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Liquid Matrices in MALDI-MS

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1. Introduction

Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) (Karas, M. & Hillenkamp, F., 1988; Tanaka, K. et al., 1988), in addition to elecrospray ionization mass spectrometry (ESI-MS) (Fenn J. B. et al., 1989) have developed into practical analytical tools in proteomics and glycomics as both have higher throughput and sensitivity than previous mass spectrometric techniques in this area. In MALDI-MS, one benefit is the detection of mainly singly charged ions, whereas ions are detected in a multiply charged state in ESI-MS. This benefit enables easy interpretation of the mass spectra acquired and thus MALDI-MS finds particular use in mixture analysis. On the other hand, a weak point of MALDI is difficulty in selecting appropriate matrices and preparation methods for each sample. Therefore development of an analyte-specific, polarity independent matrix is still required.

In MALDI the matrix is essential for ionizing the analytes that are then detected as ion peaks in the mass spectrometer. Thus the general structure of matrices has a benzene ring for absorbing N_2 laser energy and hydroxyl groups to have high affinity with analytes such as peptides, proteins and carbohydrates. In addition, the matrices have some functional groups to work as a proton donor and/or a proton acceptor to help with ionizing analytes. So far, many matrices have been reported for biopolymers and synthetic polymers. The most common matrices for biopolymers are α-cyano-4-hydroxycinnamic acid (CHCA) for peptides, 3,5-dimethoxy-4-hydroxycinnamic acid (sinapic acid or sinapinic acid, SA) for proteins and 2,5-dihydroxybenzoic acid (DHB) for carbohydrates (Fig. 1). Typically, the matrices are dissolved in solvent and then mixed with analytes solution on MALDI sample plate. After volatilization of the solvent, solid crystals containing analytes and matrix are formed on the plate. The crystals are irradiated by the laser in mass spectrometer to ionize the analytes. On the other hand, a "liquid matrix" forms a liquid droplet containing analytes and matrix on the plate. We show here the properties of liquid matrices and differences from conventional solid matrices.
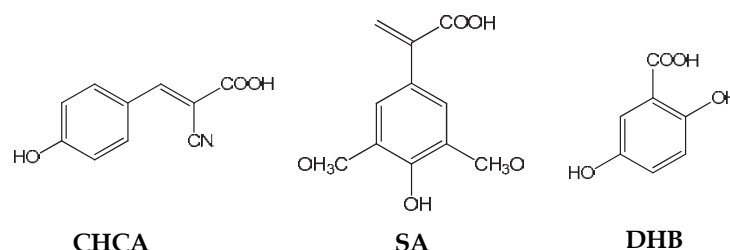

Fig. 1. Conventional MALDI matrices: CHCA, SA and DHB.

2. Conventional MALDI matrices

CHCA is the most common matrix for peptides and classified as a "hot" matrix which induced fragmentation. Typically, CHCA solution is prepared by dissolving CHCA in water/acetonitrile (1:1 v/v) with 0.1% trifluoroacetic acid (TFA) at 10 mg/mL. 0.5 μL of the CHCA solution is mixed on the plate with 0.5 μL of peptide solution dissolved in 0.1% TFA water. After volatilization of the solvent, solid crystals containing the analyte and CHCA are formed. As the analyte is co-crystallized with an excess of solid matrix, the crystal state depends on the matrix species. CHCA is known to make a thin layer of many small granular white crystals. Analyte ions are uniformly detected across the co-crystal spot when the laser irradiates the co-crystal surface. However, as a result of the nature of the thin co-crystal surface, upon irradiation with the laser the intensity of the ions from any given point in the co-crystal spot begins to decrease as the laser penetrates the thin layer. Thus, CHCA have been useful for automatic analyses using a raster function that continually moves the laser to a fresh position on the co-crystal surface.

On the other hand, DHB is the most common matrix for carbohydrates and classified as "cool" matrix compared with CHCA. For example, DHB solution is prepared by dissolving DHB in 50% aqueous acetonitrile at 10 mg/mL. 0.5 μL of the DHB solution was mixed on the plate with 0.5 μL of carbohydrate solution dissolved in water. After volatilization of the solvent, solid crystals containing the analytes and DHB are formed. DHB is known to make needle-shaped crystals. Analyte ions are detected from only a few small areas called "sweet spot" or "hot spot". This has made the application of DHB difficult because of long measurement time to find the "sweet spot" and poor reproducibility of the results.

3. Liquid matrices

Ionic liquid matrices (ILMs) introduced by Armstrong et al. were reported to have not only the property to make a homogeneous spot surface of analyte-matrix mixture but also the suitable properties for ionization of analytes (Anderson, J. L. et al., 2002; Armstrong, D. W. et al., 1999, 2001; Carda-Broch, S. et al., 2003). The essential point is that the ILMs consist of a conventional solid MALDI matrix, *e.g.*, CHCA, DHB or SA and an organic base, *e.g.*, tributylamine, pyridine or 1-methylimidazole which enables a relative state of 'liquidity' under vacuum conditions (Tholey, A. & Heinzle, E., 2006). The constituent solid matrices probably contribute to the ionization process. Several ILMs have been described and increased sensitivity analyses at the fmol or amol level have been reported for peptides and carbohydrates (Bungert, D. et al., 2004; Cramer, R. & Corless, S., 2005; Crank, J. A. & Armstrong, D. W., 2009; Fukuyama, Y. et al., 2008a; Kaneshiro, K. et al., 2011; Laremore, T. N. et al., 2006, 2007; Mank, M. et al., 2004).

Our group reported high sensitivity analyses of oligosaccharides using an optimized 1,1,3,3-tetramethylguanidine (TMG) salt of *p*-coumaric acid (G_3CA) and a TMG salt of CHCA (G_2CHCA) as liquid matrices (Fig. 2) (Fukuyama, Y. et al., 2008a). G_3CA was made by mixing *p*-coumaric acid (CA) with TMG at a 1:3 molar ratio in methanol. After evaporation of the methanol, they were dissolved in methanol at 9 mg/mL to be used as matrix solution. The matrix solution was mixed with analyte solution at a 1:1 ratio (v/v). 0.5 μL of the analyte-matrix mixture solution was spotted on a MALDI plate. After evaporating solvent, a small liquid droplet of analyte-matrix mixture was remained on the plate (Fig. 2) (Fukuyama, Y. et al., 2008a). These small droplets were irradiated by UV laser light and analyzed in the mass spectrometer.
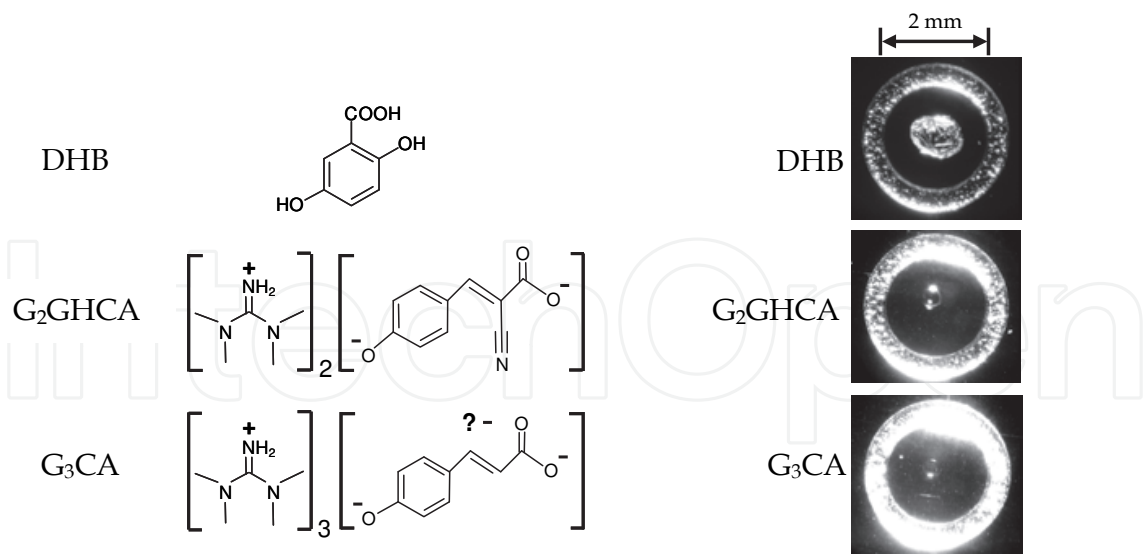
Fig. 2. Structure of matrices (left), and stereoscopic microscope photographs of analyte-matrix mixtures on a mirror-polished stainless-steel plate (right). The location of the third negative charge on the CA moiety in G$_3$CA has not been clarified.

3.1 Homogeneity

Fig. 3 is ion intensity distributions on analyte-matrix surfaces of ILMs (G$_2$CHCA and G$_3$CA) and DHB for [M-Na]$^-$ of Analyte-1 (Table 1, Fig. 4) using an incorporated automatic analytical function (Fukuyama, Y. et al., 2008a). The ion [M-Na]$^-$ was uniformly detected across the sample spot when using the ILMs whereas it was detected in only a few small areas called "sweet-spots" using DHB (Fig. 3). G$_2$CHCA gave near-perfect uniform distribution (Fig. 3). It was noted that analyses using the ILMs were carried out easily and rapidly when compared to DHB.
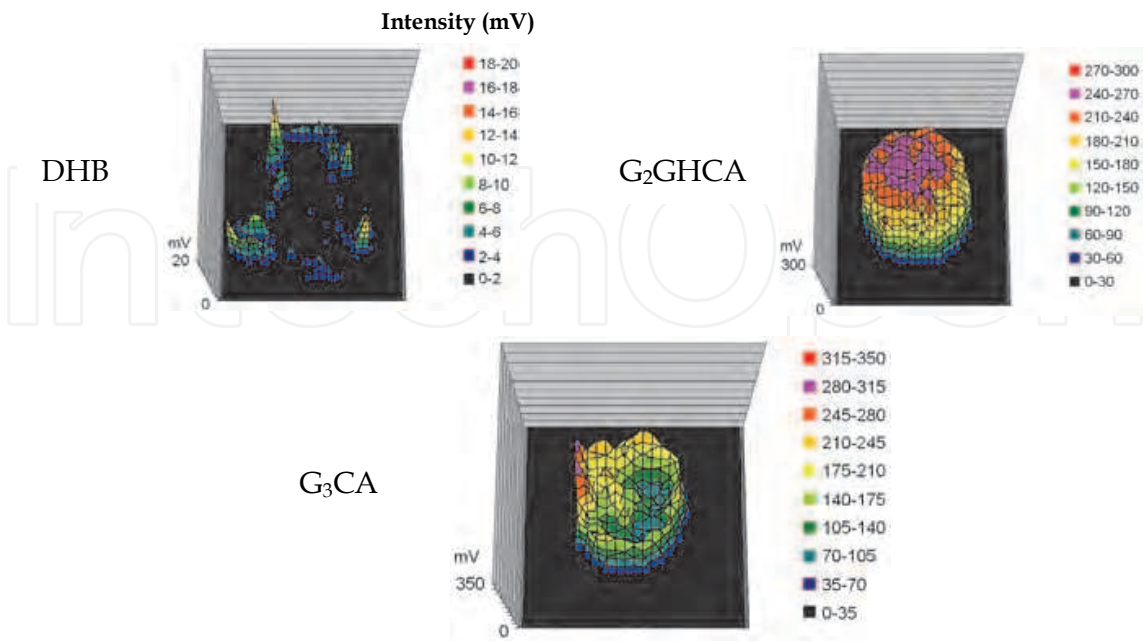

Fig. 3. Ion intensity distributions of analyte-matrix surface (810 μm × 810 μm) using DHB and ILMs (G$_2$CHCA and G$_3$CA) for [M-Na]$^-$ of Analyte-1 (in Table 1).

Analyte-#	oligosaccharides	n^a	FW
1	Neocarratetraose-41,3-di-O-sulfate (2Na$^+$)	2	834.6
2	Neocarrahexaose-41,3,5-tri-O-sulfate (3Na$^+$)	3	1242.9
3	Neocarrahexaose-24,41,3,5-tetra-sulfate (4Na$^+$)	4	1345.0
4	Neocarradodecaose-41,3,5,7,9,11-hexa-sulfate (6Na$^+$)	6	2467.9

[a] n corresponds to the number of repeating units in the oligosaccharides (see Fig. 4).
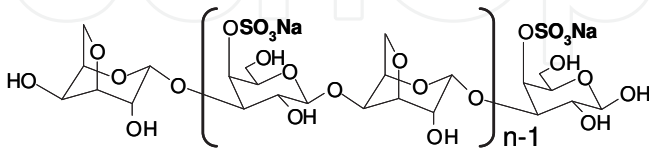
Table 1. Carrageenan oligosaccharides.

Fig. 4. Structure of carrageenan oligosaccharides. n corresponds to the number of repeating units in the oligosaccharides (see Table 1).

3.2 High sensitivity analyses of carbohydrates

Our group demonstrated the highly sensitive detection of sulfated/sialylated/neutral oligosaccharide molecules (Table 1 and 2, Fig. 4) using G$_3$CA and G$_2$CHCA (Fukuyama, Y. et al., 2008a). As a result, all oligosaccharides were detected with high sensitivity (*e.g.* 1 fmol) using the ILMs, especially using G$_3$CA, in both positive and negative ion extraction modes (Table 3 and 4) (Fukuyama, Y. et al., 2008a).

Analyte-#	oligosaccharides	M.W.
5		2302.1
6		2224.0
7		1719.4
8		1235.1
9		1865.8
10		1281.3

GlcNAc:■ ; Galactose:○ ; Glucose:● ; Mannose:◉ ;
Fucose:▽ ; NeuAc:◆ ; PA: Aminopyridine

Table 2. Sialylated and neutral oligosaccharides.

Analyte-#	Positive: [M+Na]$^+$			Negative: [M-Na]$^-$		
	DHB	G$_2$CHCA	G$_3$CA	DHB	G$_2$CHCA	G$_3$CA
1 (2S)	1 p	100 f	1 f	100 f	10 f	1 f
2 (3S)	1 p	10 f	5 f	100 f	1 f	1 f
3 (4S)	ND	100 f	10 f	1 p	10 f	1 f
4 (6S)	ND	10 f	1 f	ND	1 f	1 f

^{a}The highest sensitivity (mol/well) is shown for each analysis when 1 pmol – 1 fmol/well analytes were analyzed using MALDI-QIT-TOF mass spectrometer. ND denotes that analyte molecular ions are not detected.

Table 3. Detection limits of sulfated oligosaccharide molecules (Analyte-1 – 4 in Table 1).^{a}

Analyte-#	Positive: [M+Na]$^+$			Negative: [M-Na]$^-$		
	DHB	G$_2$CHCA	G$_3$CA	DHB	G$_2$CHCA	G$_3$CA
5	1 p	10 f	10 f	50 f	1 f	1 f
6	ND	100 f	100 f	1 p	100 f	100 f
7	100 f	10 f	10 f	100 f	25 f	10 f
8	100 f	10 f	10 f	ND	ND	ND
9	10 f	1 f	10 f	10 f	100 f	1 f
10	10 f	1 f	1 f	10 f	100 f	10 f

^{a} The highest sensitivity (mol/well) is shown for each analysis when 1 pmol – 1 fmol/well analytes were analyzed using MALDI-QIT-TOF mass spectrometer. ND denotes that analyte molecular ions are not detected.

Table 4. Detection limits of sialylated and neutral oligosaccharide molecules (Analyte-5 – 10 in Table 2).^{a}

Furthermore, 3-aminoquinoline/CHCA (3-AQ/CHCA) reported by Kumar et al. (Kolli, V. S. K. et al, 1996) is one of most widely used liquid matrices (Fig. 5). It was reported to work for highly sensitive analyses of peptides and proteins, additionally for oligosaccharides (Fukuyama, Y. et al., 2009). Several tens of attomole of oligosaccharides were detected with this matrix (Table 5) (Fukuyama, Y. et al., 2009).
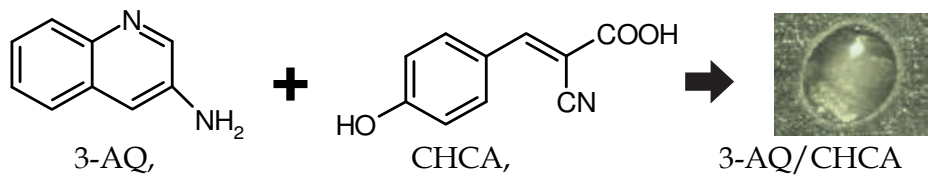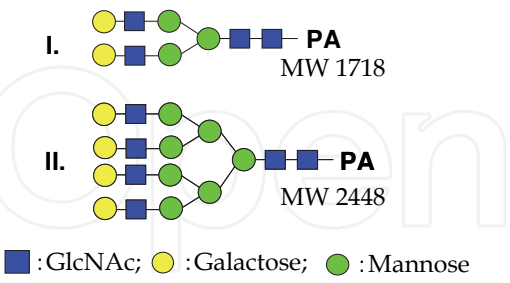

Fig. 5. Liquid matrix: 3-AQ/CHCA.

				oligosaccharides	
				I	II
MALDI-QIT-TOFMS		pos	DHB	50f	10f
			3-AQ/CHCA	50a	100a
		neg	DHB	100f	100f
			3-AQ/CHCA	1f	5f
MALDI-TOFMS	lin	pos	CHCA	1p	50f
			DHB	500f	50f
			3-AQ/CHCA	500a	50a
		neg	CHCA	500f	100f
			DHB	50f	50f
			3-AQ/CHCA	5f	500a

I. □○—... PA MW 1718

II. □○—... PA MW 2448

■ :GlcNAc; ○ :Galactose; ● :Mannose

a The highest sensitivity (mol/well) is shown for each analysis when 10 amol – 1 pmol/well analytes were analyzed. ND denotes that analyte molecular ions are not detected.

Table 5. Detection limits of PA-labeled oligosaccharide molecules with 3-AQ/CHCA and conventional solid matrices.*a*

Additionally, a labeling function of this matrix allowed the analyses of oligosaccharides on attomole level (see section 3.5) (Kaneshiro, K. et al., 2011).

3.3 Suppression of dissociation of acidic groups acids and acidic sugars

In sulfated and sialylated oligosaccharide analyses using MALDI-MS, dissociation of sulfated groups and sialic acids are observed and thus intact molecular ions are difficult to detect. Fig. 6 and Fig. 7 show results of evaluation of sulfated (Table 1, Fig. 4) and sialylated (Table 2) oligosaccharides using DHB and optimized G_2CHCA and G_3CA (Fukuyama, Y. et al., 2008a). As a result, dissociation of sulfate groups and sialic acids were suppressed using the liquid matrices in both positive and negative ion extraction modes.

3.4 Durability of ionization

One concern in automatic MALDI analyses is amount of time dedicated to the raster scanning function during automated analyses on crystalline solid matrices such as CHCA. We have reported comparison of an optimized liquid matrix CHCA butylamine salt (CHCAB) and CHCA for uniformity and durability of ionization (Fig. 8) (Fukuyama, Y. et al., 2010). Homogeneous property was confirmed using CHCA, however durability of ionization was not so long (<100 laser shots) (Fig. 8). On the other hand, peptide was ionized from whole area of analyte-matirx mixture on plate using CHCAB (Fig. 8). All these peaks showed long ionizing durability (>500 laser shots). The homogeneous property and long durability of ionization using the liquid matrix enabled irradiation on just 1-3 discrete positions with a laser for MS and MS/MS (Fukuyama, Y. et al., 2010). As a result, it was confirmed that automatic analytical time became shorter than that required using CHCA (one-third or one-quarter of the total analytical time) (Fukuyama, Y. et al., 2010).

3.5 Reaction in liquid (digestion, separation and labeling)

In addition to oligosaccharide analysis, optimized liquid matrices were applied to glycopeptide analysis. Ribonuclease B (RNase B) digests containing several peptides and glycopeptides were analyzed using DHB and G_3CA (Fukuyama, Y. et al., 2008a). The results
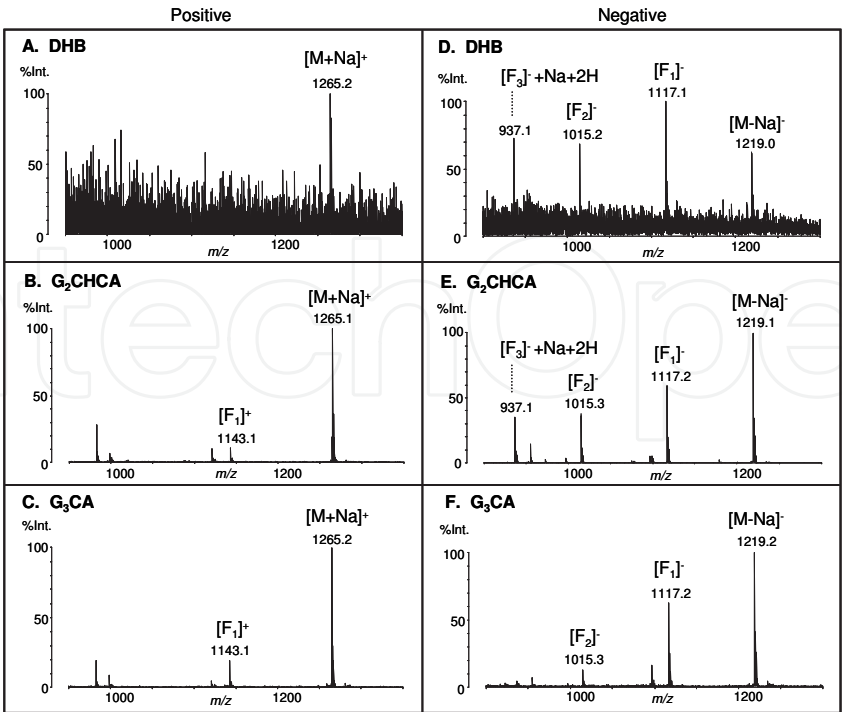
Fig. 6. Positive and negative ion mass spectra of Analyte-2 (100 fmol/well) with DHB (A and D), G_2CHCA (B and E) and G_3CA (C and F) using MALDI-QIT-TOF mass spectrometer. $[Fn]^+ = [M+Na-nSO_3Na+nH]^+$. $[Fn]^- = [M-Na-nSO_3Na+nH]^-$.
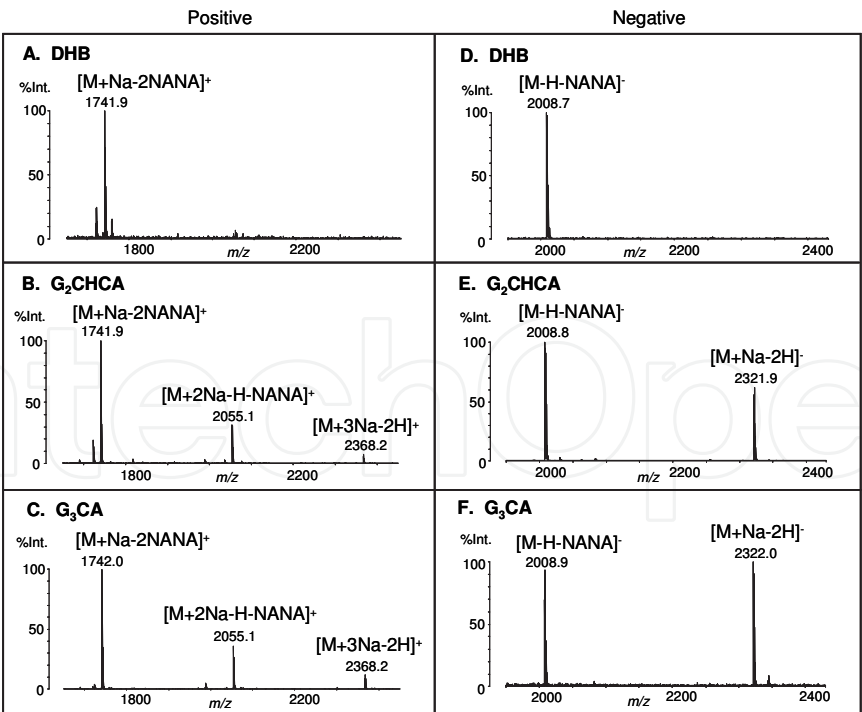

Fig. 7. Positive and negative ion mass spectra of Analyte-5 (100 fmol/well) with DHB (A and D), G_2CHCA (B and E) and G_3CA (C and F) using MALDI-QIT-TOF mass spectrometer. Dissociation of N-acetylneuraminic acid (NANA; sialic acid) was suppressed using G_2CHCA or G_3CA (B, C, E and F).
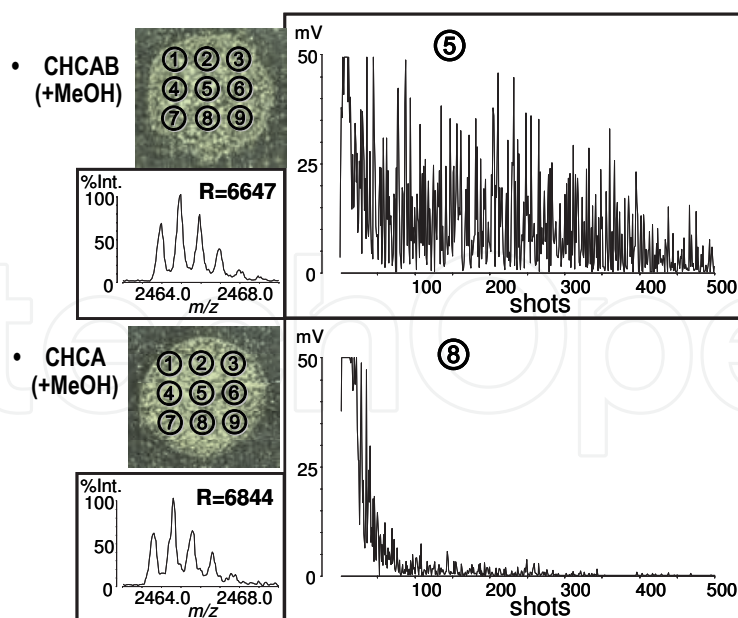
Fig. 8. Photos of analyte-matrix mixtures using optimized CHCAB and CHCA for ACTH18-39, and ionizing durability graphs of ⑤ for CHCAB and ⑧ for CHCA by manual evaluation using MALDI-TOF mass spectrometer. 500 shots of laser was irradiated to each of ①~⑨ on the photos. Almost same results were obtained for ①~⑨. CHCAB and CHCA had homegeneous property especially by adding MeOH.

shows that a series of five glycopeptides ions were preferentially detected with both positive and negative ion extractions using ILMs (Figure 9B, C, D, F, G and H) whereas they were detected only with positive ion extraction using DHB (Figure 9A and E) (Fukuyama, Y. et al., 2008a). On this basis, it may be possible to confirm the presence or absence of glycopeptides in a mixture by comparing the negative ion mass spectra obtained using the liquid matrix and DHB.

Furthermore, we confirmed on-target digestion of neutral glycoproteins: RNase B and asialofetuin and acidic glycoprotein: fetuin using liquid matrix GCA or G_3CA (Fukuyama, Y. et al., 2008b). Glycoprotein was dissolved in water and mixed with the liquid matrices and dithiothreitol (DTT). The mixture was dropped on a stainless-steel plate for reduction at 60°C for 1h. Then, trypsin was added on the mixture for digestion at 37°C for 3hs. Finally obtained mixtures were analyzed with MALDI-QIT-TOF mass spectrometer. Glycopeptide ions of RNase B digests using liquid matrix were preferentially detected in both positive and negative ion modes (Fukuyama, Y. et al., 2008b). However, glycopeptides of asialofetuin were detected with low S/N ratio and dissociation of sialic acids was observed for fetuin (Fukuyama, Y. et al., 2008b). Although the on-target digestion requires further development, these results suggest that liquid matrices can work not only as a matrix, but also a reaction medium for rapid digestion and MS analyses.

On the other hand, on-target desalting within 3-AQ/CHCA droplet and selective detection of glycopeptides ions was reported (Sekiya, S. et al., 2008). Sekiya et al. found that 3-AQ/CHCA has a property to concentrate hydrophilic compounds on a small surface area of a matrix droplet (Sekiya, S. et al., 2008). Then it was confirmed by analyzing glycoprotein digests that glycopeptides were ionized from the center hydrophilic small area on 3-AQ/CHCA droplet whereas peptides were detected from the outer area on it (Fig. 10) (Sekiya, S. et al., 2008).
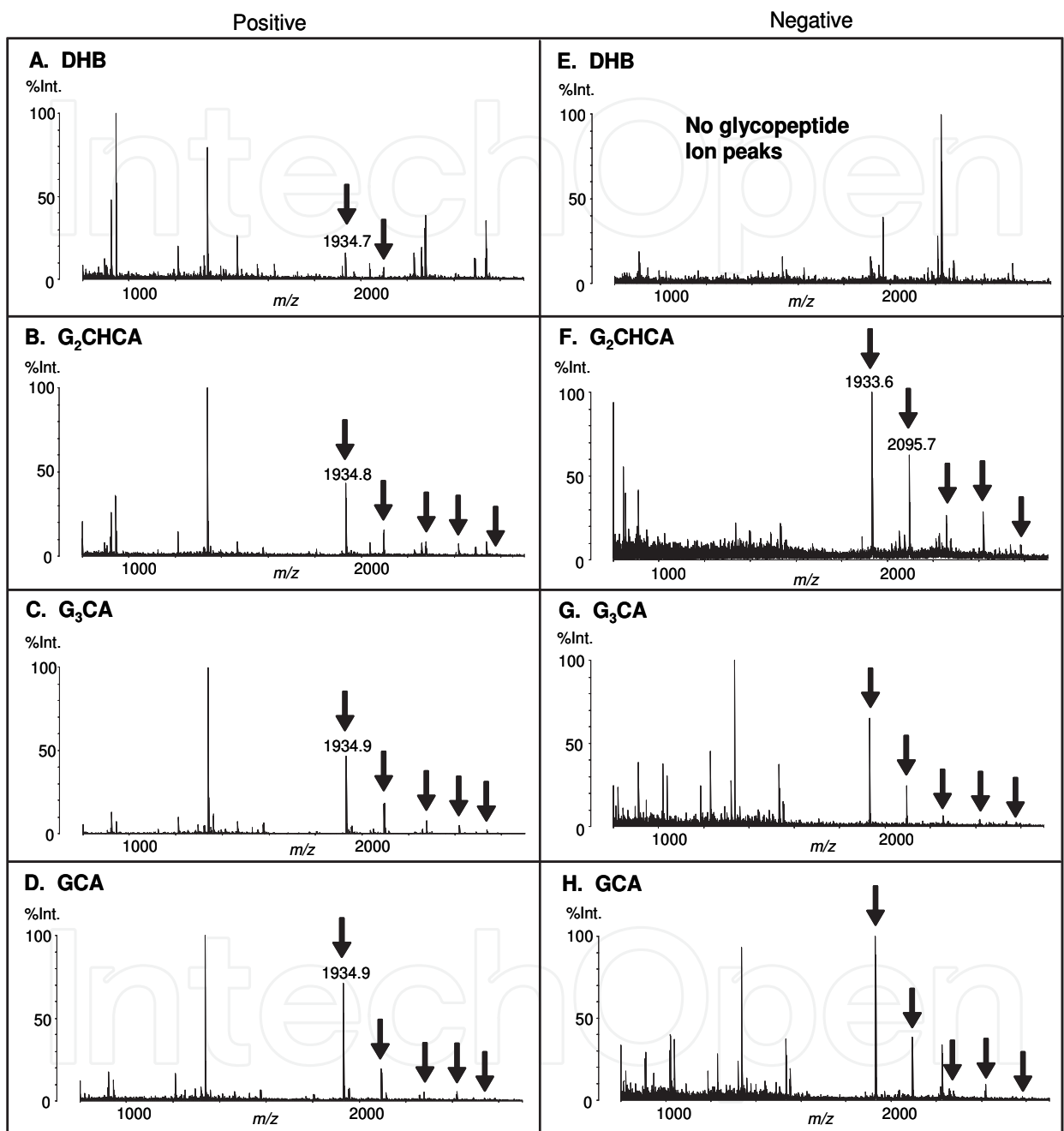
Fig. 9. Positive and negative ion mass spectra of RNase B digests (*ca.* 1 pmol/well) with DHB (A and E), G₂CHCA (B and F), G₃CA (C and G) and GCA (D and H) using MALDI-QIT-TOF mass spectrometer. Arrowed peaks are derived from glycopeptide ions.
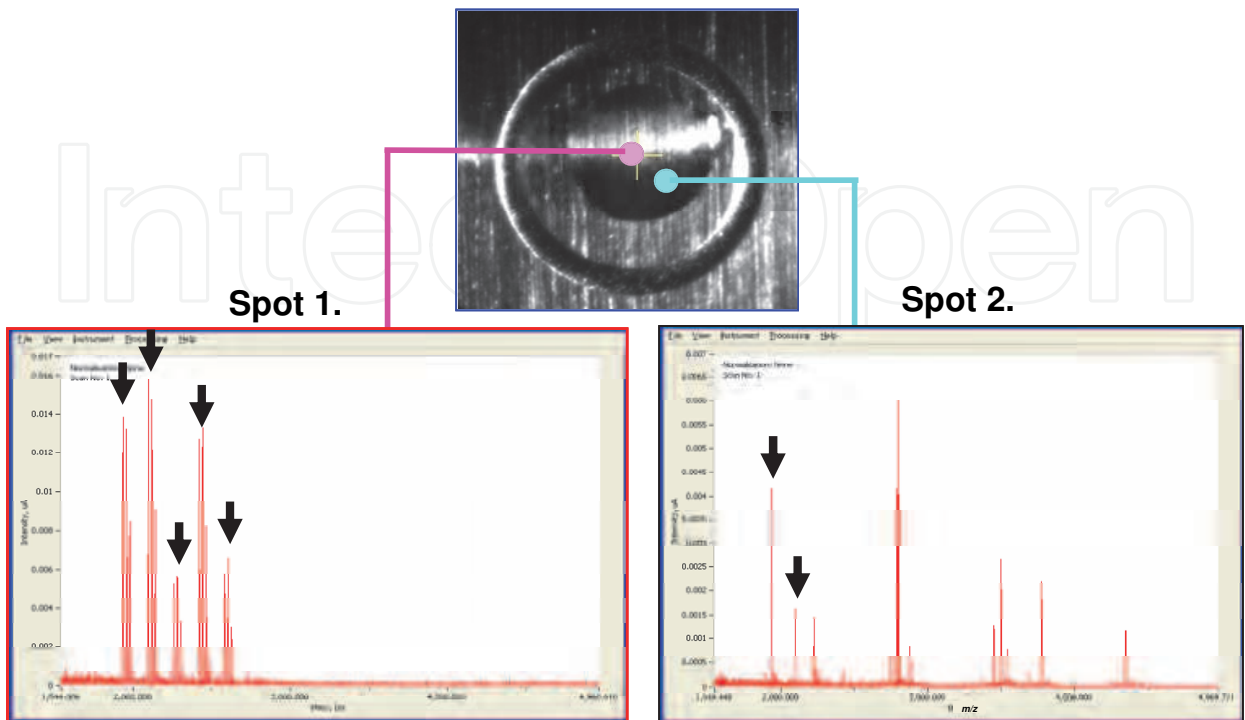
Fig. 10. Mass spectrum of RNase B Lys-C digests using 3-AQ/CHCA at a spot 1 and spot 2, respectively. Arrowed peaks are derived from glycopeptide ions.

Addionally, Kaneshiro et al. reported a high sensitive AQ-labeling method of glycans on a MALDI target using 3-AQ/CHCA (Kaneshiro, K. et al., 2011). Glycans were detected as AQ-labeled molecular ions on attomolle level (Table 6 and 7) (Kaneshiro, K. et al., 2011).

structure	name	M.W.
	NA2	1,641
	NA4	2,372
	A1	1,933
	A2	2,224

■ : GlcNAc   ○ : Galactose
● : Mannose   ◆ : Sialic Acid

Table 6. *N*-linked glycan standards.

	positive ion mode		negative ion mode	
	DHB	3-AQ/CHCA	DHB	3-AQ/CHCA
NA2	10 fmol	100 amol	ND	50 amol
NA4	5 fmol	50 amol	ND	50 amol
A1	100 fmol	500 amol	100 fmol	10 amol
A2	100 fmol	500 amol	100 fmol	50 amol

[a] 1 amol-1 pmol/well of analytes were analyzed using MALDI-QIT-TOF mass spectrometer. ND denotes that analyte molecular ions were not detected.

Table 7. Detection limits of *N*-linked glycan with DHB and 3-AQ/CHCA.[a]

3.6 Quantitative capability

Quantitative analysis is challenging area in MALDI. One of the reasons is inhomogeneous crystal surface using solid matrices. We confirmed that normalized ion peak intensities of peptides have a high correlation with loaded amounts at 1fmol-100 pmol range using 3-AQ/CHCA (Fig. 11) (Fukuyama, Y. et al., 2009).
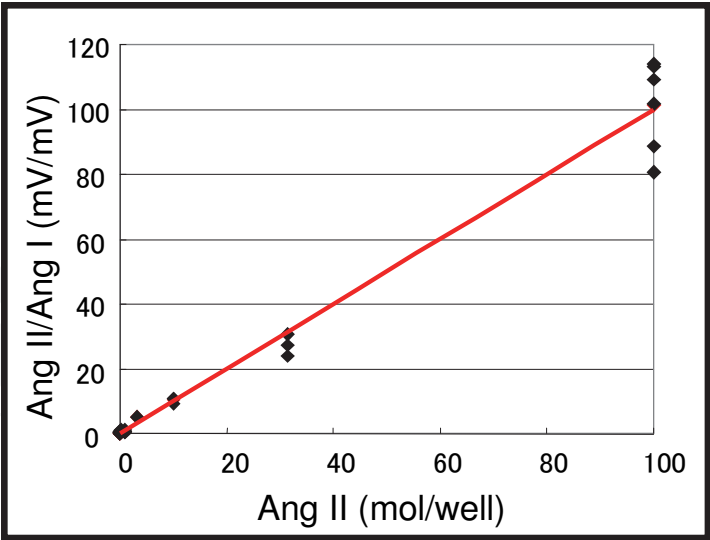

Fig. 11. Dynamic range for absolute quantification of angiotensin II (Ang II) (1 fmol - 100 pmol) using angiotensin I (Ang I) as an internal standard with 3-AQ/CHCA. Ion peak intensity (mV) of the Ang II was normalized by that of the Ang I. MALDI-QIT-TOFMS was used.

4. Conclusion

Liquid matrices are a relatively new area in MALDI. However they have great potential to overcome issues of conventional solid matrices. This chapter indicates that with liquid matrices it is possible to improve sensitivity and homogeneity, suppress dissociation of labile sites like acidic groups and acidic sugars of carbohydrates, increase the durability of ionization, enable quantitative analyses and on-target reactions such as digestion, separation and labeling in MALDI. A rapid and highly sensitive analytical method for any analytes is a difficult but attractive goal and liquid matrix research may open a new insight into this.

5. Acknowledgment

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This volume, of a two volume set on ionic liquids, focuses on the applications of ionic liquids in a growing range of areas. Throughout the 1990s, it seemed that most of the attention in the area of ionic liquids applications was directed toward their use as solvents for organic and transition-metal-catalyzed reactions. Certainly, this interest continues on to the present date, but the most innovative uses of ionic liquids span a much more diverse field than just synthesis. Some of the main topics of coverage include the application of RTILs in various electronic applications (batteries, capacitors, and light-emitting materials), polymers (synthesis and functionalization), nanomaterials (synthesis and stabilization), and separations. More unusual applications can be noted in the fields of biomass utilization, spectroscopy, optics, lubricants, fuels, and refrigerants. It is hoped that the diversity of this volume will serve as an inspiration for even further advances in the use of RTILs.

How to reference

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