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Confirmation of Synthesis of Sparingly Soluble Compounds by Accurate MALDI-TOF Mass Spectrometry

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Introduction

The MALDI method is tolerant to various characteristics of samples, and thus, for example, can be used to perform mass spectrometry of poorly soluble compounds that are difficult to measure with LC-MS. For the analysis of less polar compounds, an ionizing agent is sometimes added to the sample and matrix to promote ionization. They must be mixed and dissolved, and then spotted and dried on a sample plate to form cocrystals. Therefore, it is necessary to dissolve all components in the same solvent. Meanwhile, for highly accurate mass measurement in MALDI-TOF MS analysis, it is desirable to perform mass calibration using internal standards. However, calibrants with similar physical properties and molecular weight to the sample compound may not be easily found.

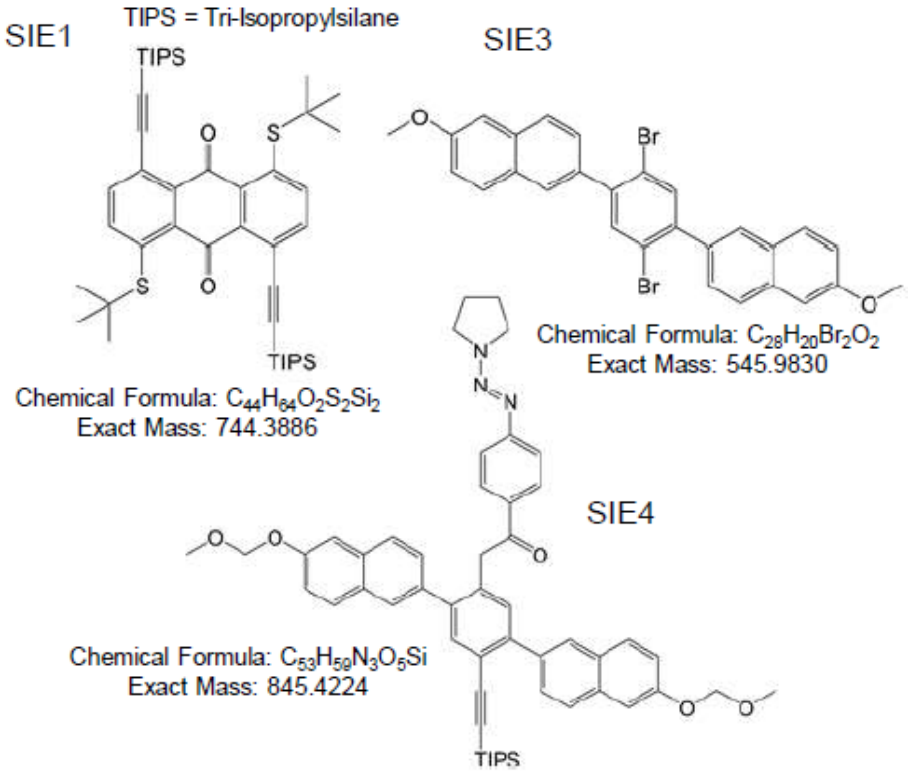

Figure 1 Structures of poorly soluble compounds

Figure 2 iMScopeTM QT - LCMS-9030

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	SIE1	SIE3	SIE4
$[M]^+$	744.38808	545.98246	845.42185
$[M+H]^+$	745.39590	546.99028	846.42967
$[M+Na]^+$	767.37785	568.97223	868.41162
$[M+K]^+$	783.35178	584.94616	884.38556
$[M+NH_4]^+$	762.42245	564.01683	863.45622

Table 1 Theoretical monoisotopic masses of poorly soluble compounds

MS Data Acquisition Parameters

Instrument	iMScope QT
Pitch (Spatial resolution)	10 [µm]
Polarity	Positive
Mass range	300 – 1000 (SIE1 & SIE4) 400 – 600 (SIE3)
Data point (X)	32 [points]
Data point (Y)	32 [points]
Data point	1,024 [points]
Sample voltage	3.70 [kV]
Detector voltage	2.20 [kV]
Number of laser shots	50 [shots]
Laser repetition rate	10000 [Hz]
Laser diameter setting	1
Laser intensity	55 / 65 (SIE1 & SIE4 / SIE3)

Data Analysis

Mass spectra	IMAGEREVEAL MS

Table 2 Data acquisition and analysis conditions for mass spectrometry

2. Methods

DHB (50 mg/mL) was dissolved in 70% acetonitrile aqueous solution containing 0.1% TFA and used as the external standard. Mass calibration was performed using DHB cluster ions (3M to 7M) as the standard peak.
A trace amount of each sample was dissolved in chloroform and used directly for analysis. DCTB (10 mg/mL) was used as a matrix and was dissolved in chloroform. Sodium trifluoroacetate (2 mg/mL) dissolved in tetrahydrofuran was added as a cation donator for SIE3. These were mixed and a small amount was spotted on the SUS target, dried, and used for measurement.

3. Results

Accurate mass confirmation for synthetic compounds

We synthesized three poorly soluble compounds (SIE1, SIE3, SIE4; Fig. 1 and Table 1) which are the material for molecular loop (SIE1) and the intermediate products for carbon nano tubes (SIE3 and SIE4). They were measured with the iMScopeTM QT - LCMS-9030 (Fig. 2) under the analytical conditions shown in Table 2, with or without the sample compound, and peaks derived from the sample were confirmed (Fig. 3 (a, b), Fig. 4 (a, b), and Fig. 5 (a, b)). As a result, SIE1 and SIE4 were observed as [M+H]+ ions, and SIE3 was observed as [M]+ ions (Table 1). Then, the accurate mass was measured three times (Fig. 3 (ce), Fig. 4 (c-e), and Fig. 5 (c-e)), and the average value was calculated (Table 3). It was found that the accurate mass of each compound could be measured with an accuracy within 1 ppm of the theoretical value. In this case, we have simply confirmed the exact mass by accurate mass measurement, but this approach is also useful for formula prediction and structure analysis of unknown compounds.

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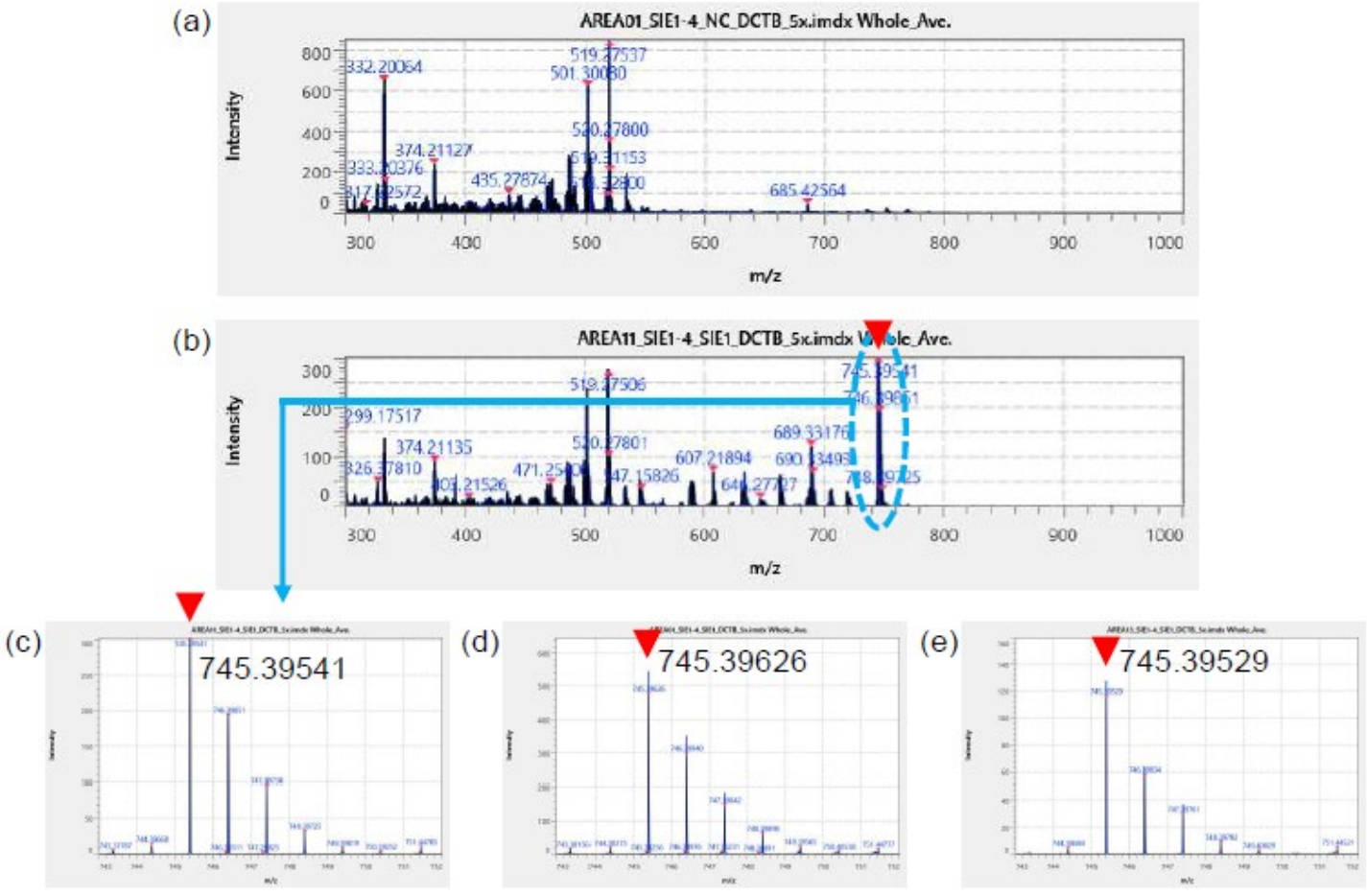

Fig. 3 Measurement results for SIE1
Mass spectra of negative control (no sample) (a) and SIE1 (b) and enlarged mass spectra of repeated measurements of SIE1 (n = 3) (c-e)

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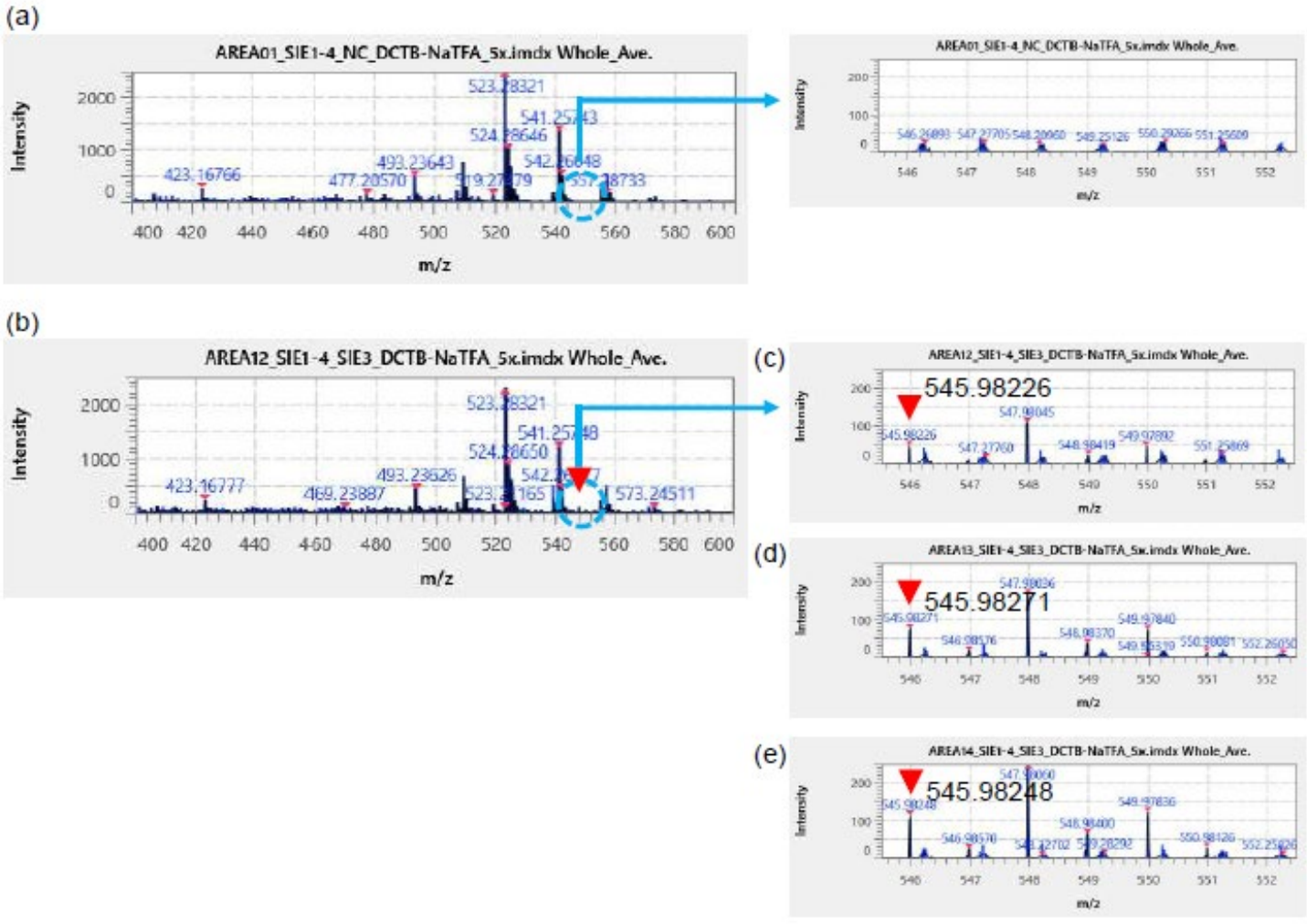

Fig. 4 Measurement results for SIE3
Mass spectra of negative control (no sample) (a) and SIE3 (b) and enlarged mass spectra of repeated measurements of SIE3 (n = 3) (c-e)

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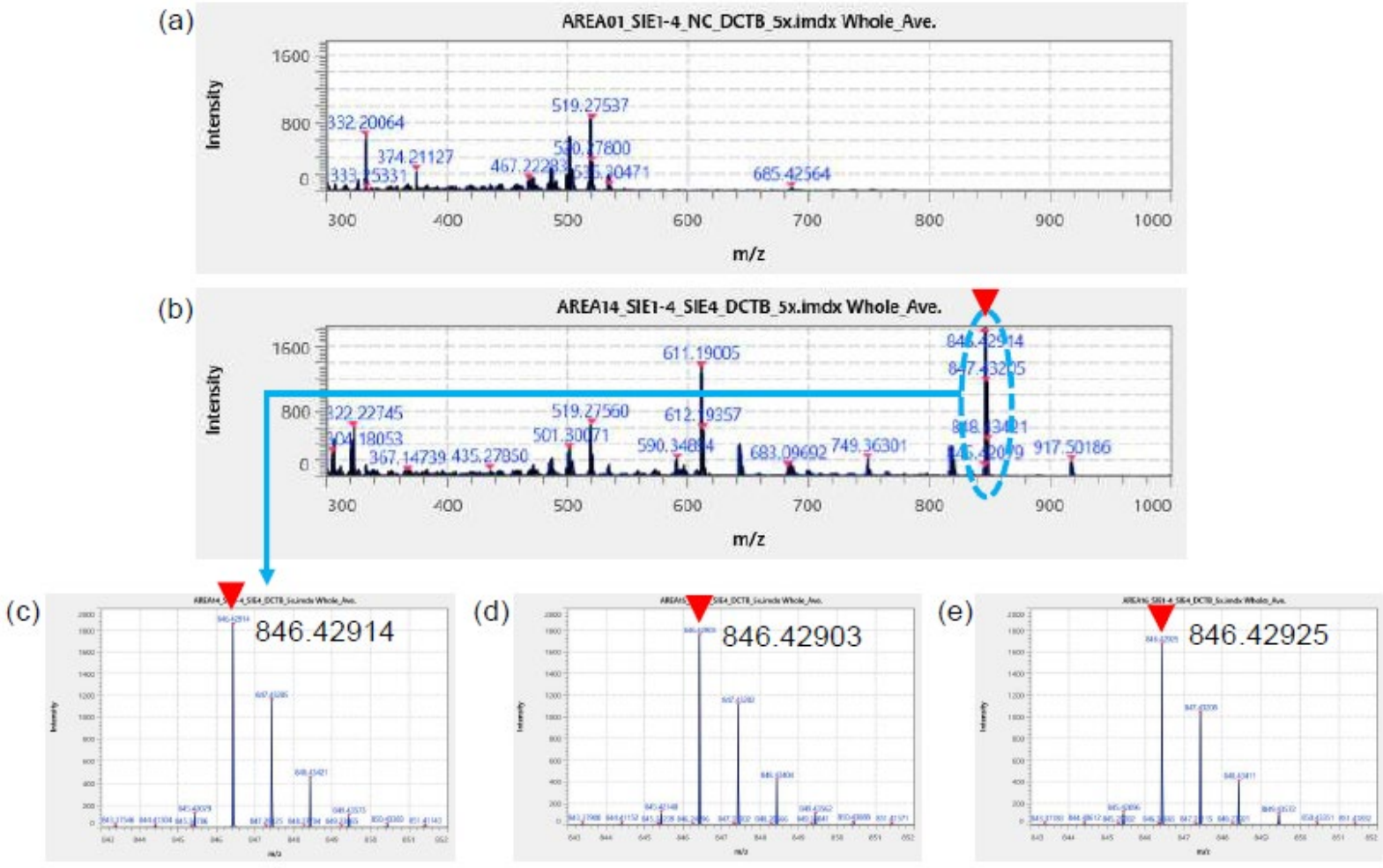

Fig. 5 Measurement results for SIE4
Mass spectra of negative control (no sample) (a) and SIE4 (b) and enlarged mass spectra of repeated measurements of SIE4 (n = 3) (c-e)

	SIE1			SIE3			SIE4		
	m/z	Difference		*m/z*	Difference		*m/z*	Difference	
		mDa	**ppm**		mDa	**ppm**		mDa	**ppm**
Theoretical	745.3959			545.9825			846.4297		
Measured 1	745.3954	-0.49	**-0.66**	545.9823	-0.2	**-0.37**	846.4291	-0.53	**-0.63**
Measured 2	745.3963	0.36	**0.48**	545.9827	0.25	**0.46**	846.429	-0.64	**-0.76**
Measured 3	745.3953	-0.61	**-0.82**	545.9825	0.02	**0.04**	846.4293	-0.42	**-0.50**
Average (of absolute value)	745.3961	0.49	**0.65**	745.3961	0.16	**0.29**	846.4304	0.53	**0.63**

Table 3 Summary of accurate mass spectrometry results

4. Conclusion

Examples of poorly soluble compounds include liquid crystal materials in liquid crystal displays, poorly soluble resin materials used in industrial products, and synthetic polymers, all of which are indispensable in our daily lives. It is very useful to be able to confirm the synthesis of these compounds with accurate mass spectrometry. With the iMScope QT – LCMS-9030, accurate mass measurement is achievable even with external calibration methods. As a result, even in the case of poorly soluble compounds, analysis can be performed easily without the need to find suitable internal calibrants or perform solvent studies. When combined with LC/MS, the iMScope QT provides accurate mass spectrometry for compounds with a variety of physical properties. The original purpose of iMScope QT is to perform high spatial resolution MS imaging integrated with microscope images. It has been reported that liquid crystal materials can be analyzed by laser desorption ionization (LDI), and we believe that MS imaging of (organic) liquid crystal displays can be used for impurity analyses. In addition to MS imaging, we propose this attractive and practical new MALDI application for poorly soluble compounds.

Acknowledgements

We would like to thank the Laboratory of Synthetic Organic Chemistry (Eric Sidler from the Mayor group), Department of Chemistry, University of Basel for kindly providing us with the phenylene-ethynylene derivatives.

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