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ARTICLE

Chiral imprinting in molten gallium

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Abstract:

Chiral imprinting in molten gallium can be attained by ultrasonic irradiation of molten Ga overlayed by an aqueous solution of D- or L- tryptophan. The products are micro/nanoparticles of Ga encapsulating molecules of one of the enantiomers. After leaching of the enantiomer in pure water, molecular templates are left on the surface of the gallium particles, enabling the entrapment of the specific enantiomer from a solution of the racemate and yeilding an enantiomeric excess of 6-12%. The extent of the enantiomeric excess was determined using polarimetry and circular dichroism measurements.

Keywords: molten gallium, chiral imprinting, D- or L-tryptophan, enantiomeric excess.

Introduction:

Chirality is a key factor in many molecular recognition processes, which have various applications in chemical and biological systems[1,2]. A chiral molecule is one that has two mirror-images which are not superimposable in three dimensions. The two forms of chiral molecule are classified as enantiomers. Discovering efficient methods to prepare, control and detect enantiomerically pure chiral compounds is critical for the development of pharmaceuticals, agrochemicals and food additives. Well known examples of chiral molecules are: ibuprofen (one of the most significant anti-inflammatory drugs, also known as "neurofen"), *L*-Dopa (a drug for the Parkinson disease), aspartame (artificial sweetener) and geraniol (rose-like scent in perfumes).

In recent years, chiral metal nanoparticles and nanostructures have been used in asymmetric catalysis[3-5], chiral separation[6-8] and enantioselective detection[9,10]. Gold nanoparticles (GNPs) are very attractive in nanoscience and technology[11, 12] due to their ease of preparation, controllable particle size, narrow size distribution, good solubility in buffer solutions and convenient modification via the Au-S bond. It is therefore not surprising that GNPs were also used for enantioselective adsorption[9] and recognition[13]. Yang et al. synthesized thiolated b–CD modified GNPs and dispersed them in running buffer for chiral separation of enantiomers[6]. Shukla et al.[9] employed D- or L-cysteine-modified GNPs for enantioselective adsorption of propylene oxide. Duran Pachon et al.[14] imprinted palladium with two derivatives of chiral cinchona alkaloids by chemical reduction of Pd ions in aqueous solutions of these compounds. The chirally imprinted metallo-organic hybride precipitated imediately and showed some enantioselectivity in catalytic hydrogenation reactions. It was found that after extraction of the dopant from the hybrid material the palladium retained some chiral character.

Recently we reported on the formation of gallium particles by ultrasonic irradiation of molten gallium in warm water[15,16]. We also demonstrated that some organic compounds, such as phenanthroline

and congo red, could be entrapped to some extent in the gallium particles when the process was performed in aqueous solutions of these compounds. In the current work we checked the possibility to create gallium particles which are enantio-selective by preparing them in aqueous solutions of D- or L-tryptophan, and thus induce some kind of imprinted chirality in their structure. The chiral imprinting was investigated by measuring the circular dichroism (CD) and optical rotatory dispersion (ORD) of the solution.

Experimental section

Chemicals: D, L, DL – Tryptophan ($C_{11}H_{12}N_2O_2$, 204.23 g/mole) and Gallium (Ga, 69.7 g/mole, 99.99%) were purchased from Sigma-Aldrich. Solutions of these compounds were prepared by dissolving weighted amounts in 250 ml double distilled water.

Experimental setup and procedure: A granule of gallium (~0.5 g) was inserted into a glass test tube containing 14 mL of aqueous solution of one of the compounds: D, L, or DL – Tryptophan, each of 50mM concentration. The test tube was dipped in a water bath at 55^{o}C and the tip of an ultrasonic transducer was dipped to the solution, ca. 2 cm above the gallium. The ultrasonic transducer used was model No. 51-05-290 produced by Ultrasonic Power Corporation, Freeport, Illinois. When the gallium was all molten, ultrasonic irradiation was applied for 3 min., causing dispersion of the gallium and formation of a grey suspension of particles. These were separated by centrifugation at 6000 rpm for 10 min., followed by three cycles of rinsing with pure water and separation by centrifugation.

The leaching experiments of the D-, L-, and DL- tryptophan from the Ga spheres were performed as previously reported[18], by immersing the gallium particles in pure water for a period of two weeks, with occasional sampling and measuring the concentration of the leached tryptophan by UV-vis. spectroscopy. After that period the gallium particles were separated, washed twice with pure water, dried under vacuum and 0.25 g were then immersed in 10 mL portions of a 50 mM racemic solution of DL-tryptophan for 7

days with shaking. After that period, the solutions were filtered and examined by polarimetry and circular dichroism techniques.

Analytic equipment: SEM images were obtained with an FEI Inspect microscope model S, operated at 20kV. A small amount of Ga particles powder was sprinkled on a SEM sample holder, coated with a carbon tape. No gold coating of the sample was needed due to the conductivity of the gallium particles. UV-vis. spectra were measured using a Cary 100 spectrophotometer (Varian), operated by LabSphere software. X-ray diffraction (XRD) measurements were performed with a Bruker D8 Advance X-ray diffractometer using Cu Kα radiation operating at 40 kV/30 mA with a 0.02 step size and a 1 s step. Elemental analysis was performed by the SEM energy dispersive X-ray spectroscopy (EDS). Circular dichorism measurements have been performed using the CD spectrometer (Applied Photophysics, Chirascan). The optical rotation measurements were performed by JASCO digital polarimeter (model P-1010, λ=589 nm) using the quartz cell (5mL, L=50mm) at room temperature. Racemic (DL) trptophan, enatiomeric ecxess of L tryptophan, and enatiomeric excess of D tryptophan were qualitatively analyzed by using Chiral HPLC. Chiralpak® AD-H, column (4.6 mm ID, 250 mm L) (Daicel Chiral Technologies (china) co., LTD) on a Surviyor LC Pump Plus HPLC instrument (Thermo Scientific, USA) were employed at room temperature.

Results

Physical characterization of the Ga particles

Gallium particles were formed by ultrasonic irradiation of molten gallium in an aqueous solution of D-, L- or DL tryptophan, as described in the experimental section. After sonication, the particles were separated by centrifugation, rinsed with pure water and dried. Analysis of the solid particles by XRD (**Figure 1**) showed perfect matching of all the signals with the database for gallium, indicating that they were composed of crystalline gallium. Examination of the particles by SEM (**Figure 2**) revealed that the

particles were spherical, in the micrometric size-range and below. Energy dispersive x-ray spectroscopy (EDS) analysis confirmed that the sole component was gallium.

Entrapment of tryptophan in the micro/nanoparticles of gallium

Based on our results in entrapment of some organic compounds in Ga particles[18], we extended this study to check whether entrapment of chiral molecules can occur, and would they imprint chirality in the gallium spheres so that preferred entrapment of one enantiomer over the other would be attained. This was examined with the D- and L- enantiomers of tryptophan, by performing the ultrasonic formation of gallium particles in 50 mM aqueous solutions of either of them. The particles were separated by centrifugation and washed three times with distilled water to remove any residues of unentrapped tryptophan on their surface. After drying, the particles were immersed in 10 mL of pure water for prolonged leaching. Aliquots of 200 μL were taken occasionally for UV-vis analysis, to determine the presence of tryptophan and its concentration in the leaching solution. The spectrum of tryptophan has two absorption bands in the UV range at 216 and 275 nm, the latter has a known extinction coefficient of ε_{275}=5650 M^{-1} [17]. The UV-vis spectra of the tryptophan aqueous solutions before sonication, after sonication with molten gallium (and separation of the particles) and of two portions of the rinsing water were recorded, and are presented in **Figure 3A** for the D-tryptophan experiments. A difference between the concentrations before (50 mM) and after (45 mM) sonication was observed, indicating that ca. 10% of the compound was absent from the solution after sonication. This could be adsorbed on the surface of the Ga particles or entrapped within them. We have collected altogether 8% of the entrapped D-tryptophan molecules. About 5% were surface-residing molecules that were removed by rinsing with water, whereas the rest 3% can be attributed to a longer leaching process. No changes in the shape or the intensity of the spectrum were observed in a control experiment without gallium, showing that sonication alone does not affect the tryptophan itself. **Figure 3B** presents the absorption spectra of the aliquots of the leaching solution as a function of time. It demonstrates

constant increase in the concentrations of D-tryptophan during 15 days. Experiments were performed also with solutions of the L-enantiomer and the racemic DL- tryptophan following the same procedure. Similar results were obtained in these cases: about 6-9% decrease in the intensity of the UV-vis signals after the sonication, and leaching of the entrapped material that lasted for 7-15 days.

Chiral imprinting

Following the leaching experiments, the gallium particles were separated and dried for 2 days under vacuum. 250 mg of the dried particles were immersed in 10 mL solution of 50 mM DL-tryptophan to check for any induction of chirality in the racemic solution due to preferred interaction with the imprinted gallium particles. The results below were obtained from an experiment that was performed with gallium particles which were formed in an aqueous solution of L-tryptophan. After immersion in DL solution and shaking for 7 days, a sample of that solution, together with samples of the original L-solution before and after sonication and a sample of the leaching solution were taken for polarimetric measurements. Each of the sample solutions was analyzed 10 times and the average rotation values are given in **Table 1**. The measured optical rotation of the original L tryptophan solution was -0.1526 deg. and after sonication (with molten gallium) it dropped to -0.1245 deg., indicating depletion of L-tryptophan molecules in the solution as a result of entrapment. This result is much higher (18% entrapped) than the decrease in the intensity of the absorption signals on the UV-Vis spectrum which was 10%. The measured rotation in the leaching solution after 15 days was -0.0171 deg., indicating that 61% of the entrapped L-tryptophan was leached. Finally, measuring the rotation in the DL-solution, after 7 days of immersion of the "empty" gallium particles, gave a value of +0.0161. Obtaining a positive rotation is indicative of an excess of the D-tryptophan. The excess of the D-enantiomer points out to the preferred penetration of the L-tryptophan into the gallium particles. The low values of the standard deviations demonstrate the reproducibility of the measured chirality values.

To validate these results, an experiment was conducted under similar conditions with gallium particles that were formed in an aqueous solution of D-tryptophan. These particles were also immersed in a DL- solution for 7 days with shaking, after which the polarity of that solution, as well as the polarities of the original D-solution before and after sonication and of the leaching solution, were measured. The results are summarized in **Table 2**; this time an excess of the L-tryptophan was found in the solution. Further confirmation of the imprinting concept was obtained from a third experiment with gallium particles that were formed in DL-tryptophan solution. As expected, the results in this case (**Table 3**) showed very low values of polarization in all the solutions, emphasizing the occurrence of the mono-imprinting effect in the previous two cases.

The extent of chirality, i.e. the enantiomeric excess (%ee), can be calculated from the results of the polarimetric measurements. The specific rotation [α] of a sample is related to the observed rotation a by the expression:

[1] $$[\alpha] = \frac{\alpha}{C \times l}$$

Where C is the concentration (in g/mL) and l is the optical length (dm)[18]. In our experiments, the concentration of the DL solution in which the L-imprinted particles were immersed was 50 mM (0.0102 g/mL) and the optical length of the cell was 0.5 dm. The specific rotation of D- or L- tryptophan is 30.0 deg.[19]. Thus, for the DL solution after immersion of the L-imprinted Ga particles (α=+0.0161) the enantimeric excess was 10%, while for the DL solution after immersion of the D-imprinted particles (α=-0.0122) the enantimeric excess was ca. 8%.

The polarimetric results were followed by Circular Dichroism (CD) measurements. **Figure 4A** presents four experimental curves: *a*) the original L-tryptophan solution. *b*) The same solution after sonication with molten gallium. *c*) The leaching solution after 15 days immersion of the L-formed particles. *d*) The DL- solution in which the L-imprinted particles were immersed. For each of these curves a matching

Gaussian fit was added. Curves *a*-*c* have similar shapes with peaks at the same wavelength (224 nm), while the peak in curve *d* is inverted and weaker but appears at the same wavelength as the others.

These results confirm that some L-tryptophan was entrapped in the gallium particles during their formation (lower intensity of the peak in curve *b*) and leached out when they were immersed in water (curve *c*), while immersing these particles in a DL-solution induces some enrichment of the D-enantiomer in the solution due to preferred penetration of the L-tryptophan into the particles (curve *d*). Inverted curves were observed in similar measurements with D-tryptophan solution (**Figure 4B**): entrapment and leaching of the D-enantiomer and enrichment of the L-enenatiomer due to preferred penetration of D-tryptophen into the D-imprinted particles.

The enantiomeric excess can be calculated from the intensity ratio between curves *d* and *a* in each case; in Figure 4A curve *d* represents the excess of the D-enantiomer in the DL-solution (after immersion of the L-imprinted particles) while curve *a* represents the pure L-solution. In Figure 4B, curve *d* represents the excess of the L-enantiomer in the DL-solution while curve *a* is for the pure D solution. For example, the calculation for Figure 4A is:

[2] $$\%ee = \frac{peak(d)}{peak(a)} \times 100\% = \frac{1.20m\,\mathrm{deg}}{11.99m\,\mathrm{deg}} \times 100\% = 10\%$$

A similar calculation for the opposite case yields an enantiomeric excess of 12%. Taking into account the limited accuracy of the measurements, these values can be considered as similar. It should be emphasized that neither stirring and heating nor ultrasonic bath were found to induce dispersion of the molten metals into such spheres.

Determination of the yield of enatiomeric excess of D, L tryptophan using Chiral HPLC analysis:

The finaly quantification of enatiomeric excess of D and L tryptophan was carried out by chiral HPLC analysis. **Figure 5a** shows the chiral HPLC analysis of pure recemic mixture of DL tryptophan, and it was consider as a 50:50 of D and L tryptophan. The enatiomeric excess was calulated using the equation-3 followed by a chromatography data:

[3] $$\%ee = \left[\frac{Area(Dtrp) - Area(Ltrp)}{Area(Dtrp) + Area(Ltrp)}\right] \times 100\% = \left[\frac{6429861 - 4948666}{6429861 + 4948666}\right] \times 100\% = \sim 13\%$$

The results confirm that L-tryptophan was imprinted on the gallium particles during their formation, while immersing these particles in a DL-solution induces ~13 % ee enrichment of the D-enantiomer in the solution due to preferred penetration of the L-tryptophan into the Ga particles (**Figure 5b)**. The similar results were also observed in L-imprinted Ga particles (**Figure 5c**), and enrichment of the L-enenatiomer (~11 %ee) due to preferred penetration of D-tryptophen into the D-imprinted Ga particles.

Discussions

Previously we showed that ultrasonic irradiation of molten gallium in warm water induces the formation of gallium spheres in the size range of several micrometers and below. When this procedure was applied to molten gallium in aqueous solutions of some organic compounds, a certain amount of these compounds was found to be entrapped within the spheres. The entrapped molecules could partially leach out when the particles were immersed in pure water. SEM and TEM images of the gallium spheres revealed some evidences that at least part of the gallium spheres were hollow, so we assumed that small volumes of the solutions were encapsulated within the spheres during their formation, and the entrapped compounds could leach out through defects or pinholes in the gallium shells. In this work we performed the same procedure with a chiral compound, L- or D- tryptophan, and here too, entrapment and leaching were observed. However, particles that were formed in a solution of L-tryptophan, immersed in pure water for leaching and then immersed in a DL-solution for 7 days, induced some D-chirality in that solution by allowing preferred penetration of the L-enantiomer into the gallium particles. Opposite chirality was detected in the DL-solution when particles that were formed in a D-tryptophan solution were immersed for several days. The apparent effect of the molecules which are dissolved in the sonicated solution on the properties of the

resulting particles suggests that the entrapment occurs via adsorption of the solute molecules onto the surface of the solidifying particles, resulting in imprinting of molecular templates in the gallium. After separation of the particles from the solution, some of the adsorbed molecules are removed by rinsing, while others that reside in these templates can diffuse out slowly when the particles are immersed in pure water. This concept is different from our previous explanation for the entrapment of solution within the hollow spheres.

The occurrence of molecular imprinting on the surface of the gallium spheres can be associated with the lack of GaO(OH) crystallites that were obtained whenever ultrasonic cavitation of gallium was performed in pure water. An example of such particles, covered with crystallites, is shown in the SEM image in **Figure 6**, and the identification of these crystallites as GaO(OH) was done by X-ray diffraction[17]. It is reasonable to assume that the presence of the entrapped molecules on the gallium surface interferes with the formation of GaO(OH) crystallites. Both molecular imprinting and GaO(OH) formation are fast and competing processes that occur on the surface of the Ga spheres in parallel to their solidification. The fact that in the presence of organic solutes no GaO(OH) crystallites were observed implies that the imprinting process is faster. It should be considered that the formation of GaO(OH) involved several steps: decomposition of water to $H^{\cdot}$ and $OH^{\cdot}$ radicals, reaction of gallium with $OH^{\cdot}$ and dissolved oxygen and crystallization. Therefore it is possible that molecular imprinting in the fast-solidifying gallium particles is more facile.

Another evidence for a surface modification of the gallium spheres comes from the fact that they do not recombine to form bulk gallium after the ultrasonic irradiation is ceased, although the temperature in the test tube is still higher than the melting point of gallium. In a previous work that described the creation of gallium spheres in water we argued that the fast formation of GaO(OH) crystallites on the surface prevents the merging. However, when organic compounds were dissolved in the water no crystallites

were formed but still no merging occurred. Based on the imprinting concept, we can claim now that this may be the factor that prevents the merging.

The extent of the enantiomeric excess in the two cases were calculated from the data obtained by both polarimetry, CD and Chiral HPLC measurements. The results are summarized in Table 4, showing good agreements between the two methods for each case and between the two cases for each method.

In principle, imprinting is a physical reaction of the solute compound with the soft gallium, rather than chemical. Thus, it may be possible to induce imprinting in particles of gallium or other metals also from solutions of inorganic materials, ions or even suspensions. Moreover, the extent of imprinting and enantiomeric excess can be a function of the experimental conditions, such as the concentration of the material, the power of sonication and the temperature. These factor will be further investigated.

Conclusions

1. Gallium particles, formed by ultrasonic cavitation in a solution of D- or L-tryptophan, were found to entrap some of the compound from the solution. We previously suggested that small volumes of the solutions were encapsulated within the spheres during their formation, and the entrapped compounds could leach out through defects or pinholes in the gallium shells

2. Immersion of the particles encapsulated with tryptophan enantiomer for several days in pure water for leaching was conducted followed by immersion for several days in a DL-solution, induced some opposite chirality in that solution by allowing preferred penetration of one of the enantiomers into imprinted gallium particles. The extent of enantiomeric excess is ca. 12%

3. This observation indicated that entrapment can occur also via imprinting of molecular templates on the surface of the gallium spheres during their solidification.

4. Such surface modification can explain why no GaO(OH) crystallites were formed on particles that were formed in aqueous solution of organic compounds, unlike the cases where gallium particles were formed by a similar procedure in pure water.

5. GaO(OH) formation and molecular imprinting are two fast processes that occur on the surface of the particles during their formatiom. The former is a multi-step chemical reaction whereas the latter is a physical process that is eventually favorable.

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Figures

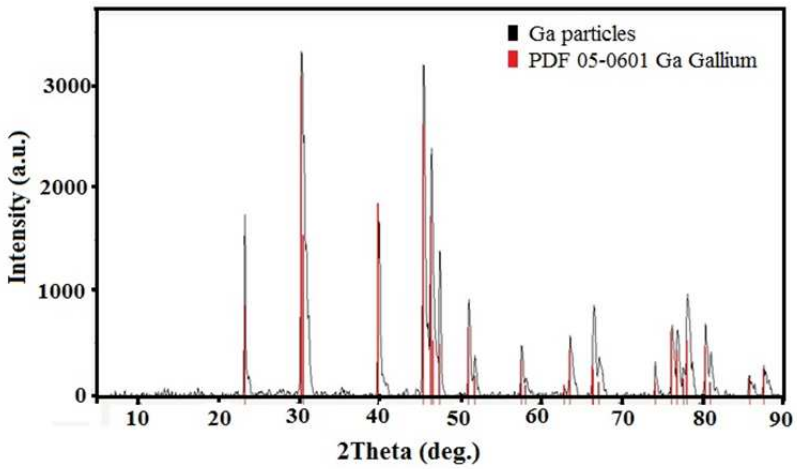

Figure 1: XRD pattern obtained from the dried gallium particles, in comparison with the database for crystalline gallium.

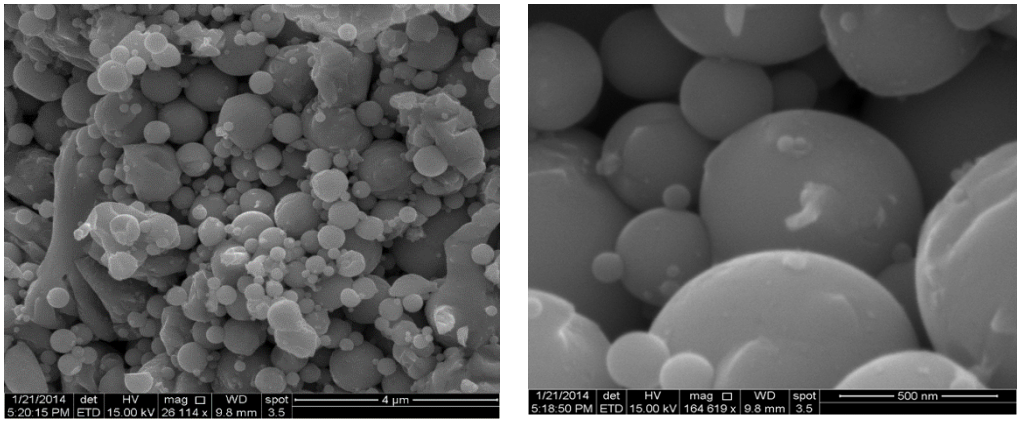

Figure 2: SEM images of Ga particles which have been synthesized in L tryptophan solution. A) A large cluster of gallium particles. B) A close view, showing particles as small as 40 nm.

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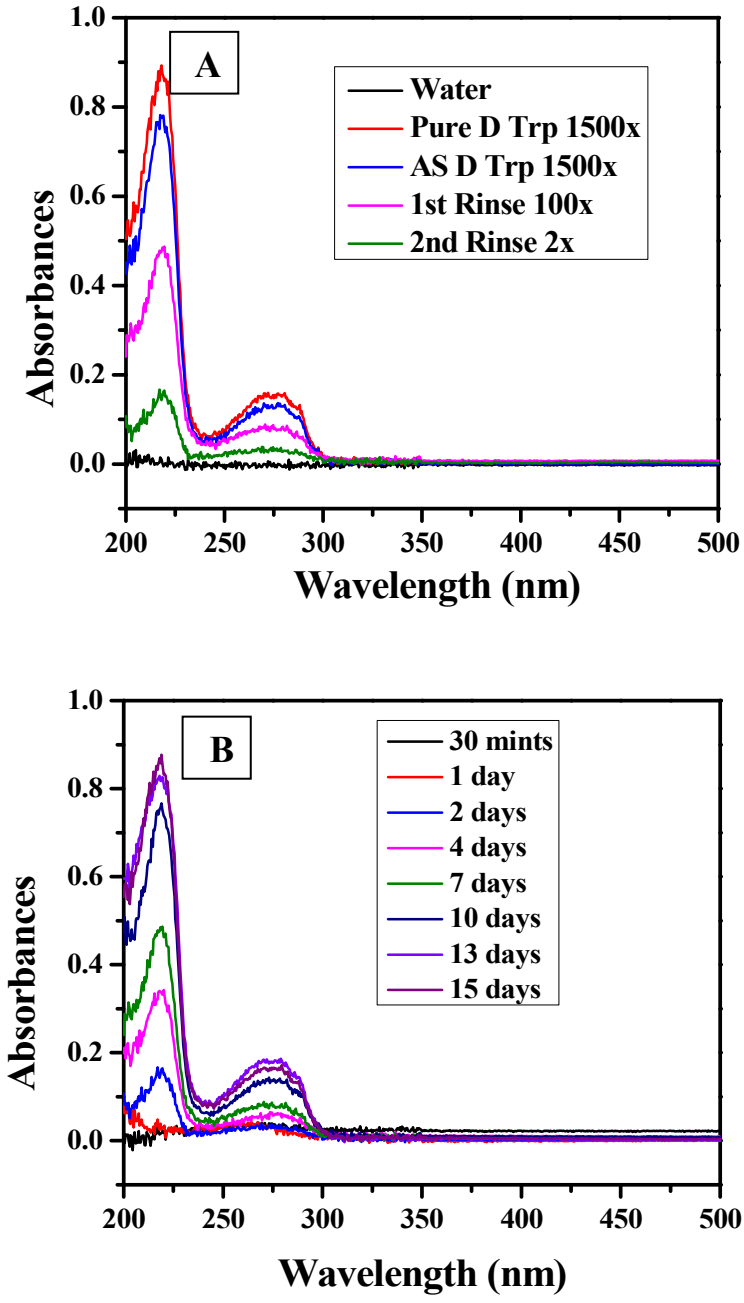

Figure 3: UV-vis. spectra of samples of D tryptophan solution. A) Before sonication without gallium, after sonication with gallium and the rinsing water of the particles after separation. The dilution factor of each curve is indicated 1500 times. B) Spectra after various leaching times. The dilution factor for all the curves is 20.

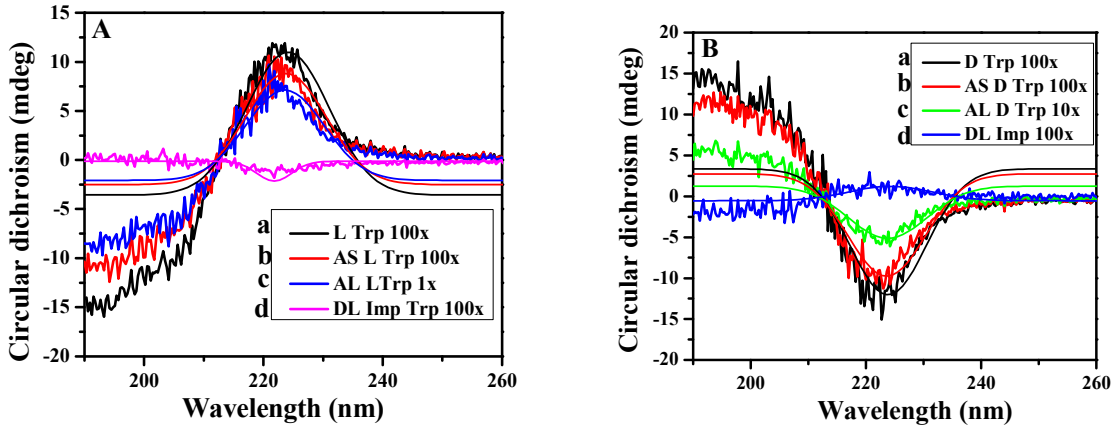

Figure 4: Circular dichroism spectra the various solutions. (A) L-tryptophan solution before sonication (black) and after sonication (red) with molten gallium, the leaching solution containing L-tryptophan (blue) and L-depleted DL-solution (pink). (B) D-tryptophan solution before sonication (black) and after sonication (red) with molten gallium, the leaching solution containing LD-tryptophan (green) and L-depleted DL-solution (blue).

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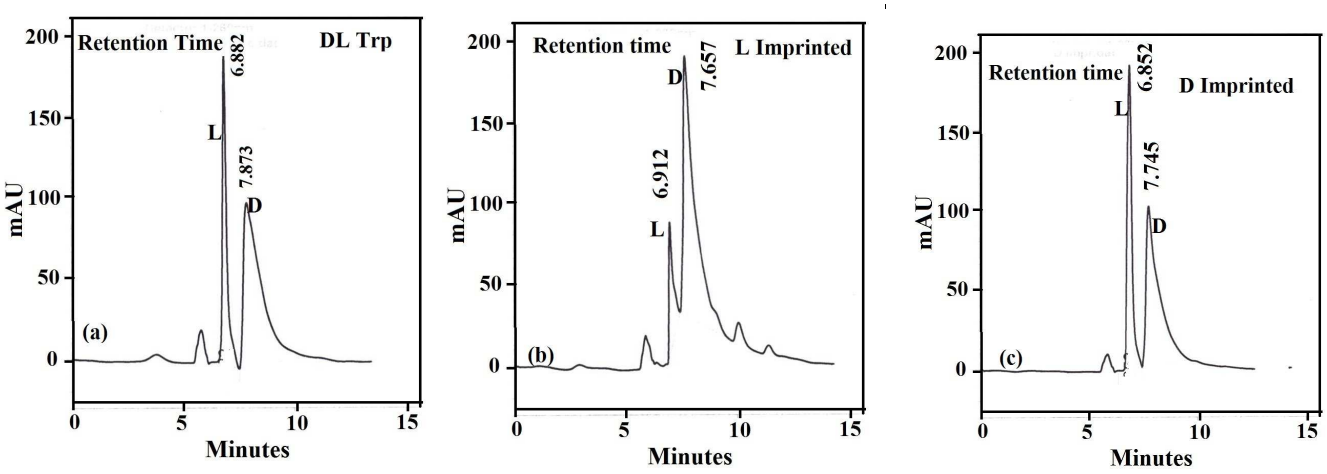

Figure 5: Chiral HPLC of (a) Recemic mixture of DL tryptophan, (b) L imprinted (D-Trp is excess ~12.6%), (c) D imprinted (L-Trp is excess ~10.8%)

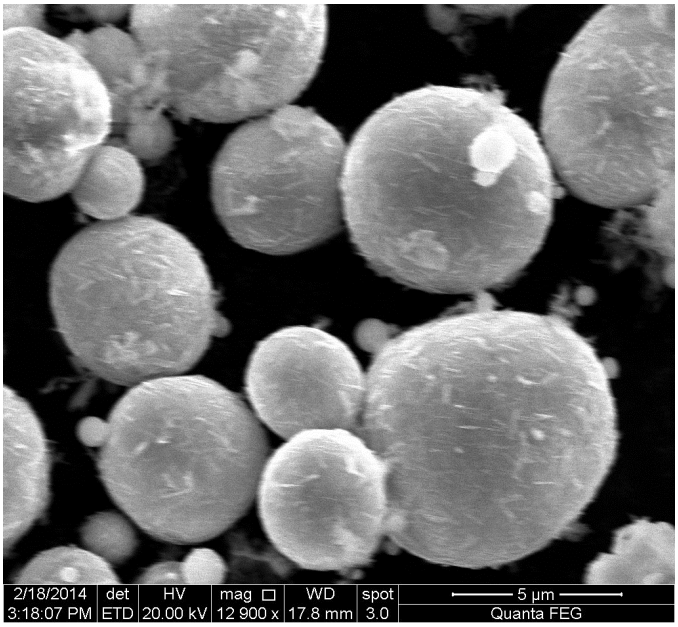

Figure 6: Gallium particles that were formed by ultrasonic cavitation of molten gallium in pure water at 55 ^{o}C. Crystallites of GaO(OH) are observed on the surface of the particles.

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Tables

Table 1: Results of the polarometric measurements in the various L-tryptophan solutions and in the DL-solution, in which L-imprinted Ga particles were immersed.

Sample	Average rotation angle (deg.)	Std. deviation
Pure water (blank)	0.0001	0.0002
Pure L-tryptophan solution	-0.1526	0.0002
L-tryptophan solution after sonication.	-0.1245	0.0003
Solution after 15 days leaching.	-0.0171	0.0002
DL- solution after immersion of the L-imprinted Ga particles	0.0161	0.0002

Table 2: Results of the polarometric measurements in the various D-tryptophan solutions and in the DL-solution, in which D-imprinted Ga particles were immersed.

Sample	Average rotation angle (deg.)	Std. deviation
Pure water (blank)	0.0001	0.0002
Pure D-tryptophan solution	0.1561	0.0004
D-tryptophan solution after sonication.	0.1450	0.0003
Solution after 15 days leaching	0.0079	0.0002
DL- solution after immersion of the imprinted Ga particles	-0.0122	0.0025

Table 3: Results of the polarometric measurements in the various DL-tryptophan solutions and in the DL-solution in which DL-imprinted Ga particles were immersed.

Sample	Average rotation angle (deg.)	Std. deviation
Pure water (blank)	0.0001	0.0002
Pure DL-tryptophan solution	0.0006	0.0010
DL-tryptophan solution after sonication.	-0.0044	0.0024
Solution after 15 days leaching	0.0011	0.0002
DL- solution after immersion of the imprinted Ga particles	0.0016	0.0003

Table 4: results of the calculated enentiomeric excess %*ee* in the DL solutins in which D- or L- imprinted Ga particles were immersed.

Method	% enantiomeric excess	
	L-imprinted Ga	D-imprinted Ga
Polarimetry	8	10
Circular Dichroism	10	12
Chiral HPLC	11	13