PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Mass Spectrometry Instrumentation for Chemists and Biologists

R. D. Craig, R. H. Bateman, B. N. Green and D. S. Millington

Phil. Trans. R. Soc. Lond. A 1979 **293**, 135-155
doi: 10.1098/rsta.1979.0085

Phil. Trans. R. Soc. Lond. A **293**, 135–155 (1979) [135]
Printed in Great Britain

Mass spectrometry instrumentation for chemists and biologists

By R. D. Craig, R. H. Bateman, B. N. Green and D. S. Millington
VG-Micromass Ltd, 3 Tudor Road, Altrincham, Cheshire WA14 5RZ, U.K.

[Plate 1]

Like Gaul, a mass spectrometer may be divided into three parts: source, analyser and detector system. The status of each is reviewed.

Recent developments concerning the ion source region include improved techniques for chemical ionization (c.i.), field desorption (f.d.) and negative ion formation. There has also been significant work with pyrolysis probes, high pressure liquid chromatography (h.p.l.c.) interfaces and improved fast pumping for use with atmospheric pressure ionization (a.p.i.) and direct coupling of capillary column gas chromatographs.

Commonly used analysers are now either the quadrupole r.f. filter or single/double focusing magnetic deflexion instruments. Magnetic instrument developments reviewed include improvements to sensitivity (*Z*-focusing and image curvature correction), higher scan speeds (laminated magnets), mass indication and marking, peak jumping when using multiple ion detection (m.i.d.) and reverse geometries (permitting mass analysed ion kinetic energy spectroscopy; Mikes) and linked scan (providing metastable ion information).

Detection systems are discussed in detail and include consideration of computer data acquisition and display. Important are simultaneous foreground/background systems, library search, wide dynamic range, precision mass measurement at low resolution (higher sensitivity) and multiple ion detection at either low or high resolution. The use of linked scan and Mikes as specific ion detectors is considered.

Introduction

Mass spectrometric techniques for the chemist and biologist are still rapidly developing and this review is therefore only a snap-shot picture at one point in time. The next decade is likely to see further significant advances in ion source development and analyser design and especially in the use of the mini-computer and microprocessor to simplify operation and improve the data acquisition facility.

This is not to say that instruments being designed today will be obsolete in 10 years. Provided there is inherent flexibility in basic design concept, fresh innovations may be accommodated by additional accessories or modifications.

Being associated with new instrument development the authors may be biased towards areas of closest personal involvement. Nevertheless an attempt is made to give a broader picture of mass spectrometric instrumentation as it affects the chemist and biologist.

1. Ion sources

(*a*) *Electron impact ionization* (*e.i.*)

Ionization of sample molecules in the vapour phase at low pressure (less than about 10^{-5} Torr (1.3×10^{-3} Pa), giving a mean free path greater than 100 cm) by 70 eV electron beam is

still the paramount mode of ionization for routine organic analysis. Ion beam intensity is linear with concentration, independent of matrix effects and stable with time. E.i. is suitable for quantitative analyses.

However, many important compounds fragment under electron bombardment and their 70 eV e.i. spectra show small or negligible molecular ion peaks. Lowering the electron energy will produce simplification of the spectra and relative enhancement of molecular ion peaks but absolute intensity falls sharply as the ionization potential is approached.

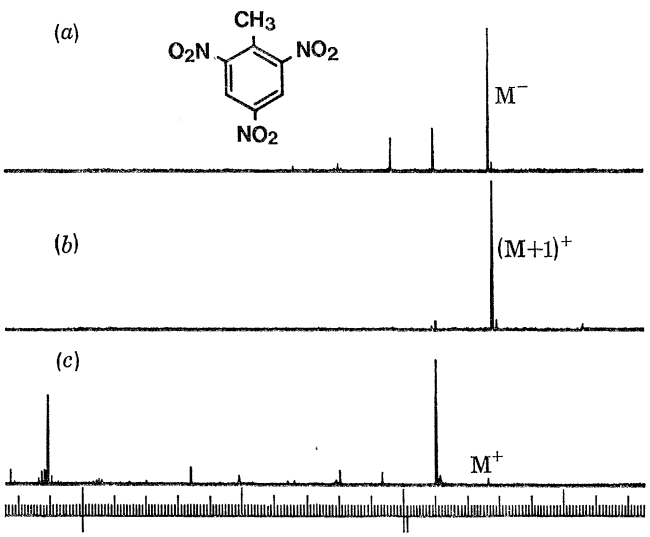


FIGURE 1. TNT spectra for three different ionization modes: (*a*) negative ion c.i.; (*b*) positive ion c.i.; (*c*) electron impact. Note mass marked chart with the use of Hall probe: negative lines indicate masses 100 and 200.

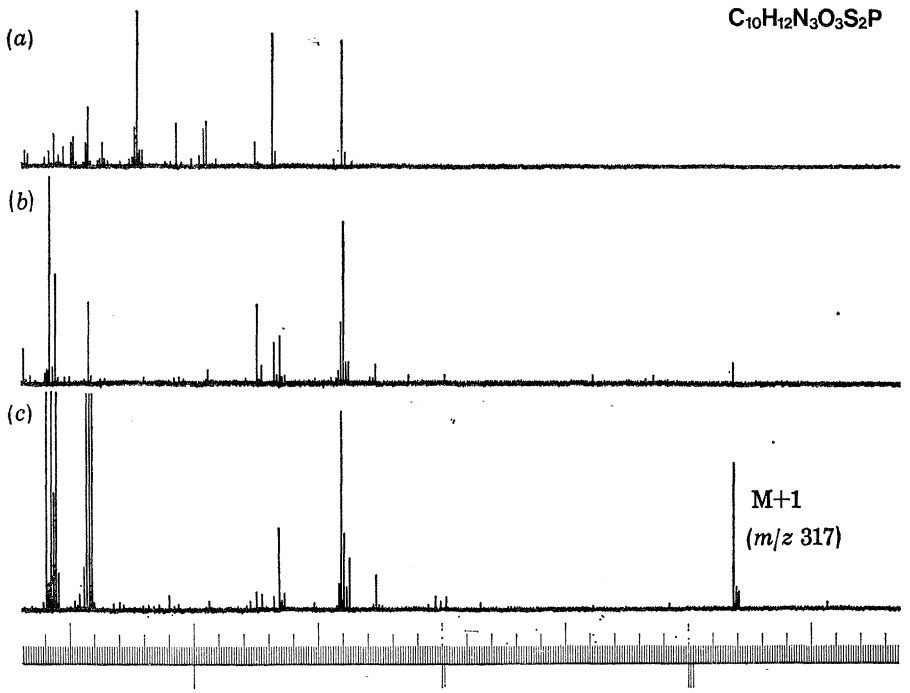


FIGURE 2. Electron impact (*a*), methane (*b*) and isobutane (*c*) c.i. spectra of a pesticide. Note relative enhancement of protonated molecular ion peak with isobutane as reactant gas.

Compounds that dissociate under e.i. may, however, respond to one of the 'softer' ionization techniques described below.

(*b*) *Chemical ionization*

In chemical ionization (c.i.) the ionization chamber is filled with a reactant gas (for example methane) at relatively high pressure (*ca.* 0.2 Torr (27 Pa), corresponding to a mean free path

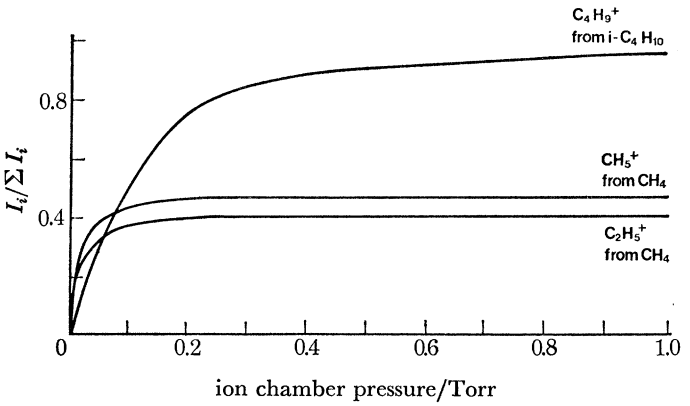


FIGURE 3. Reactant ion intensity plotted against pressure for methane and isobutane, based on work of Field & Munson (1965, 1969). Note higher pressure for optimization when using isobutane. 1 Torr ≈ 133 Pa.

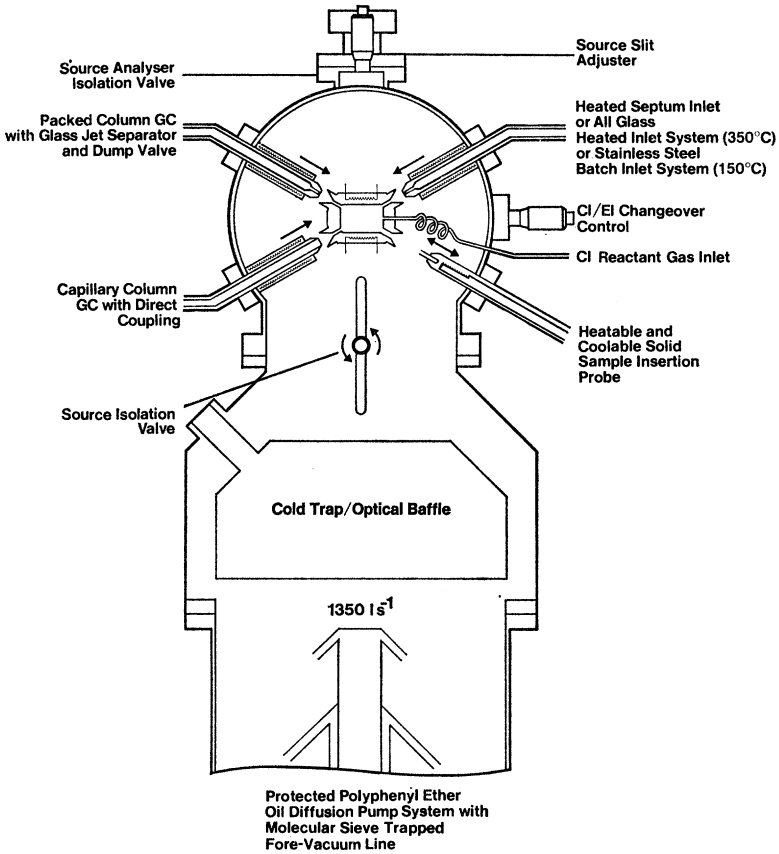


FIGURE 4. Ion source pumping with 15.2 cm bore diffusion pump. Short straight pipework and large source housing provides following pump speeds at ionization chamber: 1000 l s^{-1} for helium, 530 l s^{-1} for methane, 280 l s^{-1} for isobutane.

of *ca.* 0.25 mm) and electrons of energy 100–300 eV are injected to form reactant ions, for example CH_5^+, which may produce intense protonated molecular ion beams giving characteristic c.i. spectra with intense $[M+1]^+$ peaks. Examples are shown in figures 1 and 2. In general, c.i. sensitivity is comparable to or better than that with e.i. Also, the results are more predictable and better understood by chemists than those produced by e.i.

Common reactant gases, in increasing order of 'softness' (see figure 2), are methane, isobutane and ammonia.

Field & Munson (1965) and Field (1969) showed that the methane and isobutane reactant ion intensity varied with pressure as shown in figure 3. However, the optimum reactant gas pressure for maximization of intensity of the sample c.i. spectra depends on individual instrument design.

For effective c.i. work, high speed pumping at the ion chamber is essential. A suitable arrangement is shown in figure 4.

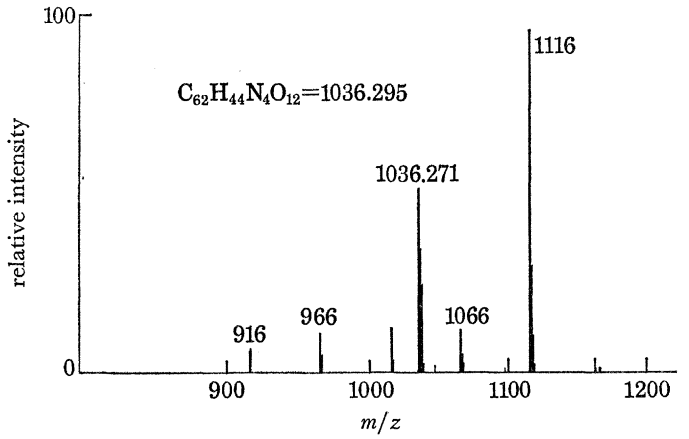


FIGURE 6. Precision mass determination, with a 30 cm double focusing mass spectrometer, of capped porphyrin with the use of data system and perfluoroheptyl-s-triazine as reference (peaks at 916, 966, 1066, 1116). F.d. sample ions suppressed the f.i. reference ions; it was therefore necessary to automate the emitter current supply so that heating only took place while the scan was in the region of 1036.

(*c*) *Negative ions*

The relatively high density of slow moving electrons generated by the c.i. mode of source operation produces copious negative sample ions for many compounds, especially those such as toluene with a large cross section for resonance electron capture (figure 1). Recent work (Hunt 1977; Hunt *et al.* 1977) has emphasized the future importance of negative ion c.i. as a specific method of detection of certain compounds in biological matrices and as an aid to structural elucidation by reaction of sample molecules with judiciously chosen negative reactant ions (Jennings 1978; Hunt 1978).

(*d*) *Field desorption*

Field desorption (f.d.), in which a solid sample is deposited onto a field emitter (figure 5, plate 1) and introduced to the ion source via a vacuum lock, is the most relevant current technique for ionization of large or labile molecules. Facility for rotation of the emitter to align with source electrodes and for three-dimensional positioning, is necessary to optimize

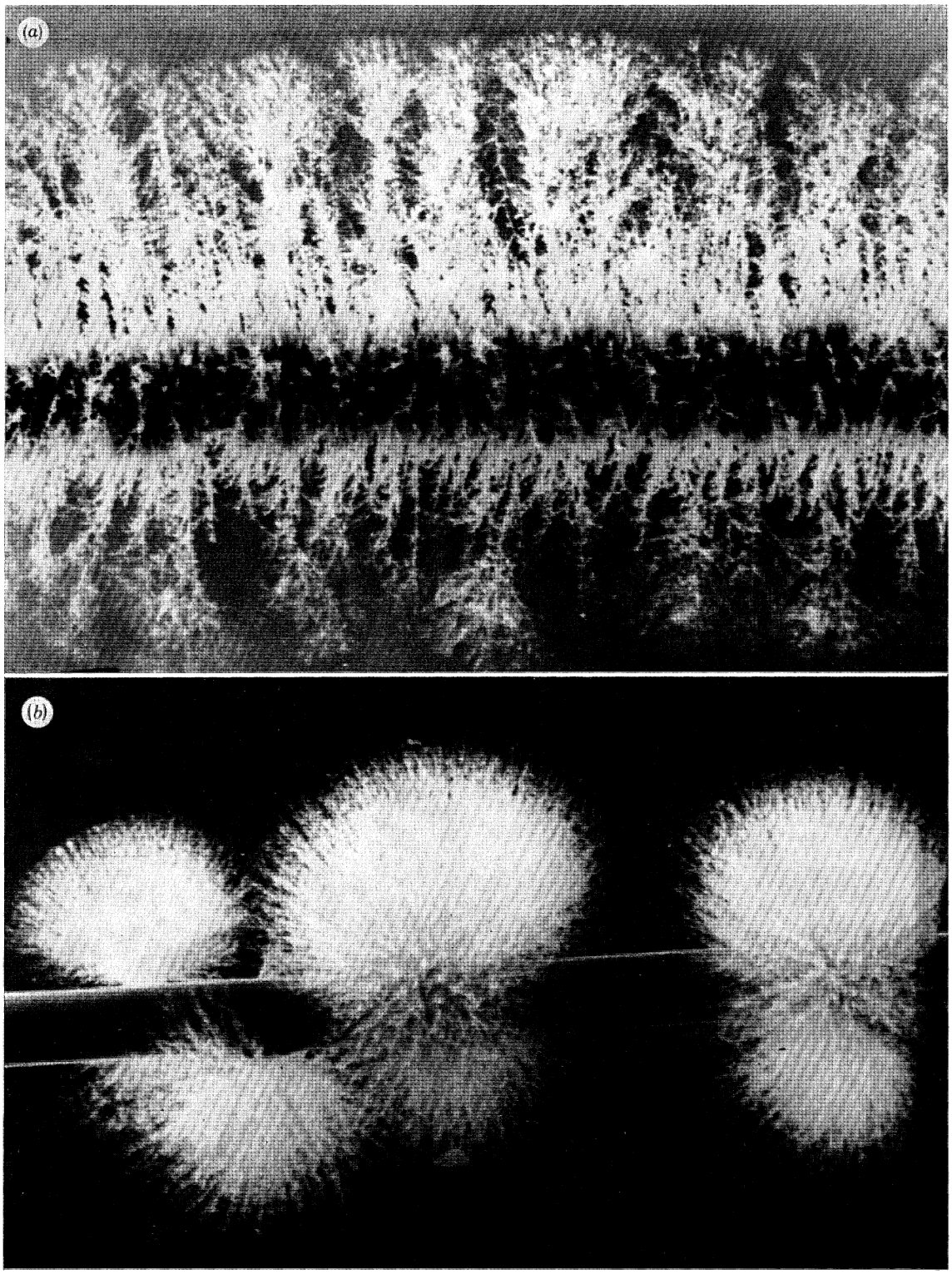


FIGURE 5. Field emitters prepared by D. W. Jopling & A. W. Payne (1978, personal communication) with the use of benzonitrile techniques (Beckey, Hilt & Schulten 1973) on a 10 μm tungsten wire: (*a*) typical good emitter; (*b*) defective emitter.

(*Facing p.* 138)

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

ion beam intensity. The emitter temperature may be regulated to provide constant ion beam intensity (Schulten & Nibbering 1977).

F.d. in many cases produces only molecular ion peaks, so precise mass measurement is often necessary to deduce the molecular formula. Using precision mass measurement by data system and a combination of pulsed f.d. and field ionization (f.i.) with vapour reference sample, we have obtained the results shown in figure 6 and table 1.

TABLE 1. PRECISION F.D. MASS DETERMINATION BY DATA SYSTEM FOR TWO PORPHYRIN SAMPLES

(Results are for computer average of approximately 10 scans per sample from m/z 1200–850 (see figure 6) at 100 s per decade. Resolving power 2000.)

elemental composition	observed mass	error (parts/10^6
$C_{62}H_{44}N_4O_{12}$	1036.286	−8.8
$C_{61}{}^{13}C_1H_{44}N_4O_{12}$	1037.290	−8.7
$C_{63}H_{54}N_6O_5$	974.419	+2.8
$C_{62}{}^{13}C_1H_{54}N_6O_5$	975.413	−5.9

(*e*) *Atmospheric pressure ionization*

An atmospheric pressure ionization (a.p.i.) source with a ^{63}Ni foil β-emitter as initiator has been described by Carroll *et al.* (1974). A suitable quadrupole mass spectrometer arrangement is shown in figure 7 (McKeown & Siegel 1975). With the fast pumping system shown in figure 4 it is feasible to fit an a.p.i. source to a magnetic instrument. The alternative use of a corona discharge as initiator is described by Carroll *et al.* (1975).

In favourable cases (Dzidic *et al.* 1975) an a.p.i. source will detect down to 30 fg (3×10^{-14} g) with the use of single ion monitoring. This compares with a detection level of 200 fg obtained by S. A. Penkett & B. N. Green (1977, personal communication) using conventional g.c.–e.i. mass spectrometry as shown in figure 8.

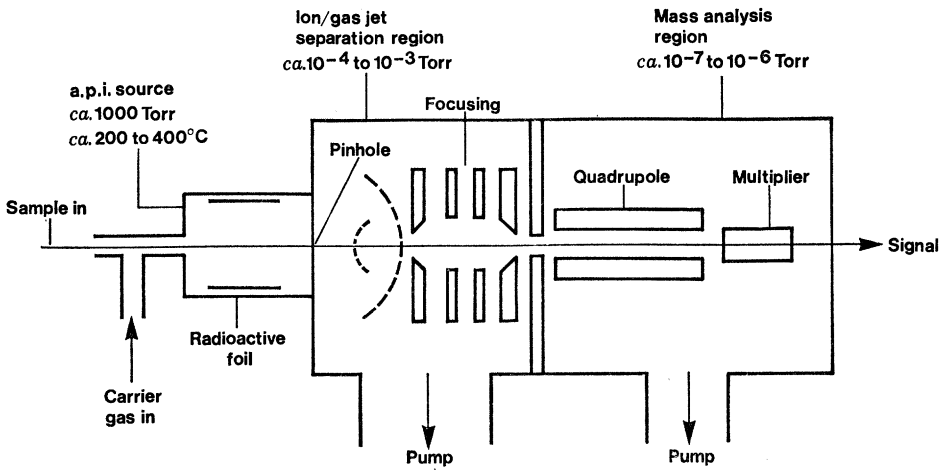


FIGURE 7. Diagram of atmospheric pressure ionization (a.p.i.) mass spectrometer based on McKeown & Siegel (1975).

(*f*) *Ionization of large molecules*

Several groups have reported on new ionization modes which may be suitable for looking at large or labile molecules such as polypeptides. These include work by Stimpson *et al.* (1978)

on the electrohydrodynamic source; by MacFarlane & Torgerson (1976) on a radioactive ^{252}Cf source used in coincidence mode on an 8 m time-of-flight mass spectrometer; by Posthumus *et al.* (1978) on laser induced desorption and by Benninghoven *et al.* (1976) and Benninghoven & Sichtermann (1977) on the use of primary ions in the kiloelectronvolt range.

The latter two techniques may readily be incorporated on some existing mass spectrometers.

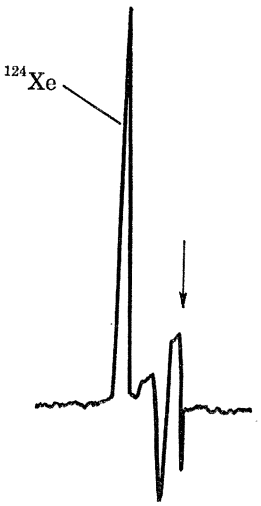


FIGURE 8. ^{124}Xe isotope in air (84×10^{-12} concentration by volume) is a useful measure of sensitivity at levels around 1 part/10^{12}. This example, taken by injection of 20 ml of air into a routine g.c.–m.s. system (e.i. mode), showed a detection limit of 2 parts/10^{12} (20×10^{-14} g). Point of injection is arrowed.

(*g*) *Pyrolysis mass spectrometry*

In pyrolysis mass spectrometry (see Risby & Yergey 1978), 10 μg or less of sample is introduced by probe through a vacuum lock and pyrolysed close to the electron beam. Spectra are normally taken during and after pyrolysis into a small reservoir by repetitive rapid scans.

The technique has been used for 'fingerprinting' paints and fibres (Hughes *et al.* 1977*a*, *b*, 1978; Saferstein & Manura 1977), an important development in forensic science, and for categorizing large biological molecules such as bacteria (see, for example, Meuzelaar & Kistemaker 1973; Meuzelaar *et al.* 1977; Sellier *et al.* 1976; Irwin & Slack 1976).

(*h*) *High pressure liquid chromatography* (*h.p.l.c.*) – *mass spectrometry*

Recent developments for the difficult problem of interfacing h.p.l.c. to the mass spectrometer (also providing means for rapid routine introduction of solid samples in solution) are (*a*) the endless belt (McFadden *et al.* 1976), (*b*) the direct introduction method described by Baldwin & McLafferty (1973*a*, *b*) and Arpino *et al.* (1974), (*c*) the modified membrane separator described by Jones & Yang (1975) and (*d*) the moving wire method described by Scott *et al.* (1974). An alternative arrangement of the endless belt probe, suitable for magnetic instruments and due to Yorke & Burns (1979), is shown in figure 9.

Horning *et al.* (1974) describe interfacing h.p.l.c. to an a.p.i. mass spectrometer by using preheated carrier gas, an evaporator and a solvent collector. At present these techniques are applicable only to compounds that survive e.i. or c.i. conditions on a conventional direct probe and to liquid chromatography solvent systems that do not contain electrolytes.

(*i*) *Interface with gas chromatography*

For interfacing gas chromatography (g.c.) with the ion source the simplest techniques generally prove to be the most reliable. Thus for most g.c. columns with flow rates of 10–60 ml min^{-1}, a single stage glass jet separator is both efficient and reliable. For the fast developing field of open tubular column g.c.–m.s., direct coupling to the ionization chamber is the simplest and most sensitive method but requires fast ion source pumping (figure 4).

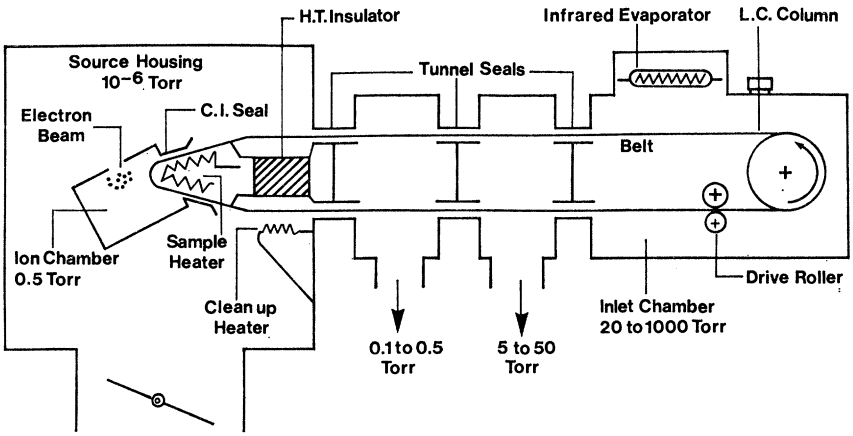


FIGURE 9. Endless belt probe by Yorke & Burns (1979) for introduction of solid samples in solution or high pressure liquid chromatograph.

2. MASS ANALYSER SYSTEMS

The most commonly used mass analysers are the quadrupole, single focusing magnetic (magnet only) and double focusing magnetic (magnet and electric analysers). For pulse ionization techniques the time-of-flight mass spectrometer may be appropriate. Ion cyclotron resonance mass spectrometers have application for the study of ion–molecule reactions at low pressures.

(*a*) *Quadrupole mass analysers*

The quadrupole mass analyser, or more correctly mass filter, is used mainly for routine g.c.–m.s. analysis up to mass 500. Currently the most commonly used rod size is 12.7 cm × 0.64 cm diameter but these show substantial fall-off in sensitivity at higher masses (figure 10), and a larger rod system is preferable.

The quadrupole has particular application in some other specialist fields, for example in pyrolysis studies where rapid scanning or peak switching may be necessary. A combined pyrolysis–quadrupole–data system instrument is now available to record 100 masses in 14 ms.

Quadrupole analysers are also valuable in crossed beam ion molecule reactions where the potential of the secondary ion production region may have to be floated relative to the primary ion potential. This is achieved by operating the quadrupole rod assembly at potentials up to several kilovolts relative to earth. Special advantages of the quadrupoles are their compactness and simple programming by microprocessor or minicomputer.

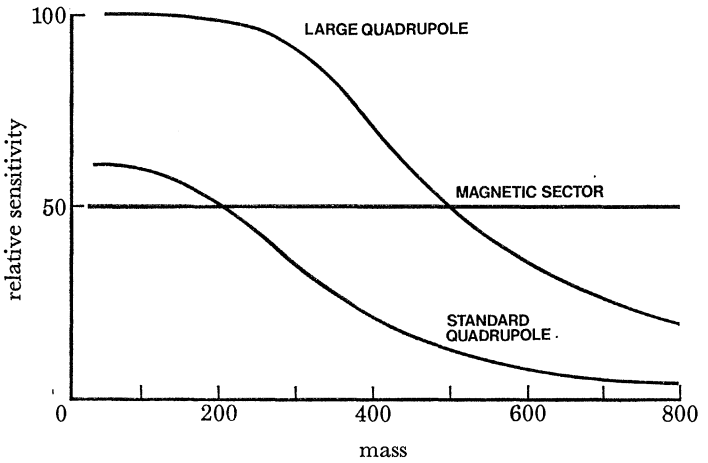


FIGURE 10. Experimental comparison by D. C. Smith (1978, personal communication) of sensitivity *v.* mass for two quadrupoles with that for commercial single focusing magnetic sector spectrometer of 16 cm radius and without *Z*-focusing (standard rods, 12.7 cm long × 0.64 cm diameter; large rods, 23 cm long × 1.3 cm diameter).

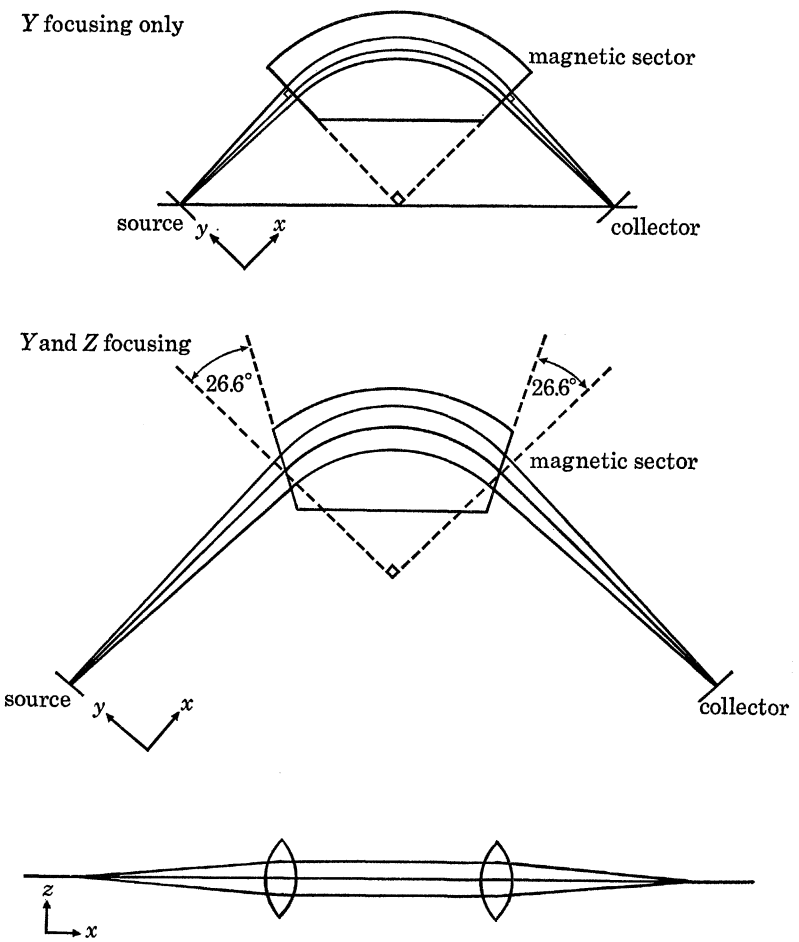


FIGURE 11. Single focusing mass spectrometer geometry for *Z*-focusing (Cross 1951) compared with conventional geometry. Sensitivity gain with *Z*-focus is a factor of between 3 and 4.

(*b*) *Single focusing magnetic analysers*

Single focusing magnetic instruments are increasingly being replaced for organic analysis by double focusing geometries which offer many additional advantages (see §2*c*).

An interesting development of the single focusing analyser has been the commercial realization of the additional sensitivity obtainable by the use of extended geometries as proposed by Cross (1951) which, when used with the same size magnet and at the same resolution as previously, increase sensitivity by a factor of between 3 and 4 (see figure 11).

Both types of magnetic instrument (single and double focusing) provide good quantitative analyses as a result of their low mass discrimination (figure 10) and flat-topped peaks (figure 12). Results on intensity ratio measurements are summarized in table 2, while table 3 shows the achievable reproducibility for multiple ion detection (m.i.d.) on g.c.–m.s. analysis.

TABLE 2. ACHIEVABLE REPRODUCIBILITY OF PEAK HEIGHT RATIOS FOR A C_1–C_4 HYDROCARBON MIXTURE TAKEN ON A 16 CM SINGLE FOCUSING INSTRUMENT

peak ratio	27/15	27/16	27/26	27/28	27/29	27/41	27/42	27/43
mean	2.435	2.101	1.470	0.4951	2.251	1.726	2.703	1.527
standard deviation	0.004	0.003	0.001	0.0007	0.004	0.002	0.004	0.004
coefficient of variation (%)	0.171	0.165	0.079	0.131	0.193	0.144	0.140	0.281

TABLE 3. REPRODUCIBILITY ACHIEVABLE WITH MULTIPLE ION DETECTION IN G.C.–M.S. ANALYSIS OF ISOTOPE PEAKS OF $C_{12}Cl_{10}$ ON 16 CM SINGLE FOCUSING MASS SPECTROMETER FITTED WITH ELECTRON MULTIPLIER DETECTOR

(Figures in parentheses are coefficients of variation.)

quantity injected on g.c.	496/498	500/498
300 pg	0.700 (±0.5%)	0.841 (±0.8%)
20 pg	0.688 (±4.4%)	0.854 (±5.4%)

Scan speeds of magnetic analysers have been increased by the use of laminated magnets, and scan rates of 30 ms per decade change in mass (for example, m/z 500–50) are possible.

A temperature stabilized Hall probe is commonly used to provide mass indication and marking (figure 1), also to generate field-controlled scans to reduce scan cycle times and improve reproducibility for precision mass measurement.

High molecular mass compounds are readily handled by magnetic analysers, and Fales (1966) has shown an e.i. spectrum to m/z 3600. The same compound has been run on a single focusing 30.5 cm radius instrument by ourselves and is shown in figure 13. Compact designs for much higher mass analysis, for example to m/z 30 000, are available if future innovation in ionization techniques should justify such an instrument.

(*c*) *Double focusing analysers*

Double focusing analysers focus for both direction and energy (figure 17) and thus may be used with high energy spread ion sources. They also have low aberration coefficients and so are compatible with very high resolution.

High resolution is a requirement for the separation (figure 14) of ions of the same nominal mass but having different elemental composition, and the effect of double focusing on sensitivity at high resolution is shown in figure 15. For the very highest resolutions (*ca.* 100 000) the

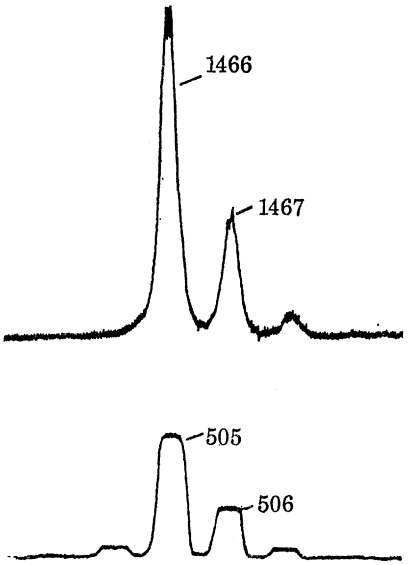


FIGURE 12. Adjustment of collector slit width on magnetic instrument provides either high resolution or flat-topped peaks. Results for a commercial single focusing instrument of 16 cm radius.

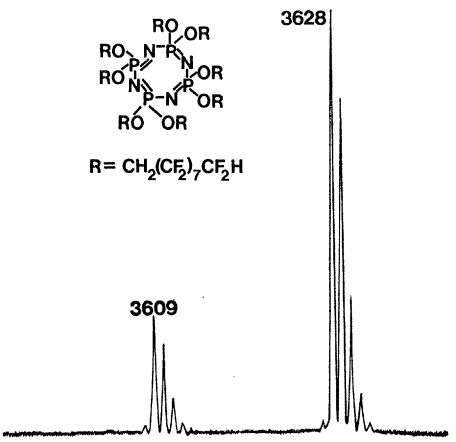


FIGURE 13. Spectra in m/z 3600 region taken on single focusing 30.5 cm radius spectrometer.

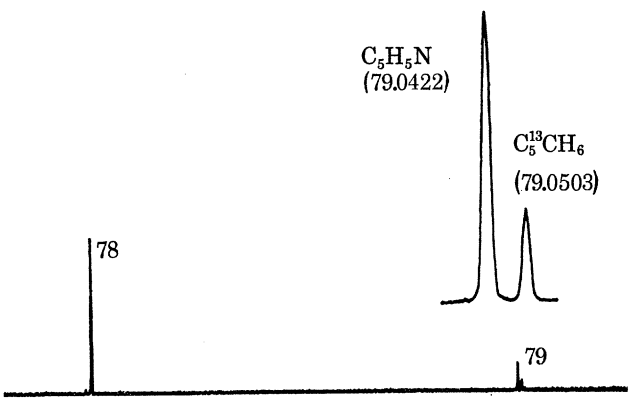


FIGURE 14. Inset shows separation of mass 79 doublet due to benzene–pyridine mixture, taken at resolving power = 20500 on a medium resolution double focusing instrument (12.5 cm radius).

source and collector slits on a 30 cm radius instrument will be only 1 or 2 μm wide, yet to maintain sensitivity the effective length should be *ca.* 1000 μm. There is thus a need for image curvature correction (Coggeshall 1947; Boerboom 1972). Figure 16 illustrates the problem.

Intense ion bombardment, as occurs under c.i., may rapidly damage the source slit edges, thus reducing the maximum obtainable resolving power.

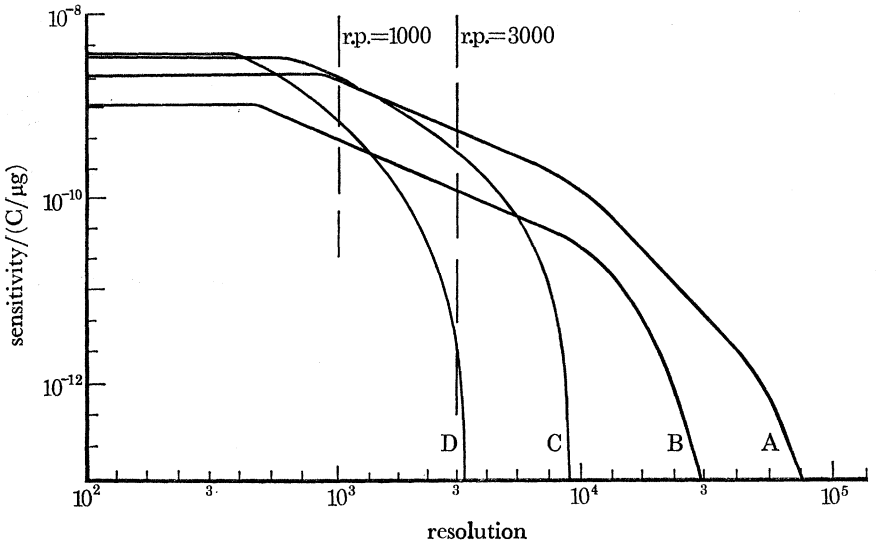


FIGURE 15. Calculated variation of sensitivity with resolving power for four mass spectrometers. A, 30.5 cm double focus; B, 12.5 cm double focus; C, 30.5 cm single focus; D, 16 cm single focus.

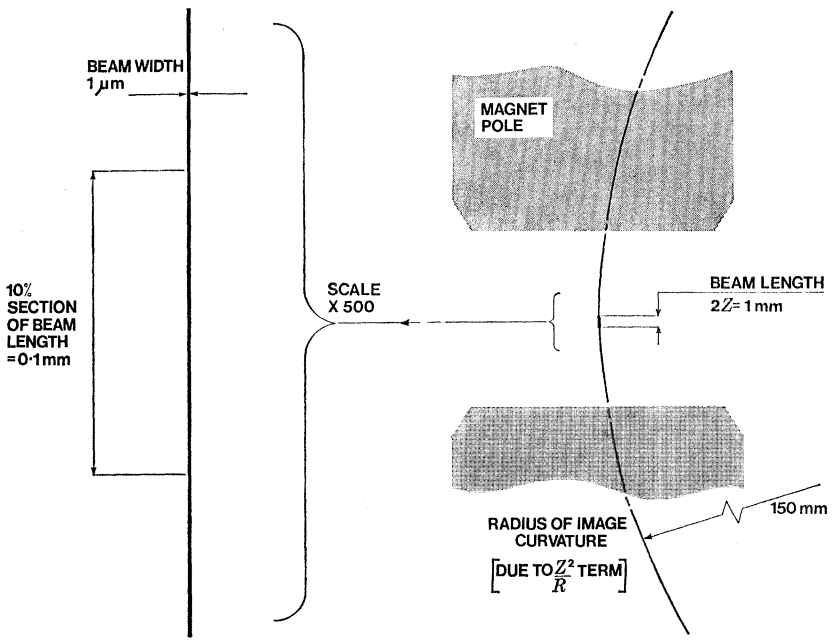


FIGURE 16. For the highest resolving powers (*ca.* 100000) available on 30 cm radius instruments the slit widths and beam widths can only be 1 or 2 μm yet the effective Z length is generally 1000 μm (1 mm). Limiting factors are image curvature Z^2/R due to magnet fringe field and the ability to align beam and collector slit over 1000 μm length.

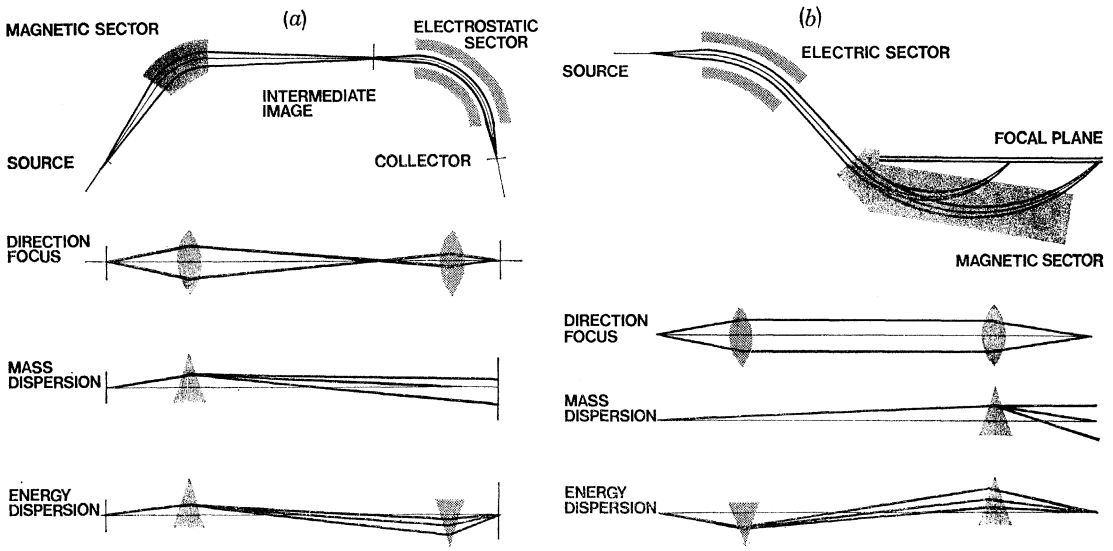


FIGURE 17. (*a*) Modified Nier–Johnson geometry and focusing.
(*b*) Modified Mattauch–Herzog geometry and focusing.

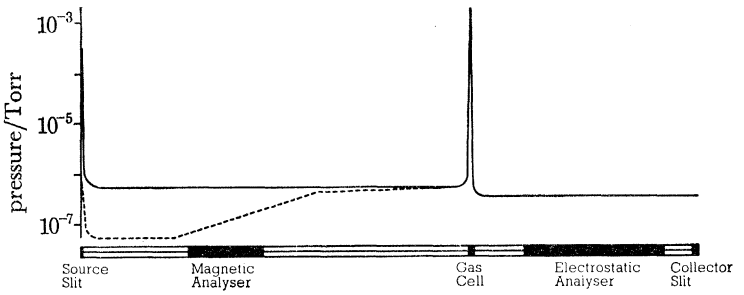


FIGURE 18. Variation of pressure along flight path of mass spectrometer designed for MIKES operation (Morgan *et al.* 1978). ——, C.i.; – – –, e.i.

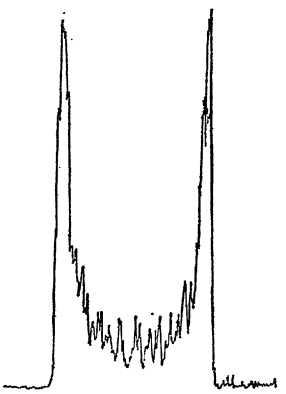


FIGURE 19. MIKES spectral shape for the $C_5H_3^+$ ion from the unimolecular fragmentation of doubly charged benzene ions. Separation of peaks on energy scale is a direct measure of the kinetic energy (2.75 eV) release on dissociation (Jones *et al.* 1972). Depth of trough between peaks is an indication of the degree of collimation of the spectrometer.

The two basic types of double focusing system in common use are derivatives either of the Nier–Johnson geometry (figure 17*a*) or the Mattauch–Herzog geometry (figure 17*b*). Variations on the original designs are given by Hintenberger & König (1957).

The Mattauch–Herzog type is equivalent to two half analysers without the formation of a real intermediate image. This is a limitation in some applications, but the analysers are of smaller angle and there is a focal plane so a flat-plate detector may be used.

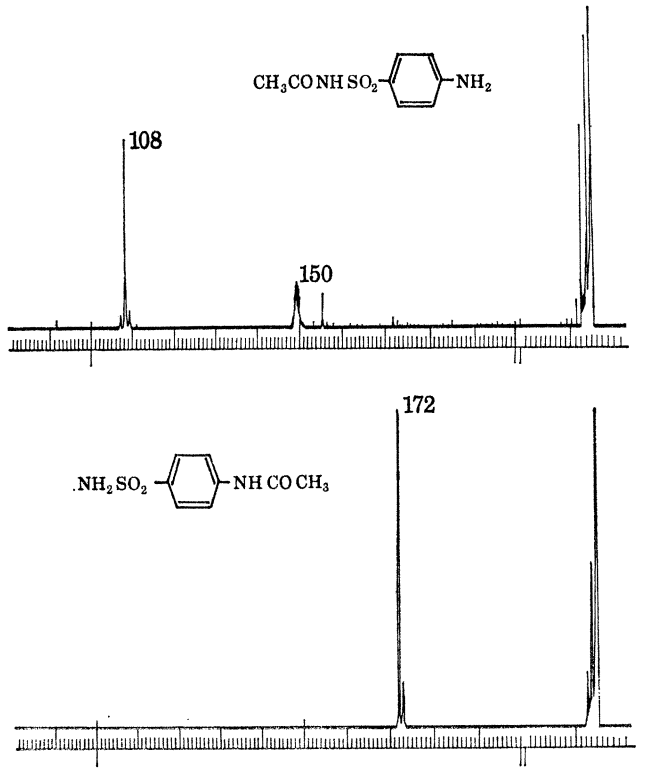


FIGURE 20. Comparison of linked scan spectra for two isomeric compounds for which the e.i. spectra were closely similar.

By the principle of conjugate foci the object and image (source and collector) may be interchanged. Early instruments generally had the electric analyser preceeding the magnet but J. H. Beynon (1974, personal communication) proposed use of a 'reversed' geometry, in which the magnet came first (figure 17*a*), for work with mass analysed ion kinetic energy spectroscopy (MIKES). According to this technique a selected ion (parent or fragment) is studied by tuning the magnetic field to the appropriate value and scanning the electric analyser voltage to obtain the kinetic energy spectrum of fragmentation of the selected ion, occurring either spontaneously in the field-free region between the analysers or induced by collisions in a short gas cell placed at the intermediate focal point (figure 18). An instrument for MIKES is described by Morgan *et al.* (1978). Figure 19 shows a characteristic kinetic energy release peak shape.

Another method of looking at fragmentation spectra (metastable ion spectra) is the linked-scan technique (Boyd & Beynon 1977; Millington & Smith 1977). This technique is applicable to any double focusing geometry and is based on simultaneously scanning both electric and magnetic sectors so that the B/E ratio is maintained constant (figure 20). The fragmentations

recorded are those occurring in the first field-free region, that is between ion source and first analyser. The effects have been enhanced by placing a collision gas cell immediately after the source object slit (Morgan *et al.* 1978).

3. Ion detection and data acquisition systems

(*a*) *Ion detectors*

(i) *Electron multipliers*

The ion detector most commonly used in organic mass spectrometry is the electron multiplier. The positive ions strike a metallic surface with 1–10 keV energy and yield about one secondary electron per incident ion (Van Gorkhom & Glick 1970). These initial electrons are accelerated to about 100 eV to strike a second surface, yielding more electrons. The process is repeate 10–20 times so that at the output there may be as many as 10^8 electrons for one incident ion.

Multipliers are either of the multiple dynode (individual electrodes) type or 'Channeltron' (continuous electrode) type. The dynode type offers better statistics (smaller Poisson probability of zero yield on ion impact on account of the higher incident voltages generally used). The incident voltages are typically 5–10 keV on a magnetic instrument where the positive ion acceleration potential adds to the multiplier voltage. For the quadrupole the ion energy in the analyser is only a few electronvolts, so if a Channeltron is used the incident ion energy is only about 1.5 keV.

The dynode type multiplier also provide wider dynamic range (from single ions per second to 10^{-9} A input current), compared with a maximum input current of about 10^{-11} A for a typical Channeltron.

Electron yield from negative ions is nearly independent of ion energy above 500 eV (Goodings *et al.* 1972) and does not have the same statistical limitation of the Poisson distribution.

Detection of negative ions on a magnetic instrument requires no changes to the detector provided the ion accelerating voltage is at least 500 V greater than the multiplier voltage. For a quadrupole a positive deflector electrode may be used for work with positive ion detection; the same electrode will then attract any negative ions and yield positive ion secondaries, which will be recorded by the multiplier.

Because of the limitations due to ion statistics, the maximum useful gain of a multiplier is generally about 10^5. Higher gain may lead to excessive output electrode currents, affecting both linearity and life of the multiplier.

(ii) *Faraday detectors*

Faraday detectors, in which the ions strike an electrode connected directly to a sensitive amplifier, are used for the most accurate quantitative work with the use of flat-topped peaks (for example in precision isotopic ratio measurement). The electrode is often in the form of a deep bucket to avoid errors due to loss of secondary electrons. Alternatively, or additionally, electric or magnetic fields may be used to prevent the loss of or to suppress these secondary electrons.

The lower level of measurement with a Faraday detector system is generally set by the Johnson noise of the input resistor and bandwidth of the amplifier. Typical peak–peak noise figures achievable are: 1.5×10^{-15} A with a 0–95% rise time of 0.6 s (100 GΩ resistor with

2 pF capacitance); 1.5×10^{-13} A with a 0–95% rise time of 6 ms (1 GΩ resistor with 2 pF capacitance).

The detection sensitivity of the Faraday system, for comparable time constants, is less than that of the electron multiplier, as shown in table 4, but for precisions better than 1% the Faraday detector is preferable.

Amplifier drift may be minimized by use of a chopper. This may be either of the mechanical or electrical (Varactor diode) type.

TABLE 4. MINIMUM CURRENT REQUIREMENTS FOR ELECTRON MULTIPLIER (SCHIFF & EVANS 1936) AND FARADAY DETECTOR SYSTEMS FOR DIFFERENT PRECISIONS OF MEASUREMENT

(Assumptions are 1 s peak width and amplifier time constant of 0.2 s. Reduction of these parameters (for example 10 ms peak width and 2 ms time constant) increases required current levels *pro rata*. Multiplier noise is ignored, i.e. it is assumed that every incident ion produces an equal number of electrons at multiplier output. Faraday figures are based on assumption that Johnson noise is the limiting factor and is standard deviation.)

precision sought	Faraday detector/A	multiplier detector/A	gain in sensitivity
just detectable (in absence of background)	1.4×10^{-15}	1.0×10^{-18}	1400
to 10% (2σ value)	0.7×10^{-14}	1.6×10^{-16}	44
to 1% (2σ value)	0.7×10^{-13}	1.6×10^{-14}	4

(iii) *Photographic plates*

Photographic plates offer the advantage of integrating a complete spectrum over the exposure time, an advantage when using pulsed or variable intensity ion sources. To be suitable for ion detection the plates must have special low-gelatine emulsion. As a consequence they are especially sensitive to mechanical pressure and a slight touch will produce an 'image'. Plates may be received from the manufacturer with such blemishes.

Other limitations are nonlinearity and narrow dynamic range (about 50:1). Sensitivity is comparable with an electron multiplier used in the scan mode, for example 5000 atomic ions of 20 keV in an image of 0.02 mm² will produce a detectable image.

There are electrical alternatives to the photographic plate, for example the channel plate, but the problems of adapting these to routine analytical mass spectrometry have yet to be overcome.

(*b*) *Specific ion detection*

Signal:noise can be improved by use of specific ion detection. The basis is that instead of taking a normal scan, or rather normal repetitive scans if in g.c.–m.s. mode, the spectrometer is set to look only at a few specific ion masses or at ions arising from specific metastable ion transitions. In this way, time wasted, between peaks and in looking at spectral regions where there is no valuable information, is cut out. Signal:noise may consequently be improved by two or three orders of magnitude and compound identification established on smaller amounts.

(i) *Multiple ion detection*

The first (Hammar *et al.* 1968) and simplest form of specific ion detection (generally used in detection of a g.c. effluent) was low resolving power multiple ion detection. This is illustrated in figure 21 and may be used with either quadrupole or magnetic (single or double focusing) instruments.

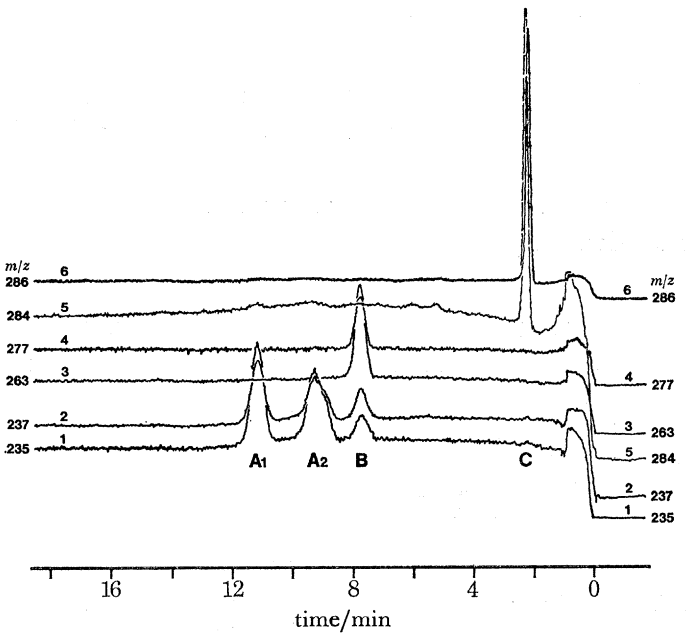


FIGURE 21. Six-channel m.i.d. chromatogram of three pesticides.
Compounds are: A, DDT (two isomers); B, dieldrin; C, HCB. All were at sub-nanogram level.

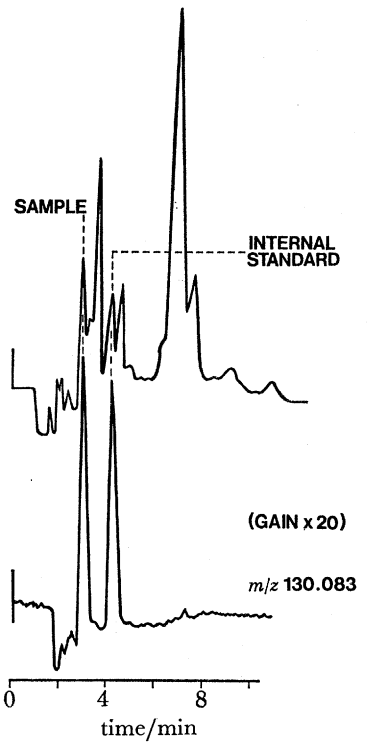


FIGURE 22. Upper trace shows a single ion chromatogram for m/z 130 taken at low resolving power (500). Lower trace shows same single ion chromatogram but taken at high resolving power (5000). Note substantial gain in signal : noise ratio due to elimination of 'chemical noise', even though mass spectrometer sensitivity was reduced by a factor *ca.* 10 to obtain the higher resolution. The sample was a flavour additive and the internal standard was an isomer.

A later development, applicable only to high resolution spectrometers, was high resolving power multiple ion detection. Here, because of the greater specificity at high resolution, it is usually only necessary to pick one mass for each compound being sought. A common case is where compound X, for example a carcinogenic compound in a natural extract, is to be determined and it is required simultaneously to monitor compound Y, ideally an isotopically labelled version of X, as internal standard. Figures 22 and 23 show examples of high resolution selective ion monitoring (Millington 1977).

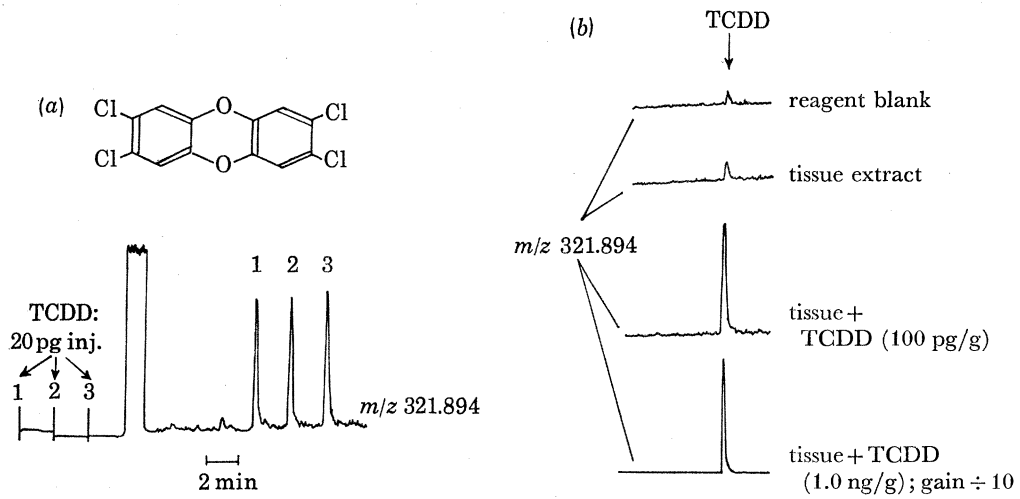


FIGURE 23. Detection of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) by high resolution single ion monitoring with capillary column g.c.–m.s. (*a*) Replicate injection of a 20 pg standard; (*b*) results in purified extracts of human liver tissue.

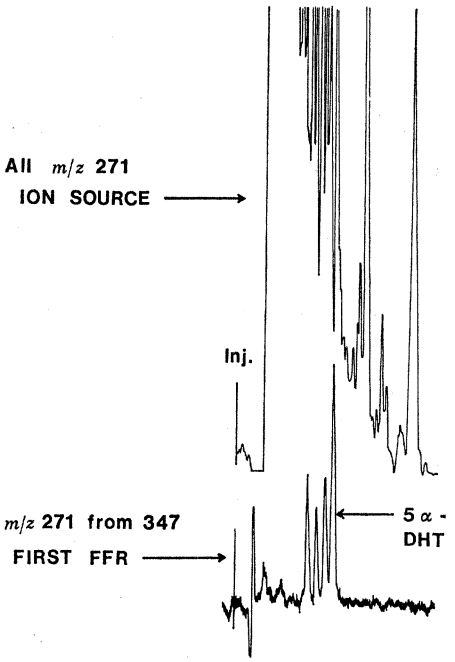


FIGURE 24. Comparison of metastable peak monitoring (via linked scan) with normal single ion detection of identification of 5α-dihydrotestosterone (5α-DHT) and its isomers at sub-nanogram levels in a crude human plasma extract (Gaskell & Millington 1978).

(ii) *Linked scan*

Another form of specific ion detection is obtained by operating a double focusing mass spectrometer in the linked scan (l.s.) mode. The instrument may be set under l.s. (figure 24) to record only fragment ions of mass B arising from metastable ions of mass A that dissociate in the first field-free region. An alternative method for looking at the total metastable ion spectrum was described by Daly *et al.* (1973).

The l.s. specific ion technique, being dependent on metastable peak intensity, is generally less sensitive than high resolving power m.i.d., but for particular samples may offer advantage because (*a*) there is a relatively intense metastable peak or (*b*) there is a limit to the usefulness of high resolving power owing to interfering ion backgrounds. L.s. is up to an order of magnitude more specific than high resolving power m.i.d.

(iii) *Mass analysed ion kinetic energy spectroscopy* (MIKES)

Kondrat & Cooks (1978) have used MIKES as an alternative to g.c.–m.s. for the analysis of natural products and drugs. Samples were introduced via the solid insertion probe and MIKE spectra taken for selected primary ions. Potential advantages of MIKES over conventional g.c.–m.s. are: (1) It is more rapid than g.c.–m.s., (2) it is more sensitive than g.c.–m.s. for cases where the g.c.–m.s. detection level is significantly limited by 'chemical noise' (for example column bleed), (3) it gives more specific identification than g.c.–m.s., and (4) it can be used with f.d. and for samples not suitable for g.c.

MIKES, as with l.s., can be used specifically to detect ions of mass B arising from dissociation of metastable ions of mass A. However, MIKES looks at transitions occurring in the second field-free region as opposed to the first for l.s. Kondrat & Cooks (1978) report a detection sensitivity ($S/N \approx 5$) of 600 pg by using MIKES in this mode.

(*c*) *Data acquisition systems*

(i) *G.c.–m.s. data handling*

The enormity of the task of handling spectral data in most g.c.–m.s. applications necessitates use of a computer acquisition, filing and library search system. For example, in the capillary column chromatogram of a typical natural flavour there are about 100 g.c. peaks in about 50 min. Assuming only one spectrum containing 20 useful peaks were taken per component there would be 2000 peaks to measure and record. In practice, with magnetic scanning, the computer may take a spectrum every 0.8 s and measure all masses from m/z 500 to m/z 25, a total of nearly 2×10^6 peak heights, in 50 min.

All of this peak height information is stored in the computer filing system along with the corresponding chromatogram taken with exactly the same time scale. Any one mass spectrum, say that corresponding to a chromatogram peak at 102.4 s, may be recalled within 2 s for television screen type display either as a normal spectral plot or as a listing of peak intensities. Furthermore, either display may be printed out (hard-copy) within a further few seconds. Additionally, (*a*) The selected spectrum may be searched for in the computer spectral library of typically 30 000 spectra in tens of seconds on the basis of the best match for the eight most intense peaks, and (*b*) The recall, view, print and spectral search on a particular spectrum may proceed while further spectra are being recorded and stored, provided the data system has the so-called 'foreground/background' facility.

(ii) *Precision mass measurement*

Precision mass measurement of a peak to determine the exact mass relative to $^{12}C = 12.0000$ u allows the elemental formula of the ion to be deduced. Mass measurement may be done by peak matching on an oscilloscope (Nier 1957) which takes about 2 min and gives a precision of about 0.3 parts/10^6, provided the reference compound has a suitable peak at the same nominal mass.

In early work, with peak matching, mass measurements were commonly made at high resolution (resolving power 10000 or above) to improve precision and avoid problems of unresolved doublets or interference from reference peaks. However, for much g.c. work, only one pure component is eluted at a time and the probability of a significant doublet is small. By using the data system and a reference compound, such as C_2I_4, with a few, very mass-deficient peaks, advantage can be taken of the much higher sensitivity (figure 15) at lower resolving power (1000). Precisions obtained for such measurement with e.i. and c.i. on a double focusing instrument are given in tables 5 and 6.

TABLE 5. SUMMARY OF PRECISION MASS DETERMINATIONS WITH E.I. OBTAINED BY DATA SYSTEM, FROM CAPILLARY COLUMN G.C.–M.S. AT LOW RESOLUTION WITH THE USE OF A MEDIUM RESOLVING POWER DOUBLE FOCUSING MASS SPECTROMETER AND C_2I_4 AS REFERENCE

(Resolving power = 1000; 2 s scans; sample was a mixture of polycyclic aromatic hydrocarbons.)

g.c. peak	elemental composition	observed mass	error (parts/10^6)
A	$C_{14}H_{10}$	178.0784	+1.7
B	$C_{16}H_{10}$	202.0782	+0.5
C	$C_{18}H_{14}$	230.1084	−4.3
D	$C_{18}H_{12}$	228.0932	−2.6
E	$C_{20}H_{12}$	252.0956	+7.1

TABLE 6. SUMMARY OF PRECISION MASS DETERMINATIONS WITH C.I. OBTAINED BY DATA SYSTEM, FOR CAPILLARY COLUMN G.C.–M.S. AT LOW RESOLUTION WITH THE USE OF A MEDIUM RESOLVING POWER DOUBLE FOCUSING MASS SPECTROMETER AND C_2I_4 AS REFERENCE

(Resolving power = 1000; 2 s scans; sample was a mixture of protonated fatty esters.)

g.c. peak	elemental composition	observed mass	error (parts/10^6)
A	$C_9H_{19}O_2$	159.1376	−5.8
B	$C_{11}H_{23}O_2$	187.1688	−5.2
C	$C_{13}H_{27}O_2$	215.2004	−3.0
D	$C_{15}H_{31}O_2$	243.2295	−11.9
E	$C_{16}H_{33}O_2$	257.2454	−10.4

TABLE 7. OPERATION OF DATA SYSTEM

(Data system was given mass 386.3550 (cholesterol) and asked to search for all possible elemental compositions for various uncertainty windows in mass. Program allowed for unlimited number of H atoms, up to 29 C atoms and up to 5 N or O atoms.)

uncertainty in mass							
parts/10^6	160	80	40	20	10	5	2.5
$10^{-3} m_u$	6.2	3.1	1.6	0.8	0.4	0.2	0.1
no. of possibilities	35	18	10	5	3	2	1

A common question is what mass measurement precision is necessary to identify uniquely an elemental composition. A comprehensive answer is impractical here but, as an example, M. J. Wallington (1978, personal communication) considers the possibilities when trying to identify the elemental composition of an ion at mass 386.3550 with any number of H atoms, up to 29 C atoms and up to 5 N or O atoms as possible elemental constituents. The number of possible compositions obtained for different uncertainties is shown in table 7.

(iii) *Other applications of data systems*

Other applications of data systems in organic mass spectrometry include: (1) enhancement of chromatogram resolution through use of the underlying mass spectral data, as proposed by Biller & Biemann (1974); (2) isometric or multicolour displays of mass fragmentograms to provide a 'third dimension' of information; (3) control of key mass spectrometric functions such as setting up the parameters for multiple ion detection (mass, sensitivity and zero offset programmes); (4) accurate quantitative measurements with the use of the new wide dynamic range (6×10^6:1) signal measurement devices; (5) time averaging of data to improve signal: noise and precision (for example in kinetic energy measurements (Morgan *et al.* 1978) or metastable ion spectra from f.d.). A review of computer applications in mass spectrometry was recently published by McLafferty & Venkataraghavan (1978).

Conclusions

In g.c.–m.s. the greater sensitivity at higher mass and the use of flat-topped peaks for quantitative measurements, combined with the advent of the new fast scan magnets, give advantages to the single focusing magnetic instrument over the quadrupole. However, the full advantages of magnetic instruments, such as precision mass measurements on fast g.c. scans and the specific ion detection techniques which can give both greatly improved signal:noise and more nearly unique identification, are only realized with a double focusing geometry.

The importance of the computer and microprocessor, both in control and data acquisition, will be more evident in future generations of mass spectrometer. As the newer and more powerful analytical techniques of double focusing mass spectrometers become simpler to use, these instruments are likely to be adopted increasingly in routine laboratories.

The authors thank their colleagues at VG-Micromass, and especially Dr David Yorke and Dr Patrick Turner for help in acquiring data for this paper.

References (Craig *et al.*)

Arpino, P. J., Dawkins, B. G. & McLafferty, F. W. 1974 *J. chromatogr. Sci.* **12**, 574–578.
Baldwin, M. A. & McLafferty, F. W. 1973*a* *Org. Mass. Spectrom.* **7**, 1111–1112.
Baldwin, M. A. & McLafferty, F. W. 1973*b* *Org. Mass Spectrom.* **7**, 1353–1354.
Beckey, H. D., Hilt, E. & Schulten, H. R. 1973 *J. Phys.* E **6**, 1043–1044.
Benninghoven, A., Jaspers, D. & Sichtermann, W. 1976 *Appl. Phys.* **11**, 35–39.
Benninghoven, A. & Sichtermann, W. 1977 *Org. Mass Spectrom.* **12**, 595–597.
Biller, J. E. & Biemann, K. 1974 In *Proc. 22nd Ann. Conf. Mass Spectrom. and Allied Topics* (*ASMS*), pp. 430–432.
Boerboom, A. J. H. 1972 *Int. J. Mass Spectrom. Ion Phys.* **8**, 475–492.
Boyd, R. K. & Beynon, J. H. 1977 *Org. Mass Spectrom.* **12**, 163–165.
Carrol, D. I., Dzidic, I., Stillwell, R. N. & Horning, E. C. 1974 *Analyt. Chem.* **46**, 706–710.
Carrol, D. I., Dzidic, I., Stillwell, R. N., Haegele, K. D. & Horning, E. C. 1975 *Analyt. Chem.* **47**, 2369–2373.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Coggeshall, N. D. 1947 *J. appl. Phys.* **18**, 855–861.
Cross, W. G. 1951 *Rev. scient. Instrum.* **22**, 717–722.
Daly, N. R., McCormick, A., Powell, R. E. & Heys, R. 1973 *Int. J. Mass Spectrom. Ion Phys.* **11**, 255–276.
Dzidic, I., Carroll, D. I., Stillwell, R. N. & Horning, E. C. 1975 *Analyt. Chem.* **47**, 1308–1312.
Fales, H. M. 1966 *Analyt. Chem.* **38**, 1058–1059.
Field, F. H. & Munson, M. S. B. 1965 *J. Am. chem. Soc.* **87**, 3289–3294.
Field, F. H. 1969 *J. Am. chem. Soc.* **91**, 2827–2839.
Gaskell, S. J. & Millington, D. S. 1978 *Biomed. Mass Spectrom.* **5**, 557–558.
Goodings, J. M., Jones, J. M. & Parkes, D. A. 1972 *Int. J. Mass Spectrom. Ion Phys.* **9**, 417–420.
Gross, M. L. (ed.) 1978 *High performance mass spectrometry: chemical applications* (*A.C.S. Symposium Series*, no. 70). Washington, D.C.: American Chemical Society.
Hammar, G. C., Holmstedt, B. & Rhyage, R. 1968 *Analyt. Biochem.* **25**, 532–547.
Hintenberger, H. & König, L. A. 1957 *Z. Naturforsch.* A **12**, 443–452.
Horning, E. C., Carroll, D. I., Dzidic, I., Haegele, K. D., Horning, M. G. & Stillwell, R. N. 1974 *J. Chromatogr.* **99**, 13–21.
Hughes, J. C., Wheals, B. B. & Whitehouse, M. J. 1977*a* *Analyst* **102**, 143–144.
Hughes, J. C., Wheals, B. B. & Whitehouse, M. J. 1977*b* *Forensic Sci.* **10**, 217–228.
Hughes, J. C., Wheals, B. B. & Whitehouse, M. J. 1978 *Analyst* **103**, 482–491.
Hunt, D. F. 1977 *Prog. analyt. Chem.* **6**, 359–376.
Hunt, D. F., Stafford, G. C., Shabanowitz, J. & Crow, F. W. 1977 *Analyt. Chem.* **49**, 1884–1893.
Hunt, D. F. 1978 In Gross (ed.) 1978, pp. 150–178.
Irwin, W. J. & Slack, J. A. 1976 *Analytical Pyrolysis* (*Proc. 3rd Int. Symposium*), pp. 107–116.
Jennings, K. R. 1978 In Gross (ed.) 1978, pp. 179–187.
Jones, E. G., Beynon, J. H. & Cooks, R. G. 1972 *J. chem. Phys.* **57**, 2652–2658.
Jones, P. R. & Yang, S. K. 1975 *Analyt. Chem.* **47**, 1000–1003.
Kondrat, R. W. & Cooks, R. G. 1978 *Analyt. Chem.* **50**, 81a–86a.
McFadden, W. H., Schwartz, H. L. & Evans, S. 1976 *J. Chromatogr.* **122**, 389–396.
MacFarlane, R. D. & Torgerson, D. F. 1976 *Int. J. Mass Spectrom. Ion Phys.* **21**, 81–92.
McKeown, M. & Siegel, N. W. 1975 *Am. Lab.* **7**, 89–99.
McLafferty, F. W. & Venkataraghavan, R. 1978 In Gross (ed.) 1978, pp. 310–324.
Meuzelaar, H. L. C. & Kistemaker, P. G. 1973 *Analyt. Chem.* **45**, 587–590.
Meuzelaar, H. L. C., Kistemaker, P. G., Eshuis, W. & Boerboom, H. A. J. 1977 In *Advances in mass spectrometry*, vol. **7B**, pp. 1452–1456. London: Heyden & Son.
Millington, D. S. & Smith, J. 1977 *Org. Mass Spectrom.* **12**, 264–265.
Millington, D. S. 1977 *J. Reprod. Fert.* **51**, 303–308.
Morgan, R. P., Beynon, J. H., Bateman, R. H. & Green, B. N. 1978 *Int. J. Mass Spectrom. Ion Phys.* **28**, 171–191.
Nier, A. O. 1957 In *Nuclear masses and their determination* (ed. H. Hintenberger), pp. 185–193. Oxford: Pergamon Press.
Posthumus, M. A., Kistemaker, P. G., Meuzelaar, H. L. C. & Ten Noever de Brauw, M. C. 1978 *Analyt. Chem.* **50**, 985–991.
Risby, T. H. & Yergey, A. L. 1978 *Analyt. Chem.* **50**, 326–332.
Saferstein, R. & Manura, J. J. 1977 *J. Forensic Sci.* **22**, 748–756.
Schiff, L. I. & Evans, R. D. 1936 *Rev. Scient. Instrum.* **7**, 456–462.
Scott, R. P. W., Scott, C. G., Monroe, M. & Hess, J. 1974 *J. Chromatogr.* **99**, 395–405.
Sellier, N., Jones, C. E. R. & Guiuchon, G. 1976 In *Analytical pyrolysis* (*Proc. 3rd Int. Symposium*), pp. 309–318.
Schulten, H. R. & Nibbering, N. M. M. 1977 *Biomed. Mass Spectrom.* **4**, 55–61.
Stimpson, B. P., Simons, D. S. & Evans, C. A. 1978 *J. phys. Chem.* **82**, 660–670.
Van Gorkhom, M. & Glick, R. E. 1970 *Int. J. Mass Spectrom. Ion Phys.* **4**, 203–218.
Yorke, D. A., Burns, P., Green, B. N. & Millington, D. S. 1979 In *Proceedings of the 27th Annual Conference on Mass Spectrometry and Allied Topics*, Seattle. (In the press.)

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

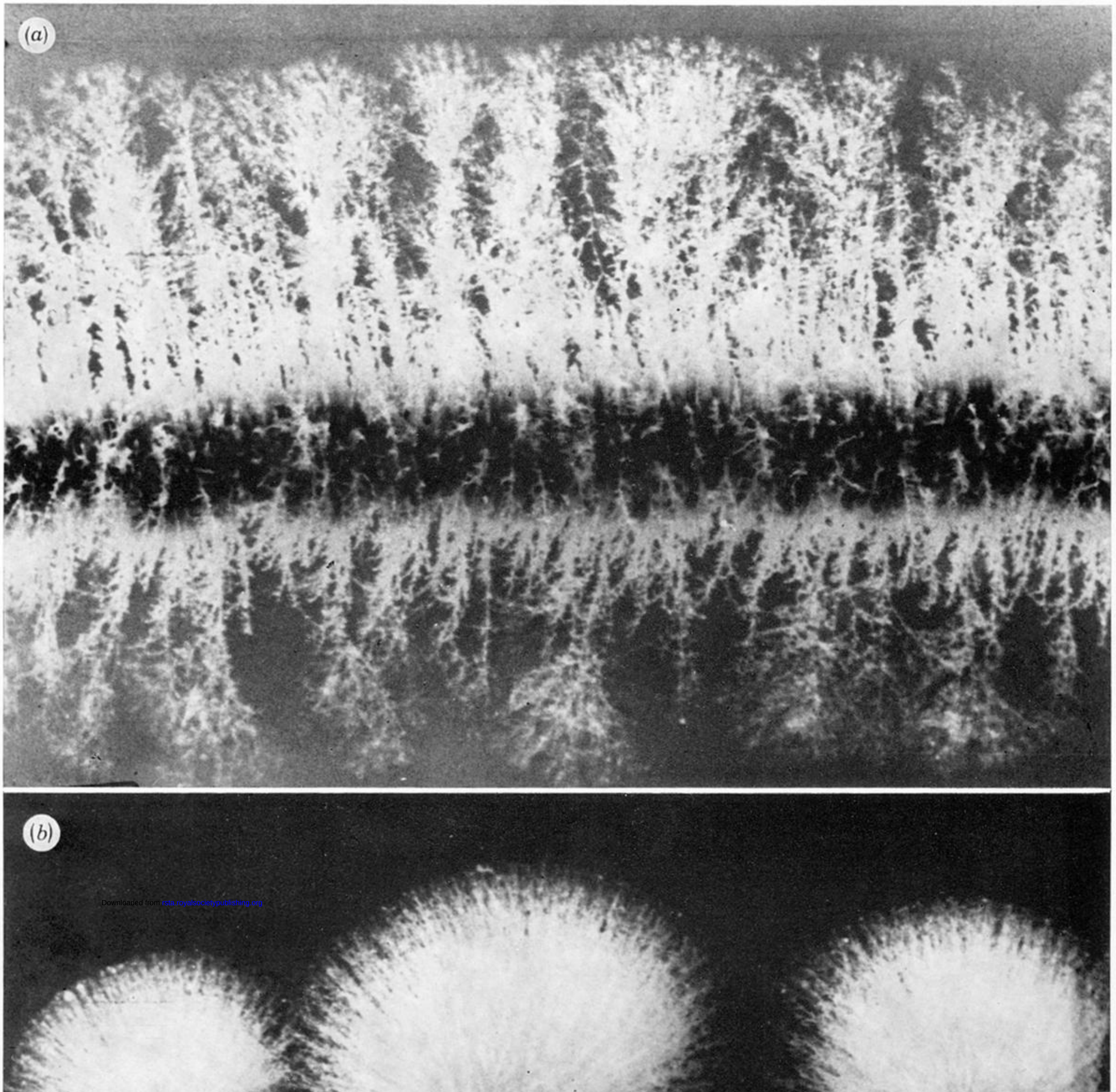
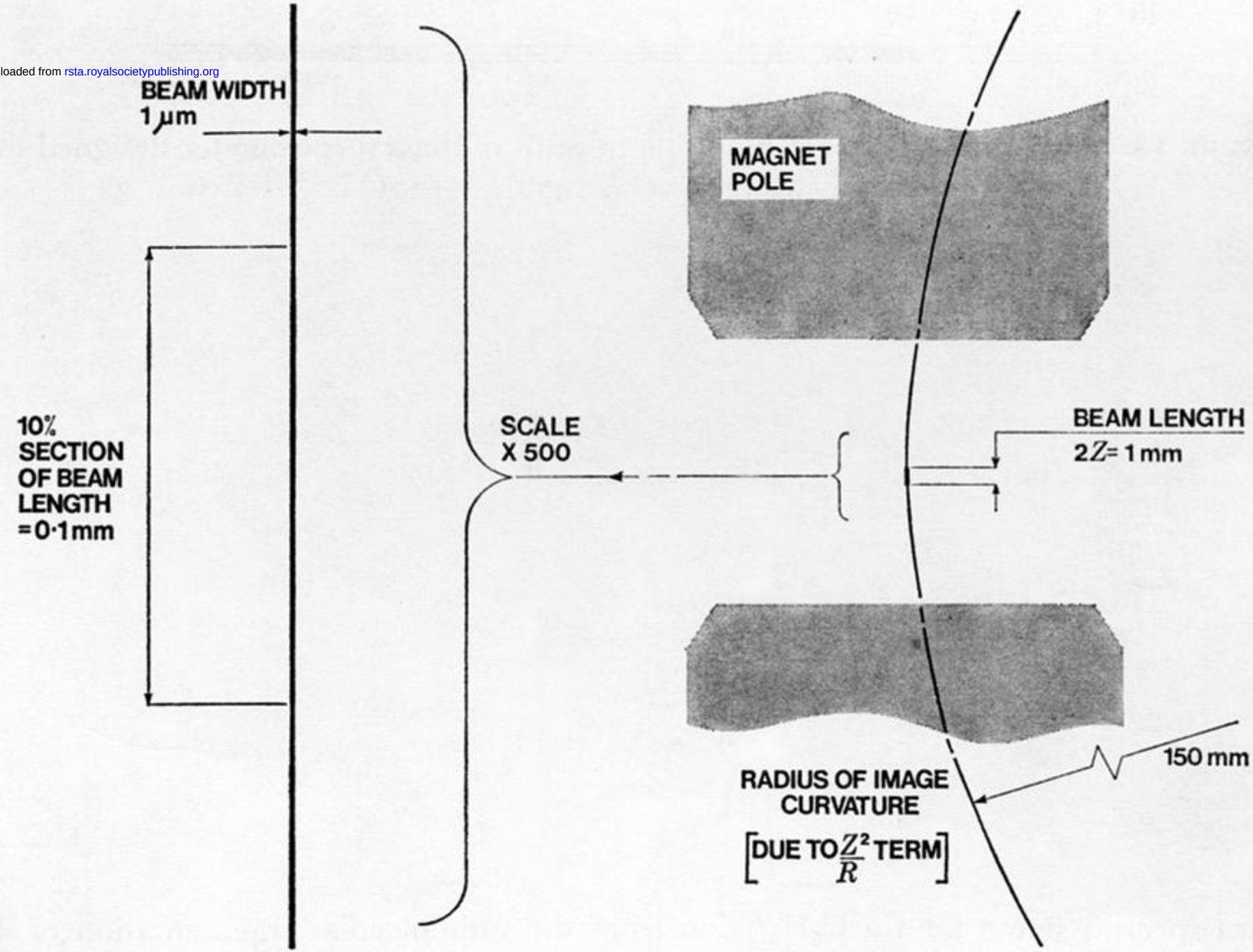


FIGURE 5. Field emitters prepared by D. W. Jopling & A. W. Payne (1978, personal communication) with the use of benzonitrile techniques (Beckey, Hilt & Schulten 1973) on a 10 μm tungsten wire: (*a*) typical good emitter; (*b*) defective emitter.



GURE 16. For the highest resolving powers (*ca.* 100 000) available on 30 cm radius instruments the slit widths and beam widths can only be 1 or 2 μm yet the effective Z length is generally 1000 μm (1 mm). Limiting factors are image curvature Z^2/R due to magnet fringe field and the ability to align beam and collector slit over 1000 μm length.

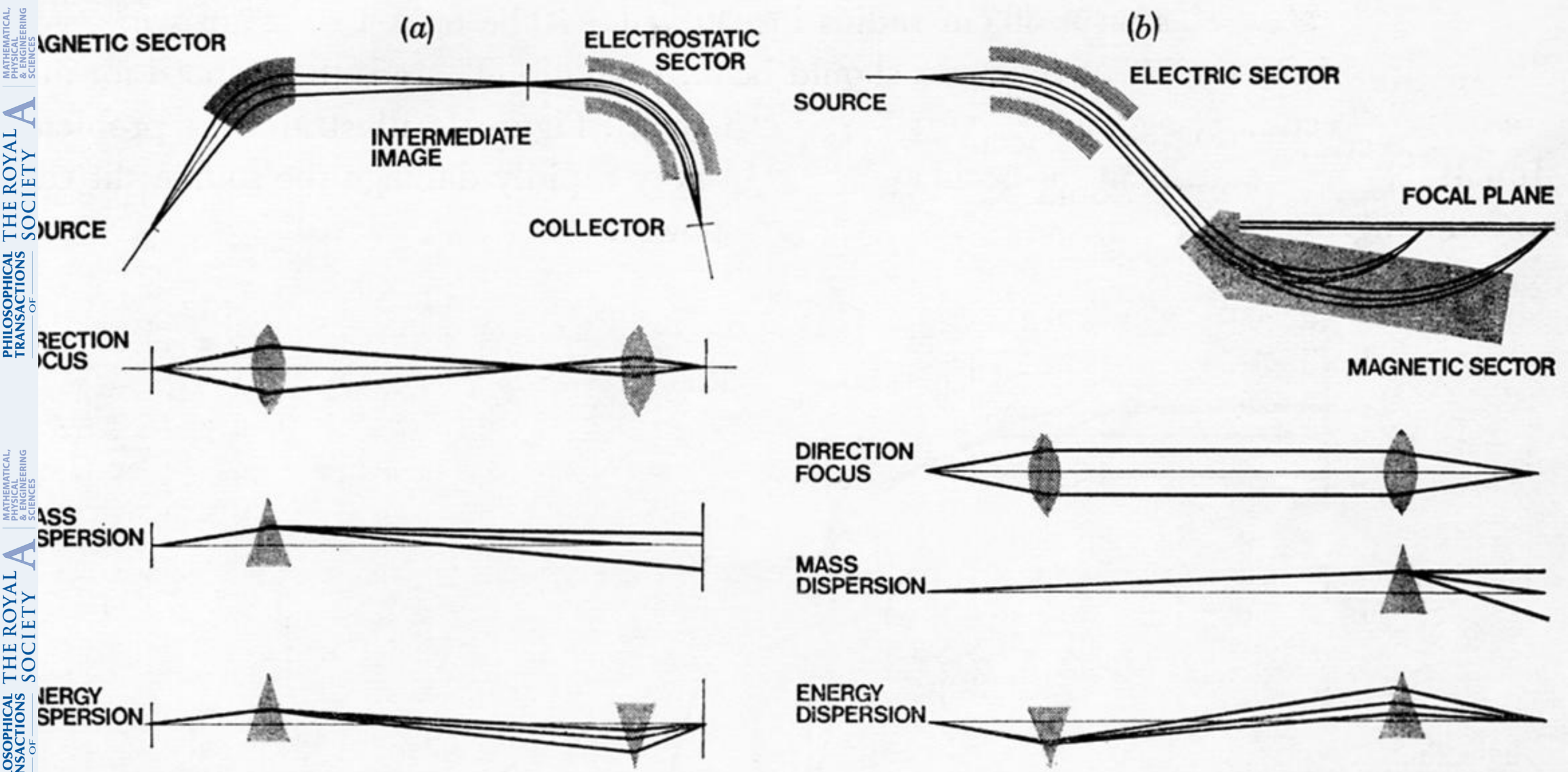


FIGURE 17. (*a*) Modified Nier–Johnson geometry and focusing.
(*b*) Modified Mattauch–Herzog geometry and focusing.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES