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Magic matrices for ionization in mass spectrometry

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ABSTRACT

The initial discovery that a heated inlet tube of a mass spectrometer is an ionization source producing ions from volatile, nonvolatile, small, and large molecules with charge states similar to electrospray ionization has been advanced to ionization requiring only the vacuum inherent with a mass spectrometer and a suitable matrix. This spontaneous ionization method was first applicable with the matrix 3-nitrobenzonitrile. Here we report that over 40 compounds have now been discovered that spontaneously convert molecules to gas-phase ions when exposed to sub-atmospheric pressure, some with remarkable sensitivity (10 fmol of protein insulin). The commonality of all matrices is the ability to sublime, preferably near room temperature, through exposure to vacuum, and the ability to create charge separation under these conditions. The effect of vacuum, airflow, temperature (−80 to +150 °C) and pH (1–9) on the effectiveness of these newly discovered matrices to ionize peptides and proteins is presented. Compounds with and without acidic hydrogen atoms act as matrices and ionize specific compound classes. The new matrices extend applications from peptides, proteins and drugs to compound classes without basic functionality such as lipids and synthetic polymers in the negative and positive modes. Mass resolution and ion mobility spectrometry aspects are also discussed.

1. Introduction

During the 50 years covered by this special issue, great strides were made in learning how to extend mass spectrometry (**MS**) to high-mass compounds. In these efforts, the use of solvents or small-molecule matrices were the most important factors for success. Fast atom bombardment by Barber and coworkers [1] introduced liquid matrices, and matrix-assisted laser desorption/ionization (MALDI) by Karas and Hillenkamp [2] introduced small molecule solid matrices for use in MS. In any method capable of ionizing large molecules such as proteins, either high voltage as in electrospray ionization (ESI) [3] or high energy input [4,5] were employed. Recently, we introduced a method in which only the energy provided by the vacuum is necessary to spontaneously convert small or large molecules into gas-phase ions upon exposure of a matrix containing analyte to the vacuum of the mass spectrometer [6–9].

This discovery originated from a systematic study that led to the discovery of laserspray ionization (LSI), a method in which laser ablation of a common MALDI matrix, 2,5-dihydroxybenzoic acid (2,5-DHB), at atmospheric pressure produced multiply charged ions from peptides and proteins [10,11]. It was initially assumed that the laser was essential for ionization, however, the discovery that the laser is only a means of ablating matrix–analyte into the heated inlet tube of the mass spectrometer where ionization is initiated led to the term matrix assisted ionization *inlet* (MAII) [12,13]. In MAII, matrix–analyte sample on a substrate can be dislodged by tapping against the inlet aperture in a fashion that particles enter the heated inlet tube linking atmospheric pressure and the vacuum of the mass analyzer producing ions from incorporated analyte. A solution–analyte mixture can substitute for the solid matrix–analyte and similarly produce analyte ions in the inlet [14,15]. In this solvent assisted ionization *inlet* (SAII) method, as with LSII and MAII, the heated inlet is the ion source. These *inlet* ionization methods produce charge states nearly identical to ESI. Because the inlet tube was heated in these experiments [16], it was postulated that charged particles/droplets are produced by a thermal process and upon desolvation produce the observed bare ions [17,18]. Types of gases, higher initial

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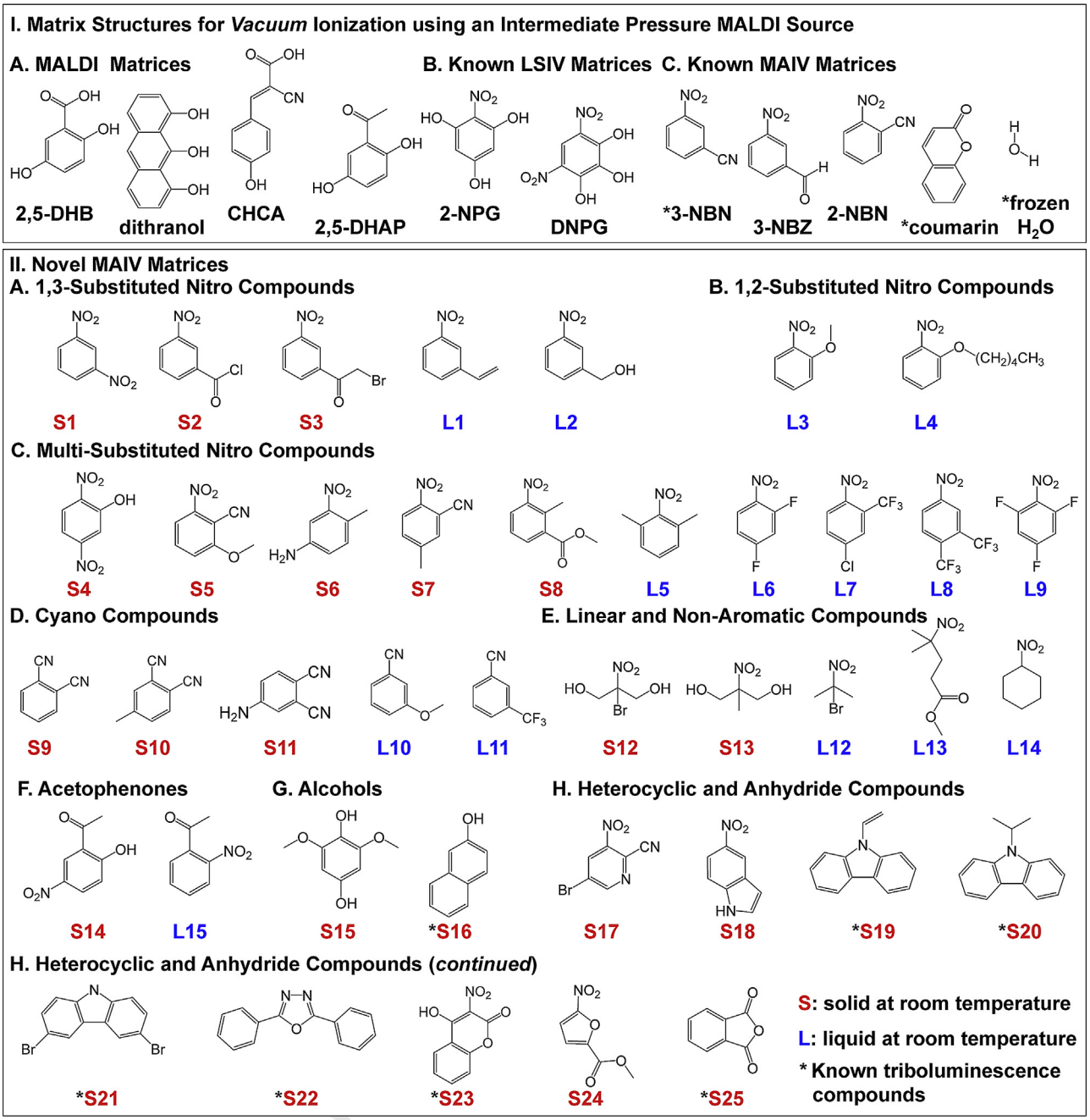
pressure, downstream pressure, rf voltages, and collision with surfaces have been parameters shown to enhance analyte ion formation [13,16,18–20].

The finding that similar charge states are produced by laser ablation in a vacuum MALDI source using select matrix compounds in the absence of conductive heat led to the terminology of laserspray ionization *vacuum* (LSIV) [19]. In LSIV a heated inlet tube is not required. It was postulated that laser ablation of the matrix provided the thermal energy necessary to produce the charged droplets. Analyte ions are observed so long as collisions with gas-phase molecules or surfaces provide desolvation of the matrix. Without a source of energy other than the laser,



Scheme 1. (I) Structures of known matrix compounds for (A) MALDI, (B) LSIV, and (C) MAIV. (II) Structures of novel MAIV matrix compounds arranged by: (A) 1,3-substituted nitro compounds: 1,2-dinitrobenzene (S1), 3-nitrobenzoyl chloride (S2), 2-bromo-3′-nitroacetophenone (S3), 3-nitrostyrene (L1), 3-nitrobenzyl alcohol (L2); (B) 1,2-substituted nitro compounds: 2-nitroanisole (L3), 2-nitrphenyl pentyl ether (L4); (C) multi-substituted nitro compounds: 2,5-dinitrophenol (S4), 6-nitro-*o*-anisonitrile (S5), 3-methyl-4-nitroaniline (S6), 5-methyl-2-nitrobenzonitrile (S7), methyl-2-methyl-3-nitrobenzoate (S8), 1,3-dimethyl-2-nitrobenzene (L5), 2,4-difluoronitrobenzene (L6), 4-chloro-1-nitro-2-(trifluoromethyl) benzene (L7), 3,4-bis(trifluoromethyl) nitrobenzene (L8), 3,4,5-trifluoronitrobenzene (L9); (D) cyano compounds: phthalonitrile (S9), 4-methylphthalonitrile (S10), 4-aminophthalonitrile (S11), 3-methoxybenzonitrile (L10), 3-(trifluoromethyl)-benzonitrile (L11); (E) linear and non-aromatic compounds: 2-bromo-2-nitro-1,3-propanediol (S12), 2-methyl-2-nitro-1,3-propanediol (S13), 2-bromo-2-nitropropane (L12), methyl-4-methyl-4-nitropentanoate (L13), nitrocyclohexane (L14); (F) acetophenones: 2′-hydroxy-5′-nitroacetophenone (S14), 2′-nitroacetophenone (L15); (G) alcohols: 1,4-dihydroxy-2,6-dimethoxybenzene (S15), 2-naphthol (*S16); (H) heterocyclic and anhydride compounds: 5-bromo-3-nitropyridine-2-carbonitrile (S17), 5-nitroindole (S18), 9-vinyl carbazole (*S19), 9-isopropyl-9H-carbazole (*S20), 3,6-dibromocarbazole (*S21), 2,5-diphenyl-1,3,4-oxadiazole (*S22), 4-hydroxy-3-nitrocoumarin (*S23), methyl-5-methyl-2-nitrobenzoate (S24), phthalic anhydride (*S25). Matrices are numbered and designated by physical state at room temperature (solid, red = S and liquid, blue = L). *Indicates the matrix compound is reported to triboluminesce (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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