Molecular Design of Low Molecular-weight Aqueous Gels Bearing an Azo-hydrazone Tautomeric Group Useful as a Solvent Polarity Probe

Masato Amaike, Hideki Kobayashi, and Seiji Shinkai*
Chemotransfiguration Project, Japan Science and Technology Corporation (JST), 2432 Aikawa, Kurume, Fukuoka 839-0861

Novel low molecular-weight gelators for aqueous gels were exploited by systematically search varying sugars and adjusting hydrophilic/lipophilic balance. The azonaphthol group was used as a lipophilic group, which was also useful as a measure of the microscopic solvent polarity. From the azo-hydrazone tautomerism the polarity in the gelator aggregates was estimated to be much less polar than that in the gelation media.

In general, "aqueous gels" stand for the gels composed of crosslinked polymers whereas "organogels" stand for the gels composed of one-dimensional aggregates of low molecular-weight compounds. However, there are a limited number of "aqueous gels" composed of such aggregates of low molecular-weight compounds.[1] Since the sol–gel phase transition temperature (T_{gel}) in these "aqueous gels" is adjustable by the gelator concentration, they are readily applicable to thermocontrol of enzyme activities, membrane properties, etc. in aqueous solution at desired temperatures. To the best of our knowledge, however, the basic strategy to design such gelators is not yet demonstrated clearly. So far, we have devoted our research effort toward exploitation of novel sugar-integrated gelators[2–7]: a merit of this system is that one can systematically design various gelators utilizing abundant basic skeletons in a carbohydrate family. In the research process we found, with serendipity, that one mannose-based gelator can gelate water.[4] The finding implies that if we carefully search for sugars as well as for appropriate hydrophobic substituents, several new aqueous gelators may be further discovered, which may be useful to specify what is the basic strategy to design such aqueous gelators. With these objects in mind we designed gelators **1b**, **1c**, and **2b–2d** bearing a sugar moiety and an azocresol or azonaphthol moiety within a molecule. The azocresol or azonaphthol moiety is introduced as a probe to detect the micropolarity in the gel aggregates through an azo-hydrazone tautomerism.[8] Compounds **1a** and **2a** are used as reference compounds without the sugar moiety.

a: R = MeO
b: R = β-D-glucopyranosyl
c: R = β-D-galactopyranosyl
d: R = α-D-glucopyranosyl
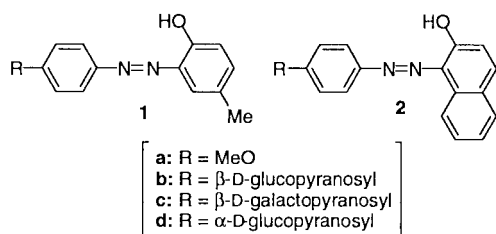
These compounds were synthesized by diazotization of the corresponding aromatic amines followed by coupling with cresol or 2-naphthol. The products were identified by ^{1}H NMR and IR spectral evidence and elemental analyses.

We prepared gels by two different methods: gelator and solvent (ethanol or water) put in a closed capped tube and heated until the solid was dissolved. The solution was cooled to room temperature. Then, water was added gradually. The mixture was heated again until a clear solution was obtained. The solution was cooled to room temperature (Method A). The mixture of water (without any organic solvent) and gelator in a closed capped tube was heated until the solvent boiled and was kept at this temperature for a few minutes. The solution was cooled to room temperature (Method B). To determine the T_{gel} value, we set an inverted capped tube containing the gel in a thermocontrolled oil-bath. We raised the bath temperature at a rate of 1 °C min^{-1} and determined the T_{gel} value where the gel melted down.

Table 1. Gelation test using Method A in water-EtOH mixed solvents [a]

	Water/ EtOH (v/v)					
	100/0	90/10	80/20	70/30	60/40	50/50
1a	P	P	-	-	-	-
1b	S	S	-	-	-	-
1c	P	P	-	-	-	-
2a	P (P)[b]	P	-	-	-	-
2b	P (G)[b]	G	G	G	Gp	S
2c	P (P)[b]	G	G	G	G	S
2d	P (G)[b]	P	P	P	P	P

[a] [Gelator] = 4.00×10^{-3} mol dm^{-3}, G: stable gel, Gp: partial gel, S: solution after cooling, P: precipitation. [b] Test using Method B.

Firstly, we synthesized a few cresol derivatives (such as **1b** and **1c**), but they were either too soluble or precipitated (Table 1). Secondary, therefore, we replaced the cresol moiety with the naphthol moiety. Compounds **2b–2d** thus synthesized were again precipitated from 100% water, but addition of EtOH changed these mixtures into translucent aqueous gels. Thus, their gelation abilities were carefully checked at various EtOH concentrations (0–50 vol%: Table 1). α-D-Glucose-based **2d** was scarcely dispersed into water–EtOH mixed solvents. On the other hand, **2b** and **2c** were able to gelate the mixed solvents at 10–40 vol% EtOH. Measurements of their T_{gel} values established that the β-D-galactose-based **2c** gel is more stable (by ca. 20 °C in T_{gel}) than the β-D-
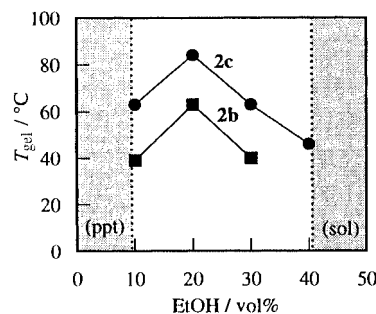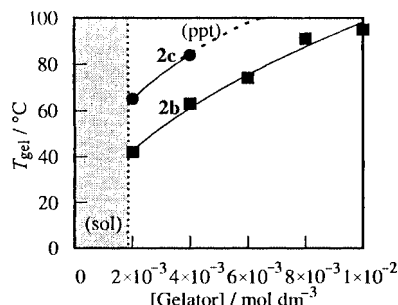

Figure 1. T_{gel} for **2b** and **2c** plotted against EtOH content: [gelator] = 4×10^{-3} mol dm^{-3}

glucose-based **2b** gel (Figure 1). For both **2b** and **2c** the most stable aqueous gels were obtained at water/EtOH = 80/20 v/v: this reason is not yet clarified. On the other hand, **1a** and **2a** without the sugar moiety only precipitated.


Figure 2. T_{gel} for **2b** and **2c** plotted against gelator concentration: water/EtOH = 80/20 v/v

Fixing the water/EtOH ratio to 80/20 v/v, we measured their T_{gel} values as a function of gelator concentration (Figure 2). The stable aqueous gels were obtained even at 2.00×10^{-3} mol dm^{-3} (0.87 g L^{-1}), indicating that these two compounds can act as excellent gelators for water–EtOH mixed solvents. Gelator **2c** resulted in precipitate above 4.00×10^{-3} mol dm^{-3}, whereas gelator **2b** resulted in the translucent gels up to 1.00×10^{-2} mol dm^{-3}. The results indicate that **2c** is more cohesive and tends to precipitate with the stronger intergelator interaction than **2b**, whereas **2b**, featuring the moderate intergelator interaction, can gelate water–EtOH mixed solvents in the wide concentration range.

It is known that when sugar derivatives act as gelators of organic solvents, equatorial OH groups tend to enhance the cohesiveness because they are mostly used for the intermolecular hydrogen-bonding interaction whereas axial OH groups are mostly used for the intramolecular one.[6] In the present system, **2b** with three equatorial OH groups should show the higher cohesiveness than **2c** with one axial OH group and two equatorial OH groups. The results in Figures 1 and 2 indicate the higher cohesiveness for **2c** rather than for **2b**, however. This implies that the major driving force for molecular aggregation in water is different from that in organic solvents.

We previously found that when certain gelators, which are not soluble in solvents at their boiling points, are enforced to be dissolved at the higher temperature in a sealed tube, the resultant solutions frequently provide very stable organogels.[6b,c] We applied Method B to **2a–2d** (4.00×10^{-3} mol dm^{-3}) in 100% water (above 100 °C). Very interestingly, **2b** and **2d** gave the stable aqueous gels with T_{gel} 122 °C and 116 °C, respectively. This implies that the gelation includes some irreversible process.

As mentioned in introduction, the azonaphthol group features an azo-hydrazone equilibrium, which is useful as a measure of the micropolarity.[8] Figure 3A shows an absorption spectral change in **2c** at various water–EtOH mixed solvents. The spectral change in **2a** and **2b** is almost the same, indicating that the sugar structure does not affect the absorption spectra in these homogeneous solutions. The λ_{max} 415 nm and λ_{max} 500 nm are assignable to the azo form and the hydrazone form, respectively, indicating that the azo form increases in less polar EtOH-rich solvents. On the other hand, Figure 3B shows the absorption spectra of **2b** and **2c** in the gel phase (water/EtOH = 80/20 v/v). It is clearly seen that the fraction of the azo form is
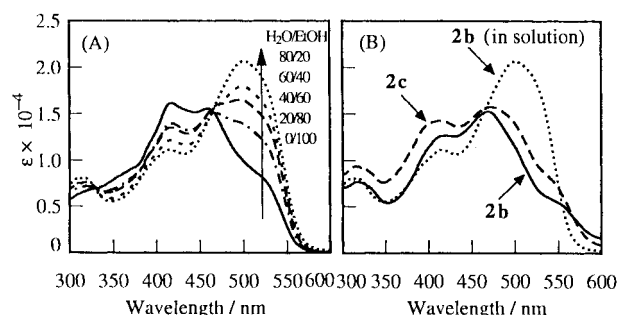
Figure 3. (A) Absorption spectra of **2c** (2.00×10^{-5} mol dm^{-3}) at various water-EtOH mixed solvents; (B) Absorption spectra of **2b** (2.00×10^{-5} mol dm^{-3}) in solution (⋯⋯) and **2b** (——) and **2c** (– –) (2.00×10^{-3} mol dm^{-3}) in the gel phase: water/EtOH = 80/20 v/v

increased, indicating that these gelators favorably adopt the azo form when aggregated in the gel phase. Since a plot of $\varepsilon_{500}/\varepsilon_{415}$ vs EtOH vol% shows a good linear relationship (data not shown here), one can estimate from this calibration curve that the micropolarities of the water/EtOH 80/20 v/v gels of **2b** and **2c** correspond to 13.9 and 23.1 vol% water, respectively. The results support the concept previously proposed by us[2,4,9] and Weiss[10] that gelator molecules in the aggregates are not so "wet" with solvent molecules (water molecules in this system).

In conclusion, the present study demonstrated that new gelators for aqueous gels can be systematically exploited by combination of combinatorial search of appropriate sugars with adjustment of a hydrophilic/lipophilic balance. In addition, it was shown that the micropolarity in the gelator aggregates is much less polar than the gelation media. We are currently extending the present aqueous gel system to examination of visual detection of their morphological structures, sugar-induced chirality of the gelator aggregates, color change by the tautomerism shift, control of biological events by the sol–gel phase transition, etc.

References and Notes
1 For such aqueous gels, see. K. Hanabusa, T. Hirata, D. Inoue, M. Kimura, H. Touhara, and H. Shirai, *J. Colloids Surfaces*, **A169**, 307 (2000) and references cited therein.
2 a) K. Yoza, Y. Ono, K. Yoshihara, T. Akao, H. Shinmori, M. Takeuchi, S. Shinkai, and D. N. Reinhoudt, *Chem. Commun.*, **1998**, 907. b) N. Amanokura, K. Yoza, H. Shinmori, S. Shinkai, and D. N. Reinhoudt, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 2585.
3 K. Inoue, Y. Ono, Y. Kanekiyo, S. Kiyonaka, I. Hamachi, and S. Shinkai, *Chem Lett.*, **1999**, 225.
4 K. Yoza, N. Amanokura, Y. Ono, T. Akao, H. Shinmori, M. Takeuchi, S. Shinkai, and D. N. Reinhoudt, *Chem. Eur. J.*, **5**, 2722 (1999).
5 N. Amanokura, Y. Kanekiyo, S. Shinkai, and D. N. Reinhoudt, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1995.
6 a) R. Luboradzki, O. Gronwald, M. Ikeda, S. Shinkai, and D. N. Reinhoudt, *Tetrahedron*, **56**, 9595 (2000). b) R. Luboradzki, O. Gronwald, A. Ikeda, and S. Shinkai, *Chem. Lett.*, **2000**, 1148. c) O. Gronwald, K. Sakurai, R. Luboradzki, T. Kimura, and S. Shinkai, *Carbohydr. Res.*, in press.
7 Also, see classic examples for sugar-integrated gelators: S. Yamasaki and H. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **69**, 561 (1996) and references cited therein.
8 a) G. Gabor, Y. Frei, D. Gegiou, M. Kaganowitch, and E. Fischer, *Isr. J. Chem.*, **5**, 193 (1967). b) J. Schreiber, J. Socha, and K. Rothschein, *Collect. Czech. Chem. Commun.*, **35**, 857 (1970). c) S. Kishimoto, S. Kitahara, O. Manabe, and H. Hiyama, *J. Org. Chem.*, **43**, 3882 (1978). d) J. Kelemen, *Dye. Pigm.*, **2**, 73 (1981).
9 K. Murata, M. Aoki, T. Suzuki, T. Harada, H. Kawabata, T. Komori, F. Ohseto, K. Ueda, and S. Shinkai, *J. Am. Chem. Soc.*, **116**, 6664 (1994) and references cited therein.
10 R. Mukkamala and R. G. Weiss, *J. Chem. Soc.,Chem. Commun.*, **1995**, 375.