A new role for layered double hydroxides hybrid materials—uptake and delivery of small molecules into the gas phase

Pedro D. Vaz* and **Carla D. Nunes**

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Hydrotalcite (HT) intercalated tryptophan (trpH) and phenylalanine (pheH) hybrid materials have been prepared by the reconstruction method. Based on elemental analysis results, such materials were found to be prepared with the general formulas $[Mg_6Al_2(OH)_{16}](trp)_{1.42}(OH + anions)_{0.58}\cdot 4H_2O$ and $[Mg_6Al_2(OH)_{16}](phe)_{1.26}(OH + anions)_{0.74}\cdot 4H_2O$, respectively. After characterization by powder X-ray diffraction and Fourier Transform Infrared Spectroscopy, the amino acid intercalated clays were used directly in Matrix Assisted Laser Desorption Ionization Mass Spectrometry experiments, where the clay was used as the matrix. The guests were detected in negative mode as $[trpH–H]^-$ at m/z 203 and as $[pheH–H]^-$ at m/z 164. From the mass spectrometry experiments no interference of ions from the clay was detected, meaning that such inorganic material is stable under the laser radiation and more important that it is adequate for use in such experiments. For the experiments using this particular approach we propose an alternative term—HALDI—standing for *H*ost *A*ssisted *L*aser *D*esorption *I*onization mass spectrometry.

Introduction

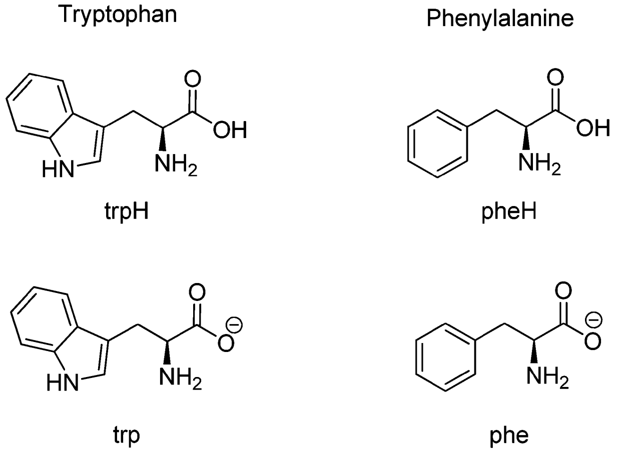
Layered double hydroxides are an important class of natural occurring minerals whose synthesis in the lab is easily accessible.[1] Such materials, also known as anionic clays have the capability of anion swelling, making them very versatile. In addition to the rich intercalation chemistry that can be played with, it also shows a wide range of variations of its composition. This latter aspect is based on the versatility of the general formula $[M^{2+}{}_{1-x}M^{3+}{}_x(OH)_2](A^{m-})_{x/m}\cdot nH_2O$ where both M^{2+} and M^{3+} can be varied,[2] and A^{m-} is usually a simple anion such as Cl^-, NO_3^- or CO_3^{2-}. In its general formula, x measures the amount of M^{3+} relative to $(M^{3+} + M^{2+})$, correlating with the spacing between layers. Moreover, the spacing changes concomitantly with both the size of the intercalated anions and the degree of hydration, and many works have dealt already with this, ranging from the intercalation of simple organic and inorganic anions to complicated biological ones.[3–6]

Among the possible strategies for introducing anions, rehydration of a calcined precursor has proved advantageous compared to direct anion-exchange,[3] as competition between anions can be efficiently prevented, as long as carbonate, the anion found in the minerals, is excluded. For this reason, manipulation of the materials under an inert atmosphere is usually crucial. In another interesting route, the synthesis of the double hydroxide is carried out in the presence of the anions chosen to be part of the final material.[7,8]

Although the nature of the anions can be wide-ranging, if they carry proper functional groups, they can undergo further reactions, namely coordination to a metal center.[9] Furthermore, calcined hydrotalcite itself has also been shown to catalyze reactions, such as the aziration of oxiranes[10,11] or aldol condensations,[12] serving as an environmentally friendly catalyst which is able to be reused several times. In a different perspective, such materials are also able to play a key role in analytical/environmental chemistry. In this aspect there are reported works on the use of such clays in the uptake of metals, and of other relevant environmental compounds, such as persistent organic pollutants (POPs).[13–15] More important are the applications in human health, where many works have been published and from these some patent applications have also resulted.[5,6,16] In particular, it has been shown that such materials can act as amino acid/peptide reservoirs and adsorbents.[17]

Mass spectrometry is a powerful technique which has been rising in interest by either the development of more sensitive spectrometers and also by newly available techniques.[18] In particular matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) is a very adequate method for studying biomolecules (peptides, proteins, oligonucleotides and oligosaccharides), polymers or more generally high molecular-weight analytes.[19] MALDI-MS provides a soft and efficient ionization method of thermolabile and non-volatile organic compounds.[20] The major drawback of this particular technique is that the commonly used organic matrices usually interfere with low molecular weight analytes.[21] Despite this, some solutions are being developed to circumvent such problem.[22] In particular, the use of inorganic oxide materials (including mesoporous materials) have proved to be quite adequate for such a task.[23–28] Some of these approaches show stability under highly energetic

CQB, Department of Chemistry and Biochemistry, Faculty of Science, University of Lisbon, 1749-016, Lisbon, Portugal.
E-mail: pmvaz@fc.ul.pt, cmnunes@fc.ul.pt; Fax: +351 217500088; Tel: +351 217500877



Scheme 1

conditions, thus originating mass spectra with matrix free signals.

In this work, we report the use of amino acid intercalated hydrotalcite (hereafter denoted as HT) as a suitable reservoir and host, for the analysis of amino acids by MALDI mass spectrometry. Tryptophan and phenylalanine (Scheme 1) intercalated hydrotalcite clay materials were prepared and used directly for MALDI analysis.

As an advance, this work uses the amino acid intercalated hybrid material "as-is" instead of using the bulk matrix and layering the analyte on top of it or by co-crystallizing it, as is usually described.[26,27] The herein reported procedure facilitates the analysis as well as giving HT an additional application. As a result, mass spectra are obtained with a clear identification of low-molecular weight analytes. This and other features will be discussed in the following sections.

Results and discussion

Structural characterization

Anionic clays offer a variety of solutions for the intercalation of guest species inside its interlayer spacing. This is due to the versatile chemistry that is offered. In particular, the introduction of guest species can be made by simple ion exchange, by reconstruction of the bi-layer structure and by co-precipitation during the synthesis of the clay itself.

In this work, the reconstruction method was employed, Fig. 1, by taking advantage of the memory effect displayed by the hydrotalcite material (hereafter denoted as HT). In this way, HT lamellar material was first submitted to a calcination process at 823 K for 4 h to eliminate the CO_3^{2-} anions from the interlayer region, as described in our previous work.[9] During this process, the structure of the lamellar material collapses, and is thereafter rebuilt when the deprotonated amino acids trp and phe are intercalated inside the interlayer space by using dimethylformamide (dmf) at 343 K.[9,29] The deprotonation of the amino acids is carried out in deionized water in the presence of KOH and the resulting solution is then added to the HT suspension leading to the preparation of the composite materials HT–trp and HT–phe.

The intercalated resulting materials were characterized by means of FTIR and powder XRD (Fig. 2). The FTIR spectra of both composite materials are dominated by the vibrations of the clay host material. Particularly, there is a broad and intense band assigned to the νOH groups in the 2600–3700 cm^{-1} range. Likewise two intense bands are observed at 1369 cm^{-1} and 1588 cm^{-1}, which are assigned to the δOH modes of the basal layer or of water molecules in the interlayer spacing. The lattice vibrations of the clay sheets are also observed. Those corresponding to the M–O (M = Mg, Al) vibrations appear at 670 cm^{-1} and 560 cm^{-1}, whereas those due to the M–O–M (M = Mg, Al) vibrations appear as a broad band at 451 cm^{-1}. Such findings are in good agreement with previous results.[29]

Despite these intense spectral features the guest molecules, either trp or phe can also be detected. For example, for the HT–trp material, a sharp band is observed at 3404 cm^{-1} corresponding to the νNH modes, and at 3080 cm^{-1} and 3048 cm^{-1} due to the νCH modes. A set of 5 bands at 1664, 1591, 1458, 1412 and 1360 cm^{-1} is also detected due to its strong intensity, being due to νCOO^-, νCC and δCH modes of the guest molecule, respectively. Finally a band appearing at 744 cm^{-1} is also observed and is due to the CH_2 rocking mode. All these values are in agreement with those evidenced by the tryptophan molecule itself (Fig. 2), although some of these bands show a deviation relative to the free molecule, since the guests are deprotonated, thus bearing a net negative charge, and are held inside the gallery of the material where intermolecular host guest interactions occur. These are expected to be established by means of hydrogen bonds between the COO^- of the amino acids and the M–OH (M = Mg, Al) groups from the clay. Interactions of this type between the guests and existing OH^- and/or H_2O cannot be ruled out.

The results of elemental analyses of materials HT–trp and HT–phe show that the N content is below what would be expected based on a complete reconstruction with the amino acids.

The N contents found for HT–trp and HT–phe were 4.20% and 2.02%, respectively. These values are slightly lower than the maximum expected values of 5.90% and 3.21%, by the same amount. It could suggest that incorporation of some carbonate during reconstruction of the layered structure would take place, leading to a multiphase sample.[30] Alternatively, the high content of hydrogen found may be explained by the uptake of OH groups or other anions. In this way, on the basis of the amount of nitrogen for the two materials, the contents of trp and phe incorporated are 71% and 63%, respectively, the rest being fulfilled by other anions from the solution (including hydroxide and fatty acids, as will be addressed later). In this way, the reconstructed clays can be rationalized as $[Mg_6Al_2(OH)_{16}](trp)_{1.42}(OH + anions)_{0.58}\cdot 4H_2O$ for HT–trp and $[Mg_6Al_2(OH)_{16}](phe)_{1.26}(OH + anions)_{0.74}\cdot 4H_2O$ for HT–phe.

In the case of the HT-phe material, again some weak spectral features are observed. Indeed, the bands at 3005 and 2966 cm^{-1} correspond to the νCH modes, whereas those appearing at 1571, 1414 and 1308 cm^{-1} are due to the νCOO^-, νCC and δCH modes of the phe guest molecules. As described above for the HT–trp material, there is also some deviation of

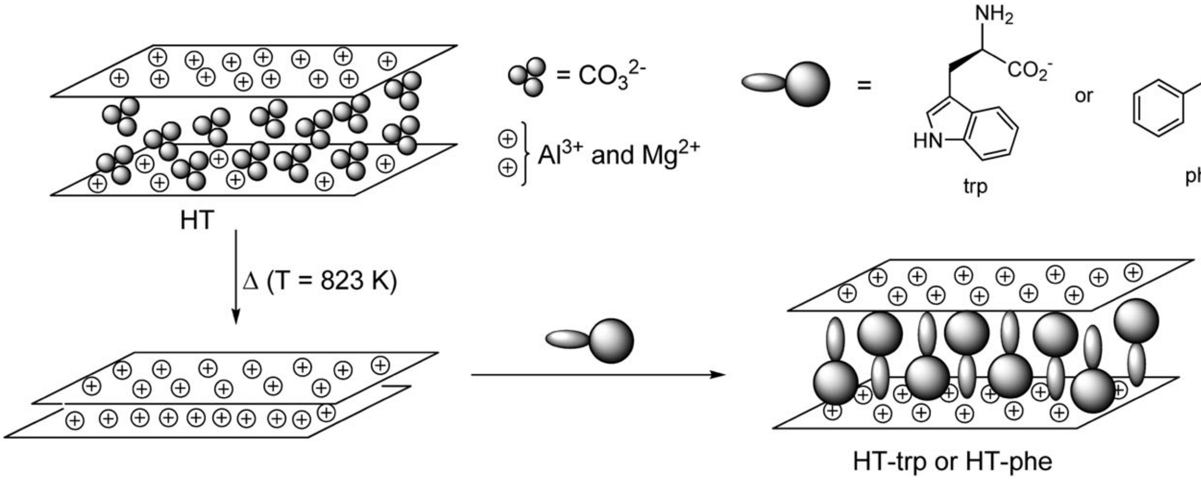


Fig. 1 Preparation of the amino acid intercalated HT materials.

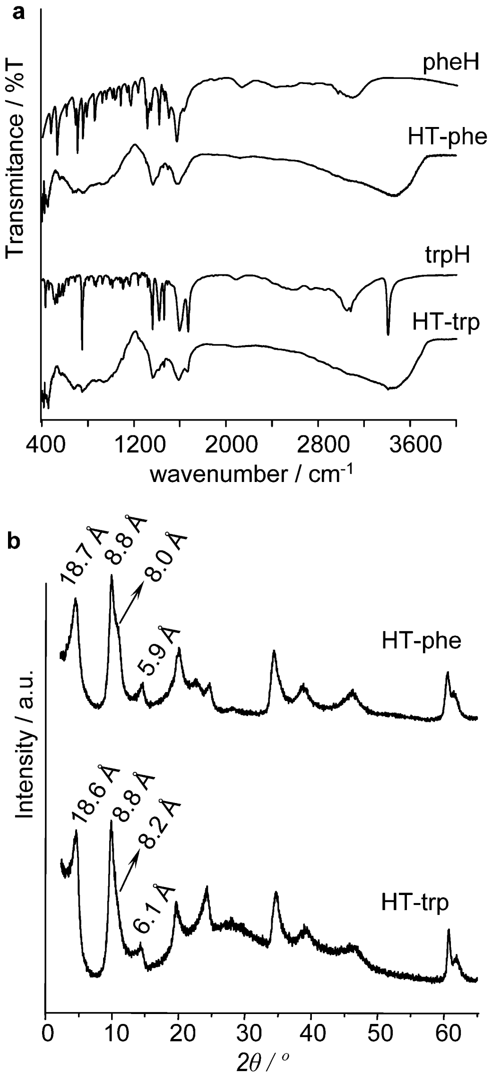


Fig. 2 FTIR spectra (a) and powder X-ray diffraction data (b) of the amino acids and amino acid intercalated HT materials. The spectra/diffractograms are shifted for clarity.

the bands compared to the free pheH molecule. Overall, the subtle changes observed in the bands of both composite materials suggest that the structures of the anionic amino acids were not affected during immobilization in the material.

Results from the powder XRD analysis show that the obtained patterns for these lamellar materials are typical of this type of reasonably well-ordered materials, exhibiting sharp and symmetric *003* reflections (Fig. 2b).[31] The calculated *d* parameters were found to be 18.6 Å and 18.7 Å for both HT–trp and HT–phe materials, respectively. Assuming the HT sheets to be 4.8 Å thick,[1,3] it is possible to estimate the gallery height of HT–trp and HT–phe to be 13.8 Å and 13.9 Å, respectively, indicating that these guest molecules are in the upright position. Another interesting feature is the observation of a shoulder at $2\theta = \sim 11°$ just after the peak indexed to the *006* reflection. This shoulder is due to the *003* diffraction peak of reconstructed HT with OH^- groups which may arise from the hydroxide solution used to deprotonate the pheH and trpH guests. This phenomenon has already been described previously by Aisawa,[29] where it has also occurred although a slightly different reconstruction method was employed. Such results are in agreement with others previously reported.[32] Most recently, Costantino[33] has also reported the intercalation of phe in hydrotalcite (among other anions) by an anion exchange procedure, reporting a *d* value of 17.3 Å which is also in agreement with data reported in the present work.

Diffuse reflectance UV/Vis experiments carried out on the composite clay materials yielded typical spectra.[34] From this data, it is possible to determine the band-gap of the amino acid composite materials, which was calculated to be 2.55 eV and 2.58 eV for HT–trp and HT–phe materials, respectively. This value is smaller than that reported for calcined Zn/Al materials, which were estimated to be *ca.* 3.22 eV.[34] This is not surprising given that the materials reported in the present work have anions which may behave as electric conductors, thus lowering the resulting band-gap energy.

Mass spectrometry analysis

The composite materials HT–trp and HT–phe were used in MALDI experiments carried out in a high resolution FTICR spectrometer. In these experiments no other entity was used as a matrix to promote the ionization of the analytes. In this way,

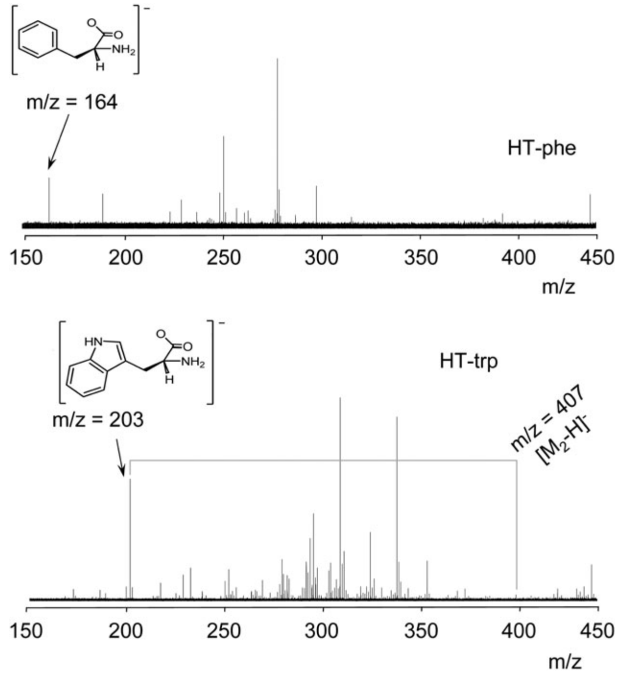


Fig. 3 MALDI–MS spectra of the amino acid intercalated HT materials.

the composite hybrid materials were used "as-is" directly in the MALDI experiments. The MALDI MS spectra of trp and phe obtained by using HT–trp and HT–phe as matrices are shown in Fig. 3. Given that both the trp and phe guest molecules are already in the anionic form inside the intragallery spacing of the HT material the mass spectra were also acquired in negative mode.

The MS spectrum of trp shows a characteristic ion at *m*/*z* 203 $[trpH - H]^-$ (with an error of about 1.6 ppm), observed with high intensity. It is also possible to detect a peak with low intensity at *m*/*z* 407 attributed to the deprotonated tryptophan dimer, $[(trpH)_2 - H]^-$, with an error of 3.4 ppm, which indicates that the ionization process is mild enough to permit the observation of dimeric structures. For phe, the MALDI mass spectrum shows a similar aspect to that of trp. In fact the characteristic ion peak at *m*/*z* 164 $[pheH - H]^-$ is clearly observed. Contrary to the trpH MS spectrum, the dimeric structure is not detected.

A relevant feature found in the mass spectra is the population of peaks found. At first glance it was thought that its origin would be from ionized fragments from the HT matrix itself. The quest for peaks containing Al, Mg or combinations of both metals has been pursued without success, thus making it clear that the matrix itself does not interfere in the analysis. However, closer inspection of the peaks has shown that several peaks, for instance at *m*/*z* 227, 254, 255 and 283, are due to long-chain fatty acids, such as myristic, palmitoleic, palmitic and stearic acids, as well as a peak from a polysiloxane—at *m*/*z* 447. These are summarised in Table 1.

These peaks from both the fatty acids and polysiloxane are very likely to be contaminants from the silicone grease used in the glass ground joints during the reconstruction process for the intercalation of the amino acids in HT. This was found to be reproducible after several attempts of preparing the HT–amino acid hybrid materials. The relatively high intensities of these peaks in the MS spectra cannot be intended to be quantitative, since many parameters are involved, such as the different ionization efficiencies from the species involved.[35] It should be mentioned that peaks resulting from the HT material itself (based on Mg and Al) have not been detected.

This may come from the fact that inorganic matrices are stable during the laser desorption process, as previously described by others.[27] Other factors, such as a uniform dispersion of the analyte throughout the HT clay, are also relevant.[29,32] Other authors have also reported this effect on inorganic-based matrices, although both the matrix and the sample preparation method differ from this one.[22,26]

Usually, the most common choice of matrices relies on α-cyano-hydroxycinnamic acid or on 2,5-dihydroxybenzoic acid (DHB). Many other works, however, also dealt with the successful use of inorganic materials as suitable matrices. Among these, one can find glycerol suspended cobalt powder[19,23] or glycerol suspended silicon particles.[36] Mainly these have been employed in the analysis of large compounds.

Recently, mesoporous materials have also been employed as adequate matrices in such MALDI experiments.[26–28] From these works, only that reported by Lee *et al.* dealt with the analysis of small lightweight bio-molecules, *i.e.*, with less than 300 Da.[28]

Most recently, anatase TiO_2 has also been used in MALDI.[22] The major advance of that work was that it was used for the analysis of small molecules, namely 2-chloroaniline and caffeine among others. The key achievement was that the resulting mass spectra of the different analytes did not suffer from interference from the matrix due to the stability of the inorganic material during the laser desorption process, depending on the TiO_2 polymorph.

Despite all the examples provided by the previous works described above, none of them relied on the use of a composite organic–inorganic hybrid material, as reported here. Although the MS results show the positive identification of the analytes of interest together with the interferences found and described above it can also be considered as advantageous, based on the following description. Given that such clays will intercalate virtually any anion it can be used as a selective anion scavenger in complex samples and be then used directly in MALDI experiments for analysis.

In this context, a word should be given on the mechanism of gas-phase ion formation. The first assumption is that one must bear in mind that the ions already exist within the interlayer spacing of the clay, meaning that there is not a true ionization process. Instead, ions or more accurately clay-trapped ionized species are ejected from the clay interior, which are then delivered into the gas phase on their way into the MS spectrometer. In addition, the ejected ions leave *loci* of positive charge that must be balanced. This may be accomplished by water molecules present within the gallery that dissociate thereafter. Such water molecules were most probably incorporated during both the synthesis and the sample preparation procedures (see Experimental Section). The gas-phase ion formation may thus occur by two pathways. The first—thermal

Table 1 Calculated and experimental molecular weight of fatty acids, polysiloxane and amino acids detected in high-resolution MS experiments

Molecule	Ion Formula	Calculated MW	Experimental MW	Error (ppm)
Myristic acid	$[C_{14}H_{28}O_2 - H]^-$	227.201654	227.201991	0.2
Palmitoleic acid	$[C_{16}H_{30}O_2 - H]^-$	253.217304	253.217328	0.0
Palmitic acid	$[C_{16}H_{32}O_2 - H]^-$	255.232954	255.232828	0.5
Stearic acid	$[C_{18}H_{36}O_2 - H]^-$	283.264254	283.264346	0.3
Polysiloxane	$[C_{13}H_{36}O_2Si_4 - H]^-$	447.136632	447.136590	0.5
trpH	$[C_{11}H_{12}N_2O_2 - H]^-$	203.082601	203.082271	1.6
trpH dimer	$[(C_{11}H_{12}N_2O_2)_2 - H]^-$	407.172479	407.174417	4.8
pheH	$[C_9H_{11}NO_2 - H]^-$	164.071702	164.071634	0.4

mechanism—could be rationalized by the heat generated by the laser irradiation which is then transferred to the guest species inside the clay and consequently sublimed. The second—excess energy mechanism—may be explained by a high energy absorption by the clay which is transferred to the guests. The latter will therefore reach an excited state and concomitantly will be ejected into the gas phase on their way to the MS spectrometer. While the first pathway seems to be less possible to occur given that the clay may act as thermal insulator,[37] the second one seems to be more likely to occur; however this requires further studies which are presently ongoing work, and in fact agrees with established mechanisms in MALDI.[19] In fact, the MALDI laser irradiates with an energy of 3.68 eV which is higher than the experimental value for the band-gap energy found for the herein reported clays. These values were estimated to be 2.55 eV and 2.58 eV for HT–trp and HT–phe, respectively, as mentioned previously. In this way it is very likely that the excess charge transfer does occur from the host clay into the guest analytes.

Conclusions

The results described and discussed above show that a purely inorganic host material may serve as a matrix in MALDI-MS experiments successfully. Moreover the nature of the host material in uptaking proper guest molecules which are held in its interior, combined with the ability of expelling them when needed inside the MS instrument gives it an increased interest. From an analytical point of view it can be advantageous, since such materials are known to uptake guests covering a wide range of molecular weights and from different origins. Numerous examples are known, from simple inorganic anions to DNA.[3–6] In this way it has been demonstrated that this material may in fact adsorb many species, even in low concentration when working with complex matrices, showing that such materials can compete with other methods such as stir bar sorptive adsorption/extraction.[38,39] In addition, during the MS experiments there is no interference from the host material, *i.e.*, no ions from the host material are detected, showing that the clay is stable under such conditions, which is an advantage over other systems. Even from an economical point of view, one can take advantage of the memory effect of the clays and in this way a given sample may be reused in several uptake/analysis experiment cycles, as long as a calcination step is performed in between.

The ionization process is probably based on a process of excessive energy transfer from the clay to the analyte, after laser irradiation, which induces the ejection of the ions into the gas-phase, as already discussed previously by others. Since the use of the composite material is "as-is" we also propose the use of a derived term—HALDI—standing for *H*ost *A*ssisted *L*aser *D*esorption/*I*onization mass spectrometry.

Experimental

General

All preparations and manipulations were performed by using standard Schlenk techniques under dry nitrogen atmosphere. Commercial grade solvents were dried and deoxygenated by standard procedures [$HC(=O)N(CH_3)_2$ (dmf) over CaH_2], distilled under nitrogen, and kept over 4 Å molecular sieves. L–Tryptophan (trpH), L–phenylalanine (pheH) and carbonate intercalated Mg, Al-hydrotalcite (HT) were purchased from Aldrich Co. The intercalation of the amino acids was performed by the reconstruction method by adopting a procedure from the literature.[9] Prior to the intercalation experiments, commercial hydrotalcite was calcined (823 K for 4 h) in order to eliminate all the carbonate anions and kept under a nitrogen atmosphere to prevent the reuptake of carbonate.[9]

Powder XRD data were collected with a Phillips PW1710 diffractometer by using graphite-filtered Cu-Kα radiation. FTIR spectra were measured with a Nicolet Nexus 6700 FTIR spectrometer by using KBr pellets (for bulk amino acids) in the absorbance mode and also with diffuse reflectance (for clay materials). All FTIR spectra were measured with 2 cm^{-1} resolution.

All MS experiments were performed on an APEX Ultra Fourier transform ion cyclotron resonance (FTICR) mass spectrometer (Bruker Daltonics, Billerica, MA, USA) equipped with a 7.0 Tesla actively shielded superconducting magnet. The vacuum was maintained by means of mechanical vacuum pumps followed by turbomolecular pumps in two different regions: ion source (maintained at approx. 6.0×10^{-6} mbar) and cell region (maintained at approx. 4.0×10^{-10} mbar). The ions were generated from an external Apollo II dual ESI/MALDI source (Bruker Daltonics), equipped with a N_2 laser (λ = 337 nm; 3.68 eV), in the negative ion mode. The laser energy at the target position was 80–100 μJ and the laser pulse length was 4 ns. The laser power was adjusted to obtain satisfactory mass resolution (> 60 000) and signal-to-noise ratio. The spectra shown are the average of 32 spectra with 20 laser shots per spectrum. The MALDI plate used was a MTP AnchorChip™ 400/384 T F (Bruker Daltonics).

Preparation of the materials HT–A (A = trp or phe). A mixture of trpH (7.30 mmol) or pheH (7.30 mmol) in freshly distilled dmf (10 mL) and deionized type II water (20 mL) with KOH (1 equiv.) was stirred until complete solubilization. This solution was then added to a suspension of calcined HT (1.00 g) in freshly distilled dmf (25 mL) at 343 K, and the reaction mixture was stirred at the same temperature for 48 h. All the manipulations were carried out under a dry N_2 atmosphere to prevent the uptake of carbonate anions. The resulting materials were then filtered off, washed with deionized type II water (3 × 20 mL), and dried in a desiccator under vacuum.

HT–trp. Elemental analysis found: C 21.53, H 4.85, N 4.20. IR (KBr): $[\tilde{\nu}]$ = 3404, 3080, 3048, 1664, 1591, 1458, 1360, 1293, 670, 560, 451 cm^{-1}.

HT–phe. Elemental analysis found: C 18.79, H 4.96, N 2.02. IR (KBr): $[\tilde{\nu}]$ = 3005, 2966, 1571, 1414, 1308, 1269, 670, 560, 451cm^{-1}.

Preparation of samples for MALDI experiments. Particle matrix suspensions were prepared by dispersing the composite clay samples in deionized water at a concentration of 10 mg mL^{-1}. A 2 μL aliquot was pipetted onto the stainless steel target plate and allowed to dry before analysis.

Acknowledgements

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