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Statistical Approach To Understand MALDI-TOFMS Matrices: Discovery and Evaluation of New MALDI Matrices

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A statistical approach is described to better understand the role of the matrix during a MALDI-TOFMS experiment. Potential matrix molecules were selected based on a rational experimental design and subsequently screened in order to investigate whether a certain compound can act as a matrix for synthetic polymers. The tested compounds were selected from a pool of 11 000 molecules based on descriptor calculations and a subsequent D-optimal design selection procedure. This approach selected 59 organic compounds that were then investigated for their ability to act a matrix for synthetic polymers in MALDI-TOFMS experiments. Within this contribution, we focus on the discussion of new MALDI-TOFMS matrixes that were discovered in the course of the screening. At least 10 new matrices were identified, and 5 of these were subsequently tested more closely with a variety of different synthetic polymers of different molecular weights revealing good to excellent performance of these new matrices.

In recent years, the mass spectrometric analysis of (biological) macromolecules became feasible due to the invention of soft ionization methods, such as electrospray ionization and matrix-assisted laser desorption/ionization (MALDI), which was rewarded with the Nobel price in chemistry in 2002 "for the development of methods for identification and structure analyses of biological macromolecules" to J. B. Fenn and K. Tanaka.[1] Today, MALDI time-of-flight mass spectrometry (MALDI-TOFMS) is perhaps the most important mass spectroscopic technique currently used for polymer analysis[2] and is a very useful tool for the determination of absolute molecular weights, molecular weight distributions and end groups of synthetic polymers.[2−4] Excellent overviews over these possibilities as well as limitations are presented in the literature by Hanton (see ref 2) and Nielen (see ref 3). A successful MALDI experiment is a multistep event consisting of the following: sample preparation, sample excitation and disintegration of the condensed phase, generation and separation of charges, and ionization of the analyte molecules followed by extraction, separation by the mass-to-charge (m/z) ratio, and detection of the molecules within the mass spectrometer.[5] An important parameter for the excitation part of the MALDI experiment is, unsurprisingly, a sufficient absorption by the MALDI matrix at the applied laser wavelength.[5,6] Furthermore, an attempt is usually made to "match" matrix and analyte polarity for good analytic results.[3] However, one of the most difficult parts in MALDI analysis seems to be the sample preparation, since this step is crucial for the success of the MALDI experiment.[2] Samples are usually prepared as films on a sample target, and afterward, the sample is irradiated with a pulsed laser to form a plume in the vacuum. Subsequently, the plume (or "trail of smoke") physically expands in the vacuum leading to fewer and fewer collisions of primary formed ions or excited-state matrix molecules with neutral analyte molecules. Simulations of this plume formation have revealed that a UV-MALDI plume can be described as a very fast (and almost explosive) solid-to-gas-phase transition.[7,8] Moreover, these simulations revealed that at low applied laser energies/cm^2 (fluences) the plume was mainly formed due to desorption, whereas at higher fluences more ablation was observed leading to larger clusters of material contained in the plume.[8] The most likely reactions to form primary ions are, for example, energy pooling of two excited matrix molecules to yield matrix radical cations (see eq 1) or excited-state proton-transfer reactions (see eq 2).[9]

$$\text{matrix} + \text{matrix} + 2h\nu \rightarrow \text{matrix}^* + \text{matrix}^* \rightarrow \text{matrix} + \text{matrix}^{+\bullet} + e^- \quad (1)$$

$$\text{matrix} + \text{matrix} + h\nu \rightarrow \text{matrix}^* + \text{matrix} \rightarrow (\text{matrix} - H)^- + (\text{matrix} + H)^+ \quad (2)$$

Analyte ions are mainly formed by secondary reactions in the expanding plume. These are then separated and detected by a time-of-flight (TOF) mass spectrometer. One explanation as to why the observed ion distributions of a MALDI experiment might be dominated by secondary reactions in the MALDI plume and do

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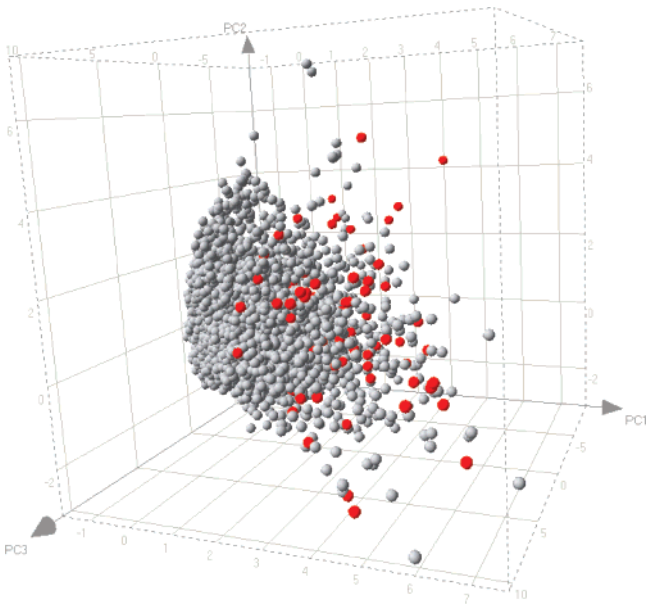

Figure 1. Loading plot for the 10 000 compound data set for the first three principal components (PCs). Compounds selected for screening are colored red.

not occur during the primary very short (3−5 ns) laser pulse is the fact that reactions between ions and neutral species will continue for as long as there are collisions in the expanding plume. The time required to reach collision-free densities in the plume is many microseconds.[10] Secondary reactions include, for example, proton transfer (eq 3 represents the arguably most important secondary reaction) between primary protonated matrix and analyte molecules, cation transfer (for synthetic polymers, agents giving rise to cation formation are often added deliberately to the sample preparation), or electron-transfer reactions.[10] These three factors are mainly responsible for the observed ion distribution in a MALDI-TOF mass spectrum.

$$(\text{matrix} + \text{H})^+ + \text{analyte} \rightarrow \text{matrix} + (\text{analyte} + \text{H})^+ \quad (3)$$

Even if recent years have provided much deeper insights into the general MALDI process (see discussion above), it is in some cases still relatively unclear (apart from the straightforward observation that a matrix has to absorb light at the laser wavelength[5,6]) why certain molecules can act as matrices and others not or, in other words, how to optimize or choose a matrix's chemical structure in such a way as to obtain better results for the analysis of otherwise difficult analytes. In an attempt to correlate the performance of a matrix in a MALDI experiment with its chemical structure, we have started a screening program, which will hopefully lead to the development of quantitative structure−property relationships (QSPR). In this first report, we will focus on experimental details and the discovery and evaluation of new MALDI matrices, while any QSPR models that will be developed, will be published separately in the near future.[18]

EXPERIMENTAL SECTION

A library of potential matrix molecules together with inorganic salts was purchased from Sigma Aldrich (Oakville, ON, Canada) and supplied as Combikits. The known MALDI matrices, α-cyano-4-hydroxycinnamic acid (CHCA), 2,-(4-hydroxyphenylazo)benzoic acid (HABA), *trans*-3-indoleacrylic acid (IAA), 2,5-dihydroxybenzoic acid (DHB), 1,8,9-anthracenetriol (dithranol), and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) were from Sigma Aldrich and were used as received. Analytical grade solvents were purchased from Biosolve Ltd. (Valkenswaard, The Netherlands). The 3-kDa poly(ethylene glycol) (PEG) was obtained from Polymer Source (Nektar, San Carlos, CA), while 8-kDa poly(ethylene glycol) was obtained from Sigma Aldrich. Poly(ethyloxazoline)s[11] and star-shaped poly(ϵ-caprolactone)s[12] were prepared as described in the literature.[11,12] Poly(methyl methacrylate) (PMMA) standards were obtained from PSS (Polymer Standards Service, Mainz, Germany).

All MALDI experiments were performed on a Voyager-DE STR Biospectrometry Workstation (Applied Biosystems, Foster City, CA) time-of-flight mass spectrometer in reflectron mode. All spectra were obtained in the positive ion mode. Ionization was performed with a 337-nm pulsed nitrogen laser. All data were processed using the Data Explorer software package (Applied Biosystems). For the screening, the instrument settings were as follows: laser intensity, 2500; delay time, 350 ns; acceleration voltage, 25 kV; mass range, 1000−8000 Da. All spectra are averaged over 500 laser shots over the complete sample area.

Samples were prepared using the multiple-layer spotting approach described recently.[13,14]Matrixes in the respective solvents (10 mg/mL) were deposited as first layers on the MALDI target. NaI (100 mg/mL in acetone) was used as a second layer and PMMA (10 mg/mL in $CHCl_3$) as final layer of the sample for the screening. For subsequent experiments involving different polymers, the polymer concentration was 20 mg/mL in $CHCl_3$.

RESULTS AND DISCUSSION

In order to gain a deeper understanding of the role of the matrix for a successful MALDI experiment and in order to develop quantitative models of the matrix performance, we chose a screening approach coupled with rational compound selection to evaluate a library of potential MALDI matrix molecules.

Initially, the Aldrich Catalog was searched for compounds that fall into a molar mass range between 100 and 500 g/mol and contain at least one aromatic ring as the presence of a π-system is necessary for the absorption of the 337-nm wavelength laser light typically used for UV-MALDI experiments. Subsequently, inorganics and organometallics were removed from the data set and a number of 1D, 2D, and 3D descriptors were calculated. Principal component analysis was carried out to reduce the data dimensionality. A D-optimal design algorithm[15] was subsequently used to select 59 compounds for screening out of a possible 10 000 compounds.

As there is currently no real agreement on which molecular features contribute to a molecule being a successful matrix in a

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Table 1. Chemical Names and Signal-to-Noise (S/N) Ratios of the 10 New MALDI Matrixes with the Highest S/N Ratios, Discovered Using a Screening/Rational Selection Approach

no.	name:	best solvent:	S/N ratio (PMMA 4 kDa)
1	galvinoxyl (free radical)	acetone	23.1
2	disperse red 13 acrylate	chloroform	20.6
3	disperse red 1	chloroform	19.2
4	disperse red 1 acrylate	acetone	18.4
5	disperse red 1 methacrylate	chloroform	17.4
6	4,4′-methylenebis(*N*,*N*-diglycidylaniline)	chloroform	15.7
7	*N*-(4-nitrobenzoyl)-L-glutamic acid diethyl ester	chloroform	15.2
8	(*S*)-(+)−2-methylbutyl 4-(4-decyloxybenzylideneamino)cinnamate	chloroform	14.4
9	α-naphtholphtalein	chloroform	14.1
10	2,4-di-*tert*-butyl−6-(5-chloro-2*H*-benzotriazol−2-yl)phenol	chloroform	12.6

MALDI experiment, we endeavored to screen a maximally diverse subset of compounds. D-Optimal designs maximize the |**XX**'| determinant, with **X** being the variance−covariance matrix. The determinant will be at a maximum for compound sets, which have a maximum variance, i.e., span a large chemical compound space. While the selection of diverse compound sets can also be achieved using other methods such as self-organizing maps[16] or clustering techniques,[17] D-optimal designs have been shown to give rise to slightly better results in the past. Figure 1 shows a loading plot for the first three principal components. Selected compounds are marked in red. A detailed account of the data preparation and selection procedure will be published elsewhere.[18] Here, we want to discuss the first results of the experimental screening, which led to the discovery of novel MALDI matrices and the subsequent closer investigation of these new matrices using a variety of synthetic polymers. In this way, their performance and limitations for the analysis of synthetic polymers can be evaluated.

The screening was carried out by depositing the potential MALDI matrix as a first layer from a number of solvents with different polarities (chloroform, acetone, and methanol). This is important, since it was shown previously that a good matrix/solvent combination is crucial in order to obtain high-quality MALDI-TOF MS spectra,[13,14] and it is generally attempted to "match" matrix and analyte polarity for good analytic results.[3,19] In this respect, it was, for instance, observed that the best MALDI spectra, with respect to S/N ratio, were obtained when the matrix and the polymer had similar retention times in a gradient HPLC experiment, also indicating a similar polarity of the two components of the MALDI sample.[20] This effect will be addressed in more detail later. After the complete drying of the first layer, the second (NaI in acetone) and third layers (4-kDa PMMA in chloroform) were spotted on top of one another to complete the MALDI sample. The multiple layer spotting sample preparation was chosen to avoid incompatibility of the different solvents used for the different components of the sample, e.g., the insolubility of NaI in $CHCl_3$, leading to precipitation of certain components during the solvent evaporation, which is generally believed to be unadvantageous for MALDI experiments. In this respect, it was observed that the addition of tetrahydrofuran to an azeotropic mixture of CH_2Cl_2 and 1,1,1,3,3,3-hexafluoro-2-propanol used for the sample preparation of poly(ethylene terephthalate) (PET) resulted in molar mass discriminations and in greatly increased shot-to-shot variability during MALDI experiments most likely due to a precipitation of the PET during solvent evaporation.[21] Each sample was prepared and measured four times resulting in 708 MALDI spectra to be measured and evaluated. The 4-kDa PMMA polymer was chosen as a model for synthetic polymers and was measured with relatively high laser intensities (compare Experimental Section) in reflectron mode, since the main goal of the screening was to see whether a certain compound can act as a matrix. All measured spectra were evaluated with respect to the absolute signal intensity at 4000 m/z, and their signal-to-noise (S/N) ratio was calculated. A binning approach was chosen to cover the different performances of the investigated compounds: a compound was considered a matrix if the found signal intensity (averaged overall 4 measurements for a certain matrix/solvent combination) was higher than 100 counts, and a compound was considered to be a good matrix if the found signal intensity was higher than 500 counts. Before the actual screening was started, six known MALDI matrices (CHCA, HABA, IAA, DHB, dithranol, DCTB) were subjected to the described screening parameters and these known matrices were correctly identified as good performing matrices giving a first indication of the suitability of the applied screening approach to correctly identify potential matrix molecules. Utilizing this approach and taking all investigated solvents for crystallization into account, 27 of the 59 investigated compounds can be considered as matrices of which 17 were good matrices at the chosen experimental settings. During these investigations, it was observed that each matrix has a preference for a certain solvent for the matrix crystallization, which is consistent with previous literature findings.[13,14] Figure 2 illustrates this effect for one of the investigated compounds (6-*tert*-butyl-2,3-naphthalenedicarbonitrile). It is obvious that 6-*tert*-butyl-2,3-naphthalenedicarbonitrile was able to act as a matrix for PMMA if it was crystallized from chloroform and acetone but not if crystallized from methanol. However, the best results in terms of signal intensity and S/N ratio were obtained if the first layer of the sample was deposited from chloroform as clearly observable from the MALDI-TOFMS spectra in the top part of Figure 2 (note that all spectra are measured with the same instrument settings). This finding can be correlated to microscopy pictures obtained from 6-*tert*-butyl-2,3-naphthalenedicarbonitrile deposited from the three investigated solvents. The pictures were obtained using cross-polarizers in the microscope and give therefore a good indication of the crystallinity of the sample. Matrix deposited from chloroform shows the highest crystal density, whereas deposition from acetone shows less crystals and deposition from methanol shows only a few crystals. This result correlates very well with

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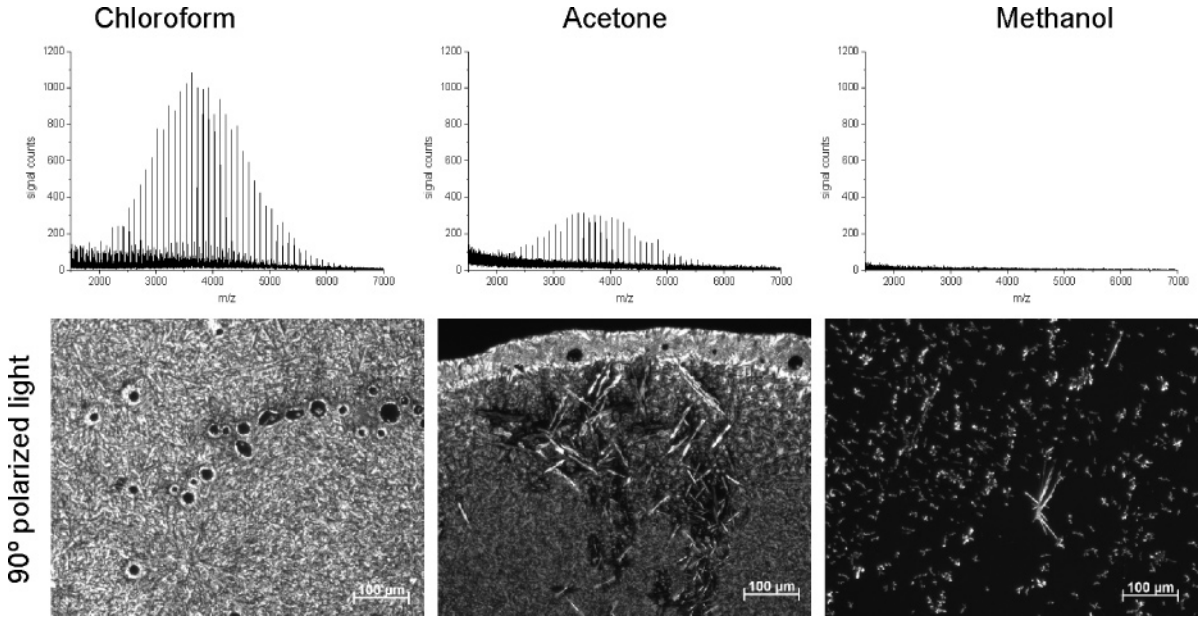

Figure 2. MALDI-TOFMS spectra (top) of a 4-kDa PMMA standard analyzed with 6-*tert*-butyl-2,3-naphthalenedicarbonitrile as the matrix applying three different solvents for the matrix crystallization. Bottom: Microscopy pictures of 6-*tert*-butyl-2,3-naphthalenedicarbonitrile deposited from the three respective solvents and observed with 90° polarizers.

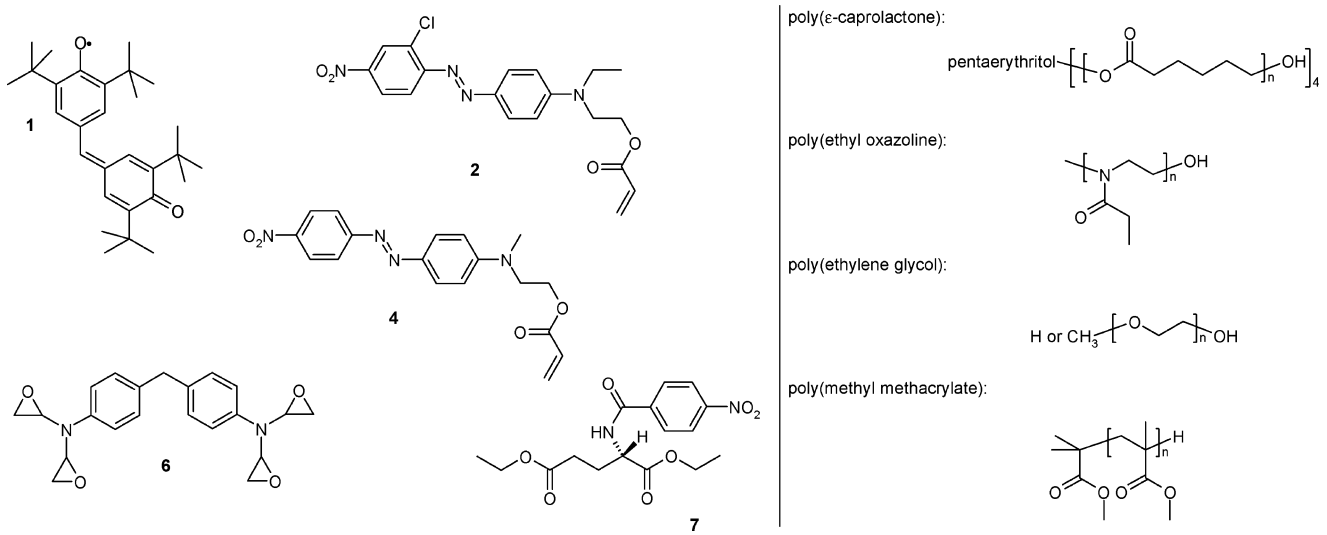

Figure 3. Left: Structures of more closely investigated MALDI-TOFMS matrices for synthetic polymers that were discovered in the course of the large matrix screening. Right: Structures of the investigated synthetic polymers.

the spectral quality and was also observed for other investigated compounds. Moreover, this effect is described in the literature.[13,14] Generally speaking, crystalline matrices give rise to better MALDI-TOFMS results. In this respect, it was proposed that proteins (and other analytes) bind to the surface of matrix crystals[22] and that an increase of the mainly hydrophobic interactions between crystal and analyte improve the spectral quality in MALDI experiments.[23] These investigations demonstrate why it was necessary to perform the screening using different solvents for the matrix crystallization. Table 1 summarizes some of the results of the screening by listing all compounds that were able to act as a MALDI matrix and provided S/N ratios greater than 10 for the investigated 4-kDa PMMA. It should be clearly noted here that the selection of different experimental parameters, such as laser intensity or matrix concentration, might result in different S/N ratios or a different order of the molecules presented in Table 1 since these parameters can effect matrix performance in a negative as well as positive fashion. Nevertheless, the compounds presented in Table 1 are promising new candidates for MALDI matrices, and it was observed that most of them performed best if crystallized from chloroform or acetone. Generally, methanol provided the worst results during the screening, and *zero* compounds were identified as good matrices if crystallized from methanol. In order to test the new matrices in greater detail, five of these compounds were investigated with synthetic polymers of different molecular weights and chemical structure. Matrixes **1**, **2**, **4**, **6**, and **7** were further investigated with respect to their MALDI-TOF behavior in the presence of poly(methyl methacrylate), poy(ethyloxazoline), and poly(ϵ-caprolactone) as well as poly(ethylene glycol) as analytes.

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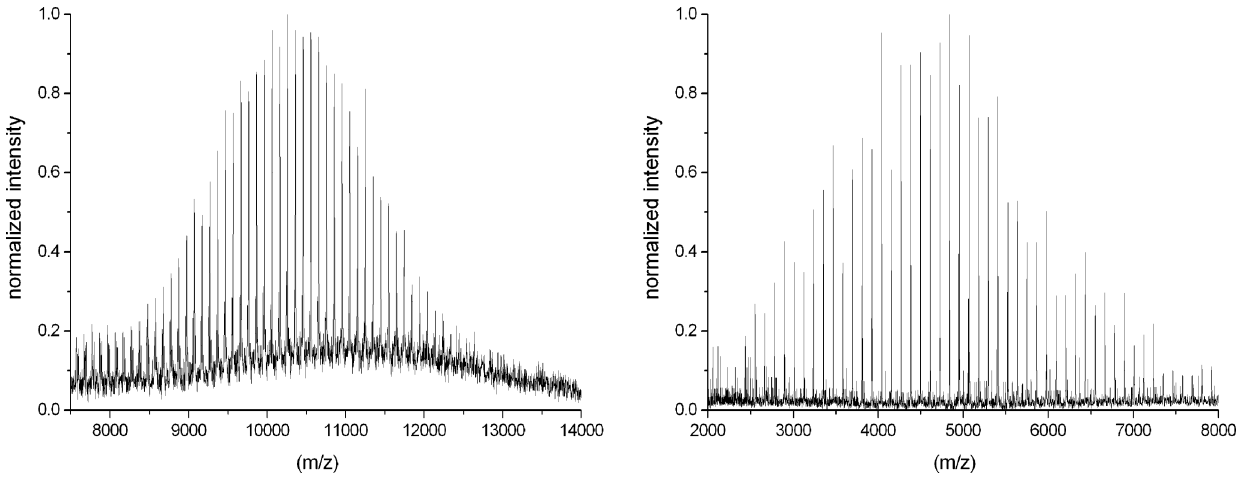

Figure 4. Left: MALDI-TOFMS spectrum of a 10-kDa poly(ethyloxazoline) obtained with **1** as the matrix (deposited as first layer of the sample from acetone) and NaI as cationizing agent (deposited as second layer of the sample from acetone). Right: MALDI-TOFMS spectrum of a 5-kDa, 4-arm, star-shaped PCL utilizing **1** as the matrix.

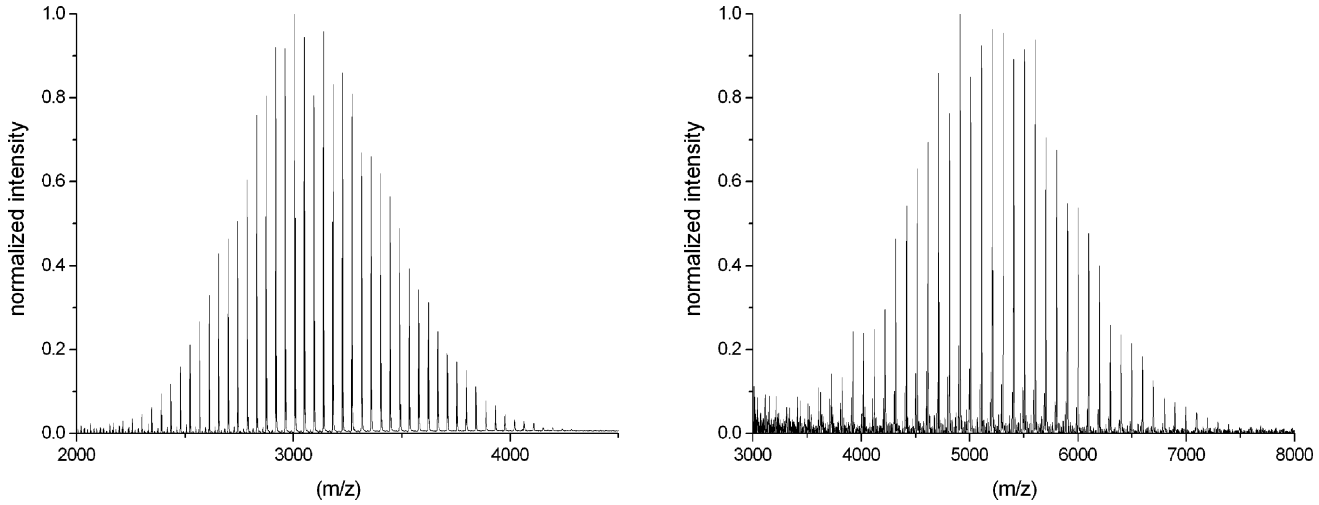

Figure 5. Left: MALDI-TOFMS spectrum of a 3-kDa poly(ethylene glycol) obtained with **2** as the matrix. Right: MALDI-TOFMS spectrum of a 5-kDa poly(ethyloxazoline) utilizing **2** as the matrix.

The chemical structures of the more closely investigated matrices as well as the chemical structures of the applied polymers are provided in Figure 3. Compounds **3** and **5** were "skipped" in the row of most effective matrices, since we expected similar performance for all disperse red derivatives. Nevertheless, it might be interesting in the future to investigate these and the other matrices of Table 1 in greater detail. Generally, **1** showed the best results and was able to ionize all of the investigated polymers (see Figure 3, right). This might be due to the fact that it is a stable radical and is therefore able to ionize the analytes in a straightforward fashion by electron abstraction. This will be interesting to investigate in detail in the future and also in combination with the investigation of other stable radicals as MALDI matrices. It should be noted here that **1** provided the highest signal intensities during screening, when crystallized from $CHCl_3$. However, for a further evaluation, acetone was chosen since in this case also very high intensities in combination with a better signal-to-noise ratio were observed. Figure 4 displays the MALDI-TOFMS spectra of the 10-kDa poly(ethyloxazoline) and a 5-kDa PCL, obtained with **1** as a matrix (crystallized from acetone) and sodium iodide as "cationizing" agent. The spectra show the expected monomer spacing between peaks of 99 and 114 Da, respectively. These results clearly demonstrate that **1** can act as a matrix and that single positively charged analyte ions with the attached cationizing agent are observed in the spectrum, as is usual for MALDI-TOFMS of synthetic polymers. Similar fitting end-group assignments and the respective monomer spacings were also observed for the other investigated polymers as well as for matrices **2** and **4**. These also provided excellent analytical results especially for the investigated poly(ethylene glycol)s, but were not able to provide suitable spectra of the higher molecular weight polymers (PCL 10 kDa, PEtOx 10 kDa, PMMA 14 kDa). This indicated that the screening approach really identified **1** as the most potent new matrix of the investigated set of compounds since it was able to provide good-quality spectra of all investigated polymers. Moreover, matrices **5** and **6** seem to further support this trend, since they were only able to ionize PEGs and low molecular weight PMMA, but not any of the other synthetic polymers. This needs to be further investigated in the future, but might be an indication that matrix potential and corresponding spectral quality is an intrinsic property of a certain compound, since the more closely investigated matrices seem to confirm the trend in the S/N ratios

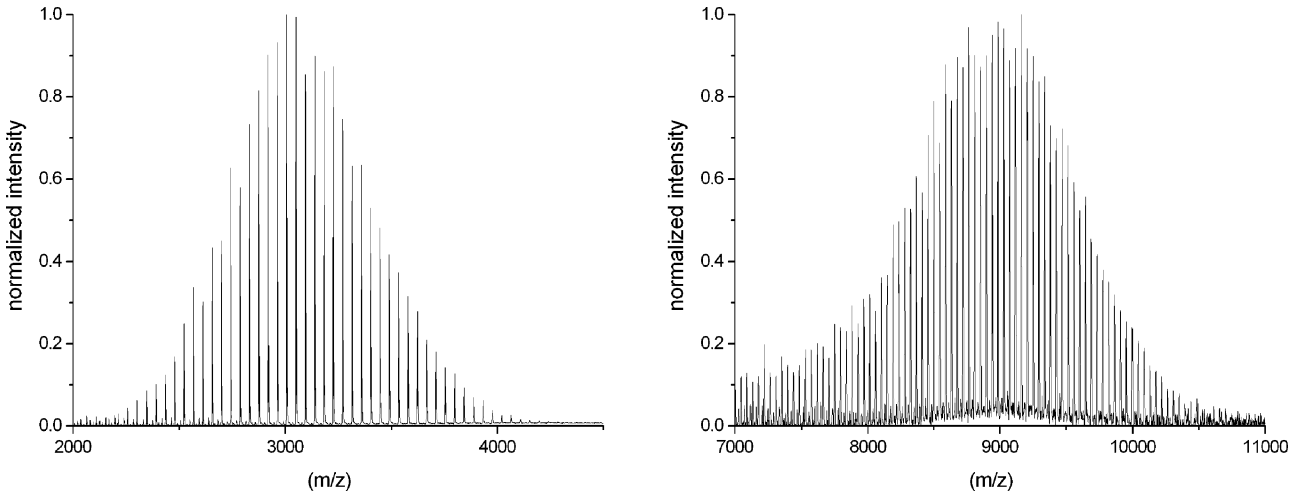

Figure 6. MALDI-TOFMS spectra of a 3- (left) and a 8-kDa (right) poly(ethylene glycol) obtained with **4** as the matrix.

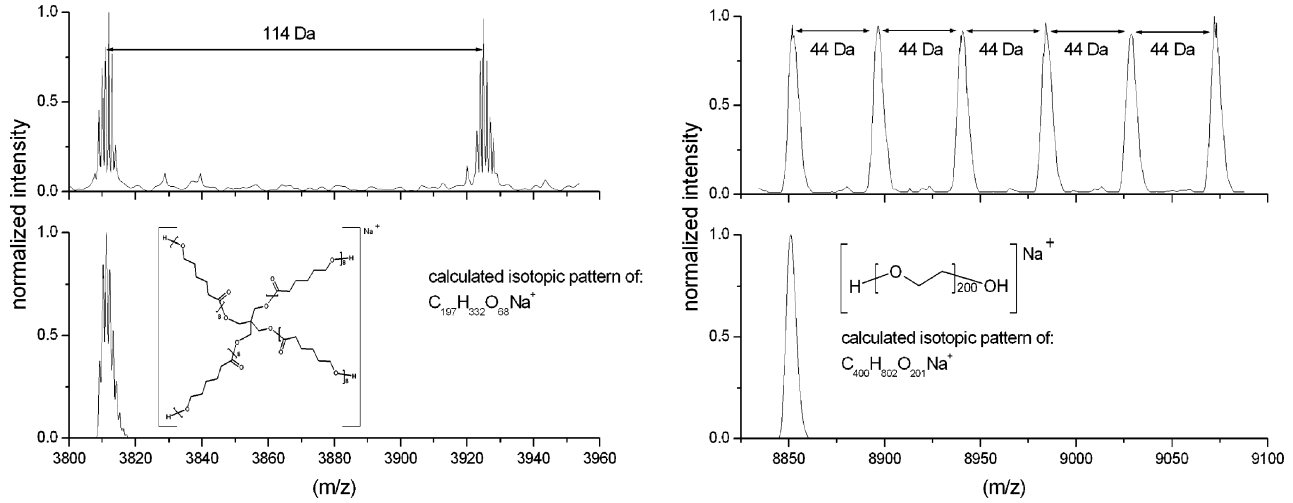

Figure 7. Zoom into the MALDI-TOFMS spectra (top) of PCL obtained with **1** as a matrix (left, see also Figure 4, right) and PEG obtained with **4** as a matrix (right, see also Figure 5, right) with corresponding simulated isotopic patterns (bottom) and correct end-group analysis.

established with PMMA 4 kDa (see Table 1) also with other synthetic polymers. In other words, a certain compound might have the ability to act as a matrix "programmed" in its chemical structure and depending on its descriptors. Figure 5 displays MALDI-TOFMS spectra of PEG 3 kDa (left) and PEtOx 5 kDa (right) obtained with matrix **2**. Well-resolved spectra with the expected monomer spacings (44 and 99 Da, respectively) and fitting end-group assignment were observed demonstrating the potential of **2** to act as a MALDI matrix. Analogous conclusions are valid for **4** as revealed by the MALDI-TOFMS spectra of PEG 3 kDa (left) and PEG 8 kDa (right) shown in Figure 6. Spectra similar quality were obtained for the low molecular weight PEG and PMMA (not shown) utilizing matrices **6** and **7**. The results clearly demonstrate that a large variety of novel MALDI matrices was discovered by applying a screening/rational compound selection approach and that especially **1** and the disperse red derivatives are good candidates for routine analysis of synthetic polymers. It should be noted here that all experiments were performed in the reflector mode of the MALDI and that the investigation of these matrices in the less demanding linear mode might reveal an even broader applicability. However, these settings were chosen since only spectra of the highest possible quality were desired. Moreover, it was observed that the novel matrices and especially **1** performed similarly or even better in terms of the obtained S/N ratio or signal intensities if compared to very well-established MALDI matrices, such as dithranol or DCTB. Dithranol, for instance, which was used throughout the screening as a comparison and is generally accepted as a excellent matrix, can provide a S/N ratio of 20 and higher if crystallized from $CHCl_3$ and subjected to the screening parameters. Moreover, it was observed that the novel matrices can provide spectra with good resolution and without undesired adduct formation, two additional very important parameters if a matrix should be selected for a certain analytical problem. Figure 7 shows the end-group analysis of a 4-arm PCL star-shaped polymer (analyzed with matrix **1**, left) and a PEG (analyzed with matrix **4**, right), both showing good agreement between calculated and observed isotope patterns providing first evidence that these molecules are able to provide easy-to-interpret MALDI spectra without the formation of undesirable adducts. Further investigations should indicate whether these compounds are also suitable for more difficult analytes (e.g., poly(acrylic acid), non-polar and unfunctionalized polymers, such as poly(ethylene) and poly(propylene)) or even higher molecular weight synthetic polymers. Finally, this research clearly demon-

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strates that combinatorial approaches in materials science[24] are fruitful and provide the synthetic as well as the analytical chemist with accurate and interesting new results in an accelerated fashion.

CONCLUSION

Applying a screening/rational selection approach to evaluate a large library of compounds for their ability to act as MALDI matrices led to the discovery of at least 10 new MALDI-TOFMS matrices. These matrices were selected on the basis of their performance in terms of observed signal-to-noise ratio and observed signal intensity during the screening experiment. Five of these new matrices were investigated more closely with a variety of different synthetic polymers of different molecular weights, revealing that especially **1** (a free radical) and disperse red derivatives act as very potential matrices during MALDI-TOFMS experiments. These compounds were able to provide high-quality MALDI spectra with correct end-group assignments for a variety of different polymers and are therefore promising new matrices that might provide not only the synthetic polymer chemist with crucial analytic data in the future. Furthermore, we hope that this approach will lead to the development of quantitative structure−property relationship models, which, in turn, could lead to a better understanding of the MALDI mechanism and therefore be useful for the development and discovery of new and better MALDI matrices in the future.

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