International Journal of Mass Spectrometry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

Direct analysis of complex mixtures by mass spectrometry

R. Graham Cooks*, Alan K. Jarmusch, Michael Wleklinski

Department of Chemistry and Center for Analytical Instrumentation Development, Purdue University, West Lafayette, IN 47907, USA

ARTICLE INFO

Article history:
Received 10 May 2014
Received in revised form 30 June 2014
Accepted 30 June 2014
Available online xxx

Keywords:
Tandem mass spectrometry
Energy transfer
Ion/surface collisions
Metastable ions
Ion kinetic energy
Fragmentation

ABSTRACT

Mixture analysis can provide information on individual components if the sample is first subjected to chromatographic separation. Two critical capabilities, soft ionization and the ability to mass-select and then dissociate ions of a particular *m*/*z*, coalesced in 1975, allowing direct analysis of complex mixtures by mass spectrometry. Chemical ionization was used as the soft ionization method and mass-analysis used the ion kinetic energy spectrometer (MIKES). Soft molecular ionization produces a set of ions that are structural surrogates of the neutral molecules; they can be mass-selected and allowed to spontaneously dissociate (*i.e.* as metastable ions) or fragmented upon energy transfer *e.g.* in the course of collision-induced dissociation (CID). The second stage of mass analysis provides information about the atomic connectivity in the precursor ion and by implication in the original molecule. This review focuses on the development of complex mixture analysis by mass spectrometry and allied topics. Discussion of the activation techniques associated with (collision-induced dissociation, surface-induced dissociation and metastable ion dissociation) emphasizes the importance of energy transfer phenomena and the internal energies distributions of ions to explain the observed mass spectra. The translational to internal energy transfer in collisions is readily accessed in the MIKES where the second stage mass analyzer is a kinetic energy/charge analyzer. Collisions in the keV range can also be used to change ion the charge state *via* the processes of charge exchange, electron stripping, or charge inversion. New ionization sources for analysis of non-volatile compounds that were introduced during the time period (1975–1990) of this review included secondary ion mass spectrometry, plasma desorption and field ionization and they are briefly discussed. Several types of scans were developed to rapidly access information of the individual components, including chemically specific scans (*e.g.* neutral loss scans of mass 30 for nitro compounds).

1. Introduction

In 1975 two capabilities came together to allow direct, rapid analysis of complex mixtures of organic compounds by mass spectrometry. They were (i) mass-analyzed ion kinetic energy spectrometry, MIKES, a method of characterizing ions of given *m*/*z* ratio by isolating them from a mixture of ions and then performing an operation, typically collision-induced dissociation (CID), that generated a characteristic set of fragment ions from each precursor ion and (ii) chemical ionization (CI) a method of ionization that allowed control of ion internal energy including the ability to cause soft ionization so as to minimize fragmentation during ion formation. Together these two capabilities allowed a complex mixture of neutral molecules to be separated into a mixture of ions, the structures of which reflected those of the original compounds in the mixture. When ions of particular *m*/*z* ratios were selected from the ionized mixture by mass analysis and then subjected to CID, a secondary mass spectrum would be recorded from which the nature (connectivity) of the corresponding neutral molecule could be inferred. This process depended on creating an ionic surrogate of each neutral compounds of interest; to do this successfully, ionization had to be gentle. To identify the selected ion, characteristic fragment ions needed to be generated and this was originally achieved by CID in the keV energy regime. This paper details these developments and associated advances in generating and characterizing molecular ions through gas-phase and surface collisions over the period 1975–1990.

1.1. MIKES instrument

The design and operation of the mass-analyzed ion kinetic energy spectrometer (MIKES) represented a sharp break from the path being taken by primary body of MS work being performed at the time. This mainstream work achieved high mass resolution using double focusing (magnetic and electric sectors) in the keV energy range. Although the same two-sector instrumentation was used, the positions of the magnetic and electric sectors were

---

* Corresponding author. Tel.: 765 494 5263; fax: 765 494 9421.

http://dx.doi.org/10.1016/j.ijms.2014.06.035
1387-3806/© 2014 Published by Elsevier B.V.

Please cite this article in press as: R.G. Cooks, et al., Direct analysis of complex mixtures by mass spectrometry, Int. J. Mass Spectrom. (2014), http://dx.doi.org/10.1016/j.ijms.2014.06.035

reversed, and they were uncoupled instead of being using in concert to improve mass resolution. Successive ion kinetic energy and mass analysis performed on a ion beam, allowed spontaneous or collision-induced processes occurring in the region between the sectors to be characterized by kinetic energy analysis (equivalent to mass analysis but only at constant velocity) [1]. McLafferty [2] also uncoupled a two-stage instrument by reversing the positions of source and detector of a Hitachi PerkinElmer RMU-7 while at MAT in Bremen (later FinniganMAT and still later Thermo) Curt Brunneé used a reversed geometry instrument to study direct analysis of daughter ions (DADI). Significantly, but not known to community of organic mass spectroscopists, Fred White [3] had already built three- and four-sector instruments to perform beam/foil collision experiments to characterize small ions by fragmentation and Futrell and Tiernan [4] had constructed a four-sector tandem instrument to study at very low energy the reactions of mass-selected ions.

Completed in 1973 in the reverse-geometry format, (electric sector/magnetic sector) the MIKES instrument [5] allowed spontaneous dissociations as well as inelastic collisions of mass-selected ions to be studied. The resulting ion kinetic energy spectra allowed both the mass changes involved and more subtly, translational energy changes, to be measured. The fabrication of components for the MIKES instrument fell upon Tom Ridley, the skilled machinist at Purdue University. Tom recalled that the MIKES instrument was presented to him as a hand-drawn sketch on a single sheet of paper. The ion optics was based on calculations provided by Syd Evans of AEI (later Kratos). The vacuum system and electronics fell to the expertise of William Baitinger and Jonathan Amy [6] whose Instrumentation Facility (now the Jonathan Amy Facility for Chemical Instrumentation), continues to design and fabricate instrumentation in support of Purdue researchers.

1.2. Physical chemical studies using MIKES

MIKES allows precursor ions to be mass-selected in the magnetic sector and product ions to be mass analyzed using the electric sector. Operated normally, the electric sector measures ion kinetic energy-to-charge ratios; however, at constant ion velocity, m/z values can be inferred. This is the basis for the analytical MS/MS experiments done using this instrumentation and discussed further below. For ions of the known mass, the electric sector measures ion velocities which form the basis for studies of the kinematics of various collision processes. Kinematics is conveniently displayed as vectors in Newton diagrams where the origin is the center of mass of the system [7]. This methodology allows elastic collisions to be distinguished from more or less deeply inelastic processes through velocity measurements whether these involve reaction or fragmentation.

The study of metastable ions – ions that spontaneously dissociate at some time after their formation – was greatly enriched by MIKES measurements. Metastable peaks had first been reported in 1946 by Hipple, Fox and Condon [8] as the signals due to the spontaneous dissociation of ions with excess internal energy above the dissociation threshold. Excess energy is converted into vibrational, electronic, and translational energy of product ions – the latter corresponding to kinetic energy release. The kinetic energy release of metastable ions revealed details about ion structure, reaction energetics and dynamics. The fact that wide peaks are observed in MIKES (Fig. 1) is due to velocity amplification of the kinetic energy release in the fast moving fragments, an effect associated with measuring in the lab system processes that occur in the simpler center-of-mass coordinate system. Note that the reverse process is also possible in that translational energy can be converted into excess internal energy resulting in dissociation (*e.g.* collision induced dissociation) and this shows up as velocity shifts in Newton diagrams. The study of metastable ions, energy conversion (T–V) upon collisional activation and kinetic energy release (V–T) upon fragmentation, kinetic isotopic effects, mapping of potential energy surfaces for ion dissociation, measurements of thermochemical properties and of unimolecular kinetics were just some of the capabilities of this powerful device as detailed elsewhere [9].

As a specific example, the reverse critical energy for a unimolecular dissociation ($\varepsilon_0^{\neq}$ in Fig. 1a) is large and a significant fraction is released as kinetic energy ($T^{\neq}$) when reaction proceeds via a tight transition state as is often the case for skeletal rearrangements [10]. On the other hand, loose transitions, such as those corresponding to simple bond cleavage, require very little rearrangement in the transition state possess negligible reverse activation energies and are associated with small kinetic energy releases. Therefore, qualitative information on the nature of the transition state for ionic dissociations is available from MIKES via

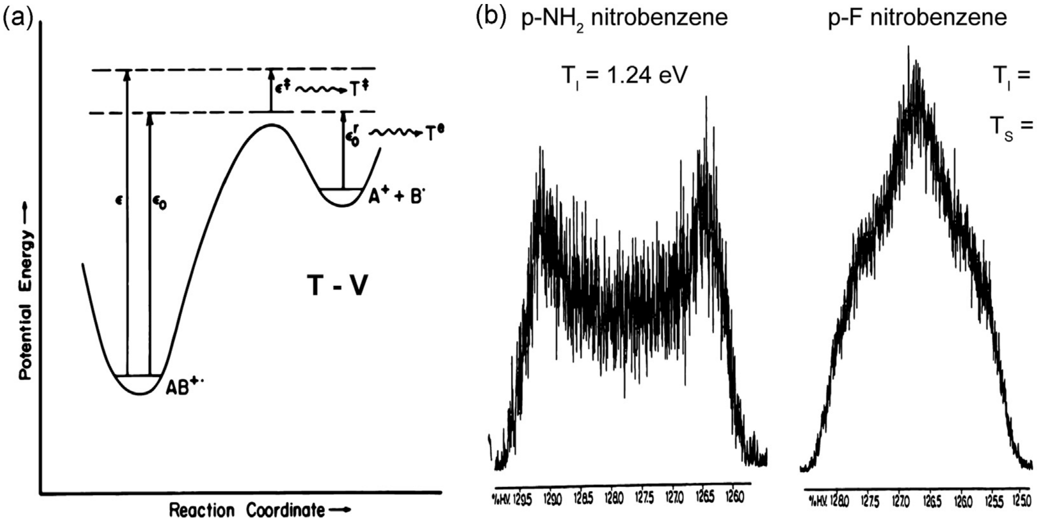

Fig. 1. (a) Reaction coordinate of an ionic dissociation of $AB^{\bullet+}$ (reproduced from reference [9]). (b) Composite metastable peaks for the $NO^{\bullet}$ loss from p-substituted nitrobenzene p-NH_2 (left) and p-F (right), where T_l and T_s refer to the kinetic energy release values of the separate reaction pathways which contribute components to the composite peak (modified from reference [16]).

Please cite this article in press as: R.G. Cooks, et al., Direct analysis of complex mixtures by mass spectrometry, Int. J. Mass Spectrom. (2014), http://dx.doi.org/10.1016/j.ijms.2014.06.035