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Supramolecular Self-organization of Potential Hydrogelators on Attracting Surfaces

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This article highlights the aggregation behaviour of potential low molecular weight hydrogelators on attracting surfaces. Our goal was the development of a method, which enables the finding of new hydrogelators that are not easily recognizable as such because they only form instable or no hydrogels in aqueous solution. To this end, a series of negatively charges azo-dyes was synthesized and positive charged glass slides were immersed into their aqueous solutions. All dyes showed supramolecular organization and significant concentration on the attracting glass surface. Microscopic investigations mostly revealed the formation of crystals. However, one compound, (1-(2-n-octylphenylazo)-2-hydroxy-6-naphthalenesulphonate, selectively formed a hydrogel on the surface whereas it does not gel in aqueous solution. This reveals the hydrogel as the stable form of this compound under equilibrium conditions. This method of surface-induced hydrogelation might facilitate the identification of new hydrogelators. Further more, it might also allow the mimicking of surface gelation as a process of biological relevance.

Keywords: Supramolecular; Self-assembly; Low molecular weight; Hydrogelator

INTRODUCTION

Self organization of molecules in water has drawn much attention and is an important topic for understanding and mimicking many processes in living organisms. In this context low molecular weight hydrogelators (LMWH) are the least understood class of molecules. Although such compounds have been found to be capable of gelling water more than hundred years ago [1], not many LMWH are known to date. Recent overviews and examples of these are presented in the reviews of Hamilton [2] and van Esch [3]. Amongst those, a hand full are known to form a hydrogel by dissolving the compound in water upon heating and subsequent cooling to room temperature. The majority of the described hydrogelators require additives. Such was already the case with the first hydrogelators found by Lipowitz in the course of his experiments about the solubility of uric acid. To obtain gels, he needed to add certain bases and salts like borax. Absence of these additions led to precipitation only. Equally are the finding with many other hydrogelators described in literature. In some cases, the addition of buffers like sodium carbonate [4,5] and others [6] are required. Jørgensen *et al.* report about hydrogelators which necessitate adding of ethanol or dimethylformamide [7]. Also, mixtures with methanol [8] and other alcohols [9] or DMSO [10,11] etc. are common. Some gels are only formed during their chemical synthesis or the subsequent workup procedure [12–14]. This is due to the fact that all hydrogelators must reach the minimal gelling concentration (MGC) at a certain temperature and precipitate in form of a gel.

The basis for gelation of LMWHs are physical interactions like hydrophobic associations and Van der Waals forces [15], hydrogen bonding [11,16], ionic bonding [17] and combination of these forces [18]. Another important factor for hydrogelling is the delicate hydrophilic/hydrophobic balance of the compounds. In an initial stage, the ordering of single molecules leads to a primary structure which then can associate to build a secondary structure of nano- to micrometer dimension, often with morphologies like fibres [18], micelles [15] or ribbons [19]. Finally, interconnection of these leads to a tertiary structure that entraps the water and forms a hydrogel. Since the

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bonds between the molecules are all non-covalent, each of these association steps is reversible. Therefore, hydrogels of LMWH represent unique and delicate systems where the right balance between order and disorder has to be found. Thus, most likely a tremendous number of possibly hydrogel forming compounds exists and cannot be recognized as such, because the molecules do not reach their MGC in water. Until now there is no established procedure that can mimic the gelation behaviour of a hydrogelator below MGC. Here, we describe a method that reveals the hydrogel forming potential of low molecular weight compounds that do not reach MGC in their aqueous solutions.

RESULTS AND DISCUSSION

Organization Properties During Synthesis

Hamada *et al.* examined the gelling properties of diverse azo-dyes composed of 2-naphthol-6-sulphonic acid and different anilines which form instable hydrogels [20,21]. Based on these findings, we synthesized a library of various regioisomers containing diverse side chains at the ortho-, meta- and para-position to the azo-group (Table I and Fig. 1). As described previously, it was found that only one of the isolated azo dyes (1-(2-n-hexylphenylazo)-2-hydroxy-6-naphthalenesulphonate (**5-*o***) forms a stable and thermoreversible hydrogel and is also capable of gelling on appropriately modified attracting surfaces [22]. However, many of the other compounds did form hydrogels during their synthesis but these gels form precipitates with time (Table I and Fig. 2).

The formation of precipitates was temperature dependent. While the hydrogels were stable at 5°C for several hours, they precipitated within minutes when warmed to room temperature. This finding seems to indicate that the hydrogels are not thermodynamically stable and the reorganization is kinetically controlled. We presume that the gelation occurred during synthesis, where the highly concentrated educts form the respective azo dye during a fairly fast reaction. Thus, the product exceeds its solubility product and also its MGC very fast. If the compound has hydrogelling abilities, it will form a gel in the first place, because this is the fastest way to remove its hydrophobic moieties out of the water. However, if this gel is not the stable form under the conditions at hand, the compound then crystallizes with time. In the cases of compounds **6-*o***, **6-*p***, and **7-*p***, it is thinkable that the solubility product is exceeded, but not MGC, which then results in the formation of an amorphous precipitate.

In all later attempts, it was not possible to obtain gels again from the precipitates by heating the reaction mixtures and subsequent cooling. Obviously, MGC of these compounds cannot be reached anew this way. This phenomenon was already described for other hydrogels as well [23].

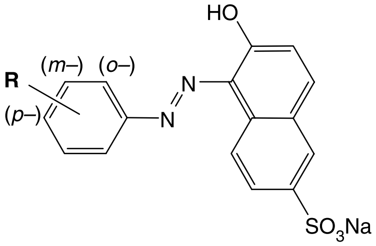

FIGURE 1 Chemical motive of the synthesized azo-dyes.

TABLE I Synthesized azo-dyes and their behaviour during synthesis: G: instable hydrogel formed during synthesis, GG: stable hydrogel formed from the aqueous solution, D: no hydrogel and no precipitate during synthesis, P: precipitation during synthesis

	R	*o-*	*m-*	*p-*
1	CF_3	G	G	–
2	C_2H_5	G	D	–
3	$n{-}C_4H_9$	G	G	G
4	$n{-}C_5H_{11}$	G	–	G
5	$n{-}C_6H_{13}$	GG	G	G
6	$n{-}C_7H_{15}$	P	–	P
7	$n{-}C_8H_{17}$	G	–	P

Organization Properties on Attracting Surfaces

To explore the self-organization properties of the isolated azo dyes, they were saturated in boiling

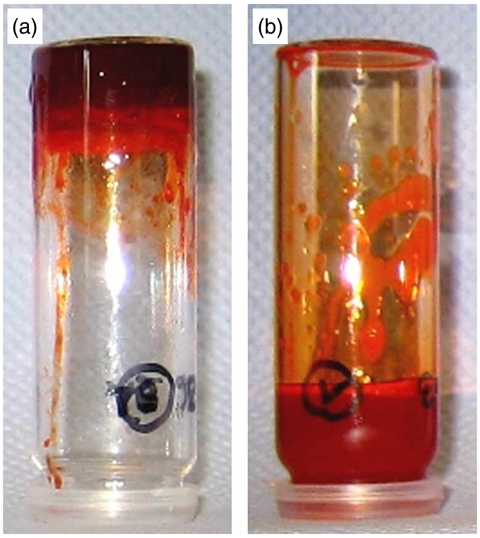

FIGURE 2 (a) Hydrogel of **5-*p*** with 4.7 wt.-% formed during synthesis at 5°C, (b) precipitated sample after warmed to room temperature.

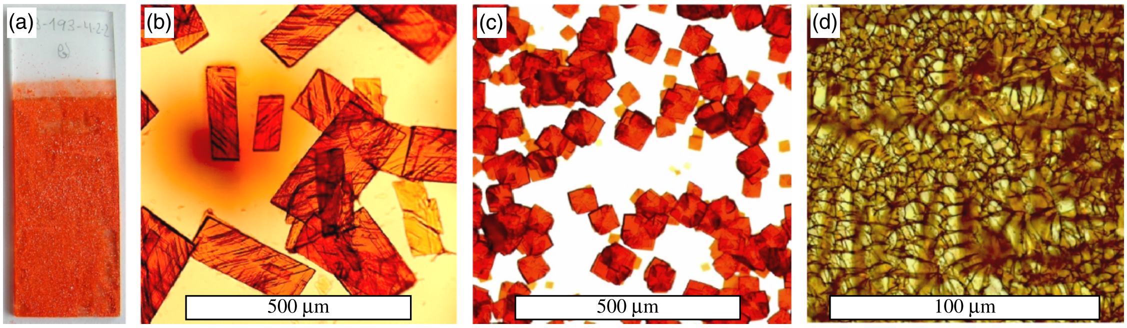

FIGURE 3 (a) Amino glass surface showing deposition of crystals of **4-*p*** formed from a solution of 0.4 wt.-%, (b) light microscopy image of such crystals, (c) light microscopy image of crystals of the **4-*o*** from a solution of 0.4 wt.-%, (d) light microscopy image of a amino glass surface after immersion into a 0,4 wt.-% solution of ***o*-7** showing the regular structuring.

water and the solution was cooled to room temperature. In all cases with the exception of **5-*o*** precipitation of crystals or amorphous substances but no hydrogelation occurred, i.e. the MGC was not reached. However, all aqueous solutions with concentrations below 1 wt.% did not show precipitates.

In order to obtain a stable self-organization form of the pure azo dyes from the aqueous solution in concentrations above MGC, we decided to explore the interactions of stable dye solutions with NH_2 functionalized surfaces. Since the negatively charged dyes show an electrostatic affinity to amino groups, they will have a higher concentration near the surface as known from many other examples [24–27]. In the ideal case, this surface concentration exceeds the concentration required for the compounds to form supramolecular structures, which will then be formed on the surface only. The amino glass slides have been immersed into solutions with concentrations of 0.4 wt.%. After 16 h, the slides were removed and examined under a light microscope. Whereas none of the dyes precipitated from their solutions under normal conditions or on unmodified glass slides, we always found depositions of the dyes on the amino glass slides. Investigations of the latter revealed 4 scenarios: cubic crystals (Fig. 3b), sheet-like crystals (Fig. 3c), amorphous aggregates mixed with crystals, and very surprisingly a highly ordered non-crystalline structure in the case of **7-*o*** (Fig. 3d). Table II summarizes the results of these experiments.

As seen in Fig. 3a, dense coatings of fairly regular crystals had been formed in many cases. The dimensions of the crystals ranged from 10 to 50 μm as for **4-*o*** but also up to some hundred micrometers as for the **4-*p***. This crystallization is noteworthy since azo dyes usually do not exhibit good crystallizing properties [28].

To get a closer look at the morphologies of the aggregates, the samples were freeze dried and examined with an environmental scanning electron microscope (ESEM). It turned out, that the crystals possess sandwich structures with stacked layers (Fig. 4a–d). In the cubic crystals, these layers are dense-packed with little to no gap visible (Fig. 4b,d) whereas the layers of the sheet like crystals seem to be stapled more loosely on top of each other (Fig. 4a,c). Mostly, the layers in the sheet like systems are of the same shape and dimension with very accurate superimposition. Therefore, the crystals are quite regular. The cubic crystals are less regular since the individual layers are often of different dimensions. Finally, it is worth noting that the sheet like morphology was only observed for the para-substituted azo dyes whereas the ortho-analogues frequently exhibited the cubic shape. This shows that the position of the alkyl-group has an important influence on the crystallizing behaviour of the dyes.

As seen in Fig. 5a, the ESEM image of the structure of freeze-dried samples of **7-*o*** is very regular in a honey-comb like fashion. The structure does not resemble crystals but exactly the structure of the xerogel of surface-induced hydrogels of hydrogelator **5-*o*** (Fig. 5b) of our previous experiments [22]. Thus, **7-*o*** obviously formed a hydrogel on the surface of the amino glass slide. In contrast to all the other investigated dyes, the hydrogel seems to be the stable form of **7-*o***. This is surprising, because

TABLE II Type of deposition of the azo-dyes on amino glass surface: C: crystallization—CC: cubic crystals, SC: sheet like crystals, G: Gelation, C&A: formation of crystals and amorphous aggregates

#	R	*o-*	*m-*	*p-*
1	CF_3	C	C	–
2	C_2H_5	C&A	C&A	–
3	$n{-}C_4H_9$	CC	CC&A	C
4	$n{-}C_5H_{11}$	CC	–	SC
5	$n{-}C_6H_{13}$	G	SC&A	SC
6	$n{-}C_7H_{15}$	CC	–	C&A
7	$n{-}C_8H_{17}$	G	–	C

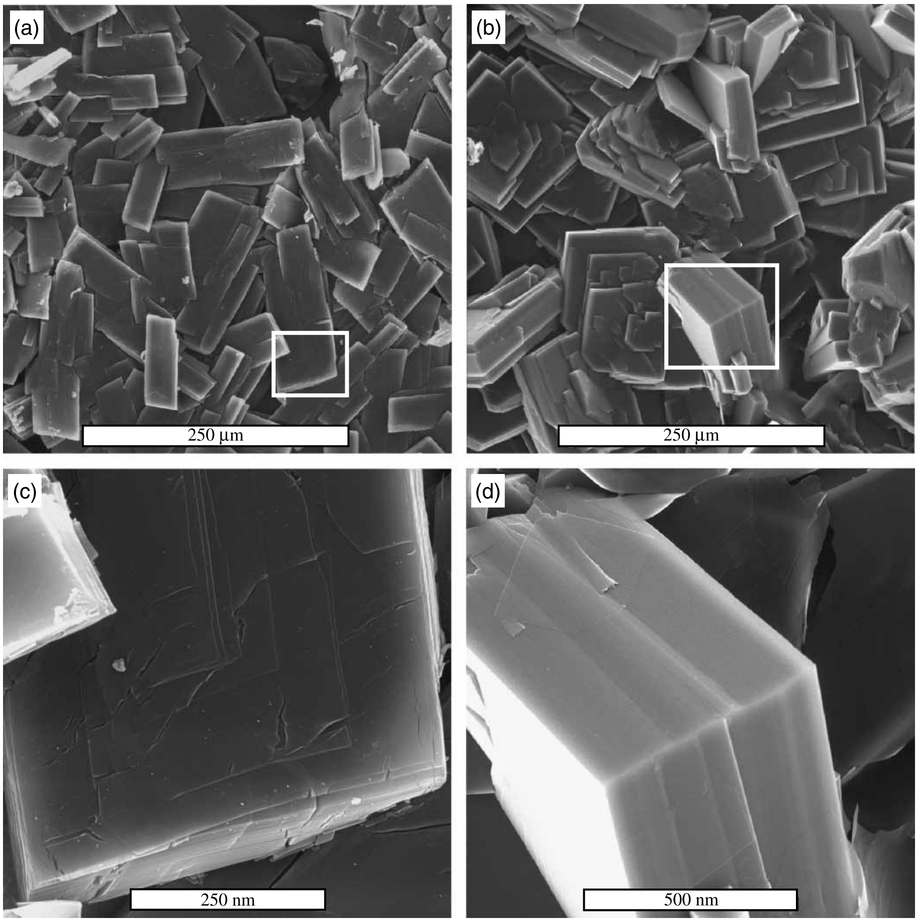

FIGURE 4 SEM images of surface grown crystals of (a) **4-*p***, (b) **3-*o***. (c) and (d) show magnifications of the highlighted areas of the pictures above.

during synthesis, **7-*o*** formed only an instable hydrogel, which precipitated rather quickly. This might be explained by the fact that the concentration of **7-*o*** then was too high or the salts or other impurities in the reaction mixture induced precipitation.

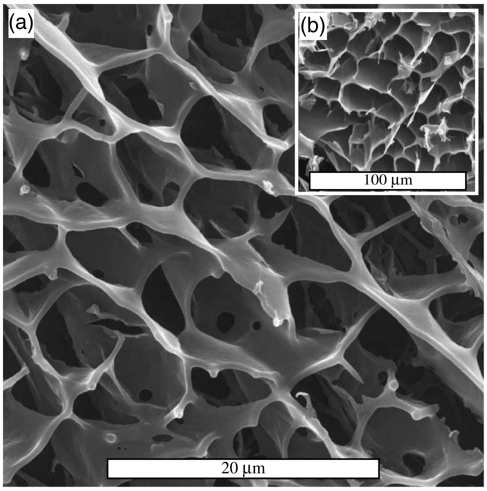

FIGURE 5 SEM images of (a) the surface induced structuring of **7-*o***, (b) of a xerogel sample of a surface-grown hydrogel of **5-*o***.

CONCLUSION

In closing, hydrogelation is undoubtedly a phenomenon that is still poorly understood and much research has to be done in order to broaden the understanding in this field. Here, it could be demonstrated for the first time, that surface-induced self-organization seems to be a useful tool to get closer insights in the potential of low molecular weight compounds to form hydrogels. This simple yet informative experiment might serve as a new procedure to find out the stable form of a compound under equilibrium conditions and thus might be a new method for the identification of potential hydrogelators which have been overseen as such previously. Furthermore, since it can be done under any chosen conditions including the application of tailored surfaces with specific recognition structures, surface-induced hydrogelation might enable the investigation of hydrogelling drugs, e.g. the pyrene-modified vancomycin, under physiological conditions [29,30].

EXPERIMENTAL

Azo Coupling

A typical method is described on the example of **7-*o***. The diazonium salt of 2-octyl-aniline was prepared by slow addition of a solution of sodium nitrite (2.42 g, 35 mmol) in water (5 ml) to a solution of the aniline (6.20 g, 35 mmol) in water (15 ml) and conc. hydrochloric acid (7.8 ml, 95 mmol) at 5°C. This solution was slowly added to a solution of 2-naphtholsulfonic acid sodium salt (8.64 g, 35 mmol) and sodium hydroxide (4.00 g, 100 mmol) in water (100 ml) at 5°C. After addition of the first 5 ml of diazonium salt solution, the mixture became viscous and started to form a hydrogel. To isolate the product after complete reaction, sodium chloride (35 g) was added and the product was precipitated at 5°C overnight. The residue was recrystallized repeatedly from a mixture of ethanol/methanol/acetone/water (3:3:4:1, v:v:v:v).

Surface-Induced Aggregation

Solutions of azo dyes have been prepared by dissolving the 0.4 wt.% of dyes in distilled and boiling water. After cooling to room temperature, amino glass slides have been placed into these solutions for 16 h. Finally, the slides were removed and investigated under the microscope in wet condition or the ESEM after freeze drying.

Visible microscopy images were measured with an Axioplan 2 imaging microscope (Zeiss, Jena, Germany). *Scanning electron microscope images* were recorded with an ESEM 2020 (Electron Scan Corporation, Wilmington, MA, USA) after previous sputtering with gold palladium in a Polaron Sputter Coater SC 7640.

Supporting Information Available

Analytical data for all azo dyes as well as the preparation procedure for the amino glasses and further azo-coupling experiments are available.

Acknowledgements

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