$ state or to the $^1\pi\sigma^*$ state. Following photoexcitation to the $^1\pi\sigma^*$ state with 239.6 nm and probing via time-delayed two-photon ionization with 266-nm radiation, the eKE distribution could be attributed to photodetachment to either the D0 or D1 states of the Im$^+$ cation. In
Figure 3
Schematic potential energy cuts along the N–H bond stretch and ring deformation coordinates ($R_{\text{NH}}$ and $Q_{\text{puck}}$, respectively) of various DNA subunits discussed in the text. The most probable conical intersections (CIs) defining the relaxation mechanisms following photoexcitation to the optically bright $1\pi\pi^*$ state are highlighted as yellow circles. As one progresses from panel $a$ to panel $f$, there is an increase in molecular complexity and the probing of specific interactions. The species for which these schematics are relevant are indicated in all cases. FC indicates the Franck–Condon region and, for simplicity, includes modes that are not indicated in the two labeled coordinates. Abbreviations: 9Me-Ade, 9-methyladenine; Ade, adenine; d(A)$^n$, adenosine di- or tri-nucleotide, for $n = 2$ or 3; dAMP$^-$, 2$'$-deoxyadenosine-5$'$-monophosphate.

Figure 4a, the photoelectron signal in the electron binding energy (eBE = $h\nu$ – eKE) regions $8.75 < \text{eBE} < 9.5$ eV and $10.25 < \text{eBE} < 11$ eV was attributed to photodetachment to the D$_0$ state and to a combination of the D$_0$ and D$_1$ states of Im$^+$, respectively. Upon integration of the photoelectron signal in these two regions, the photoelectron transients yielded time constants of $17 \pm 15$ fs and $44 \pm 15$ fs, the latter of which was taken as an upper limit for the timescale to reach the $1\pi\sigma^*$/$S_0$ CI (leading to either repopulation of $S_0$ or N–H dissociation) and accorded reasonably well with corresponding dynamics simulations by the same authors (58). These timescales, however, exceed the temporal resolution of the experiments and should therefore be taken as approximate values rather than true lifetimes. Excitation at 200.8 nm to the higher-lying $1\pi\pi^*$ state and probing with 251.6 nm led to competing dynamics (Figure 4b). The N–H dissociation pathway (along the $1\pi\sigma^*$ state) formed the dominant pathway ($\sim 80\%$) in addition to ring deformation/fragmentation (58). The lifetimes obtained were $50 \pm 30$ fs and $74 \pm 30$ fs, with the latter representing a lower limit to reach the $1\pi\sigma^*/S_0$ CI. Importantly, the longer timescale determined by these authors accords with the preceding $1\pi\pi^* \rightarrow 1\pi\sigma^*$ internal conversion that was mediated by ring deformation coordinates.

TR-HII recorded by Hadden et al. (59) compares favorably with the TR-PES measurements at 200.8 nm by Crespo-Otero et al. (58). Figure 4c shows a TKER spectrum derived from a H$^+$ velocity map image (inset) following photoexcitation with 200 nm and a pump–probe time delay of 2.5 ps. The Gaussian-like feature centered at approximately $10,000 \text{ cm}^{-1}$ arises from H atoms.
eliminated from the N–H bond along the $1\pi\sigma^*$ state (5, 7, 59). The integrated H$^+$ signal transient shown in Figure 4d reveals that this overall $1\pi\pi^* \rightarrow 1\pi\sigma^* \rightarrow$ N–H scission process occurs in 78 ± 37 fs. This timescale is in good agreement with the timescale for reaching the $1\pi\sigma^*/S_0$ CI that was experimentally determined by Crespo-Otero et al. (58) as well as the timescale for N–H fission of approximately 105 fs that was predicted theoretically by the same authors.

We close this section by discussing the most recent work on Im by Longarte and coworkers (60), who utilized TR-IYS on Im$^+$ to study the excited state dynamics over a range of excitation wavelengths of 250–217 nm using multiphoton ionization with 800 nm as a probe. Two time constants were extracted from their transients, 18 ± 4 fs and 19 ± 4 fs; the former was attributed to the timescale for $1\pi\pi^* \rightarrow 1\pi\sigma^*$ internal conversion, mediated through ring deformation coordinates, and the latter they attributed to the excited state lifetime on the dissociative $1\pi\sigma^*$ state. Importantly, the latter time constant is in very good accord with the TR-PES experiments and dynamics simulations by Crespo-Otero et al. (58) (see above). We once again note, however, that these timescales exceed the temporal resolution of the experiments.
3.2. Adenine

The excited state dynamics of Ade and its derivatives have received by far the greatest attention from gas phase spectroscopists. Two factors have contributed to this: (a) Ade is thermally stable and does not decompose upon heating, meaning that sufficient vapor pressure can be attained for it to be easily entrained into a molecular beam (Figure 1a); and (b) there is only one dominant tautomer observed in the gas phase, the biologically relevant N⁹H tautomer (Figure 2), which simplifies the analysis of the experimental data (7, 61).

Kang et al. (62) performed the earliest excited state relaxation measurements in Ade (and indeed all other nucleobases) utilizing TR-IYS of the parent cation (Ade⁺). A single time constant of approximately 1 ps was extracted from these measurements, which involved photoexcitation with 267-nm radiation to the lowest ¹ππ* state and probing through ionization from this state with a further three photons of 800-nm radiation. To account for the single extracted time constant, Kang et al. proposed a sequential ¹ππ* → ¹σσ* → S₀ internal conversion mechanism, mediated by CIs along appropriate out-of-plane vibrational coordinates, in agreement with the theoretical model put forth by Broo (63). Kang et al. (64) extended these measurements to substituted derivatives of adenine including 9-methyladenine (9Me-Ade), where the H atom along the N⁹–H coordinate is replaced by a methyl group (Figure 2). The time constant obtained from this latter measurement was very similar to that obtained from Ade, leading these authors to propose that the ¹σσ* state localized along the N⁹–H coordinate played little role in the excited state dynamics of Ade following photoexcitation at 267 nm, in concordance with the model proposed by Perun et al. (65).

TR-IYS measurements by Canuel et al. (66) with an improved time resolution showed that, following photoexcitation at 267 nm and probing with two photons of 400-nm radiation, the parent Ade⁺ transient was in fact biexponential with time constants of 100 fs and 1.1 ps. The slower decay was in good agreement with the single time constant extracted by Kang et al. (62). Canuel et al. proposed that the fast component, which was not resolved by Kang et al., contained intrinsic information regarding the deactivation mechanism of Ade in the photoprepared ¹ππ* state. These measurements once again led these authors to propose that ¹σσ*-mediated dynamics were not operative following photoexcitation at 267 nm.

To track the excited state dynamics along the entire reaction coordinate, Satzger et al. (67) performed TR-PES on both Ade and 9Me-Ade, following photoexcitation at 267 nm and probing with 200-nm radiation. As with the measurements by Canuel et al. (66), biexponential decay dynamics were observed. The time-resolved photoelectron spectra were analyzed using a global fitting procedure that fits the data to a minimal number of exponential functions across the eKE space. For Ade, only two decays were required, a fast 40-fs component and a slower component of approximately 1.2 ps, and for 9Me-Ade, these were 70 fs and 1.1 ps. Measurements for both Ade and 9Me-Ade are consistent with the time constants extracted by Canuel et al. (66) using TR-IYS. Additionally, the amplitudes as functions of the eKEs of these decay functions provide decay associated spectra (DAS) and can be interpreted as the photoelectron spectra that are decaying at a given time constant. Note that DAS can be negative, reflecting exponential growth with a given time constant. Figure 5a,b shows the DAS for Ade and 9Me-Ade, respectively. The fast and slow components in the DAS were assigned as photoionization from the ¹ππ* and ¹σσ* states, respectively.

Cursory inspection of the DAS for Ade and 9Me-Ade reveals distinct differences in the fast–time component DAS. These differences enabled Stolow and coworkers (67) to infer differences in the excited state dynamics between Ade and 9Me-Ade. In particular, for the region 1.0 < eKE < 1.5 eV, there is nonzero amplitude in the DAS of the fast component of Ade (Figure 5a), which is
absent for 9Me-Ade (Figure 5b). This was suggested to be because of another short-lived excited state that contributes to the dynamics in Ade but is absent in 9Me-Ade. The state they assigned this to was a $1\pi\sigma^*$ state localized along the N9–H coordinate, and from a simple kinetic model that takes into account the $1\pi\pi^*$ state lifetime, they estimated the lifetime of the $1\pi\sigma^*$ state to be approximately 90 fs.

The findings presented by Stolow and coworkers (67) contradict the majority of the relevant ab initio calculations, which predict that the $1\pi\pi^*/1\pi\sigma^*$ CI along the N9–H coordinate is at higher energy than the 267-nm photoexcitation (65, 68–70), and thus that H-atom elimination along this coordinate is a closed channel. Indeed, more recent work by Stolow and coworkers (61) acknowledges that the differences in the excited state dynamics of Ade and 9Me-Ade following photoexcitation at 267 nm may not be due to the participation of a $1\pi\sigma^*$ along the N9–H coordinate. This is in concordance with Rydberg tagging experiments by Ashfold and coworkers (71), who place an onset for H-atom elimination via the $1\pi\sigma^*$ state in Ade at $\leq$233 nm. This has since been further corroborated by Ullrich and coworkers (72), who used TR-PES to show that an additional decay pathway, such as that provided by a $1\pi\sigma^*$ state, may be operative at $\lambda < 238$ nm, thus lending further credence to the idea, supported by both theory and Rydberg tagging measurements, that $1\pi\sigma^*$ state–mediated deactivation occurs at much shorter wavelengths than 267 nm. Through comparative studies on Ade and 9Me-Ade using TR-HII, Stavros and coworkers (73) have also shown that H-atom elimination mediated through $1\pi\sigma^*$ states localized along both the N9–H and NH$_2$ amino coordinates occurred at 200 nm and not at 267 nm, directly in line with the Rydberg tagging measurements and TR-PES measurements discussed above.

The experimental results of the diverse techniques outlined above imply that deactivation of energy along the $1\pi\sigma^*$ state of photoexcited Ade is closed at 267 nm, as shown schematically in Figure 3b. However, the details of the decay dynamics from Ade following excitation at 267 nm (and indeed at other excitation wavelengths) remain debated in the literature, with recent literature suggesting that internal conversion from $1\pi\pi^* \rightarrow S_0$ mediated by low-lying S$_1$/S$_0$ CIs through out-of-plane ring distortions (at positions C2 and C6) is likely to be the dominant relaxation mechanism, as opposed to decay through sequential $1\pi\pi^* \rightarrow 1\pi\sigma^* \rightarrow S_0$ (70, 74–77). These mechanisms are highlighted in Figure 3b.
Cluster experiments have also emerged on Ade in which \((\text{Ade})_n(\text{H}_2\text{O})_m\) was studied, where \(n = 1, 2\) and \(m = 0, 1, 2, 3\) (78–79). TR-IYS measurements by Schultz and coworkers (79) on \((\text{Ade})_2\), probing the production of \((\text{Ade})^+\), revealed that the dynamics in the dimer initiated around 266 nm are dominated by the fast component seen in Ade, and only a very small slow component could be identified. Similar experiments on the \((\text{Ade}(\text{H}_2\text{O}))_n\) cluster, where \(n = 1, 2, 3\), reveal essentially no evidence for the slow decay component (79). This suggests that in these clusters, a new pathway opens up that outcompetes the formation of the intermediate that leads to the slower decay on a 1-ps timescale. Using ab initio calculations, Schultz and coworkers (79) argued that the likely culprits are the \(1\pi\sigma^*\) states. These were calculated to be lower in relative energy in the hydrogen-bonded clusters, which, as shown in Figure 3c, makes the \(1\pi\pi^* \rightarrow 1\pi\sigma^*\) progression energetically accessible and the dominant decay pathway. In aqueous solution, however, the \(1\pi\sigma^*\) decay pathway only becomes available at \(\leq 220\) nm (69, 77).

Although the importance of the \(1\pi\sigma^*\) state in the photophysics and photochemistry of small heterocyclic molecules is well recognized (5, 7, 53, 80), when building up Ade to its nucleotide, it is the N9 position that couples to the deoxyribose (Figure 2). Therefore, a more suitable comparison is 9Me-Ade, for which the aforementioned \(1\pi\sigma^*\) state plays no role in the dynamics at 266 nm, and is likely not to do so in the nucleotides.

### 3.3. Adenosine Nucleotide

Nucleosides (which have no phosphate) and nucleotides can be generated as neutral complexes in the gas phase by, for example, laser desorption (Figure 1b). Recent nanosecond resonant two-photon experiments on desorbed adenosine nucleosides point to faster decay than Ade (81), and a proton transfer reaction between a sugar OH at the 5′ position and the N3 position of Ade was proposed as a mechanism (82). In the nucleotide, the phosphate connects to the 5′ position, so this pathway is no longer available. In its natural form, the phosphate is deprotonated. For the nucleotides, ESI is a particularly efficient means of generating anions. Being charged, the anion can be mass-selected prior to investigation, avoiding any contamination of the sample. Moreover, ESI provides a simple route to larger complexes, such as oligonucleotides, as discussed below.

The localized charge on the phosphate has two important consequences. First, the energetics of the nucleobase’s electronic states are affected; second, there are now two possible low-energy electron detachment sites: the negatively charged phosphate and the base. The Wang group (83) has measured the photoelectron spectrum at 7.9 eV of the nucleotides and showed that only for deprotonated 2′-deoxyguanosine-5′-monophosphate (dGMP−) does the base clearly have the lowest ionization energy. Using calculations, they predicted that in all other cases, the phosphate was the lowest-energy ionization site. This was later experimentally confirmed by Chatterley et al. (84), using resonance-enhanced two-photon detachment experiments at 4.7 eV, as these experiments selectively ionize only the nucleobase. Nevertheless, because of the Coulombic interaction, the ionization energy of the nucleobase is lowered by approximately 3 eV in the deprotonated nucleotide compared to its isolated value (84). The useful implication for TR-PEI experiments is that lower photon energies can be used to probe the dynamics while accessing a similar ionization window as for the isolated nucleobase; at 267 nm, excitation is below the detachment energy of the phosphate. In Figure 5c, the results of a TR-PEI experiment with a 267-nm pump and a 400-nm probe are shown (76), which have been analyzed in the same manner as the TR-PES experiments on Ade and 9Me-Ade by Stolow and coworkers (61, 67). The dynamics in deprotonated 2′-deoxyadenosine-5′-monophosphate (dAMP−) are biexponential, as in Ade. A key observation, however, is that the DAS for both 9Me-Ade and dAMP−, as shown respectively in Figure 5b,c, are very similar. The shift in eKE between the two arises from the difference in probe photon...
energy and the ionization energy of the nucleobase in the respective systems. Once this shift is accounted for, the shapes of the DAS of the fast component show a peak of similar width in both cases, and the DAS of the slow component show a similar rise at low kinetic energy, but in dAMP− the DAS does not plateau. As the DAS are a very sensitive probe of the excited state dynamics, the implication is that the excited state dynamics of 9Me-Ade are not strongly perturbed by the addition of sugar and phosphate and have similar dynamics to those shown in Figure 3d.

The decay times of the fast components in 9Me-Ade and dAMP− are limited by the experimental temporal resolution but are likely to be similar, whereas the slower timescale is a factor of three slower in 9Me-Ade. This would seem to contradict the contention that the dynamics are similar regardless of the sugar/phosphate moiety. However, it is important to note that the molecular temperatures of these experiments were vastly different. The 9Me-Ade experiments were performed in a molecular beam (<20 K internal energy) (61, 67), whereas the nucleotides were generated at 300 K and were at equilibrium (76). Hence, the timescales may well be affected by temperature, which is a topic that has received comparably little attention but is likely to be very important. In fact, comparison of the gas-phase dAMP− timescales to those observed for transient absorption of dAMP− in aqueous solution at room temperature (1, 2) shows that these are actually very similar: a fast initial decay followed by a 340-fs decay after excitation at 260 nm (85). This, therefore, suggests that the aqueous environment may have only a very minor impact on the dynamics of the base in the nucleotide. This assertion has been supported by calculations that indicate that the 1nπ∗ state, which lies just below the bright 1ππ∗ state, increases in energy upon solvation so that in aqueous solution, it is at a significantly higher energy than the 1ππ∗ state in the Franck–Condon region (69, 76, 86–88). This is shown schematically in Figure 3e.

Taking the above information holistically, one concludes that the dynamics of 9Me-Ade occur solely on the 1ππ∗ state, as involvement of the 1nπ∗ states would be sensitive to an aqueous environment. The fast dynamics can be assigned to a rapid motion away from the Franck–Condon region, whereas the slower component represents a sampling of the CI to access the S0 ground state. This is in agreement with certain excited state calculations (69, 76, 86, 87). Notably, the dynamics of the 1ππ∗ state appear to be insensitive to the environment. The question of how temperature influences the timescales remains open and is an important question that needs to be addressed if one is to correlate gas-phase dynamics to those observed in ambient environments.

The gas-phase dynamics of the other nucleotides have also been reported (89). In particular, dGMP− is of interest, as no previous gas-phase TR-PES has been performed on isolated Gua because of the difficulty in its production in a molecular beam without thermal decomposition and because of its many tautomers. TR-IYS experiments have been reported and showed a biexponential decay (66). The TR-PEI of dGMP− is broadly similar to that of dAMP−, revealing similar DAS and dynamics, although the timescale of internal conversion is a factor of two slower in dGMP−, with a lifetime of 600 fs (89). This is comparable to the 680-fs slow component observed in a recent experiment in aqueous solution (85). The DAS corresponding to the fast component is also broader in dGMP− compared to dAMP−. Note that in Gua, recent theory has shown that the 1nπ∗ state always lies above the 1ππ∗ state, regardless of the environment (90–94). Given the similarity of the dynamics of dGMP− and dAMP−, this again provides some support for the non-active role of the 1nπ∗ state in Ade. Overall, the gas-phase dynamics broadly support the notion that the dynamics of the purine bases are similar and are dominated by relaxation on 1ππ∗ surfaces.

With the advent of liquid microjets (95), TR-PES has also recently been extended to the solution phase (96–99). Although the focus of this review is on gas-phase studies, these developments present an important connection between the isolated system and the system in solution, and the first TR-PES studies on Ade and adenosine have been reported (100). We discuss this further in Section 4.
3.4. Oligonucleotides

Oligomers of nucleotides can be readily generated by ESI, with the only major obstacle being the formation of multiply charged anions as the oligomer size increases (101–104). In multiply charged anions, the Coulomb repulsion between charged phosphate sites leads to a dramatic decrease in the phosphate’s electron affinity, so that excitation around the lowest \( \pi\pi^* \) state of the nucleobase is in competition with direct photodetachment from the phosphate (83, 84). Nevertheless, with care, singly charged oligomers can be generated and have been probed by time-resolved methods. Specifically, the dynamics of adenosine di- and trinucleotides \([d(A)]^-_2 \) and \([d(A)]^-_3 \) have been probed by TR-PEI (76). The results of a global analysis are shown in Figure 6. Figure 6a,b shows the kinetics of \([d(A)]^-_2 \) and \([d(A)]^-_3 \), respectively, and Figure 6c shows the DAS of the fast components of \([d(A)]^-_2 \) and \([d(A)]^-_3 \). The DAS of the slow components are essentially identical to the DAS of the slow component of \(dAMP^-\), which is shown in Figure 5c.

**Figure 6**

Photoelectron imaging data of adenosine di- and trinucleotides \([d(A)]^-_2 \) and \([d(A)]^-_3 \), respectively. For (a) \([d(A)]^-_2 \) and (b) \([d(A)]^-_3 \), the total photoelectron signal is shown, along with curves fitted to the data for each decay time constant. (c) The decay associated spectra (DAS) for the fast component of \([d(A)]^-_2 \) and the fast component of \([d(A)]^-_3 \). The difference between these DAS is shown in panel d and represents the DAS of the fast component of the nucleobase furthest from the charge in \([d(A)]^-_3 \), the structure of which is shown in panel f. The structure of the nucleobases in \([d(A)]^-_2 \) is shown in panel e. Abbreviation: eKE, electron kinetic energy. Panels a–c adapted with permission from Reference 76.

\(d(A)\_2^-\): singly deprotonated anion of an oligonucleotide with \(n\) adenine bases
At first glance, the dynamics of \(d(A)^-\) and \(d(A)^+\) appear very similar to those of \(dAMP^-\), suggesting that the dynamics observed in oligomers reflect those of localized Ade. There are small changes in the slower timescale, which increases slightly with increasing number of Ade, and there are small changes to the DAS. Overall, however, the observed dynamics reinforce the notion that the dynamics of 9Me-Ade are not strongly affected by the environment (Figure 3d).

This is in stark contrast, however, with observations in aqueous solution, where dramatic increases in the lifetime are observed, even for \(d(A)^+\) (2, 105). These observations have been attributed to the formation of excimers. In aqueous solution, there is a delicate balance between the solvation energy of the Ade nucleobase, the \(\pi\)-stacking interaction of two Ade nucleobases, and the solvation of this \(\pi\)-stacked dimer, which ultimately leads a fraction of \(d(A)^+\) to be \(\pi\)-stacked. UV excitation can then excite either the Ade nucleobase or an excimer state, delocalized over two bases, that has strong charge-transfer character (2). The dynamics of these excimers have been the focus of much discussion, and an excellent recent review has considered their dynamics in detail (2).

In the gas phase, the \(\pi\)-stacking interaction remains, but the solvent that stabilizes the dimer is not present. At 300 K, the entropic energy dominates the \(\pi\)-stacking interaction and the two nucleobases do not interact directly. Bowers and coworkers (106) have shown, using cryogenic ion mobility, that cooling can favor the stacked configuration and that at 80 K, the majority of \(d(A)^+\) are \(\pi\)-stacked. In the experiments described above, the internal temperature was 300 K, and therefore the dynamics appear much like those of 9Me-Ade. Hence, temperature control may provide exquisite control over conformation but will also likely affect the dynamics, as discussed before, and these factors should be explored.

Returning to the data in Figure 6, the DAS of the fast components show that the increment of a nucleobase in going from \(dAMP^-\) to \(d(A)^-\) leads to a red shift in the eKE of approximately 0.2 eV without altering the overall shape of both components. This suggests that the ionization energy has effectively increased by 0.2 eV. As the lowering of the base ionization energy in the nucleotide can be attributed to the Coulomb interaction with the phosphate, the 0.2-eV shift in \(d(A)^-\) implies that the change in this complex is screened to some extent. Also, the almost identical shape of the DAS of \(d(A)^-\) compared to \(dAMP^-\) indicates that the two nucleobases are indistinguishable in \(d(A)^-\), and this is consistent with its structure (Figure 6c). For \(d(A)^+\), a broadening in the DAS of the fast component is observed at low eKE, and the high eKE edge is identical to \(d(A)^+\) (Figure 6c).

In \(d(A)^+\), the sole deprotonated phosphate lies between two bases, with the third base further from the charged phosphate, as shown in Figure 6f. The Coulomb interaction at this Ade site is lower because it is physically further away from the charge and/or because the charge is more effectively screened. In either case, the result is a higher ionization energy (by approximately 0.5 eV) and a lower eKE, which explains the spectral broadening. In Figure 6d, these contributions have been separated by simply subtracting the fast DAS of \(d(A)^-\) from that of \(d(A)^+\). This recovers the DAS of the fast component for the single Ade base that is furthest from the charge, as shown in Figure 6f; this demonstrates the ability to probe the ultrafast dynamics of a specific nucleobase in an oligomer.

One might argue that the lack of excimer dynamics indicates that the gas phase is not a useful model for any real environment, and in many respects this is correct. However, in solution, a major decay mechanism involves the decay of an excited monomer because not all oligomers are stacked and because not all excitations form excimers (85, 107). In solution, one has almost no control or selectivity in these dynamics, and they are generally very difficult to distinguish (85). The utility of gas-phase spectroscopy lies in its ability to incrementally increase complexity and in the possibility of control, enabling specific pathways to be probed. This control could be achieved through temperature control, conformer selection [either by hole-burning (108–113) or ion mobility methods (114, 115)], and site selective experiments (as demonstrated in Figure 6d), which will ultimately be able to unpick specific interactions in a systematic manner.
4. OUTLOOK

In this review, we have attempted to capture how ultrafast gas-phase charged-particle imaging can be used to gain detailed insight into excited state dynamics, and have used Ade as a case study. By incrementally increasing complexity from a chromophore of Ade, to the nucleobase itself and site-specific chemical modifications, to nucleotides and oligonucleotides and solution-phase dynamics, one can build a comprehensive bottom-up picture of the dynamics. Of key importance is that this methodology enables specific interactions and dynamical pathways to be explored and disentangled. Take the example of Ade: The role of $1\pi\sigma^*$ states can be uncovered using H$^+$ imaging and time-resolved photoelectron imaging; the role of the $1\pi\pi^*$ states can be uncovered by building up complexity and by comparison to environments to which these states are sensitive; and the effect of nearby unscreened charges can be understood. These are all important interactions in a DNA duplex and, although one might rightly argue that gas-phase spectroscopy does not bear much on DNA in vivo, the emerging trends that can be uncovered in this systematic manner do, and they provide a basis for understanding dynamics in complex environments.

In the following discussion, we provide an outlook on the other types of interactions that can be probed using the gas-phase approach and that are of key importance. First, however, we comment that, although Im has been extensively studied with ultrafast methods (see above), the partner chromophore of Ade, 4-aminopyrimidine (Figure 2), has, to the best of our knowledge (and somewhat surprisingly), received no attention. Instead, there has been much interest in its precursor, aniline (Figure 2), specifically regarding the role of the $1\pi\sigma^*$ state (44, 116–121). Dimers of 2-aminopyridine have also received attention as a model system for proton/H-atom transfer reactions (122–124). It would certainly be of interest to understand the dynamics of 4-aminopyrimidine as a building block of Ade, and we hope that this review will go some way to catalyze such studies.

Microsolvation through clustering is the most used method in gas-phase dynamics to establish links between the intrinsic dynamics and those observed in solution. Cluster experiments have emerged on Ade, as discussed above (78, 79). However, TR-IYS on the (Ade)$_2$(H$_2$O)$_n$ cluster showed drastically different dynamics from those on Ade$_2$ or Ade(H$_2$O)$_n$ (78). Although the dynamics contain signatures of Ade dynamics, with a fast (100-fs) component and slower (1.3-ps) component, an offset in their transients at long times was also observed with a much slower decay time (>1 ns). This was attributed to the formation of an excimer on the basis of photoelectron spectra and theoretical calculations. These excimers are stabilized by the H$_2$O molecules that drive the two Ade molecules into the correct initial orientation. The observation of excimers in this controlled environment provides an excellent starting point to probe their evolution as a function of size. As already mentioned, at lower temperatures, $\pi$-stacking also occurs in isolated oligonucleotides, and their study using TR-PEI may yield a deeper understanding of the excimer states. Alternatively, $\pi$-stacking and base-pairing can be enforced by chemical substitutions that pin together the ends of two oligonucleotides, forming either hairpin or dumbbell duplexes (107). Shape selection using ion mobility methods will provide an additional dimension, and photoelectron spectroscopy of mass- and isomer-selected anions has recently emerged (104). Finally, we stress again that there is a need for an understanding of temperature effects in the excited state dynamics of DNA subunits. Temperature can be conveniently controlled in ion experiments using cryogenic ion traps of variable temperature, in which the ion of interest thermally equilibrates with the buffer gas (125, 126).

Clustering can probe the local solvation and, in the limit of infinite cluster size, represents the fully solvated system. Making a clear connection between gas-phase experiments and solution-phase experiments is generally difficult because different experimental methods are required, which often means that different observables are probed. However, methods such as TR-PES are now
being applied to solution-phase samples using liquid microjets (96, 98–100), and photoelectron spectra of nucleotides have been measured (127, 128). These are likely to be very rich areas of research in the coming years.

Most recently, excited state dynamics measurements carried out in the solution phase on subunit (and subunit motif) chromophores of biological building blocks have started to demonstrate how knowledge attained from highly differential gas-phase experiments can help guide the interpretation of the underlying dynamics of their solution-phase counterparts (129–134). Of direct relevance to the present review is the recent work by Roberts and coworkers (77) on the role of $^1\pi\sigma^*$ states in the excited state dynamics of Ade$_{aq}$. Using a combination of transient electronic and vibrational absorption spectroscopies, they showed that $^1\pi\sigma^*$ state–mediated N9–H bond fission was inactive for excitation wavelengths $\geq$ 220 nm in aqueous solution, hinting at the significant blue shifting for the onset of this channel in comparison to gas-phase measurements ($\leq$ 233 nm) (71). Indeed, this serves to illustrate the role of solvation in terms of a higher-order perturbative effect. The tantalizing prospect of extending these solution-phase measurements to study the dynamics across both Watson–Crick base pairs, Ade-Thy and Gua-Cyt, is already being realized, with preliminary results suggesting that electron-driven proton transfers, mediated in part by $^1\pi\pi^*$ states with interbase charge transfer character, are key reaction paths in these dynamics (135). The importance of base pairing versus base stacking interactions in natural double-helix DNA has been the topic of considerable debate in the recent literature (2, 136–139), and resolving these broader scientific questions remains at the frontier of research into DNA photophysics. This can surely be aided by carefully developed bottom-up experiments.

SUMMARY POINTS

1. Gas-phase femtosecond spectroscopy can be used to systematically probe how specific interactions alter the excited state dynamics in chromophores. We discuss this in the specific context of the adenine nucleobase.

2. Starting from imidazole, the role of $^1\pi\sigma^*$ states in the excited state dynamics of adenine can be gauged. In adenine water clusters, the $^1\pi\sigma^*$ states become more active because their relative energy is lowered.

3. Methylation at the N9 position of adenine mimics how the nucleobase connects to deoxyribose and phosphate and leads to comparable dynamics. The dynamics of deoxyadenosine monophosphate reveal similar timescales in both the gas and solution phases.

4. Gas-phase femtosecond spectroscopy can be applied to relatively large systems, such as di- and trinucleotides, offering a potential route to studying interactions found in nature and a platform toward understanding intrinsic dynamics in biological complexes.

5. There is a bright future for gas-phase femtosecond spectroscopy as a tool to provide deep insight into specific interactions occurring in DNA. The gas phase also offers the potential for exquisite control over molecular structure and molecular temperature, enhancing our understanding of structure–function relationships in complex biological systems.

DISCLOSURE STATEMENT

The authors are 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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LITERATURE CITED


53. This key paper proposes the generality of $\pi\sigma^*$ states as a decay mechanism.

62. This was the first paper to study the excited state dynamics of nucleobases in the gas phase.


80. This important paper experimentally demonstrated the prominent role of 1πσ* states.

81. This was a demonstration of ultrafast dynamics probed in large isolated complexes.


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Errata

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