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12-Hydroxy stearic acid appended new amphiphilic scaffolds for selective capture of hydrogen halides through supramolecular hydrogelation†

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12-Hydroxystearic acid (12-HSA) appended new amphiphilic scaffolds reveal excellent hydrogelation propensity in the presence of aqueous acids and vapors of HCl/HBr. This selective entrapment efficiency towards hydrogen halides demonstrates an unprecedented route for the successful removal of toxic chemicals, thus providing a safe and easy protocol for environment management. We anticipate that the halide derivative of the amphiphile plays a vital role in driving the self-assembly mechanism and eventually the hydrogelation phenomena.

Stimuli responsive low molecular weight hydrogelators comprising peptides have witnessed remarkable growth in recent years.[1] Low production cost, benign fate and simplified synthesis protocol render peptides as appealing synthons for biomaterial design.[2] In turn, the involvement of peptide self-assembly utilizing non-covalent interactions makes these constructs highly promising candidates for the design of smart materials with diversified applicabilities.[2,3]

Hydrogen halides are a class of toxic entities produced during the pyrolysis of numerous substances encountered during industrial transformations, and their exposure to the environment causes detrimental effects on health.[4] They are highly corrosive in nature and cause acute injury to the respiratory tract.[5] Although researchers have dedicated significant efforts to discovering materials pertaining to a plethora of applications, little progression could be achieved in the arena of halide capture, due to the inhibitory response of the anions towards gelation.[6] So the development of scaffolds for the successful removal of toxic halides selectively through supramolecular hydrogelation appears highly challenging and will be of paramount interest to society.

Aligned with this goal, herein we report two structurally related amphiphilic peptides, 12-HSA-amino tetrazole (compound: **I**) and 12-HSA-aniline tetrazole (compound: **II**) (12-HSA:12-hydroxystearic acid) that display excellent hydrogelation propensity in the presence of aqueous acids and vapors of HCl/HBr thus providing a simple cost effective protocol for the clean-up of acidic effluents (Fig. 1). Being mindful of the potentiality of the alcoholic hydroxy group of 12-HSA in undergoing nucleophilic substitution reactions, we tethered this component at the N-terminus of the compounds.[7] We coupled the heterocycle tetrazole to the amphiphile due to its salt forming tendency with hydrohalic acids.[8] Since the design consisted of a heterocycle appended amphiphile, we anticipated that in the presence of hydrogen halides (nucleophile), there could be possibilities for two units of nucleophile to participate.[6,7] One for forming the halide derivative and the other in salt formation.[7,8] These individual properties of the respective scaffolds might collectively contribute to the process of self-assembly by its enhanced hydrogen bonding likeliness and π–π correspondence employing the bottom up approach.[9]

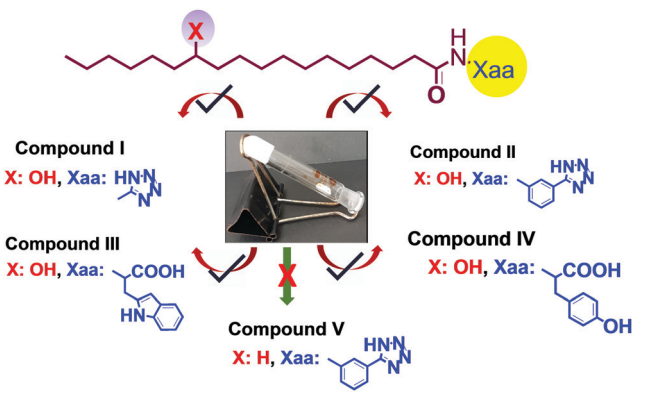

Fig. 1 The chemical structures of the heterocycle appended amphiphile leading to the formation of self-supporting hydrogels in the presence of aqueous acids and vapors of HCl/HBr for compounds **I–IV** and no gel formation for compound **V**.

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To gain insight into the feasibility of hydroxy replacement in the compounds, computational studies were performed where the heats of formation (H_f) corresponding to the heterocyclic salt of different halide derivatives were calculated using two popular semi-empirical methods, namely Austin Model 1 (AM1) and Parametric Method 3 (PM3), and DFT (Table S1, ESI†).[10] The H_f values obtained from all the procedures followed a similar trend and were found to be negative, suggesting that the probable scaffold could be held responsible for driving the self-aggregation mechanism. Additionally the parameter H_f was found to increase with an increase in the size of the halides (Table S1, ESI†). Therefore we envisioned that compounds **I** and **II** could exhibit better gelation propensities with HCl/HBr in comparison to HI.

To experimentally verify the above hypothesis, the compounds were dissolved in a methanolic water medium and concentrated hydrohalic acids (HCl/HBr/HI) were added dropwise (MeOH : water : hydrohalic acids: 3 : 1 : 1). Initially a clear solution was produced, but the gradual addition of hydrohalic acids led to complete immobilization of the solution instantaneously resulting in the formation of an opaque gel for HCl/HBr (Fig. 1). But for HI, we obtained a black suspension and were unable to draw a definitive conclusion from it, which is in accordance with the computational analysis. However none of these solvents (methanol–water–HCl/HBr) solely were competent to induce the gelation protocol. To confirm whether any other acids were able to nucleate the phenomena, the experiments were repeated with HNO_3, H_2SO_4, HCOOH, CH_3COOH, H_3BO_3, H_3PO_4, $HClO_4$ and TFA (variation in anion component). But in every case for both types of organic and inorganic acids, negative results were obtained. But gelation occurred in the presence of other alcohols like ethanol and isopropanol instead of methanol. Thus this investigation allowed us to conclude the extreme selectivity of this process towards polar protic acids HCl/HBr. With this information in hand, we decided to investigate the efficiency of the compounds in trapping the corresponding halide vapors. To achieve this, gelation experiments were performed using HCl gas as shown in Fig. 2 and Fig. S1A (ESI†).

We speculated that the methanolic solution of the compounds readily absorbed HCl vapors and subsequently formed a gel upon self-assembly. The experiment was repeated with HBr gas also, for both the compounds (Fig. S1B, ESI†). Notably in every case we ended up with a positive inference. Aligned to the investigative workflow, we started gathering experimental evidence to support the observation and first turned our attention towards the FT-IR spectra of the compounds both in the solid state, as synthesized, and in the corresponding xerogels (Fig. S2, S3 and Tables S2, S3, ESI†). We assumed that if the predictions of the nucleophilic substitution reaction were correct, then from the IR spectra some information about the formation of the C–X bond might be obtained. As evident from the spectra, in the xerogels, a small peak at 794/538 cm^{-1} (HCl/HBr) for compound **I** and 662/616 cm^{-1} (HCl/HBr) for compound **II** was noticed, with the corresponding peaks missing in the solid compounds (Fig. S2, S3 and Tables S2, S3, ESI†). This peak was attributed to the formation of the C–X (X: Cl/Br) bond under experimental conditions.[11] However the heights of the peaks were small, so arriving at a definitive conclusion was difficult. This led us to delve deeper into the NMR spectra of the compounds in d_6-DMSO since the latter provides better insights into the self-assembly process (Fig. 3 and Table S4, ESI†). In continuation with the previous assumption of hydroxy replacement, we envisioned that in the NMR spectra, the hydroxy peak in the solid molecule might be visible and disappear in the xerogels. For compound **I**, in the solid state, the chemical shifts of tetrazole and amide NHs along with 12-HSA OH appeared at 15.78, 11.95 and 4.21–4.19 ppm respectively. On the other hand, the spectra of the xerogels reflected peaks at 15.78 and 11.97 in the case of HCl and only 11.93 in the case of HBr. Similarly for compound **II**, the NHs, aromatic protons and 12-HSA OH depicted chemical shifts at 9.90, 8.12 (Ha), 7.65–7.62 (Hb & Hd), 7.28–7.25 (Hc) and 4.23–4.22 ppm respectively in the solid state and 10.29, 8.44 (Ha) & 7.78–7.74 (Hb & Hd), 7.52–7.49 (Hc) ppm in xerogel HCl and 10.29, 8.23 (Ha), 7.74–7.73 (Hb & Hd), 7.55–7.45 (Hc) ppm in xerogel HBr. The corresponding $\Delta\delta$ values (in ppm) were as follows: For amide NHs (a) 0.02 in compound **I** (xerogel HCl) and 0.39 (xerogel HCl)/0.25 (xerogel HBr) in compound **II**; (b) for aromatic H's the values correspond to 0.32 (Ha), 0.13–0.12 (Hb & Hd), and 0.24 (Hc) in xerogel HCl and 0.11 (Ha), 0.09–0.11 (Hb & Hd), and 0.27–0.20 (Hc) in xerogel HBr in compound **II**.

From the change in chemical shifts we noticed that in both the compounds neither the amide NHs nor aromatic H's (compound **II**) illustrated substantial change. Therefore their involvement in nucleating the gelation phenomena was ruled out (Fig. 3 and Table S4, ESI†).

Indeed the OH peak of 12-HSA which was clearly visible in the solid state of both the compounds, was found to disappear in the xerogel state, in line with our vision. However the NMR spectra further revealed that the completely converted derivative and the partially converted derivative remained in equilibrium as has been reflected by the occasional appearance of tetrazole NH in the NMR spectra (Fig. 3).[11] Thus from the IR and NMR spectra it was confirmed that the nucleophilic substitution reaction had taken place leading to the replacement of the hydroxy group of the amphiphile by the halides, in accordance with the prediction.

To strengthen our intuition and affirm whether the salt formation in compounds **I** and **II** has occurred, mass spectrometry of the xerogels obtained from HBr was performed (Fig. S4, ESI†). From the HRMS spectra, we obtained peaks

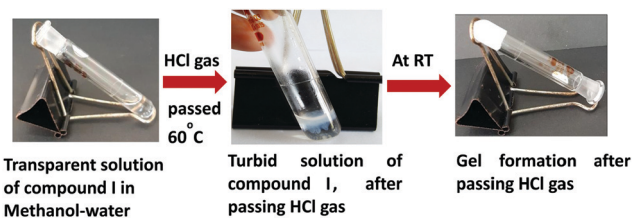

Fig. 2 The gelation phenomena occurring in the presence of HCl gas, for compound **I**.

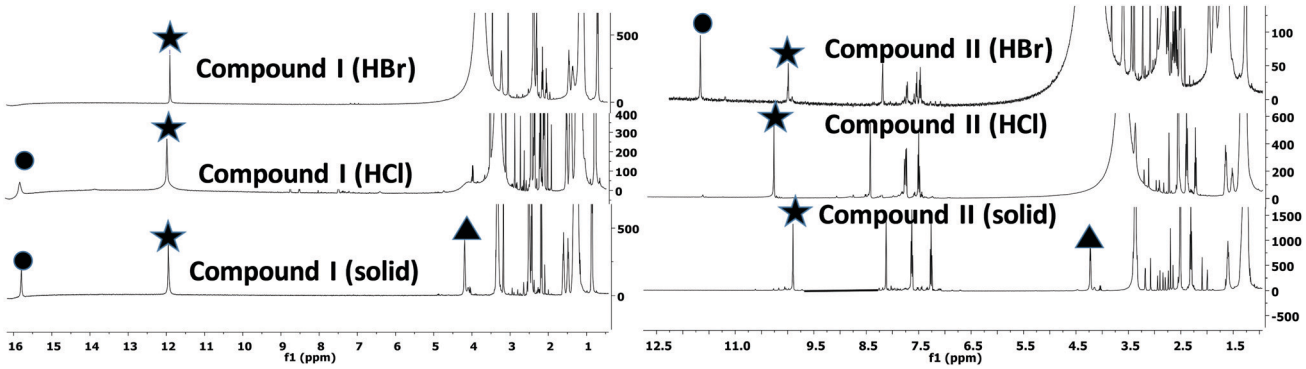

Fig. 3 The ^{1}H NMR spectra of the xerogels and solid compounds in d_6-DMSO at 25 °C; NH of tetrazole ●; amide NH ★; OH of 12-HSA ▲.

corresponding to (a) $C_{19}H_{37}Br_2N_5O$ obtained: 519.4918 $[M + 5H]^+$; calculated: 513.54 $[M]^+$ and (b) $C_{25}H_{41}Br_2N_5O$ obtained: 587.3876 $[M]^+$; calculated: 587.43 $[M]^+$ (Fig. S4, ESI†), in agreement with the bromo derivative of the heterocyclic salt of the amphiphile. Thus this experimental evidence amply manifests the formation of the halide derivative as well as the salt in the reaction medium for both the compounds.

Next, our interest lied in determining the fundamental residue responsible for driving the gelation mechanism. So we synthesized compounds **III–V** (Fig. 1). In compounds **III** and **IV**, the normal amino acids Trp (compound **III**: with indole; basic heterocycle) and Tyr (compound **IV**: phenol; acidic heterocycle), devoid of the salt forming ability, were appended with 12-HSA at the C-terminus (Fig. 1). In compound **V**, the 12-HSA moiety of compound **II** was replaced with stearic acid (SA) (Fig. 1). Interestingly compound **III** & **IV** formed stable gels, but compound **V** failed to do so, which highlights the importance of the hydroxy substituent of the amphiphile in nucleating gelation phenomena. Inspired by these results, next we decided to check whether 12-HSA alone (not in any derivatized form) could form gels. Surprisingly, we obtained negative results, indicating the importance of the maintenance of a crucial balance of both the hydrophobic and π–π interactions in driving the self-assembly mechanism and subsequently the gelation phenomena. However, failure to attain this delicate cruciality leads to negative results as was reflected by the case of 12-HSA in the underivatized form.

Overall, the computation and experimental inferences allowed us to consider the 12-HSA appended derivatives to be a new amphiphilic scaffold for the selective entrapment of hydrogen halides through supramolecular hydrogelation.

Next we attempted to characterise the hydrogels of compounds **I–IV** using standard techniques. The minimum gelation concentrations (mgc) of the compounds were as follows: (a) **I** & **II**: 4 and 6 mg ml^{-1} respectively for both HCl and HBr case; (b) **III** & **IV**: 4 mg ml^{-1} for HCl for both the compounds (Fig. S5, ESI†).[9] The gel formation time of the hydrogelators is described in Table S5 (ESI†). To determine the secondary structural aspect of the xerogels we looked deeper into the FT-IR spectra of the compounds (Fig. S2, S3, S6 and S7, ESI†). From the spectra it was clearly evident that the region corresponding to OH and NH appeared to be broad in the xerogel state. However the wavenumbers of the H-bond donors OH/NH shifted from around 3770 to 3500 and 3300 cm^{-1} for all the compounds. Similarly in the xerogels for the amide I/II carbonyl, distinct peaks were observed in the region (a) 1688/1554 cm^{-1} (HCl) & 1656/1550 cm^{-1} (HBr) for compound **I**; (b) 1650/1548 cm^{-1} (HCl) & 1650/1556 cm^{-1} (HBr) for compound **II**; (c) 1656/1516 cm^{-1} (HCl) for compound **III** and 1656/1522 cm^{-1} (HCl) for compound **IV** respectively (Fig. S2, S3, S6 and S7, ESI†). This could only happen if hydrogen bonding and van der Waals interactions were engaged in interconnecting the molecules to form an entangled fibrous network leading to hydrogel formation through β-sheet conformation.[12]

To re-confirm the conformation, we carried out PXRD analysis with the xerogels of the compounds (Fig. S8, ESI†).[13] The wide angle PXRD patterns were as follows: (a) 2θ: 19.3° (HCl)/19.2° (HBr) for d: 4.5 Å, (b) 2θ: 22.4° (HCl)/22.0° (HBr) for d: 3.7 Å, for compound **I**; (c) 2θ: 19.4° (HCl)/19.3° (HBr) for d: 4.5 Å, (d) 2θ: 22.8° (HCl)/22.3° (HBr) for d: 3.7 Å, for compound **II**; (e) 2θ: 19.1°/22.9° for d: 4.5 Å /3.7 Å (HCl), for compound **III**; (f) 2θ: 19.3°/22.6° for d: 4.5 Å/3.7 Å (HCl), for compound **IV** respectively further supporting the presence of β-sheet like extended structures stabilized by non-covalent interactions, mainly π–π correspondence.

Additionally, the formation of the parallel β-sheet structure of the compounds was further supported by our computational studies (Fig. 4 and Fig. S9, ESI†). The halide derivative was found to promote van der Waals interaction amongst 12-HSA

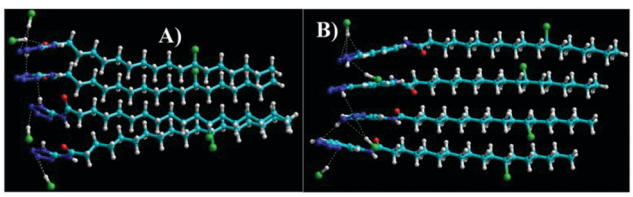

Fig. 4 Energy optimised structures of the actual construct; chloride derivatives of the heterocyclic salt of compound (A) **I** & (B) **II**, and their self-assembly patterns stabilizing β-sheets. For the formation of sheets four monomeric units have been considered. Colours of the atoms are as follows: carbon: cyan; hydrogen: white; oxygen: red; nitrogen: blue; and chlorine: green. H-Bondings are shown as dotted lines.

aliphatic chains, whilst the aromatic units reinforced the π–π interactions in the compounds resulting in successful gelation.

Thus on the basis of FT-IR, PXRD and computational data, we concluded that the compounds pack in β-sheet like structures.

To gain insight into the morphological aspect of the xerogels, field emission scanning electron microscopic studies were performed using xerogels of the same concentration. Importantly, the images of all the compounds demonstrated an entangled three dimensional fibrillar network of dimensions 20–50 nm in width and several micrometers in length, a characteristic of β-sheet structures.[13] Additionally, we noted that in compound **II** & **III**, the fibrils were more closely packed than that in **I** & **IV** which might be reflected in their mechanical strength (Fig. 5).

In continuation with the previous studies, to gain deeper insights into the mechanical integrity of the compounds, we performed rheological measurements, as it is one of the prime requirements for any hydrogel to be used as a biomaterial.

In this experiment, the elastic response (G') and viscous response (G'') were measured as a function of strain.[14] As observed from Fig. S10 (ESI†), throughout the viscoelastic region, the storage modulus (G') was higher than the loss modulus (G'') in the region 1 to 100 rad s^{-1} (angular frequency) until the application of strain of approximately 5% for compound **I** & **IV** and 40% for compound **II** & **III**. This behavior demonstrated a soft gel phase formation (Fig. S10, ESI†).[13] At this corresponding limit of maximum strain, a cross over point was noticed where the value of loss modulus (G'') slightly exceeded the value of the storage modulus (G') and transformed into a solution. Increasing the strain beyond this point, resulted in the decrease of both the modulus since intermolecular forces had won over the applied strain and the fibrils were unable to withstand large deformations. Thus from the rheological studies we noted the strain bearing ability of compounds **II** & **III** to be higher than that of **I** & **IV**, data previously supported by the morphological observation.

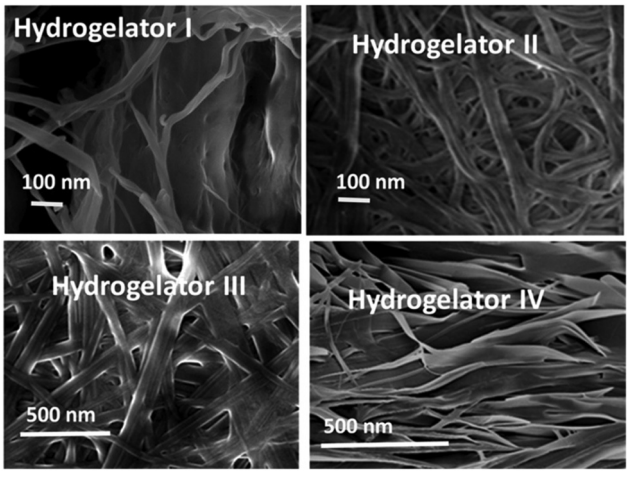

Fig. 5 FE-SEM images of the xerogels of compound **I–IV** showing the formation of the self-assembled fibrillar network. The gels were prepared in methanol water mixture in the presence of concentrated hydrochloric acid.

In summary in this paper we report the design and synthesis of a new amphiphilic scaffold containing 12-HSA at the N-terminus, that possesses the capability to entrap hazardous hydrogen halides namely HCl/HBr and form hydrogels in the form of vapors or liquids. This selective anion encapsulation procedure represents an alternate route for the effective removal of these harmful chemicals from industrial effluents, thus providing a safe and easy protocol for green management. We attribute this phenomenon to be a major contribution from the hydroxy substituent of the amphiphile. From the synthesis perspective it involved a single step reaction and therefore is cost effective. We envision that the resultant halo-entrapped hydrogels may exhibit potential applicabilities in the development of novel materials in versatile avenues.

Conflicts of interest

There are no conflicts to declare.

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