

Surface-induced hydrogelation

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The first azo dye that gels from its aqueous solution was synthesized and its moist hydrogel was investigated with electron microscopy and atomic force microscopy; the anionic azo dye in aqueous solution forms a hydrogel on cationic surfaces even at concentrations 50 times below the minimal gelation concentration.

Low molecular weight hydrogelators have been known for over a hundred years,^{1,2} but because they could never match the superior material properties of macromolecular hydrogelators, they have not been a focus of research and therefore only a few of them, mostly amino acid derivatives,³ lipids,⁴ sugar-based systems,⁵ bis-urea carboxylate derivatives,⁶ some *N*-alkylaldonamides,⁷ bolaamphiphiles⁸ and gemini surfactants,⁹ are known. Recently, the first antimicrobial hydrogelator based on the antibiotic vancomycin was described by Xing and coworkers.¹⁰ This derivative surprisingly shows an up to ten times greater antibacterial activity than the unmodified drug. It was suggested that the modified surface-active antibiotic is concentrated onto the surface of Gram-positive bacteria by gelation, increasing the activity of the drug.^{10,11} Fig. 1 illustrates the concept of this process, where the hydrophilic part of the hydrogelator must have an affinity to the surface. Upon attachment, the surface presents hydrophobic groups that have an

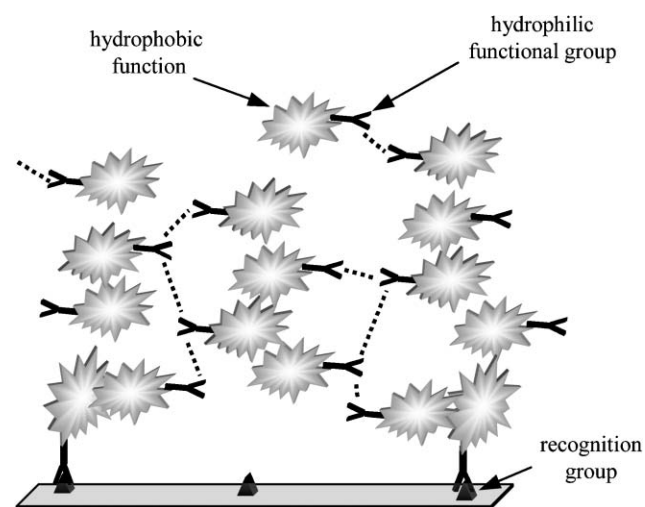


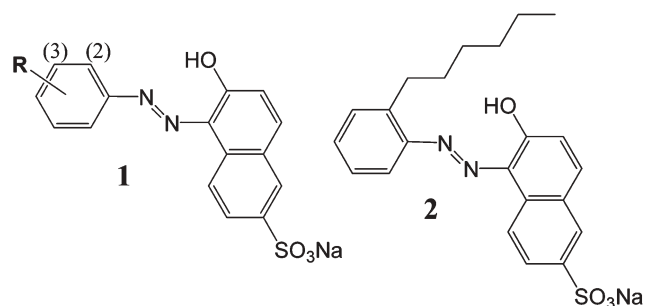
Fig. 1 Gelation of drug molecules on a surface leading to an increased local concentration.

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affinity to the remaining molecules in solution, which then start to gel even below the minimal gel concentration (MGC).

Since the phenomenon of surface-induced hydrogelation had not yet been observed, we decided to explore it with the aid of a model compound.

Negatively charged hydrogelling sulfonate-dyes have already been described by Haller and later by Hamada *et al.*^{12,13} Unfortunately, all the described dyes form gels from mixtures and do not gel in pure aqueous solution. The latter is essential for judging interactions with a complementary surface. However, azo dyes are easily detectable and contain ionic functions that represent suitable groups for their attachment to surfaces equipped with the respective opposite charge as recognition structure. Therefore, they were chosen as model structures in our experiments. In order to find a compound that gels from its aqueous solution, we synthesized a series of different dyes based on the generic structure **1**. The tendency of these molecules to either crystallize or to form a hydrogel should mainly depend on the ratio of the non-crystallizing alkyl parts *R* to the crystallizing aromatic parts of the molecule and to the position of the alkyl substituent on the benzene moiety. Therefore, we explored dyes with *R* = trifluoromethyl-, ethyl-, *n*-butyl-, *n*-pentyl-, *n*-hexyl- and *n*-octyl-sidechains at both the ortho (2)- and the meta (3)-position to the azo-group.† In the end, only the compound with an *n*-hexyl group at the ortho position, 1-(2-*n*-hexylphenylazo)-2-hydroxy-6-naphthalenesulfonate in the following referred to as ortho hexyl-dye, OHD‡, **2**, was found to form a stable hydrogel upon dissolving at least 5 wt% in hot water (80 °C) and subsequent cooling to room temperature. The gel is stable over several months and also thermoreversible with a gel transition temperature of 45 °C as determined with dynamic mechanical analysis.§



Investigating the structure of the original swollen gel as well as the freeze dried sample (xerogel) revealed a highly ordered structure. The Environmental Scanning Electron Microscope (ESEM) image of the hydrogel (Fig. 2a) shows a broccoli-like structure. This structure originates from the water-filled channels of the honeycomb-like architecture of the azo-dye seen in Fig. 2b, which shows an ESEM micrograph of the respective xerogel. The

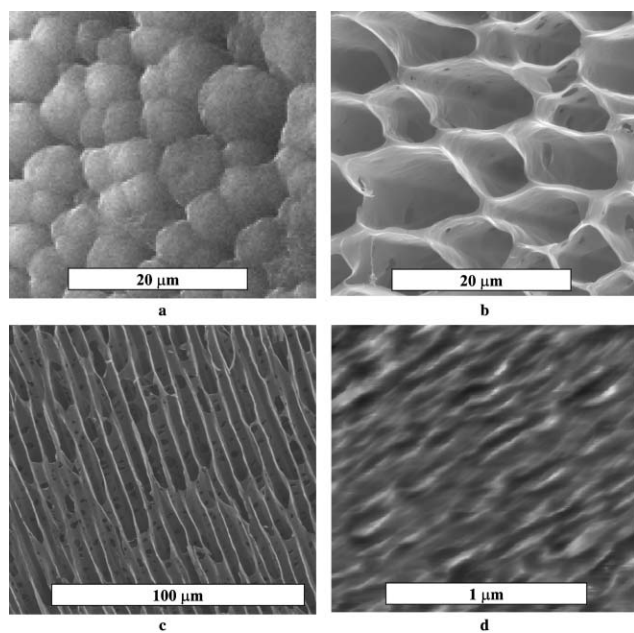


Fig. 2 a: ESEM of the OHD-hydrogel, b, c: ESEM of the OHD-xerogel from different perspectives, d: AFM of the OHD-hydrogel.

channels are highly ordered in parallel with more than 100 μm in length and a wall thickness of approximately 350 nm. The diameters of these channels range from 4 to 10 μm . Fig. 2c shows a side view of the channels.

Even from this small section, an aspect ratio above ten can be calculated. Investigations of the hydrogel with atomic force microscopy under water showed that the dye molecules assemble to give fibers of some 20 nm in thickness that are oriented in parallel (Fig. 2d).

Having established that OHD is an anionic hydrogelator with a distinguishable structure, an investigation was now undertaken into whether the compound is capable of gelling on a recognizing surface, such as an oppositely charged material. For this purpose, commercial glass slides were modified with amino groups. Then, aqueous solutions of OHD in a concentration range of 0.05 to 0.30 wt%, which is far below the MGC of 5 wt%, were prepared and the glass slides were immersed in these solutions.¶ After 16 h, the slides were removed and the amount of dye on the surface was determined by UV/VIS-spectroscopy.¶ As seen in Fig. 3 the concentration of the dye adsorbed on the amino glass slides increases significantly at a minimum concentration of about 0.10 wt% of OHD, which can be considered as minimal surface gelation concentration (MSGC). Investigating the surface-adhered dye with ESEM revealed a structure similar to that found in the gelled solution (see Figs. 2b and 3b).** Obviously, the gelling azo-dye OHD is truly surface concentrated by hydrogelation. Plain glass did not concentrate OHD at all, *i.e.* the adsorption of the dye is specific to the amino glass.

For calculation purposes, the number of NH_2 groups on the surface was determined to be 3–4 functions/ nm^2 using a standard procedure with picric acid.¹⁴ Considering the size of the azo-dye OHD, a monolayer would be 1–2 molecules per nm^2 . With this, the number of OHD molecules adhered by surface-induced gelation from a, for example, 0.25 wt% solution (20 times below MGC) is more than 200 times greater than that of a monolayer.

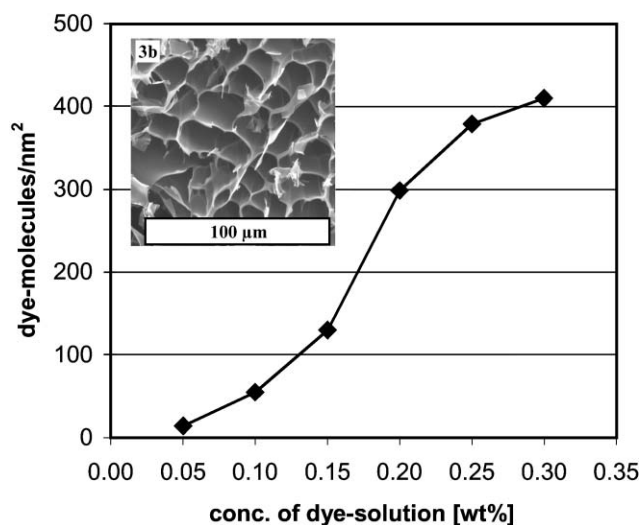


Fig. 3 Dye-molecules attached to the glass surface *versus* the concentrations of the dye solutions, 3b: ESEM image of the xerogel of a surface-adhered hydrogel.

In closing, it could be demonstrated for the first time that a hydrogelling low molecular weight compound starts to gel on a surface with attracting functions with an MSGC 50 times below the MGC. The resulting concentrating of molecules on surfaces from solutions might prove a useful concept for the design of novel drugs. The surface-induced self-organization might also be suitable for surface patterning and functional coatings of non-accessible surfaces. Our future work will be directed toward the design of biologically active hydrogelators.

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Notes and references

† For a general description of the synthesis of analogous azo-dyes see reference 12 and references therein.

‡ Key analytical data of OHD: $T_{\text{decomp.}} = 305\text{ }^\circ\text{C}$. $^1\text{H NMR}$ (300 MHz, [D6]DMSO, 25 $^\circ\text{C}$, TMS): $\delta = 15.89$ (s, 1H, OH), 8.52 (d, 1H, $J = 8.56$, H_{Ar}), 8.09 (d, 1H, $J = 1.64$, H_{Ar}), 8.02 (d, 1H, $J = 9.39$, H_{Ar}), 7.88 (dd, 1H, $J_1 = 1.64$, $J_2 = 8.56$, H_{Ar}), 7.61–7.66 (m, 2H, 15-H, H_{Ar}), 7.36–7.43 (m, 1H, H_{Ar}), 7.15–7.17 (m, 1H, H_{Ar}), 6.95 (d, 1H, $J = 9.39$, H_{Ar}), 2.61 (t, 2H, $J = 7.61$, CH_2), 1.52–1.64 (m, 2H, CH_2), 1.20–1.38 (m, 6H, CH_2), 0.81 (t, 3H, $J = 6.86$, CH_3); $^{13}\text{C NMR}$ (75.4 MHz, [D6]DMSO, 25 $^\circ\text{C}$, TMS): $\delta = 168.0$, 145.3, 145.1, 144.2, 139.7, 132.6, 129.5, 129.0, 128.4, 126.9, 126.5, 125.6, 124.0, 120.8, 119.0, 116.3, 34.9, 31.0, 30.7, 28.3, 22.0, 13.8; Elemental analysis calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_4\text{SNa}$ (MW = 434.48): C, 60.82%, H, 5.34%, N, 6.45%, S, 7.38%; Found: C, 60.53%, H, 5.24%, N, 6.38%, S, 7.37%; UV/VIS (water): $\lambda_{\text{max}}(\epsilon) = 485\text{ nm}$ ($\epsilon_{485} = 15800\text{ M}^{-1}\text{ cm}^{-1}$).

§ DMA was performed on a PaarPhysica UDS 200 Rheometer using plate diameters of 50 mm and a gap width of 1 mm. The fluid (5 wt% of **1** in water) at 60 $^\circ\text{C}$ was cooled gradually to 5 $^\circ\text{C}$ at 5 K/min. During this process a constant frequency of 0.1 Hz with an amplitude of 2% was applied and the resulting moduli G' and G'' were measured.

¶ Note that the viscosity of the dye solutions in the tested concentration range does not differ from that of water.

¶¶ The amount of dye molecules per nm^2 , AN, was calculated as follows: $\text{AN} = [(c_2 - c_1) \times V \times N]/A$. Therein, V is the slide adhered liquid volume (measured by the weight difference before and after immersing the slide in the dye solution), N is the Avogadro number 6.022×10^{23} , c_1 is the concentration of OHD in the surrounding solution, c_2 is the concentration

of the dye in the slide adhered liquid, and A is the surface area of the glass slide, $25 \times 10^{14} \text{ nm}^2$.

** Note that simple freeze drying of OHD solutions below MGC cast of glass slides did not result in a regular structure.

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