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PAPER

Extremely pH-sensitive fluids based on a rationally designed simple amphiphile†

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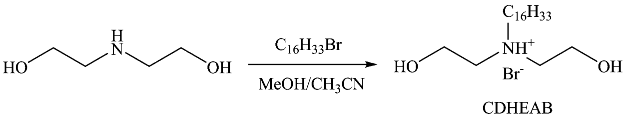
In this paper, we report on an extremely pH sensitive fluid based on a simple ammonium surfactant synthesized in our lab. The fluid was obtained simply by the addition of NaOH into a 100 mM *N*-cetyl-*N*,*N*-dihydroxyethylammonium bromide (CDHEAB) aqueous solution. The viscosity of this aqueous solution may change 10^6-fold within a narrow pH range of 4.97 to 5.78. The extremely pH-sensitive rheological performance was attributed to the critical molecular structure that allows the combination of strong hydrophobic interactions and effective hydrogen bonding upon protonation. Based on the understanding of the molecular origin of this superior rheological behavior, we are able to manipulate the responsive threshold value of the pH, which provides great advantage in the fine tuning and design of pH responsive fluids with desired pH values. Our results demonstrate that easy-to-process, extremely pH sensitive fluids can be produced by proper molecular design which covers the delicate balance between hydrophobic interactions and the electrostatic effect.

Introduction

Stimuli-responsive materials have attracted considerable interest over the past decade.[1–22] They usually exhibit a dramatic change in their properties in response to an external stimulus, such as pH,[1–6] temperature,[7–12] electric or magnetic fields,[13,14] to name a few. Among which, the stimulus of pH is of special interest owing to the attractive potential in pharmaceutical, biomedical and related fields.[23–28] It is well-known that the pH in different parts of the body varies, depending on the site and pathological conditions. Therefore, pH is often used as a trigger in the controlled release of encapsulated drugs.[22] For example, pH responsive hydrogels composed of a polyethylene glycol and polymethacrylic acid backbone have been applied for the oral delivery of insulin.[29] It is also known that the pH of a tumor is different from that of a healthy organ. In this regard, exploring materials that are extremely sensitive to pH is of special significance.[30–32] So far, the pH sensitive materials that meet this criterion are few.[33] Furthermore, most of those have appeared either involve the synthesis of complicated molecules[34–37] or the employment of a combination of a simple molecule and a commercial pH-sensitive component.[38–40] The disadvantages for the above strategies are obvious: the former requires a complicated synthesis, which is not easily handled in many labs; the overall performance of the latter may be considerably influenced by the environmental conditions due to the different response from each component. Therefore, it is very necessary to invent a system that is as simple as possible and yet has the desired performance in practical applications.

In this work, we report on an extremely pH sensitive fluid formed by a very simple structured amphiphile, *N*-cetyl-*N*,*N*-dihydroxyethylammonium bromide (CDHEAB). The synthesis of CDHEAB requires only one step (Scheme 1) with a high yield. Surprisingly, the fluidity of the fluid formed by 100 mM CDHEAB undergoes a dramatic change of 10^6 magnitude within 0.81 pH units. Meanwhile, the microstructures in the system changed synchronically with the macroscopic behavior. In the following we show these results in detail.



Scheme 1 The synthesis of CDHEAB.

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† Electronic supplementary information (ESI) available: the species distribution of CDHEAB; steady-shear rheology data and the cole–cole plot at pH 3.31 and 4.97 with various concentrations of NaBr; birefringent photographs of the upper phase at pH = 5.78 and pH = 6.00 and the steady-shear rheology of the lower phase at pH = 5.84. See DOI: 10.1039/c2sm25334h

Experimental

Materials

N-Cetyl-*N*,*N*-dihydroxyethylammonium bromide (CDHEAB) was prepared by refluxing *N*,*N*-diethanolamine and 1-bromohexadecane in a methanol–acetonitrile (1 : 3, V/V) mixture for 24 h. The product was then recrystallized five times in mixed solvents of ethanol–ethyl acetate (1 : 4–1 : 5, V/V). The purity of the surfactant was examined and no minimum value was found in the surface tension curves. Other reagents were products of AR grade and the water used was redistilled from potassium permanganate.

Sample Preparation

A concentrated NaOH solution was added to the cationic surfactant aqueous solution to reach the desired pH. Samples were mixed in a vortex after sealing and kept at 30 °C in a thermostat for 24 h before measurement. All the measurements mentioned in this work were performed at 30 °C.

Transmission Electron Microscopy (TEM)

Samples for TEM analysis were prepared by freeze-fracture replica technique (FF-TEM) according to standard techniques. Fracturing and replication were carried out in a high vacuum freeze-etching system (Balzers BAF-400D). A JEM-100CX electron microscope was employed in the microscopic observation.

Rheological studies

The rheological properties of the samples were measured at 30 °C with a ThermoHaake RS300 rheometer (cone and plate geometry of 35 mm diameter with the cone gap equal to 0.105 mm). Frequency-sweep experiments were performed at a constant stress, which was chosen in the linear viscoelastic range.

Dynamic light scattering (DLS)

Dynamic light scattering (DLS) measurements were performed with a commercialized spectrometer (Brookhaven Instruments Corporation, Holtsville, NY) equipped with a 100 mW solid-state laser (GXC-III, CNI, Changchun, China) operating at 532 nm. The scattering angle was 90° and the intensity autocorrelation functions were analyzed with the CONTIN method.

ATR-IR

The IR spectra of the studied solutions were collected with a Nicolet iN10 MX microscopic infrared spectrometer (Thermo Scientific, America) in the range of 4000 cm^{-1} to 650 cm^{-1}. The spectrometer was equipped with an attenuated total reflection (ATR) accessory with a Smart iTR (diamond). The ATR accessory is specifically suited to aqueous solutions because the large –OH water band is attenuated, and the sample bands at longer wavelengths become enhanced. The resolution was 8 cm^{-1} and 32 co-averaged scans were used.

Cryo-TEM

A small drop of sample was placed on a 400 mesh copper grid, and a thin film was produced by blotting off the redundant liquid with filter paper. This thin film was then quickly dipped into liquid ethane, which was cooled by liquid nitrogen. Observation of the cryo-sample was carried out at −183 °C.

Results

pH triggered rheological behaviors

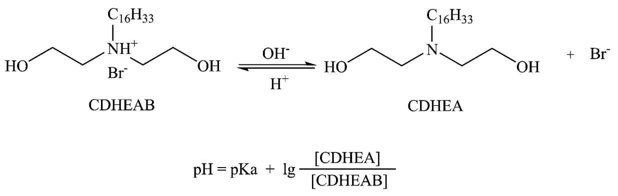
As a weak acid, cationic surfactant CDHEAB can be deprotonated and transformed into CDHEA (*N*-cetyl-*N*,*N*-dihydroxyethyl amine) with increasing pH (Scheme 2). Therefore, two species (CDHEAB and CDHEA) coexist in the solution and their relative ratio depends on the pH. According to a pH titration experiment, the p*K*a of CDHEAB was 5.90 (Fig. S1†) which can be used to calculate the composition of each component at various pH.

The original solution of CDHEAB was clear and transparent with a pH of 3.31 (Fig. 1A), and this character remains almost unchanged up to pH 4.97. Starting from pH 4.97, the viscosity of the solution increases sharply and the system becomes viscous enough so that it does not flow easily out of a tilted vial (Fig. 1B). Steady state rheology shows that the viscous systems formed between pH 4.97 and 5.50 are shear-thinning which is followed by a Newtonian plateau. In the pH range 5.50–5.62, the viscosity keeps increasing and the system turns into a transparent gel-like fluid that may support its own weight (Fig. 1C), but the steady state rheology pattern is similar to the viscous samples except that the Newtonian plateau is approximately 1000 times higher than that at pH 5.35 (Fig. 2). These rheological behaviors are typical for worm-like micelles (Fig. 2), which have been discussed adequately in literature by Kaler,[41,42] Hoffmann, and Abdel-Rahem *et al.*[43]

The gels can exist only in a narrow pH range of 0.12; at pH 5.63 the system starts to flow again, and rheology study suggests a dropped Newtonian plateau (Fig. 2). Actually, both the viscosity and shear modulus drops steeply at pH values beyond 5.62. The zero shear viscosity has dropped to 0.066 Pa s at pH 5.78 (Fig. 3). That is, the viscosity increases by about 6000 times only in the narrow pH range 5.50–5.78.

Discussions

The extremely pH sensitive rheological behavior of the 100 mM CDHEAB system is expected to be a result of the variation of the microstructures with increasing pH. To confirm this, dynamic light scattering measurements were performed for solutions with increasing pH. It can be clearly seen in Fig. 4 that in the low pH



$$pH = pKa + lg\frac{[CDHEA]}{[CDHEAB]}$$

Scheme 2 The structure transition of CDHEAB induced by pH.

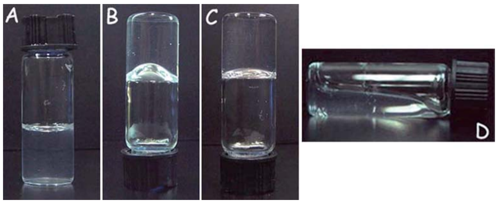


Fig. 1 Photographs of 100 mM CDHEAB aqueous solutions at: (A) pH = 3.31; (B) pH = 5.35; (C) pH = 5.53; (D) pH = 5.63.

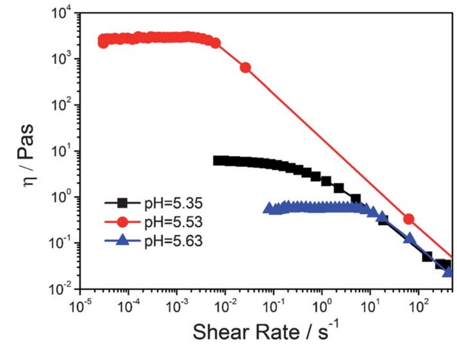


Fig. 2 The steady state shear viscosities for the 100 mM CDHEAB aqueous systems at various pH.

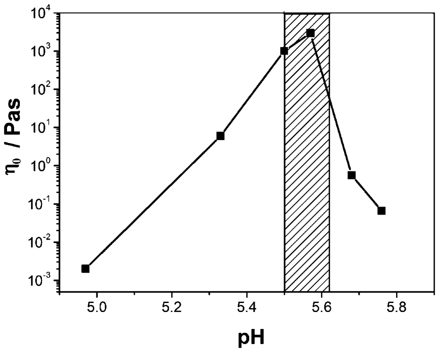


Fig. 3 The variations of zero-shear viscosity (η_0) at various pH values. The shaded area denotes the region of gel formation.

region of 3.31–4.90 where the viscosity of the systems are still very low, the average hydrodynamic radii for the particles in the system increase obviously with increasing pH. Although the apparent hydrodynamic radius R_h of the micelles indicated in this figure cannot be seriously taken as the real size of the micelles due to the presence of strong electrostatic interactions in the system,[44] the tendency of increasing micellar size with increasing pH can be confirmed.

To further check whether it is the transformation from spherical micelles to wormlike micelles that leads to the increase in the viscosity of the system, detailed analyses on the steady state rheology measurements were carried out. It has been well established that the log scaled viscosity in wormlike micellar systems increases linearly with log scaled concentration.[45–49] In this study, the pH triggered steep increase in viscosity is obviously due to the deprotonation of CDHEAB upon increasing pH. Therefore, the molar fraction of unprotonated CDHEA, which can be easily obtained from the composition–pH plot in Fig. S1,† was used as the concentration axis, whereas the zero shear viscosity η_0 was used as the *y* axis. Indeed, a perfect linear relationship was observed in the double log plot of viscosity *vs.* concentration, as demonstrated in Fig. 5. This is an important sign for the formation of wormlike micelles in the process of pH variation. However, the slope is much larger than that expected for wormlike micelles, suggesting that the micelles grow more rapidly here.

Furthermore, a dynamic rheological study was performed to check whether the system exhibited characteristic features of wormlike micelles. It is well-known for wormlike micelles that the shear modulus G_0 is proportional to the number of connections at a given concentraion.[43] In our case, the concentration of the total material that forms wormlike micelles was kept at 100 mM, therefore we may expect a constant plateau modulus G_0 at different pH. This is indeed the case. As indicated in Fig. 6 the plateau moduli tend to meet at around 10 Hz, suggesting that wormlike micelles are formed at the measured pH.

The occurrence of wormlike micelles with increasing pH is definitely related to the special molecular structure of CDHEAB. As described in Scheme 2, the proportion of uncharged CDHEA rises with increasing pH. This on the one hand decreases the electrostatic repulsions between the component molecules, however, on the other hand it affects the hydrogen bonding

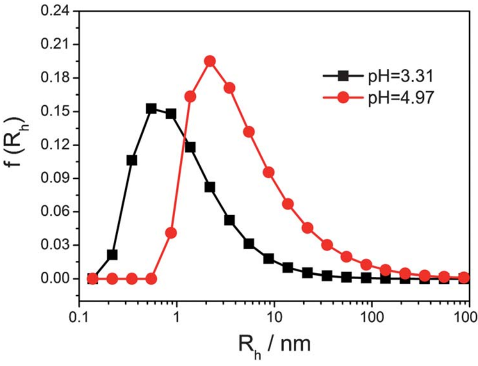


Fig. 4 The representative dynamic light scattering measurements for 100 mM CDEHAB solutions in pH range 3.31–4.97.

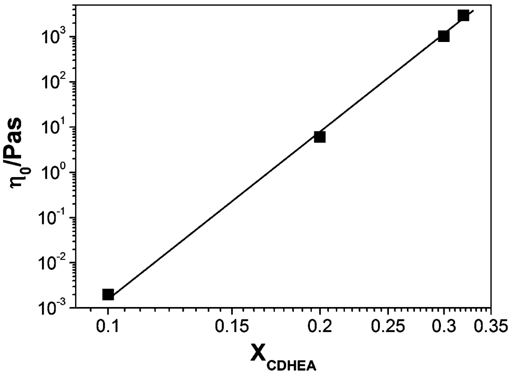


Fig. 5 The variation of zero-shear viscosity with concentration in a log–log demonstration.

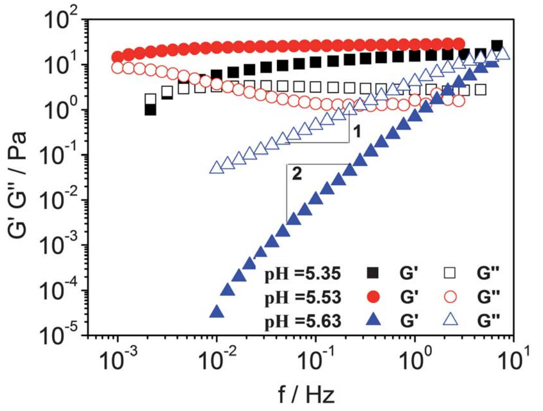
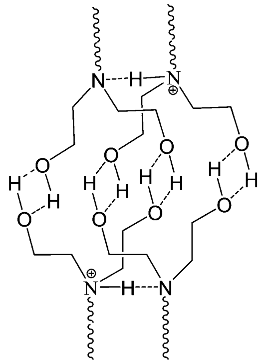


Fig. 6 Oscillating shear moduli for the 100 mM CDHEAB aqueous systems at various pH values.



Scheme 3 An illustration of the hydrogen bonding between the CDHEA(B) molecules at increased pH.

between them. For the fully charged CDHEAB molecules, only spherical micelles can be formed in their aqueous solution due to the strong electrostatic repulsions between the headgroups. However, with increasing pH, the fraction of uncharged CDHEA increases, which enables the shielding of the electrostatic repulsions between the headgroups and leads to the growth of larger elongated rod and wormlike micelles from small spherical micelles. Such a micellar growth mechanism has been well-documented in the literature. However, this usually occurs in concentrated surfactant systems;[49] if the solution is dilute, one usually observes a direct transformation from micelles to unilamellar vesicles. In this work, we found that one simply observes a micelle–vesicle transition in the 10 mM CDHEAB system with increasing pH (ESI, Fig. S2†), which coincides with the increasing turbidity. This will be further discussed in the following text (Fig. 9). In contrast, in the 100 mM CDHEAB system, the systems are all transparent in the wide pH range 3.31–5.53, albeit the viscosity keeps increasing, which is characteristic of wormlike micelles too. As to the decrease in the viscosity in the pH range 5.53–5.75, it is probably caused by a microstructure transition from wormlike micelles to lamellar structures, as can be inferred later in this work. It should be noted that in this process the wormlike micelles may first undergo branching before lamellar structures can occur. This can be inferred from both the pattern of the steady and dynamic rheological behavior for the solution at pH 5.63 where the viscosity has decreased considerably but the system is still a Maxwellian fluid with the G'' (the viscous modulus) scaling linearly with frequency and G' (the elastic modulus) with frequency squared (Fig. 6).

Hydrogen bonding will be strengthened at the start of increasing pH. It is clear that the originally protonated CDHEAB molecules gradually change into deprotonated CDHEA with increasing pH. Therefore, hydrogen bonding may occur between the N atoms from the two molecules, as demonstrated in Scheme 3. This strengthens the intermolecular interactions in the micelles and promotes micellar growth. However, the hydrogen bonding between the –OH groups also plays an important role in the extremely pH sensitive viscosity. When CDHEAB was replaced by it is analogue, CDEAB (*N*-cetyl-*N*,*N*-diethylammonium bromide), where the OH group was replaced by H, neither gel-like nor viscoelastic fluids were observed upon increasing the pH. This suggests that the intermolecular H…O…H hydrogen bonds are crucial for the occurrence of extremely pH sensitive rheological behavior. The presence of strong hydrogen bonds was further confirmed by ATR-IR (Attenuated Total Reflection-Infrared) measurements. In this method, the hydrogen bonds from water were quenched so that only the hydrogen bonds in the molecular self-assemblies were highlighted. It can be clearly observed in Fig. S3† that the vibration band for hydrogen bonding at 3442 cm^{-1} is even stronger than the asymmetric and symmetric vibration of the hydrocarbons at 2921 and 2852 cm^{-1}. This is probably caused by the multiple hydrogen bonds as demonstrated in Scheme 3:

The effect of NaBr introduced by the increasing pH should also be elucidated since it may cause a shielding effect. To this end, controlled experiments were completed by measuring the viscosity of CDHEAB aqueous solutions with increasing additional NaBr concentrations at pH 3.31 and 4.97, respectively. It was found that the viscosity increases as well (Fig. S4 and S5†), but no gel can be formed even at high NaBr concentrations of 300 mM. In contrast, the maximum NaBr in the 100 mM CDHEAB system introduced by increasing pH cannot exceed 100 mM, which is the total concentration of CDHEAB. It is clear that the micellar growth with pH is mainly caused by the increased intermolecular interactions, rather than the shielding effect from the produced NaBr. Moreover, the addition of extra NaBr may only lead to an increase in the viscosity; no viscosity drops can be induced by further increasing the concentration of additional NaBr. Therefore, the effect of NaBr produced in the process of pH variation on the rheological properties can be neglected.

Finally, we would like to focus on the molecular chain length on the pH sensitive rheological behavior. When the chain was shortened to twelve carbons, namely, replacing the cetyl group with a dodecyl group, we only observed a viscous fluid in the 100 mM solution, but not gels, no matter what the pH value is. This suggests that the strength of the worms is crucial to the formation of gels. It is well-known that each CH_2 unit contributes to the free energy of the molecular self-assembly formation. Therefore, amphiphiles with longer hydrocarbon chains may produce a larger free energy upon the formation of molecular assemblies, which is advantageous for the association process and so for 'stronger' worms.

So far, we have analyzed each of the factors that are related to the unique rheological behavior from the molecular level. It was found that each part of the molecular design is crucial to the pH sensitivity of the viscosity. The extremely pH sensitive fluids produced in this simple system resemble the mixed systems formed by CTAB and a hydrophobic salt,[50] where by increasing the amount of the hydrophobic salt, the viscosity increases as a result of the growth of wormlike micelles; the worms finally transform into stacked lamellar structures which lead to a considerable drop in the shear viscosity. This is also the case in our study. At pH 5.78 where the viscosity was as low as 0.066 Pa s, stacked lamellas were already present (Fig. 7). Actually, upon further increasing the pH, where more neutral CDHEA components occur in the system, large areas of lamella structures were formed. Fig. 8 shows the phase photo and the freeze-fractured TEM images for the microstructures formed in the pH 5.80 and 5.90 systems, respectively. At pH 5.80, the system separates into two phases. Multilamellar vesicles were observed in the turbid upper phase, whereas densely stacked lamellas occurred in the less turbid lower phase. As the pH increased to 5.90, the system transformed into a low viscous turbid homogeneous phase, in which giant multilamellar vesicles were found. In line with the occurrence of multilamellar vesicles, birefringence was observed (Fig. S6†).

The above phase sequence, therefore, verifies that the curvature for the microstructures decreases with increasing pH which leads to deprotonation of the CDHEAB molecules. As a result, the repulsive forces between the molecules in the self-assembled structures decreases so that the microstructures keep growing. It can be expected that the micelles grow rapidly and entangle into network structures so that they form gels. This rapid growth of the wormlike micelles is obviously a cooperative effect of hydrogen bonding, charge shielding, and hydrophobic interactions. It should be pointed out that both the hydrogen bonding contributed by the amide and that by the –C_2H_5OH in the head group are crucial to this extremely pH sensitive rheological behavior. When the amount of the charge neutral CDHEA component exceeds the fraction of charged CDHEAB, the repulsive forces can be effectively shielded so that zero curvature occurs which leads to the formation of planar layers. These layers do not entangle and easily slip over each other, so that the shear viscosity decreases sharply.

Fig. 7 Cryo-TEM images of the low viscosity 100 mM CDHEAB at pH 5.78.

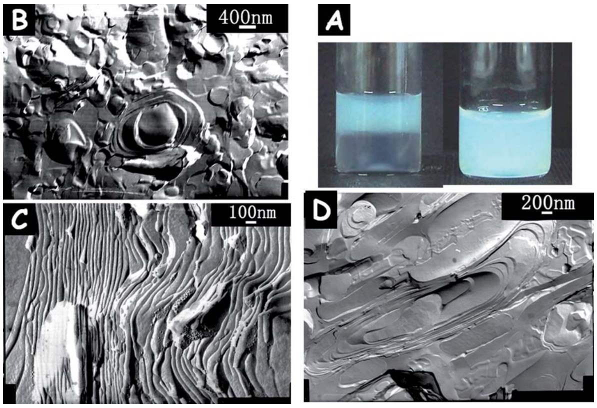


Fig. 8 (A) Photos for 100 mM CDHEAB at pH 5.80 (left) and 5.90 (right), respectively; (B and C) freeze-fractured TEM (FF-TEM) images for microstructures in the upper (B) and lower phase (C) of the pH 5.80 system, respectively; (D) is the FF-TEM image for the pH 5.90 system.

Manipulation of the phase transition pH

The main interest in studying pH sensitive molecular assemblies is to use them potentially in the biological environment.[51–56] Therefore, it is very important to produce a system that is responsive at moderate biological pH values. Since the delicate phase and microstructure transition in the CDHEAB system is mainly attributed to the decreased repulsion inside the self-assembled structures, it is believed that the strength of the repulsive forces matches the corresponding phase and microstructures. What is more important is that such a rule is adaptable not only to the special molecule of CDHEAB, but also to the family of this kind of quaternary ammonium salt. This can be conveniently and smartly used to tailor the pH required for phase and microstructure transitions. In the following we elucidate this by using results from DDHEAB (*N*-dodecyl-*N*,*N*-dihydroxyethylammonium bromide) solutions.

The 10 mM DDHEAB solution is clear and transparent (Fig. 9). Upon increasing the pH gradually, the turbidity of the system remains unchanged until a threshold pH is reached. As demonstrated in Fig. 9, the turbidity increases suddenly at pH

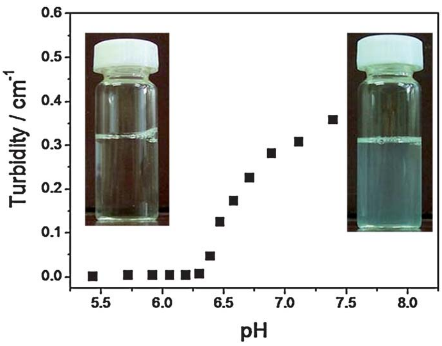


Fig. 9 Turbidity values at different pH for 10 mM DDHEAB aqueous solutions. The insets are photos of the solutions at pH 6 and 8, respectively. Measurements were made at 30 °C.

6.30. Here 6.30 is the critical pH that is required for a microstructure transition in the 10 mM DDHEAB solution, therefore it was defined as pH_{MT}. At pH_{MT}, the repulsive forces between the positively charged ammonium head groups was effectively shielded by the charge neutral amine which enables the formation of larger aggregates.

Hence, if an amphiphile that carries permanent positive charge was introduced to the DDHEAB aqueous solution, the pH_{MT} value should be increased since more bases are required to produce enough neutral DDHEA to decrease the repulsive forces in the micelles. In contrast, if some extra neutral amide exists in the system, a lower pH_{MT} is required to arrive at the same state. This was indeed the case. As demonstrated in Fig. 10, the pH_{MT} was increased when a positively charged surfactant dodecyl trimethylammonium bromide (DTAB) was introduced to the aqueous solution of DDHEAB (Fig. 10a), whereas it was decreased when a neutral alcohol dodecylhydroxy ($C_{12}H_{25}OH$) was added to the same DDHEAB solution (Fig. 10b). The extent of the decrease or increase on pH_{MT} is related to the amount of the added DTAB and $C_{12}H_{25}OH$. Therefore, we have successfully tailored the pH_{MT} value in the present system.

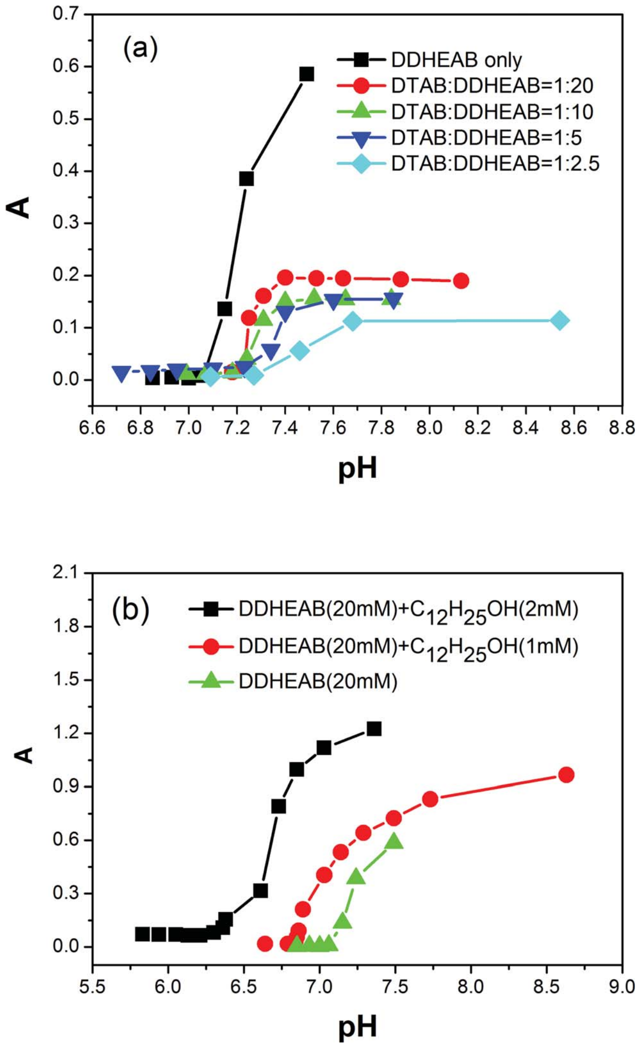


Fig. 10 The turbidity values at different pH for DDHEAB aqueous solutions with DTAB (C_T = 20 mM) (a) and $C_{12}H_{25}OH$ (b). All measurements were made at 30 °C.

Conclusion

In summary, we have reported the fabrication of extremely pH sensitive molecular self-assembling systems by creating a simple quaternary amide amphiphile. Within a narrow pH range of less than 1, the fluidity of the system can be increased by 6 orders of magnitude owing to the triggered growth of micelles. Both the ethylene hydroxyl group in the head group and the long hydrocarbon chains are found to be responsible for the occurrence of the sharply increased viscosity. The former helps to form denser molecular packing by the formation of multiple intermolecular hydrogen bonds, while the latter assists in stronger hydrophobic interactions. We were able to manipulate the responsive pH range upon understanding the rationale behind the extremely high sensitivity of these materials, which provides a great advantage in the fabrication of materials with desired responsive pH switch.

Acknowledgements

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