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Ion/surface reactions and ion soft-landing†

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Ion/surface collision phenomena in the hyperthermal collision energy regime (1–100 eV) are reviewed, with emphasis on chemical processes associated with the impact of small organic and biological ions at functionalized self-assembled monolayer surfaces. Inelastic collisions can lead to excitation of the projectile ion and can result in fragmentation, a process known as surface-induced dissociation which is useful in chemical analysis using tandem mass spectrometry. Changes in charge can accompany ion/surface collisions and those associated with a change in polarity (positive to negative ions or *vice versa*) are an attractive method for ion structural characterization and isomer differentiation. The surface-induced charge inversion of nitrobenzene and other substituted aromatics is discussed. Reactive collisions occurring between gaseous ions and surfaces depend on the chemical nature of the collision partners. These reactions can be used for selected chemical modifications of surfaces as well as for surface analysis. Particular emphasis is given here to ion soft-landing, another type of ion/surface interaction, in which the projectile ion is landed intact at the surface, either as the corresponding neutral molecule or, interestingly but less commonly, in the form of the ion itself. The ion soft-landing experiment allows for preparative mass spectrometry; for example the preparation of pure biological compounds by using the mass spectrometer as a separation device. After separation, the mass-selected ions are collected by soft-landing, at different spatial points in an array. If the experiment is performed using a suitable liquid medium, in the case of some proteins at least, biological activity is retained.

Introduction

Studies of the interactions between ions and surfaces can be traced to the backscattering experiments of Rutherford,[1] whose use of MeV ion beams impinging on thin metal films provided the first experimental basis for the theory of atomic structure. Much later, this phenomenon was developed into an analytical method of surface and near-surface analysis known as Rutherford backscattering spectrometry (RBS). A related experiment in the keV rather than the MeV energy range, based on binary elastic scattering, was developed in the 1960's into ion scattering spectrometry (ISS), a method for the analysis of the elemental composition of the outermost layers of solid surfaces.[2] This method has subsequently grown to include recoil and shadowing processes, the latter depending on angular relationships involving the positions of surface adsorbates. Another keV collision phenomenon is sputtering, the process upon which secondary ion mass spectrometry (SIMS)[3] is based. A series of binary elastic collisions leads to desorption of ions and neutral molecules from a surface struck by a primary ion beam of keV energy; the secondary ions leave with relatively low translational energies and a range of internal energies and are mass analyzed to provide elemental and molecular structural information on surface constituents.

This review covers ion/surface collision phenomena at hyperthermal energies, *viz*. in the range of laboratory energies of 1–100 eV. It particularly emphasizes collisions of organic ions with organic (monolayer) surfaces. A full treatment of the kinematics of such an experiment would require as a minimum the ability to measure (and vary) the masses and charges, the velocities and directions of the beams of ions impacting on and being scattered from the collision surface. While such capabilities are increasingly being developed,[4–7] these experiments actually developed out of studies on mass spectrometry and tandem mass spectrometry in the 1970's. As such they were less influenced by the analogy with molecular beam scattering than by analogies with two gas-phase ion processes, collision-induced dissociation (CID) and ion/molecule (I/M) reactions. In CID, inelastic collisions of ions in the keV (later the eV) energy regime are used to cause internal excitation and subsequent dissociation so as to provide information on the structure of the ion. By inference, this provides information on the structure of the neutral molecule, for which the ion is a surrogate in this chemical analysis experiment. The SID method was originally introduced to activate ions using low angle incidence in the keV collision energy regime.[8] Attempts to understand the chemical physics of di- and tri-atomic ion scattering under similar conditions revealed fragmentation due to dissociative collisions occurring in competition with neutralization of the ion beam.[9] With the widespread use of mass spectrometers like the quadrupole mass filter, in which the beam being mass-analyzed has a translational energy in the eV range, it became convenient to perform CID in this energy regime.[10,11] This development was paralleled by efforts to perform low-energy inelastic collisions at surfaces, a process which was successfully achieved in the mid-1980's.[12–14] In retrospect it is fortunate that relatively poor vacuum conditions were used in these experiments since adventitious hydrocarbons on the surface were effective in reducing the neutralization that is otherwise the dominant process when molecular radical cations collide at clean metal surfaces in high vacuum.

The earliest SID spectra showed ion/surface reaction products in addition to products of simple dissociation. These were the results of covalent bond formation between the ion and a surface atom or group, while the SID products were simply the result of inelastic collisions of the ion with the surface leading to excitation and dissociation. In the case of

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radical cations such as the benzene radical cation $C_6H_6^+$, SID fragment ions like the acetylene elimination product $C_4H_4^+$, were accompanied by products similar to $C_6H_7^+$, due to hydrogen atom abstraction from the hydrocarbons on the surface. Ion/surface reactions such as this provide information on the chemical nature of the adsorbate and the ion; they can also be used to change the chemical nature of the outermost monolayers on the surface and these changes (*e.g.*, esterification, ether formation, and other functional group specific reactions) can in principle be used to chemically tailor the properties of the surface at desired locations. Examples of such chemical reactions are increasing with evidence of surface modification being provided by both mass spectrometric experiments and independent surface analysis experiments such as electron spectroscopy.[15]

Instrumentation

Instrumentation for the study of hyperthermal ion/surface collisions has developed in an *ad hoc* fashion, following as it has instrumental developments in tandem mass spectrometry. The basic tandem mass spectrometry experiment involves mass selection of the ion of interest in the first MS stage, excitation of the ion by collision followed by its dissociation and then finally mass analysis of the resulting fragment ions in the second MS stage. Because a number of different types of mass analyzers are widely used, many combinations of two analyzers ("hybrid" instruments) can be considered when designing a tandem mass spectrometer. Numerous mass analyzer combinations have been successful in mass spectrometry utilizing CID for structural analysis of molecules and some of these combinations have also been used for ion/surface collisions in the hyperthermal energy range. The considerations which underlie appropriate choices and the performance of specific instruments have been reviewed earlier.[16]

The first instrument built for the study of hyperthermal ion/surface collisions was a hybrid device of BQ (magnet, quadruple filter) design. (It should be noted that in these and other instruments, mass spectrometric design features are denoted with the appropriate abbreviation (*e.g.* QqQ)—capitalized components representing mass analyzers.) The instrument allowed the study of polyatomic ion/surface collisions at variable collision energy and fixed incident and scattering angles. Subsequently, much work was carried out using tandem quadrupole mass spectrometers,[17] analogs of the triple quadrupole instruments that remain so popular for tandem mass spectrometry experiments based on gas-phase collision processes. Typical of later instruments which allowed more detailed examination of ion/surface collision phenomena in the hyperthermal energy regime is the BEEQ mass spectrometer[18] (Fig. 1), where B = magnetic sector, E = electric sector and Q = quadrupole. This instrument allows momentum, velocity and directional selection of the impinging ions with velocity, mass/charge and angular analysis of scattered and desorbed ions. A dc quadrupole doublet focuses the mass/charge and energy selected ion beam onto the surface and an appropriate deceleration lens system allows selection of particular collision energies in the eV or keV range. The electrically floated, EQ post-collision analyzer and detection system is mounted on a rail capable of revolution and acquisition of angle/energy resolved SID spectra.[18] Sectors have also been coupled with other analyzers such as quadrupoles,[18,19] time-of-flight (TOF),[16,20,21] and other sector[22] analyzers. Later instruments used other geometries[23–30] and/or included other analyzers such as tandem-in-time instruments like the FT-ICR MS.[31]

Quadrupole mass filters have the advantage that they use low energy ion beams and this makes them particularly attractive for soft-landing experiments in which low energy ion beams are required.[24]

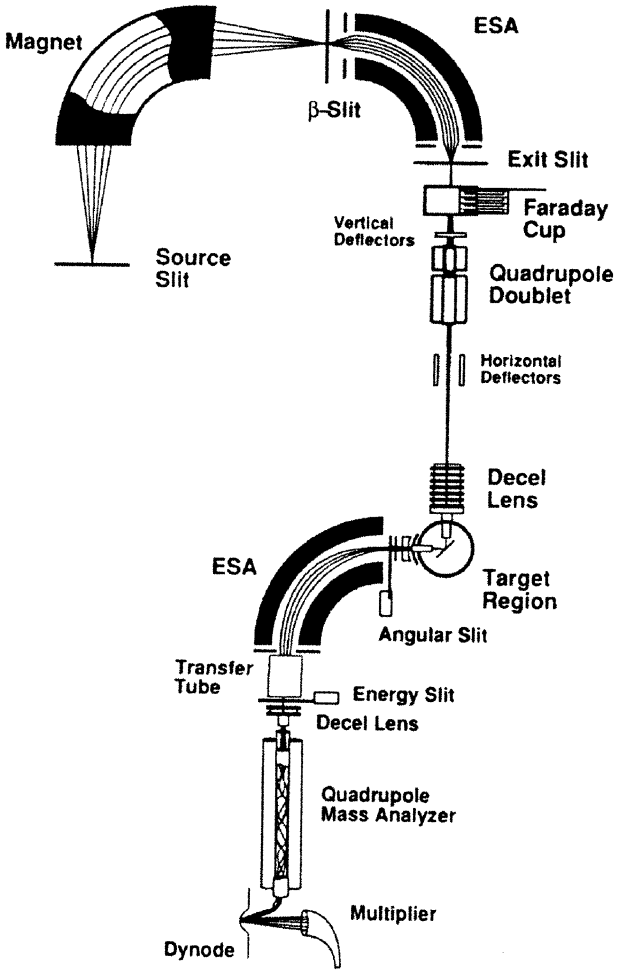

Fig. 1 Hybrid BEEQ tandem mass spectrometer used for the study of ion/surface collision phenomena. (Reproduced with permission from ref. 18).

Phenomena of interest

The phenomena observed following the collision of a polyatomic, organic projectile ion with a surface include (i) simple elastic scattering leading to reflection, (ii) surface-induced dissociation (SID) resulting from ion excitation in the course of an inelastic collision, (iii) chemical sputtering, a process in which surface molecules are ejected into the gas phase as a result of low energy chemical reactions, (iv) reactive collisions leading to chemical transformation of the ion, or the surface, or both, and (v) ion soft-landing. These processes, which occur competitively in the hyperthermal energy regime, are summarized in Fig. 2. The likelihood of chemical reactions involving the atoms of the ion and the surface is maximized at collision energies which are neither too high (where sputtering and electronic phenomena dominate) nor too low (where there is insufficient center-of-mass energy to drive chemical reactions). In most cases, hyperthermal energy collisions provide highly useful chemical information on the ions and surfaces (provided that the surfaces are not chemically inert); the information includes insights into structures and reactivities. Fundamental aspects of ion/surface collision processes include studies of energy partitioning during inelastic collisions, in particular the transfer of translational energy to vibrational energy (T → V),[32] the recently recognized non-statistical dissociation mechanisms (ion shattering)[33] and of course, comparisons of reactivity at interfaces with gas-phase and solution-phase analogs.

In parallel with experimental studies of ion/surface collision phenomena there has been an increasingly strong effort in

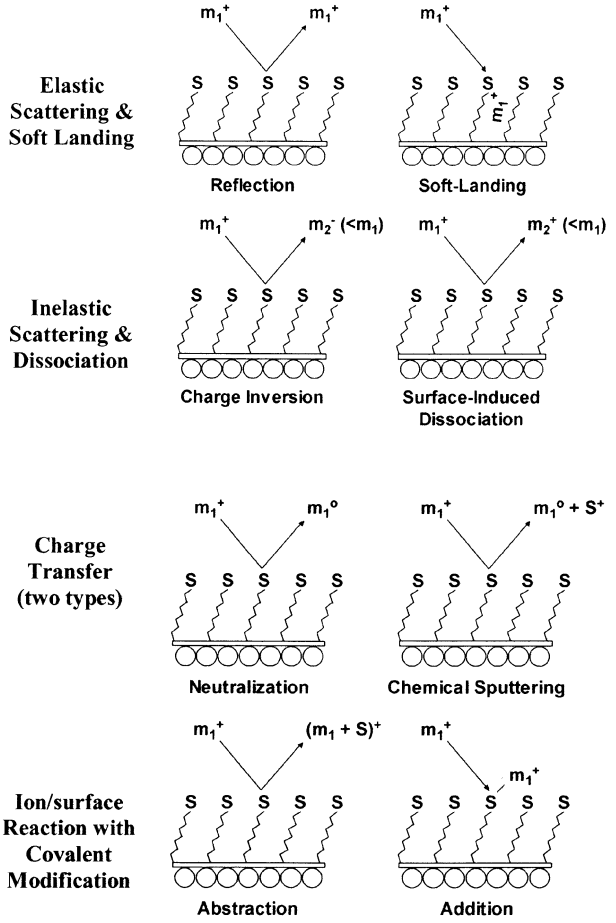

Fig. 2 Some processes associated with collisions of polyatomic ions at surfaces. There are other types of processes and categorizations.

simulations. Noteworthy early work was Sigmund's elucidation[34] of the ion/surface collisions that lead to sputtering in SIMS and the use of a binary collision model[35] which correctly predicted energy loss in binary and ternary scattering in the ISS experiment. More relevant to the hyperthermal energy range is the work of Hase in which dynamics of collisions of polyatomic ions are simulated.[36,37] A full description of these processes remains unavailable, largely due to the difficulties of adequately calculating the dynamics of interactions at a surface. Excellent progress has been made for very simple systems by Garrison and coworkers and more recently for larger ions and more complex surfaces with organic adsorbates.[38–40]

a. Inelastic scattering

During inelastic scattering a fraction of the initial kinetic energy of the ion is transferred to the surface and/or converted into ion internal energy of the scattered ion. If sufficient internal energy is acquired, the ion may dissociate either immediately at the surface (a non-statistical process known as shattering[33,41,42]) or following recoil, at some distance from the surface by standard unimolecular decay mechanisms.[43–45] The activation/dissociation process is collectively known as surface-induced dissociation (SID), an analog of collision-induced dissociation (CID). Although not nearly as widely practiced, SID has some advantages over CID including the simplicity conferred on the experiment by not having to introduce gas into the vacuum system as well as a somewhat narrower internal energy distribution deposited into the activated ions although the width of the distribution is comparable to that of low-energy CID. In addition, SID is the only fast activation method for large ions and as such it opens up all the

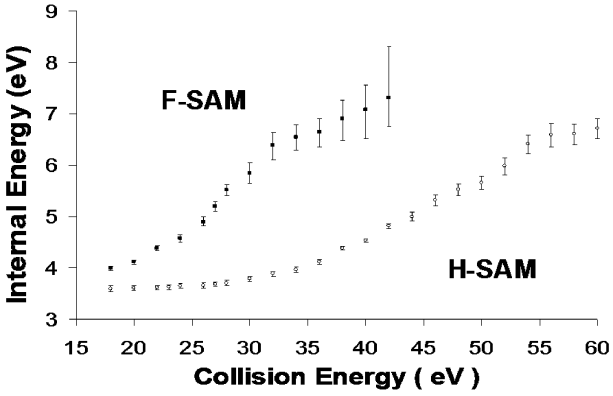

Fig. 3 Plot of internal energy *versus* laboratory collision energy for *n*-butylbenzene ion.

dissociation channels available to the molecule at each internal energy (while CID is discriminatory),[46] and this feature presents an important advantage for some MS/MS applications. The internal energy deposited in SID is very readily varied as the collision energy varies. Energy transfer, the key step in the SID process, has been studied in some detail by a number of investigators.[47–50] As an example, Fig. 3 shows the internal energy of fragmenting ions, estimated by their dissociation behavior, *vs.* their collision energy in the laboratory frame. This is essentially a plot of the average vibrational energy of the activated ion *vs.* the collision energy at a particular angle of incidence (55°). The slope of this plot is therefore a measure of energy conversion, T–V. It is clear that the internal energy transferred increases with collision energy, that it increases roughly in proportion to the translational energy and that the energy transfer efficiency (% T–V) is greater for the fluorine terminated self-assembled monolayer (F-SAM) surface (20%) than the hydrogen-terminated self-assembled monolayer (H-SAM) (12%) surface.[32]

b. Charge inversion

Among the many phenomena associated with gas-phase collisions of keV energy ions are charge inversion, electron transfer and charge stripping processes in which incident positively charged ions are converted into negatively charged ions and *vice versa*. These and related gas-phase charge changing phenomena, including charge stripping of singly-charged ions to give doubly charged ions, have proved of considerable value in the determination of thermochemical properties of gaseous ions.[51,52] Ionic collisions at surfaces too can lead to charge-changing, although their usefulness in estimating thermochemical values remains to be explored. In cases in which the scattering of projectile ions from self-assembled monolayers results in charge permutation, the scattering process can sometimes be accompanied by fragmentation of recoiled ions. This can occur at eV collision energies, in contrast to the keV energies typically used to record the corresponding gas-phase charge-changing processes.[51] Charge-changing collisions at a surface are strongly affected by the thermochemistry associated with the particular reaction and since ions do not penetrate the surface in this velocity range, by the nature of the outermost atomic layers of the surface.

Fragmentation processes associated with charge inversion can be compared with simple SID of the same ions. The results often show more extensive and analytically useful dissociation in the former case, presumably a result of the additional energy barriers imposed by the charge changing requirement.[53] Experiments using a custom-built tandem-quadrupole mass spectrometer showed larger amounts of internal energy to be deposited into the projectile, as evidenced by the more abundant fragment ions generated by surface-induced charge

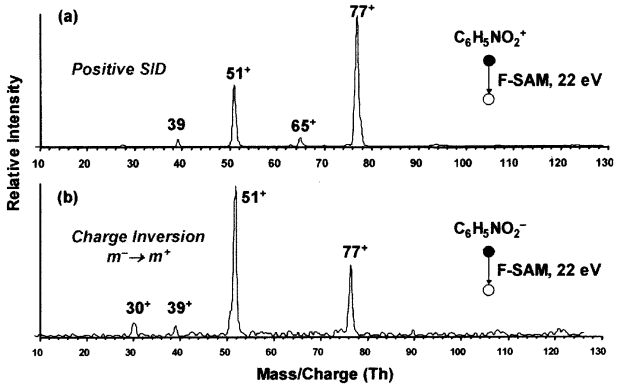

Fig. 4 (a) SID spectrum and (b) surface-induced charge inversion ($-\rightarrow +$) spectrum of nitrobenzene (m/z 123 is completely dissociated, hence absent from the spectra).

inversion than by conventional SID (Fig. 4). A representative spectrum showing the products of dissociative charge inversion of the nitrobenzene anion radical is shown in Fig. 4b, and compared with the conventional SID of the nitrobenzene molecular cation, shown in Fig. 4a. The more extensive fragmentation (and greater internal energy deposition indicated by the larger ratio of the high energy fragment, m/z 51 compared for example to m/z 77) suggests that charge inversion occurs *via* a vertical Franck–Condon transition to an excited vibronic state lying well above the barrier to dissociation.

c. Chemical sputtering

The powerful surface analytical technique of secondary ion mass spectrometry (SIMS)[3] uses keV energy projectiles to desorb ions from a surface, and hence to provide information on the elemental, isotopic and, less often, molecular nature of the surface. Energy transfer from the projectile to the surface results in a selvedge region that is in temporal and spatial non-equilibrium, where neutral and ionic components of the surface are sputtered and released into the gas phase. Specifically, the kinetic energy of the projectile is converted through collision cascades into a translationally and later a vibrationally excited interfacial region. This description makes it clear that in SIMS the projectile plays a physical role in the sputtering process although it also has a chemical role in ionization of the sputtered atoms and molecules.[54]

In SIMS physical (momentum transfer) processes release molecules from surfaces as a result of bombardment with ions of keV energies. Ionic collisions in the hyperthermal energy range also result in sputtering of surface material but instead of material being released by momentum transfer, ions are liberated in this energy regime as a result of chemical effects. Consequently, it has become common to refer to these low energy processes as chemical sputtering.[55–57] In this lower energy regime the ion beam itself constitutes a chemical reagent; chemical sputtering[58] is defined as a process in which surface molecules are ionized by chemical reactions with a hyperthermal projectile ion. The reactions can involve electron or proton (or other ion) transfer and they are strongly dependent on the chemical nature of the projectile. A specific example is found in the case of $Xe^{+\bullet}$ collisions with desorption of a surface molecule; neutralization of the projectile ion (here $Xe^{+\bullet}$) leaves a charged surface moiety, which if given sufficient energy can be desorbed into the vacuum as the ion. This occurs with or without further fragmentation, depending on the difference in ionization energies of Xe and the target.[58,59] Energy made available in the form of translational energy of the projectile is much less effective than that provided by the reaction exothermicity in causing dissociation. Surface analysis is possible using chemical sputtering[60] and an advantage of this approach is its strong restriction to the topmost atomic layers of the surface.

d. Reactive scattering

Ion/molecule reactions have long been a significant field of science, with applications to flame, plasma, atmospheric and interstellar chemistry, and implications for mechanistic and thermochemical issues across the chemical sciences. Reactive scattering from surfaces is a younger field, but one with potentially wide significance. Hyperthermal ion/surface collisions can lead to formation of new covalent bonds, often as a result of transfer/abstraction of an atom or group of atoms to/from the outermost layers of the surface by the projectile ion.[61,62] A systematic study of different projectiles under varying experimental conditions reveals that often odd-electron ions abstract hydrogen from the surface while even-electron species do not undergo reactive scattering as readily.[63] In addition to altering the chemical nature of the projectile, ion/surface reactions can be used to modify the top layers of the surface with a desired chemical reagent provided one selects reagent ions of appropriate mass and velocity.[64] An example is the silylation of hydroxyl-terminated SAMs (HO-SAMs),[65,66] which demonstrates the possibility of performing multi-step synthesis/modification using low-energy ion/surface collisions. In this case, the increased reactivity of the substituted silylium cations, which facilitates further reaction, is attributed to the local positive charge density of the central Si atom.[67] Generally, the advantages of the surface modification approach are its versatility and chemical control, features not present in more traditional plasma and other approaches.[16]

Ion soft-landing

a. Initial observations

Molecular ion deposition as described in 1977[68] and two decades later,[15] shown unambiguously in the case of organic ions using self-assembled monolayers (SAMs) surfaces as deposition substrates and the BEEQ mass spectrometer described above. This method of preparing modified surfaces by gently landing intact polyatomic ions from the gas phase into a monolayer surface at room temperature is referred to as ion soft-landing (or just soft landing) and is the basis for recent novel experiments in preparative mass spectrometry.[23] During these experiments[15,69,70] ions are trapped in the fluorocarbon, hydrocarbon and other functionalized matrices for many hours and then released, intact, upon sputtering at low or high energy or by thermal desorption. Confirmation of molecular composition is achieved by isotopic labeling and high-resolution mass measurements and more rarely, by X-ray photoelectron spectroscopy and other surface analysis methods. It is important to distinguish two processes that are *both* described as soft landing; in one the landed ion is trapped *as the ion itself*, in the other the molecule remains structurally intact but the trapped product is neutralized.

As an example of the soft-landing process,[15] Fig. 5 illustrates the deposition of $(CH_3)_2SiNCS^+$ projectile ions into a F-SAM surface (the monolayer is constructed using $CF_3(CF_2)_7(CH_2)_2SH$). Two $(CH_3)_2SiNCS^+$ ions are shown penetrating the surface to different depths, and a third is approaching the F-SAM surface. The sterically bulky and covalently-bound silyl ether ion, $(CH_3)_3SiOSi(CH_3)_2^+$ (m/z 147), was generated by electron impact on hexamethyldisiloxane, mass-selected, decelerated to 10 eV, and allowed to collide with a monolayer surface of the thiol, self-assembled onto a polycrystalline gold substrate.

The F-SAM surface was examined before and after 1 h of deposition, in both cases with the use of 60 eV $^{132}Xe^{\bullet+}$ chemical sputtering for surface analysis. When compared to

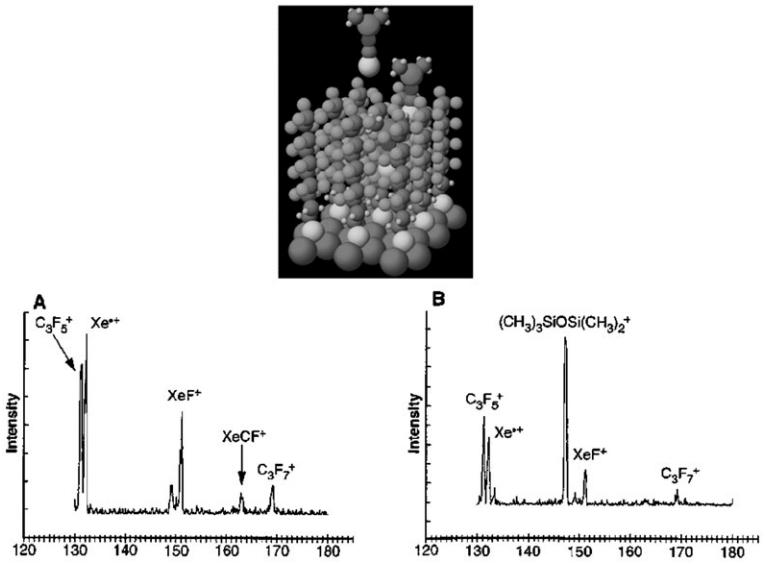

Fig. 5 3D molecular modeling representation of the soft-landing process for $(CH_3)_2SiNCS^+$ projectile ions impinging on an F-SAM monolayer surface. Mass spectrum recorded by 60 eV $^{132}Xe^{\bullet+}$ chemical sputtering of (A) an F-SAM surface and (B) the same surface after treatment for 1 h at 5 eV collision energy with $(CH_3)_3SiOSi(CH_3)_2^+$ ions (m/z 147), at a total dose corresponding to ~7% of a monolayer. (Reproduced with permission from ref. 15).

the background spectrum of an unmodified F-SAM surface (Fig. 5a), the chemically sputtered mass spectrum of the modified surface (Fig. 5b) showed a prominent new peak due to the ion at m/z 147. After storage of the treated surface in laboratory air for 1 d, the m/z 147 signal decreased by only 30% and the signal was still observable after 4 d. This is in spite of the fact that it is present in the SAM matrix as the free ion.

The ability to directly deposit intact polyatomic ions into F-SAM surfaces at low collision energies is a striking result, although the deposition occurs into only a small fraction of the available surface sites.[69] The combination of steric hindrance in the polyatomic ions and the inert and ordered matrix formed by the fluorinated alkylthiolate chains of the F-SAM surface, are believed to be important factors for successful ion soft-landing. Electrostatic interactions between the soft-landed ions and induced electric dipoles in the surface substrate may also contribute significantly to their binding to the F-SAM surface. At least in the case of small organic ions, intact soft-landing as the ion is more successful with closed-shell rather than open-shell ions, a result ascribed to the ease of neutralization of the latter.[69,70]

b. Charge preservation in the landed ion

Several pieces of evidence show that deposited polyatomic ions can be deposited into fluorinated SAM matrices so that they are initially present at the surface as charged species. This evidence includes the following: (1) the projectile ions are often liberated intact by low-energy sputtering or by thermal desorption; (2) the secondary ion yields in the chemical sputtering process show only a small dependence on the proton affinity of the projectile ion used for sputtering; and (3) there is no evidence for products other than those readily explained as the result of ionic dissociation or reaction or fragmentation due to analysis. The remarkable fact that intact ions can be held at surfaces for long periods is explained by steric trapping and the ion/induced dipole bonding noted above. The failure of the deposited ions to be removed rapidly by reaction is ascribed to the strongly hydrophobic F-SAM matrix which helps exclude reagents such as water from the surface region and to the steric bulk of the successfully landed projectile ions which help to screen the reactive charged site from attack. It would be expected that the "charge down" configuration of the deposited projectile ion will be especially stable, both because of the ion-induced dipole interactions and because of more effective steric protection from reaction with reagents approaching from the top of the monolayer. It is emphasized that the matrix may be highly disturbed and that the bulky steric substituents are thought to play several distinct roles: (1) they serve to increase the capture cross-section of ions by a polarizable medium during landing and help remove translational energy from the ion and allow its trapping; (2) their steric bulk helps to lock the ion into the matrix; and (3) they protect the reactive site from reagents, as just noted.[69]

Laskin and co-workers[71] examined the applicability of ion soft-landing to peptides colliding at functionalized SAMs at hyperthermal energies. The surfaces used for soft-landing and analysis were similar or identical to those used previously for studying this phenomenon using smaller polyatomic ions as projectiles.[15,69,70] Peptides of interest were ionized by electrospray ionization, mass-selected using a quadrupole mass analyzer, and deposited onto F-SAM surfaces by soft-landing in a Fourier transform ion cyclotron resonance (FT-ICR) instrument specially configured for studying ion–surface interactions. Both *in situ* and *ex situ* analysis of modified surfaces using FT-ICR SIMS and time-of-flight SIMS confirmed that a significant number of soft-landed peptide ions remained charged on the surface, even when exposed to air for several hours after deposition. SIMS analysis of a surface on which there were deposited doubly-charged ions of the peptide substance P showed a signal characteristic of the singly-charged ion on the surface. This signal was orders of magnitude stronger than that for the same amount of the corresponding neutral peptide, consistent with the expectation that pre-charged ions at surfaces provide much higher ion yields in SIMS.[72] Peptide ion soft-landing on F-SAM surfaces gave much greater sputtered ion signals than on hydrocarbon self-assembled monolayer (H-SAM) surfaces, which can be attributed again to the fact that ion-induced dipole interaction potential is stronger for the F-SAM surface because of its greater polarizability, which results in slower physisorption of ions from the surface and therefore better retention of the charged species.

Through the use of a modified single-stage quadrupole mass spectrometer equipped with a moving stage to facilitate soft-landing experiments, soft-landing with charge retention as seen for peptides and in some cases small organic ions[15] has also be observed for proteins.[73] Lysozyme, a protein with a molecular

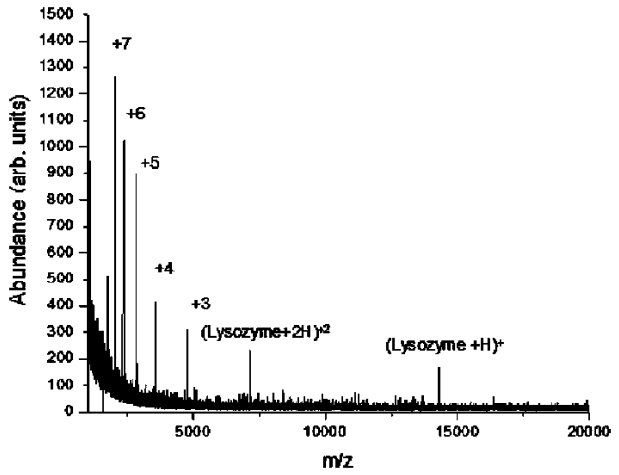

Fig. 6 LDI-MS spectrum of soft-landed lysozyme $(M + 8H)^{+8}$ on a CF_3-terminated SAM surface. (Reproduced with permission from ref. 73).

weight of 14 kDa, was ionized by conventional electrospray ionization and the species corresponding to the +8 charge state (m/z 1785–1795) was mass isolated and soft-landed on an F-SAM surface. The modified fluorinated surface was removed from vacuum and analyzed using a Bruker-REFLEX III MALDI instrument. The spectrum shown in Fig. 6 was recorded and the results show spectral features indicating that lysozyme ions ranging from one up to seven charges per molecule were released from the F-SAM. Note that all the observed ions have lower charge state values than the mass-selected soft landed ion itself, indicating that the ions are deposited in their original charged state on the surface but that partial neutralization occurs on the surface or during analysis.

c. Kinetic energy effects

During SIMS analysis of soft-landed peptides[71] fragment ions are observed together with ions due to the intact molecule. Fragmentation observed in the SIMS analysis could be the result of (i) "crash-landing" *i.e.* projectile ion dissociation upon impact with some of the fragments being retained by the organic monolayer, a known process for small organic ions[70] or (ii) the result of internal energy deposition onto the intact peptide (whether ion or neutral) by keV ion desorption during the SIMS analysis step. By varying the kinetic energy of the peptide ions upon impact at the surface over a range of collision energies (0 eV to 150 eV) these alternatives could be distinguished. If dissociation occurred during ion-surface impact an increase in fragment ion abundance with soft-landing energy would be expected. However, soft-landing of doubly-charged bradykinin at 30 eV and 150 eV collision energy resulted in a similar amount of fragmentation and, in fact, for two of the peptides investigated, bradykinin and substance P, the amount of fragmentation was independent of the energy of the soft-landing event, providing no evidence of "crash landing" in these experiments.[71]

Although no significant differences in the fragmentation pattern of deposited peptides at various soft-landing energies were observed upon static SIMS analysis, the amount of singly-protonated peptide sputtered from the surface upon 2 kV Cs^+ SIMS analysis varied significantly with the soft-landing energy, indicating a significant decrease in the soft landing efficiency with increase in the kinetic energy of the projectile ion. Similarly, soft-landing studies of small organic molecules have demonstrated that at low energies the soft-landing process is favored since other ion/surface collision channels are suppressed and that as the energy increases the probability of soft-landing decreases[69] because of competition with other processes. Interestingly, the decrease in the SL efficiency with increasing collision energy can be rationalized by the corresponding decrease in the Langevin capture cross section, which determines the probability of ion capture by the polarizable medium.

This last observation is also supported by the work performed by Kaiser and co-authors[74] who investigated the interaction of positively-charged antimony clusters Sb_n^+ with highly oriented pyrolytic graphite (HOPG) as a function of cluster size ($2 < n < 13$) and cluster kinetic energy (<600 eV) by tandem time-of-flight mass spectrometry and scanning tunneling microscopy. Based on their observations, the processes taking place when the cluster hits the surface can be classified into three main categories according to kinetic energy. As illustrated in Fig. 7, at very low kinetic energies (less than or equal to 13 eV), depending on the cluster size, soft-landing should be feasible, since no fragmentation of the cluster takes place and the result of the impact may lead to deposited clusters without or with only a weak deformation of their original structures. With increasing kinetic energy, up to about 150–180 eV, two competing processes are found: one is fragmentation (SID) of the cluster into the most stable products, the other is neutralization. The efficiency of the latter process increases with increasing particle energy from about 85% to almost 100% at 150–180 eV kinetic energy. At 150 eV and above the interaction between clusters and surfaces leads to an ultrafast heating and shattering of the projectile cluster into very small fragments. In the same energy regime, starting at about 110 eV, implantation of the clusters within the surface is also observed. During this process the cluster is presumably strongly deformed and the surface atoms are displaced from their original positions, leaving the impact area in a highly amorphous state. The authors suggest that controlled nanostructuring of surfaces using soft-landing and implantation is promising.[74]

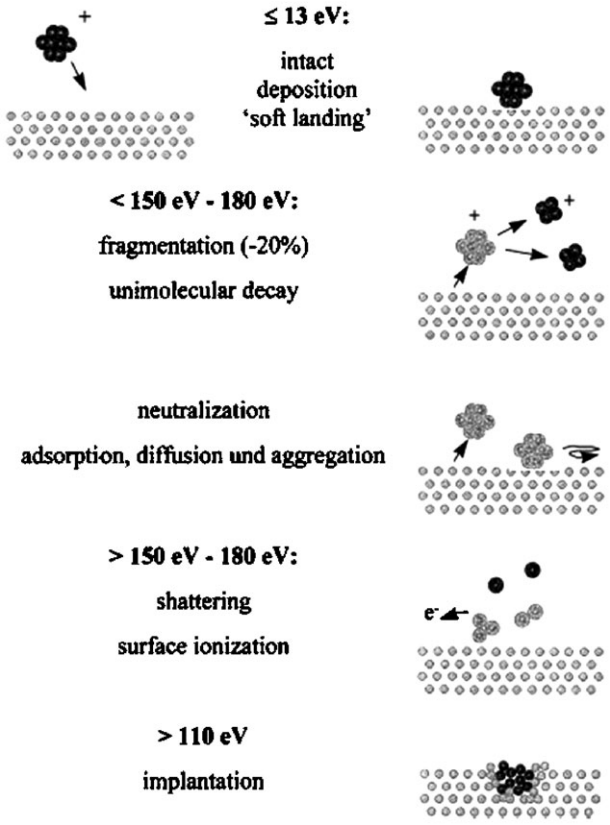

Fig. 7 Overview of the different interaction mechanisms found for the collision of antimony clusters with HOPG (Reproduced with permission from ref. 74).

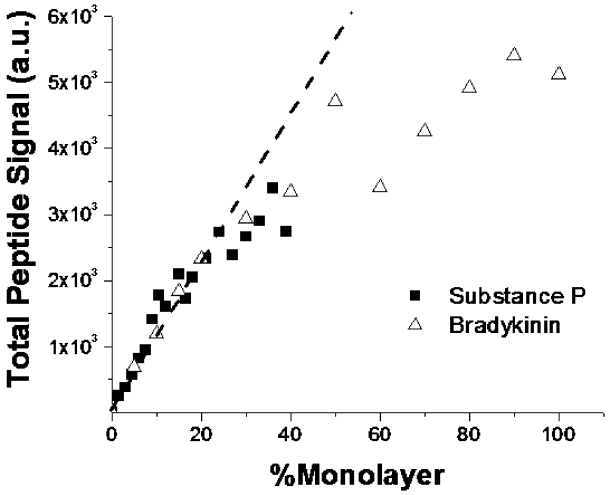

Fig. 8 Saturation plots showing the total peptide signal sputtered from the surface as a function percent of ion exposure for doubly protonated bradykinin and substance P. The exposure is expressed in percent of an equivalent of a monolayer.[76]

d. Surface and dose effects

The relative amounts of sputtered peptides were investigated[71] after soft-landing on different surfaces including H-SAM, F-SAM, carboxyl terminated SAM (HOOC-SAM) and gold surfaces. The results showed that SIMS sputtering yields of soft-landed peptides are strongly dependent on the choice of surface, a result that parallels other ion/surface collision experiments since neutralization is such a dominant effect.[75] For example, angiotensin III showed a relatively high sputtering yield from F-SAM surfaces, however, the sputtering yield was reduced to about 25% when the experiment was performed using an H-SAM surface. Further reduction to about 4% was observed on bare gold surfaces and only about 1% relative yield was obtained upon analysis from a HOOC-terminated SAM surface.

One question that must be raised[76] relates to the number of ions that must be deposited on a surface before saturation is obtained and all the subsequent ions are repelled by the surface charge. Given the evidence that soft landed small organic and peptide ions retain their charge to at least some extent, this phenomenon should be observable. Surface saturation has been observed previously upon deposition of small organic ions onto F-SAM surfaces[69] where the saturation plateau was reached when about 1×10^{13} ions (7% of a monolayer) had been deposited. More recently in the case of peptide soft landing[76] it was shown that saturation due to Coulombic repulsion also occurs before deposition of one monolayer. Accumulation experiments were performed on an F-SAM surface for various periods and the signal observed in subsequent SIMS analysis was compared to the fraction of a monolayer deposited through ion soft-landing (Fig. 8). For bradykinin and substance P saturation occurred upon deposition of about 30% of a monolayer.

The experiments involving small organic ions, peptides and proteins all show that in addition to natural physisorption of ions from the surface the loss of the soft-landed ions involves chemical reactions with adventitious chemical reagents, such as water.

e. Soft-landing in chiral enrichment experiments

An unusual application of ion soft-landing is its use in the accumulation of homochiral serine octamers. Starting from non-racemic serine solutions and taking advantage of the special properties of serine, chiral enrichment was achieved.[77] In a study performed by Nanita *et al.* serine octamers were generated by means of electrospray and sonic spray ionization of aqueous solutions of d_3-L-serine (108 Da) and D-serine (105 Da) having different molar ratios of enantiomers. A sequence of processes allowed the formation of chirally-enriched octameric cluster ions, their mass selection and their dissociation back to the monomer, *viz.* $Ser_1 \rightarrow Ser_8 \rightarrow Ser_1$. The regenerated serine monomers were shown by isotopic labeling to have an increased enantiomeric excess. Two types of experiments were performed: (1) Chiral enrichment in serine was observed in MS/MS/MS experiments in a quadrupole ion trap in which the entire distribution of serine octamers formed from non-racemic solutions was isolated, collisionally activated, and fragmented. Monomeric serine was regenerated with increased enantiomeric excess upon dissociation of the octamers when compared with the enantiomeric composition of the original solution. (2) Chiral enrichment was observed in the products of soft-landing of mass-selected protonated serine octamers. These ions were generated by means of electrospray ionization and a single quadrupole mass filter modified for ion soft-landing was used to isolate the entire isotopic distribution of protonated serine octamers (m/z 841–865) and to soft land these ions at a gold surface. Chiral enrichment of the soft-landed serine was established by re-dissolving the recovered material and comparing the intensities of protonated molecules of d_3-L-serine and D-serine after atmospheric pressure CI analysis. Both of these experiments showed comparable results, (20% *e.e.* originally, 50% *e.e.* after the processing) suggesting that formation of serine octamers depends on the enantiomeric composition of the serine solution and that the magnitude of the chiral preference is intrinsic to octamers formed from solutions of given chiral composition.

f. Soft-landing in proteomics

Molecular ion soft-landing, characterized by deposition of intact molecules on surfaces at low kinetic energies,[68] has been applied in a wide range of experiments. These include studies using chemically inert and structurally organized self-assembled monolayers (SAMs) as substrates for ion storage,[15] studies of ion mobility through ice and vapor-deposited films,[78,79] and experiments aimed at developing soft-landing as a method for preparative mass spectrometry.[25] Simple organic cations,[69,80] metal clusters,[81] polysaccharides,[27] a nucleotide,[82] and intact viruses[83–85] have all been the subject of examination by ion soft-landing. In some of these experiments it is desirable to preserve the ion in its charged state at the surface. However, in many other experiments, especially in preparative mass spectrometry, one wants to neutralize the ions and capture the corresponding neutral molecules. This becomes inevitable with surfaces such as hydrophilic liquids, the acid/base properties of which ensure neutralization of protonated (or deprotonated) ions of biological compounds produced by electrospray ionization.

In 2003, separation and collection of intact proteins from a mixture by mass spectrometry was achieved.[23] Intact, multiply-protonated proteins of particular mass and charge were selected from ionized protein mixtures and gently landed at different positions on a gold surface to form a microarray. The experiments were performed using a modified quadrupole mass spectrometer and a custom-built instrument linear ion trap (LIT).[24,86] A mixture of cytochrome *c*, lysozyme, insulin, and apomyoglobin was ionized and particular charge states of the individual proteins were selected by mass/charge, and soft landed. The electrospray ionization mass spectra of the deposited spots matched those of the authentic compounds. Fig. 9B shows the ESI mass spectrum of a mixture of the four proteins listed above, indicating the regions of the mass spectrum selected for soft-landing with a photograph of the landed material on an array shown in Fig. 9A. The ESI spectra resulting from analysis of rinse solutions for each spot are

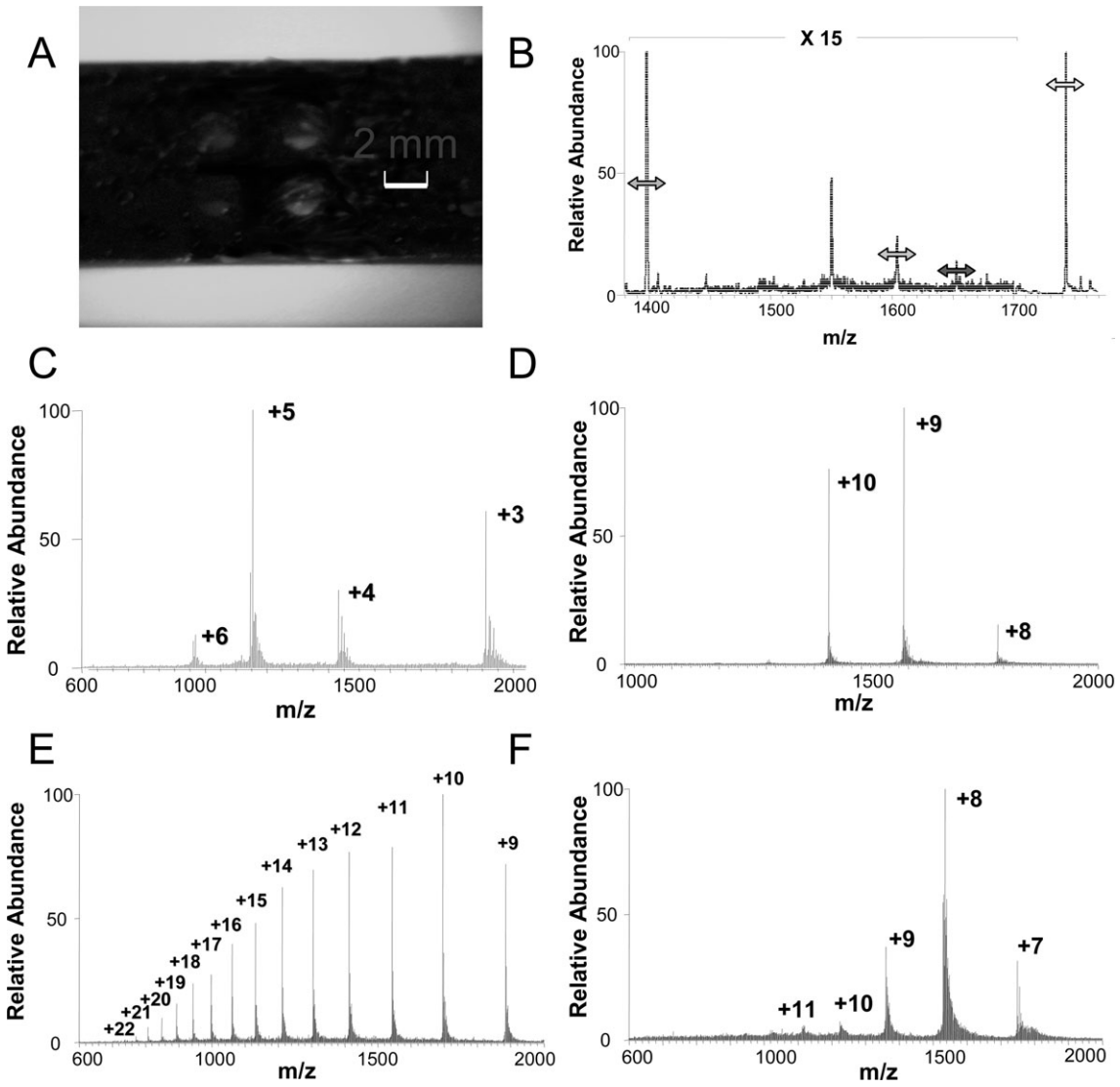

Fig. 9 (A) Photograph (in blue light) of a microarray of four proteins soft-landed onto a gold substrate; each spot is 1 mm in radius. (B) ESI mass spectrum of a mixture of 2.5 μg ml^{-1} cytochrome *c* (molecular mass 12 360 Da), 2.5 μg ml^{-1} lysozyme (molecular mass 14 316 Da), 2.5 μg ml^{-1} insulin (molecular mass 5734 Da), and 2.5 μg ml^{-1} apomyoglobin (molecular mass 16 951 Da) in methanol/water 1 : 1 used for soft-landing. The ions of +9 charge state of cytochrome *c* (*m*/*z* 1359), +11 charge state of lysozyme (*m*/*z* 1301), +4 charge state of insulin (*m*/*z* 1398), and +15 charge state of apomyoblobin (*m*/*z* 1135) were selected for ion soft-landing based on a window of 5 *m*/*z* units. Nominal charge landed for each protein was on the order of 10^{-6} C. Mass spectra of the soft-landed proteins after rinsing the spots: (C) insulin, (D) lysozyme, (E) apomyoglobin, and (F) cytochrome *c*. (Reproduced with permission from ref. 23).

shown in Fig. 9C to F and these spectra contain only multiply-charged ions of the corresponding protein (in the high-mass range, $m/z > 500$) and show no evidence for fragmentation or cross-contamination. A total of 480 μl of a solution (10^{-7} to 10^{-6} M in each protein) was sprayed, and the amounts of proteins recovered (in the 10-ng range) indicate that multilayer deposition occurs and that neutralization occurs in the course of landing. Later experiments revealed that neither the landing efficiency nor the collection of native proteins depends on the selected charge state of the proteins. However, the landing energy and type of surface used were critical parameters. Fragmentation was observed at higher energies and only hydrophilic liquid surfaces could be used reliably to retain the biological activity of the landed proteins as is now discussed.

g. Biological activity preservation during soft-landing

To investigate the biological activity of soft-landed proteins, Ouyang *et al.*[23] separated a mixture of two enzymes, trypsin and lysozyme and landed the pure proteins. In this initial experiment, extracellular enzymes containing no prosthetic groups were chosen to ensure their structural stability throughout the ionization and soft-landing process. The bioactivity of landed lysozyme was tested with hexa-*N*-acetyl chitohexaose as a substrate and the enzymatic cleavage products of the substrate were detected by MALDI. The specific activity of soft-landed lysozyme was determined from two parallel soft-landing experiments. $[Lysozyme + 8H]^{+8}$ ions were soft-landed on a gold substrate for 1 h, and the landed material was quantified by ESI-MS as judged from the intensity of the lysozyme ions with charges from 7 to 11. Quantitative results were obtained by comparison with ion intensities from a series of calibration experiments. Landed material from the parallel experiment was assayed with hexa-*N*-acetyl chitohexaose as a substrate, using ESI-MS for quantification. In this particular experiment, the amount of landed lysozyme was 1.8 ± 0.3 ng, as determined by direct quantification and 2.0 ± 0.1 ng based on the bioassay. From these results it was concluded that lysozyme retains its bioactivity virtually completely when soft landed.

The feasibility of soft-landing of delicate proteins with high biological relevance was tested by landing different kinases into vacuum and protein-compatible liquid surfaces. Bovine protein kinase A catalytic subunit (PKAc; molecular mass 40 856 Da)

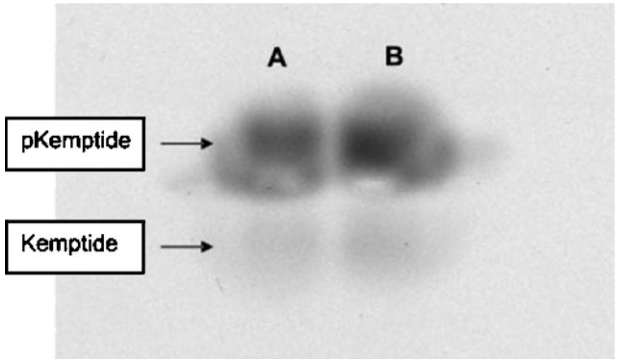

Fig. 10 Electropherogram from the assay of landed PKAc (B) and of a positive control experiment (A). PKAc molecular ions of all charge states (Fig. 4A) were soft-landed into a glycerol surface for 1 h. Enzymatic activity was assayed based on phosphorylation of fluorescently labeled Kemptide in the presence of ATP and Mg^{2+} and electrophoretic separation of labeled Kemptide and phospho-Kemptide. For the positive control experiment, 1 ng of enzyme was used. (Reproduced with permission from ref. 23).

and yeast hexokinase (molecular mass 52 360 Da) were ionized and soft-landed onto various surfaces. Gas phase PKAc ions, tentatively assigned to the original folded structure, were mass-selected and soft-landed into a glycerol/fructose/water liquid surface containing adenosine 5-triphosphate (ATP) Mg salt and its corresponding substrate Kemptide (single amino acid code, LRRASLG). Electropherogram analysis (Fig. 10) of the liquid surface after incubation by ESI-MS/MS showed the presence of phospho-Kemptide (LRRApSLG), demonstrating retention of biological activity.

Similar experiments with hexokinase in the presence of fructose yielded fructose-6-phosphate. The specific activity of the soft-landed PKAc was estimated on the basis of the phosphorylation assay and estimated ion currents. This rough estimate gave values of $\sim$50% of the specific activity of the original enzyme preparation in several different experiments. In this series of experiments sensitive, intracellular enzymes were ionized by electrospray under mild conditions (physiological pH, aqueous media), and mass-selected multiply charged ions were transferred to another hydrophilic medium represented by the glycerol liquid surface. The fact that these kinases survived this process and retained their biological activity is evidence that soft-landing of active enzymes is feasible for various eukaryotic (*e.g.*, human) cytosolic proteins. This result formed the basis for a subsequent study investigating the use of liquid surfaces as media for protein capture and preservation during a soft-landing separation process.

h. Liquid surfaces as soft-landing substrates

There are many challenges in attempting to preserve the bioactivity of proteins in the course of ionization, exposure to vacuum and soft-landing on self-assembled monolayer type surfaces. Even after the development of appropriately gentle methods of ionization, a serious problem is that SAMs are not ideal landing substrates for preservation of biological function.[87–89] The use of liquids as an alternative to SAM surfaces provides a way of preserving biological activity of the landed species. It was found that media rich in polyols and sugars allow the capture and preservation of bioactivity.[73] Retention of biological activity is strongly favored in glycerol-based surfaces but not in self-assembled monolayer solid surfaces. Soft-landing efficiency for multiply-charged hexokinase ions was found to be some four times higher for a glycerol/fructose liquid surface than for a fluorinated self-assembled monolayer surface. Soft-landing into liquid surfaces allows (i) protein purification, (ii) on-surface identification of the soft-landed material using MALDI and (iii) protein identification by in-surface enzymatic assays. Using soft-landing, pure lysozyme was successfully isolated from different mixtures including an oxidized, partially decomposed batch of the protein and a partial tryptic digest, and landed into liquid glycerol/carbohydrate substrates. These liquids could be used directly to record MALDI spectra on the soft-landed compounds provided they were fortified in advance with traditional MALDI matrices such as *p*-nitroaniline and α-cyano-4-hydroxycinnamic acid. Various proteins were soft-landed and detected on-target using these types of liquid surfaces.[73]

From a mechanistic point of view, the protecting role that polyols and sugars display on preserving the bioactivity of proteins is not easily explained.[23,73] Proteins are designed to function in environments crowded by co-solutes, but most studies of protein equilibria are conducted in dilute solution. While there is no doubt that crowding changes protein equilibria, interpretation of the changes remain controversial. A review published by Pielak and co-authors[91] combines experimental observations on the effect of small uncharged cosolutes on protein stability with a discussion of the thermodynamics of cosolute-induced nonideality and critical assessments of the most commonly applied interpretations. Protein solvation for a given (folded) state of a protein is typically viewed in terms of two steps (Fig. 11) where first the gas-phase protein is solvated in either water or osmolyte solution, both of which are interpreted in terms of hard-sphere interactions. The subsequent

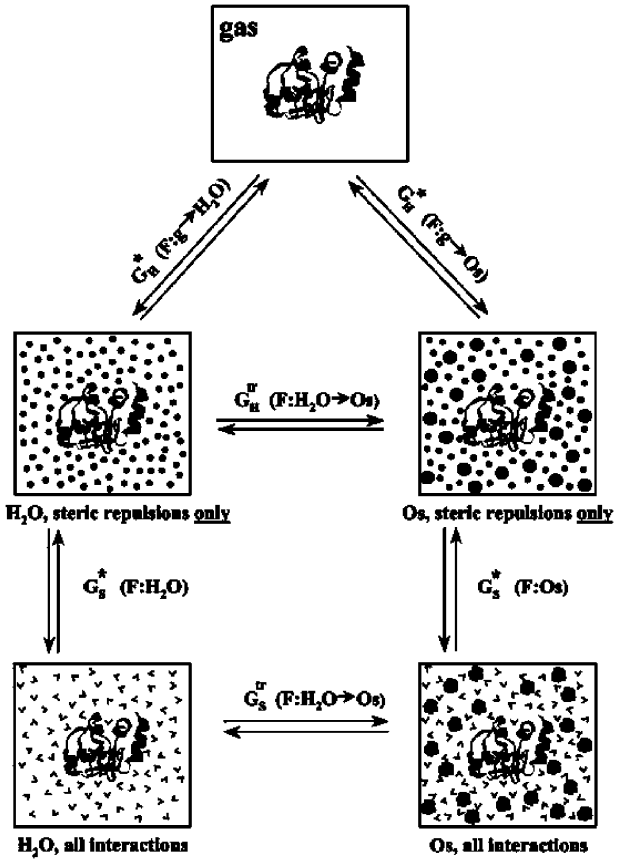

Fig. 11 Solvation process for a single protein conformational state is broken into two steps.[90] In the first step, the protein is removed from the gas phase and introduced into a water or water/osmolyte solution. The solvent and solute are represented as hard spheres and only solvent–solvent and solvent–solute interactions and steric repulsions between the protein and solvent are "turned on". In the second step, solvent–protein and solute–protein binding interactions are turned on. The transfer of a protein conformation between pure water and water/osmolyte mixture is also divided into two steps, ΔG_S^{tr} (F : H_2O → Os) and ΔG_H^{tr} (F : H_2O → Os). Abbreviations: F-Folded protein, Os-Osmolyte, g-Gas phase, G_H-free energy arising from hard-sphere exclusion effects, G_S-free energy arising from binding interactions (Reproduced with permission from ref. 91).

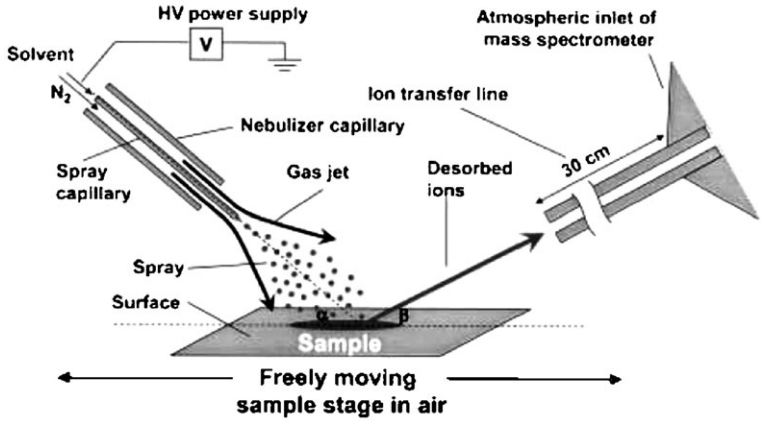

Fig. 12 Schematic of a typical DESI experiment. The sample solution was deposited from solution and dried onto a PTFE surface, and methanol–water (1 : 1 containing 1% acetic acid or 0.1% aqueous acetic acid solution) was sprayed at a flow rate of 3–15 μl min^{-1} under the influence of a high (4 kV) voltage. The nominal linear velocity of the nebulizing gas was set to 350 m s^{-1}. (Reproduced with permission from ref. 92).

step consists of soft interactions, which include phenomena such as electrostatic, van der Waals, and hydrophobic interactions.[91] Within Pielak's work, analysis of the interactions reveals that steric repulsions are the major driving force for stabilization of folded protein states.[91] Larger sugars will therefore have a more pronounced effect on stabilization than smaller sugars as a result of their greater volume occupancy. This phenomenon may be applied in understanding the interactions of proteins within cells where the crowded environment may induce similar effects.

Desorption electrospray ionization at atmospheric pressure

Mass spectrometry is performed in vacuum. However, Takats *et al*. recently introduced a novel approach, desorption electrospray ionization mass spectrometry (DESI),[92] in which mass spectra are recorded on samples in the ambient environment. The experiment is based on interaction of low kinetic energy cluster ions generated from solvent colliding with ordinary surfaces bearing organic or biological compounds of interest. DESI is carried out by directing electrosprayed charged droplets and ions of solvent onto the surface to be analyzed, as illustrated in Fig. 12. The impact of the charged particles on the surface produces gaseous ions of material originally present on the surface. The resulting mass spectra of biomolecules are similar to normal ESI mass spectra in that they show mainly singly- or multiply-charged molecular ions of these analytes. The mechanisms of DESI are not known but in at least some cases there is evidence that chemical sputtering is involved. The DESI phenomenon was observed both in the case of conductive and insulator surfaces and for compounds ranging from nonpolar small molecules such as lycopene, the alkaloid conicine, and small drugs, through polar compounds such as peptides and proteins. Changes in the solution that is sprayed can be used to selectively ionize particular compounds, including those in biological matrices. *In vivo* analysis was demonstrated by exposing a finger cut to a nitrogen assisted ethanol–water spray which resulted in a spectrum confirming the presence of carnitine and acetylcarnitine in blood.

There are many applications[92] which can be made as a result of the collision of ions with surfaces at atmospheric pressure. For example, it is possible to examine protein digest analysis from a Teflon surface; enzyme–substrate molecular recognition is achieved for systems when the kinetics of the enzymatic reaction allow the complex to be observed in the mass spectrum; chiral analysis on a limestone surface containing an amino acid; drug metabolites from skin—these are all examples. Remarkable new types of chemical analysis are possible using this experiment[92] which demonstrates just how much more powerful a method mass spectrometry might become once its vacuum constraints are lifted.

Conclusions

The collision of ions at surfaces is becoming a rich and active area of research. Processes associated with ion/surface scattering have been briefly reviewed and the analytical/practical applications discussed. Of note are the implications for surface analysis and specific chemical modification of surfaces. Exciting possibilities exist for preparative mass spectrometry, performed by soft-landing, for purification and storage of biological compounds. Various aspects of this work in our laboratory have been presented. Exploration of some of the requisite surface properties and their influence on the practical aspects of soft-landing are still under examination. Much remains to be learned about the fundamental aspects of each of these processes.

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