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Ion Sources

In the ion sources, the analysed samples are ionized prior to analysis in the mass spectrometer. A variety of ionization techniques are used for mass spectrometry. The most important considerations are the internal energy transferred during the ionization process and the physico-chemical properties of the analyte that can be ionized. Some ionization techniques are very energetic and cause extensive fragmentation. Other techniques are softer and only produce ions of the molecular species. Electron ionization, chemical ionization and field ionization are only suitable for gas-phase ionization and thus their use is limited to compounds sufficiently volatile and thermally stable. However, a large number of compounds are thermally labile or do not have sufficient vapour pressure. Molecules of these compounds must be directly extracted from the condensed to the gas phase.

These direct ion sources exist under two types: liquid-phase ion sources and solid-state ion sources. In liquid-phase ion sources the analyte is in solution. This solution is introduced, by nebulization, as droplets into the source where ions are produced at atmospheric pressure and focused into the mass spectrometer through some vacuum pumping stages. Electrospray, atmospheric pressure chemical ionization and atmospheric pressure photoionization sources correspond to this type. In solid-state ion sources, the analyte is in an involatile deposit. It is obtained by various preparation methods which frequently involve the introduction of a matrix that can be either a solid or a viscous fluid. This deposit is then irradiated by energetic particles or photons that desorb ions near the surface of the deposit. These ions can be extracted by an electric field and focused towards the analyser. Matrix-assisted laser desorption, secondary ion mass spectrometry, plasma desorption and field desorption sources all use this strategy to produce ions. Fast atom bombardment uses an involatile liquid matrix.

The ion sources produce ions mainly by ionizing a neutral molecule in the gas phase through electron ejection, electron capture, protonation, deprotonation, adduct formation or by the transfer of a charged species from a condensed phase to the gas phase. Ion production often implies gas-phase ion–molecule reactions. A brief description of such reactions is given at the end of the chapter.

1.1 Electron Ionization

The electron ionization (EI) source, formerly called electron impact, was devised by Dempster and improved by Bleakney [1] and Nier [2]. It is widely used in organic mass spectrometry. This ionization technique works well for many gas-phase molecules but induces extensive fragmentation so that the molecular ions are not always observed.

As shown in Figure 1.1, this source consists of a heated filament giving off electrons. The latter are accelerated towards an anode and collide with the gaseous molecules of
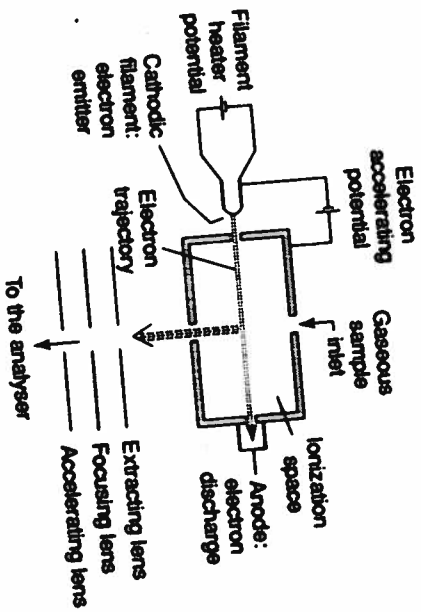
the analysed sample injected into the source. Gases and samples with high vapour pressure are introduced directly into the source. Liquids and solids are usually heated to increase the vapour pressure for analysis.

Each electron is associated to a wave whose wavelength λ is given by

$$\lambda = \frac{h}{mv}$$

where m is its mass, v its velocity and h Planck's constant. This wavelength is 2.7 Å for a kinetic energy of 20 eV and 1.4 Å for 70 eV. When this wavelength is close to the bond lengths, the wave is disturbed and becomes complex. If one of the frequencies has an energy $h\nu$ corresponding to a transition in the molecule, an energy transfer that leads to various electronic excitations can occur [3]. When there is enough energy, an electron can be expelled. The electrons do not 'impact' molecules. For this reason, it is recommended that the term electron impact must be avoided.

Figure 1.2 displays a typical curve of the number of ions produced by a given electron current, at constant pressure of the sample, when the acceleration potential of the electrons (or their kinetic energy) is varied [4]. At low potentials, the energy is lower than the molecule ionization energy. At high potentials, the wavelength becomes very small and molecules become 'transparent' to these electrons. In the case of organic molecules, a wide maximum appears around 70 eV. At this level, small changes in the electron energy do not significantly affect the pattern of the spectrum.

On average, one ion is produced for every 1000 molecules entering the source under the usual spectrometer conditions, at 70 eV. Furthermore, between 10 and 20 eV is enough to ionize most organic molecules during the ionization process. Since approximately 10 eV is enough to ionize most organic molecules, the excess energy leads to extensive fragmentation. This fragmentation can be useful because it provides structural information for the elucidation of unknown analyses.

At a given acceleration potential and at constant temperature, the number of ions i produced per unit time in a volume V is linked to the pressure p and to the electron current

Figure 1.1
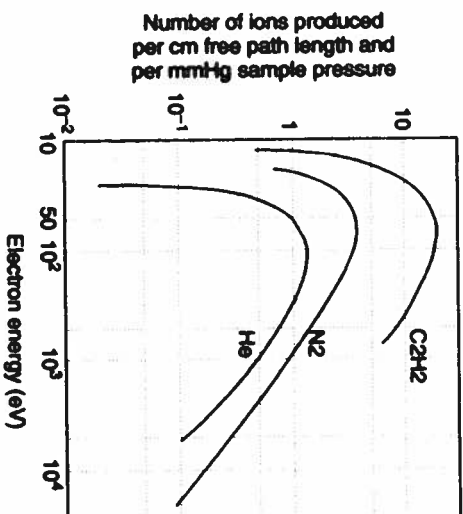Diagram of an electron ionization source.

Figure 1.2
Number of ions produced as a function of the electron energy. A wide maximum appears around 70 eV.

i through the following equation, where N is a constant proportionality coefficient:

$$I = N p i V$$

This equation shows that the sample pressure is directly correlated with the resulting ionic current. This allows such a source to be used in quantitative measurements.

Figure 1.3 displays two EI spectra of the same β-lactam compound, obtained at 70 and 15 eV. Obviously, at lower energy there is less fragmentation. At first glance, the molecular ion is better detected at low energy. However, the absolute intensity, in arbitrary units, proportional to the number of detected ions, is actually lower: about 250 units at 70 eV and 150 units at 15 eV. Thus, the increase in relative intensity, due to the lower fragmentation, is illusory. Actually, there is a general loss of intensity due to the decrease in ionization efficiency at lower electron energy. This will generally be the rule, so that the method is not very useful for better detection of the molecular ion. However, the lowering of the ionization voltage may favour some fragmentation processes.

A modification implies desorbing the sample from a heated rhenium filament near the electronic beam. This method is called desorption electron ionization (DEI).

Under conventional electron ionization conditions, the formation of negative ions is inefficient compared with the formation of positive ions.
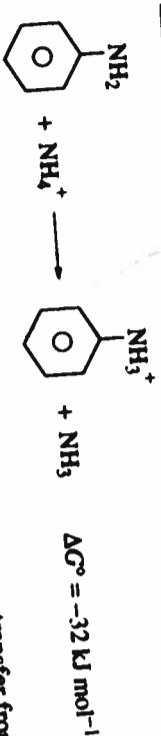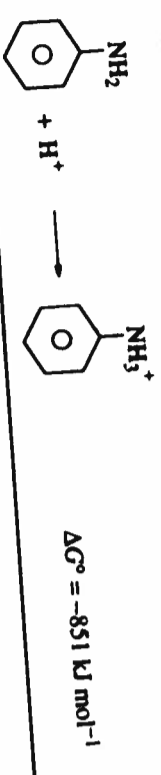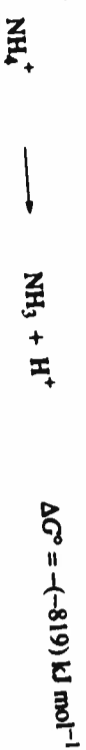
1.2 Chemical Ionization

Electron ionization leads to fragmentation of the molecular ion, which sometimes prevents its detection. Chemical ionization (CI) is a technique that produces ions with little excess energy. Thus this technique presents the advantage of yielding a spectrum with less fragmentation in which the molecular species is easily recognized. Consequently, chemical ionization is complementary to electron ionization.
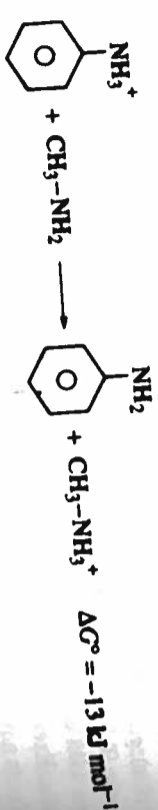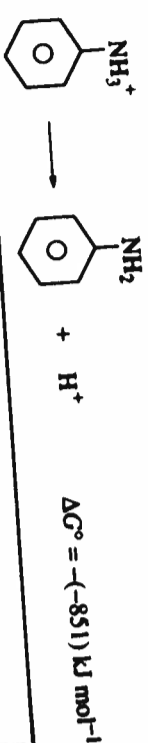
As an example, let us examine whether or not the proton transfer from protonated ammonia to neutral aniline is efficient:

NH_2 + NH_4^+ ⟶ NH_3^+ + NH_3
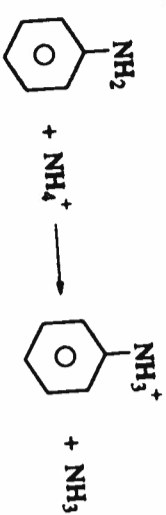
From the individual $\Delta G°$ values, equal to $-GB$, the $\Delta G°$ value for this reaction is calculated:

NH_4^+ ⟶ NH_3 + H^+ $\Delta G° = -(-819)$ kJ mol^{-1}

NH_2 + H^+ ⟶ NH_3^+ $\Delta G° = -851$ kJ mol^{-1}

NH_2 + NH_4^+ ⟶ NH_3^+ + NH_3 $\Delta G° = -32$ kJ mol^{-1}

In a standard source, the reaction being exergonic, the proton transfer from ammonium to aniline will be very efficient. Note that in the source we are dealing here with efficiency at each collision, not with equilibrium. Under the high-vacuum conditions, equilibrium is not established. This example was selected because it shows that, in the gas phase, aniline is actually a stronger base than ammonia. The importance of solvation is thus emphasized once again. On the other hand, the methylamine is more basic than aniline:

CH_3-NH_2 + H^+ ⟶ $CH_3-NH_3^+$ $\Delta G° = -864$ kJ mol^{-1}

NH_3^+ + NH_2 ⟶ NH_2 + H^+ $\Delta G° = -(-851)$ kJ mol^{-1}

NH_3^+ + CH_3-NH_2 ⟶ NH_2 + $CH_3-NH_3^+$ $\Delta G° = -13$ kJ mol^{-1}

1.17 Formation and Fragmentation of Ions: Basic Rules

The aim of this section is to give an overview of the factors determining the formation of the various types of ions encountered in the different ionization modes. Exceptions

and examples are given in the sections dedicated to the ionization methods and to the fragmentations.

1.17.1 Electron Ionization and Photoionization Under Vacuum

These reactions occur under high vacuum. Thus, no ion–molecule reaction occurs. The species formed during the ionization process is a radical cation. Ionization efficiency depends on the ionization energy of the molecule. The presence or not of the molecular ions also depends on how easy it fragments.

Fragmentation often produces both a radical and a cation. This can be represented by the following equation:

$$R-R^{\cdot})^+ \begin{cases} R^\cdot + R^+ \\ R^+ + R^\cdot \end{cases}$$

The factor that determines which of the fragments is a radical or a cation can be emphasized as a competition between two cations to capture the electron:

$$R^+ \cdots e^- \cdots R'^+$$

As the fragment with the higher propensity to retain the electron should have the higher ionization energy, the fragment observed in the spectrum as a cation is the one having the lowest ionization energy. The other one, having the highest ionization energy, takes the electron to be a radical. This is the origin of the Stevenson rule that will be explained in Chapter 7 on fragmentation.

1.17.2 Ionization at Low Pressure or at Atmospheric Pressure

The CI source operates at low pressure. Ion–molecule reactions occur and are needed for sample ionization. The MALDI source is under vacuum, but during the ionization process the pressure increases in the plume close to the target and ion–molecule reactions occur. The various sources operating at atmospheric pressure to have numerous collisions AP-MALDI. All these sources operate at sufficient pressure to have numerous collisions between ions and molecules, and reactions between these species are observed.

It is worth noting that reactions between neutrals produced by fragmentations and ions are not observed. This is due to the fact that, whatever the ionization method, only a small fraction of the analyte molecules are ionized, and their fragments are at even lower concentrations. The probability of a collision is thus too low. Similarly, under normal conditions, no collision between ions is observed.

However, reactions may be observed between an ion and a neutral both resulting from the fragmentation of one precursor ion, immediately after cleavage, provided they remain associated for some time. This time is rarely more than a few microseconds. This can occur as well under vacuum as at higher pressure.

1.17.3 Proton Transfer

Proton transfer to produce a cation or an anion is the most often observed ion–molecule reaction in sources that allow collisions. The general rule is that the proton affinity of

the proton acceptor (neutral or anion) has to be higher than the proton affinity of the donor (cation or neutral). If there is a difference in proton affinity such that the reaction is exergonic, the transfer occurs at each collision (see Figure 1.48).

The protonated molecule fragments, if necessary after activation. The fragments do not always result from the cleavage of only one bond, as this can lead to the formation of a radical fragment and a radical cation, a very unfavorable process. The pathway is thus often more complicated than for radical cations. It can be represented as follows:

$$M + H^+ \longrightarrow MH^+$$

$$MH^+ \Big\langle \begin{array}{l} F1 + F2H^+ \\ F1H^+ + F2 \end{array}$$

$$F1 \cdots H^+ \cdots F2$$
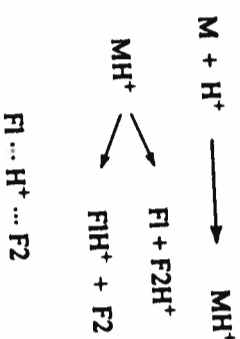
Here the competition is between two fragments for a proton. The fragment with the highest gas-phase basicity gets the proton. For negative ions a similar rule applies, but now it is the most acidic species that carries the negative charge. This is analogous to the competition seen before, about EI, between two ions for an electron.

A similar competition already exists at the ion formation stage in the source. For this reason, in the presence of a solvent having a certain proton affinity, it is not possible to see the protonated cation of an analyte having a lower proton affinity. It is, however, possible to observe an adduct with another cation, such as sodium, ammonium, and so on. The reverse is true for negative ions. Here too, adducts with anions as chloride, acetate, and so may be observed.

Similarly, if two analytes in a mixture have a marked difference of acidity or basicity, only one is observed in the spectrum: the best proton acceptor in positive ion mode, or the best proton donor in negative ion mode. However, at low concentrations the competition is less obvious, and both ions can sometimes be observed together.

1.17.4 Adduct Formation

An adduct is an ion formed by direct combination of a neutral molecule and an 'ionizing' ion other than the proton. In positive ion mode the most often observed is the sodium adduct, producing an ion with 22 mass units higher than the protonated molecule, that is $(M + 23)^+$ instead of $(M + 1)^+$. It is often accompanied by a potassium adduct, another

the sodium adduct is dominant. If ammonium salt is present it can also form adducts $(M + NH_4)^+$ because of its ability to form hydrogen bonds.

In the negative ion mode, the chloride adduct is often observed yielding $(M + 35)^-$ and $(M + 37)^-$. As for the sodium, the chloride ion is always present if the solution is not desalted. However, it produces fewer adducts than the sodium. The acetate ions, if present, produce $(M + 59)^-$ owing to their ability to form hydrogen bonds.

The addition of ammonium acetate, at low concentration, in API methods can be interesting to produce protonated or deprotonated species. Indeed, in the heated gas or heated capillary interface, ammonia or acetic acid evaporates, leaving the corresponding protonated or deprotonated species. The interest of nitrate adducts in the analysis of sugars has been recently demonstrated [109,110].

1.17.5 Formation of Aggregates or Clusters

'Dimer' ions such as $(M + M + H)^+$ or of higher order $(nM + H)^+$ are often observed. The proton can be replaced by another cation. 'Heterodimers' of the general formula $(M + M' + H)^+$, or with a metal cation or of higher order, are also observed. The corresponding ions are also observed in negative ion mode.

It should be noted that the formation of such aggregates in the gas phase causes a diminution of entropy. To be possible, the formation of such aggregates must be exothermic. Furthermore, if the partners have similar basicities or affinities for the cation, the cluster is more stable. Otherwise it dissociates, one of the partners taking the proton, or the cation, according to the relative stability. This is why associations of two or more identical molecules are observed more often or at higher abundances. Indeed, they have the same affinities of course.

The formation of oligomers has as a consequence the diminution of the number of molecules in the gas phase, and thus occurs with a diminution of the entropy. As the reaction must be exergonic to occur, it must be sufficiently exothermic, at least to compensate for the entropy loss. Once formed, the internal energy of the oligomer should be reduced, since it contains a sufficient amount of energy to dissociate. This needs a collision with a third partner, and this requires a sufficient pressure.

As a general rule, the abundance is reduced when the number of associated molecules increases. However, some specific aggregates, resulting from particularly important interactions, are present at particularly high abundance. This occurs often with organometallic compounds, as the metal tries to complete its electronic shell.

Aggregates are rarely observed in the negative ion mode, because the presence of the negative charge causes an expansion of the electronic shell, thus reducing the electric field around the negatively charged ion. This reduces the interactions between the partners.