Self-Assembling Galators -- Toward New Functional Materials

Lit. Seminar #3
Rie MOTOKI (M2)

1. Introduction

about gel

- **definition**

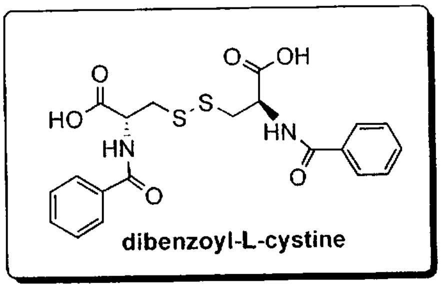
  高分子ゲル→「あらゆる溶媒に不溶の三次元網目構造を持つ高分子およびその膨潤体」
  「有限の膨潤性を示す(形のある液体、容器が不要の液体)」
  「固体と液体の中間の物質形態」

- **example**

  jerry(gelatin), collagen, albumin // polypeptide
  jam(pectin), agar(agarose) // sugar
  } natural product

  high molecular compound

  soft contact lens ——→ synthesized polymer



dibenzoyl-L-cystine

→ amino acid deriv.
hydrogel

J. Am. Chem. Soc. **1921**, *43*, 2199.

↕

low molecular compound

today's topic

- **gelation mechanism of natural product (high molecular compound)**

  structure : three-dimensional network bridged by some interactions
  (covalent bond, hydrogen bond, ionic interaction, hydrophobic effect, etc)

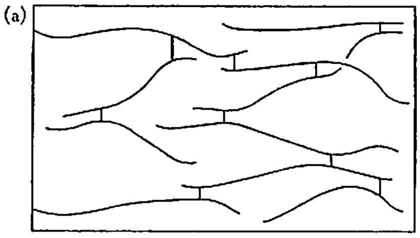
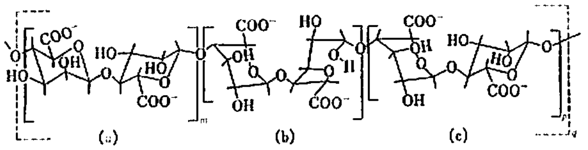
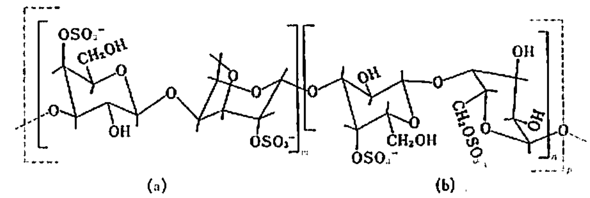


図 1 (a)線状高分子の架橋によって生ずるゲル構造,



アルギン酸



カラゲナン

図 3 電解質多糖の構造.

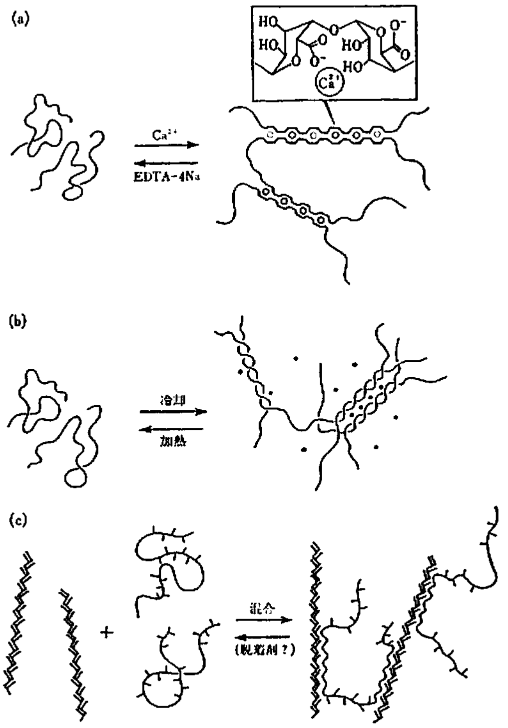
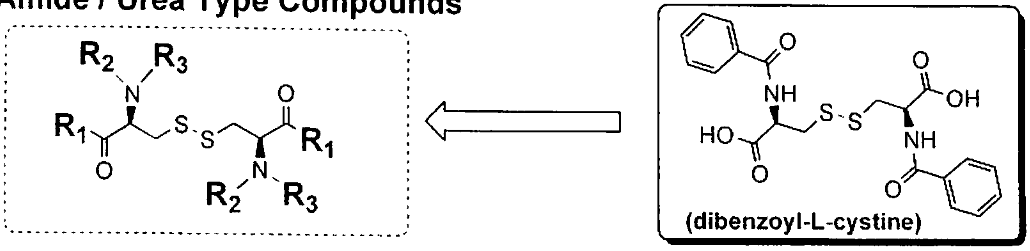


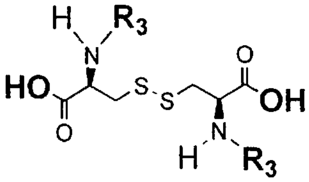
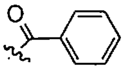
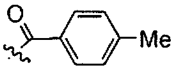
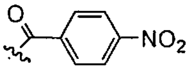
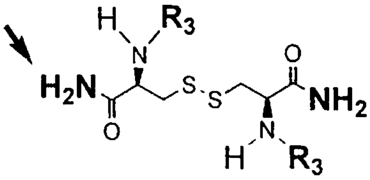
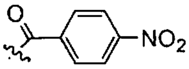
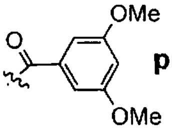
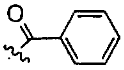
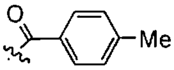
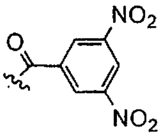
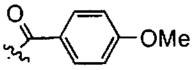
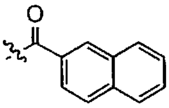
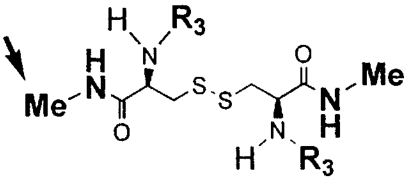
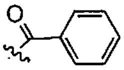
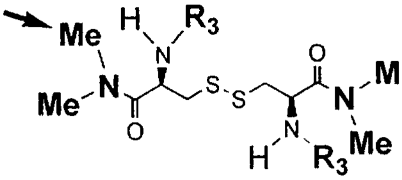
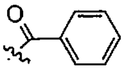
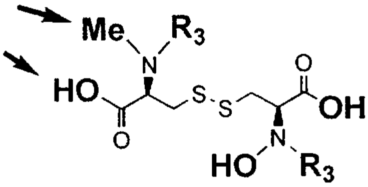
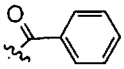
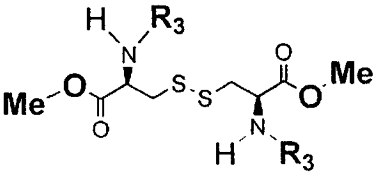
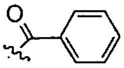
図 4 電解質多糖のゲル化機構. (a)アルギン酸ナトリウムのゾル-ゲル転移モデル(egg box junction). (b)カラゲナンのゾル-ゲル転移モデル(二重へリックス会合(domain)モデル). ● = K^+. (c)ザンサン-ガラクトマンナン混合ゲル(架橋吸着).

2. Low Molucular Weight Gelators

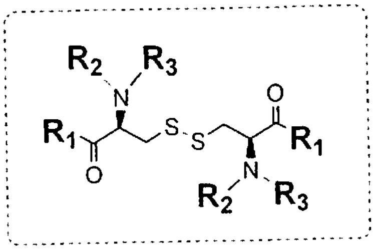
2.1 Amide / Urea Type Compounds

Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679

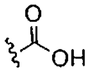


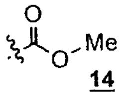
structure	entry	R_3 =	property	entry	R_3 =	property
	1		**G** (gel)	**(dibenzoyl-L-cystine)**		
	2		**recry.**			
	3		**recry.**			
	4		**G**	8		**precipitate** (沈殿)
	5		**G**			
	6		**G**	9		**jerry**
	7		**G**	10		**G**
	11		**G**			
	12		**recry.**			
	13		**precipitate**			
	14		**G**			

○ results



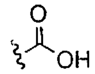
(a) comparing 1 with 14 carboxyl proton is not essential for gelation.


1

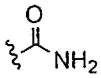

14

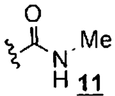
both have gelation activity

(b)gelation ability of 1 is inferior to 4-7, 10, 11.


1

<


4-7, 10

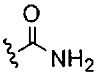

11

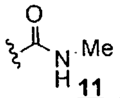
good gelator

amide carbonyl is stronger hydrogen-bonding carbonyl than carboxyl carbonyl

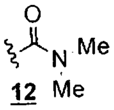
⟶ carbonyl oxygen serves as a key hydrogen-bonding unit ?

(c)comparing 5 with 11, 12


5


11

gel


12

recryst.

α-carboxyamide proton is necessary ?

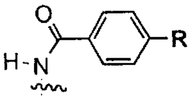
...or simply steric effect ?

(d)10 is the **best** gelator in the series.

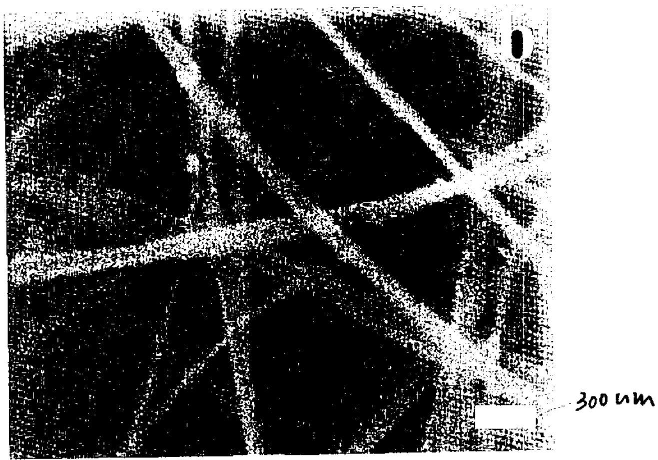
---minimum concentration of gelator par water is need (0.25mM) // gel-forming time is short (<30s)

π–π stacking of the large naphthalene group stabilize the gel ?

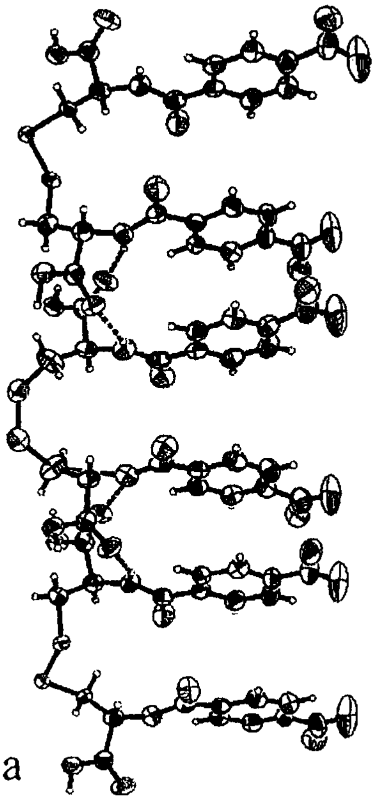
(e)gel / crystal relationship ?



R = EWG or EDG
no relation to gelation / crystallization activity.



SEM image of fiber obtained from gel 5



X-ray crystal structure of 3

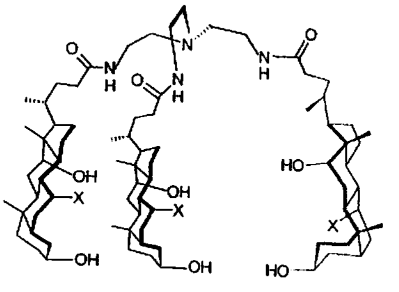
Summary

gelation is the product of intermolecular forces
(hydrogen bond + hydrohobic force (π–π stacking)
two factors impede gelation
(water solubility, crystallinity)

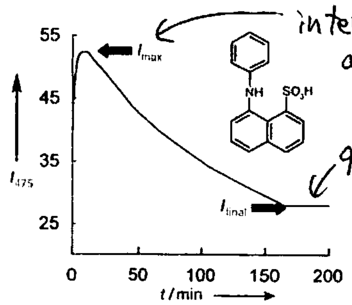
Hydrophobic Pockets in a Nonpolymeric Aqueous Gel: Observation of such a Gelation Process by Color Change**

Uday Maitra,* Samrat Mukhopadhyay, Arnab Sarkar, Photon Rao, and S. S. Indi

Angew. Chem. Int. Ed. 2001. 40. 2281



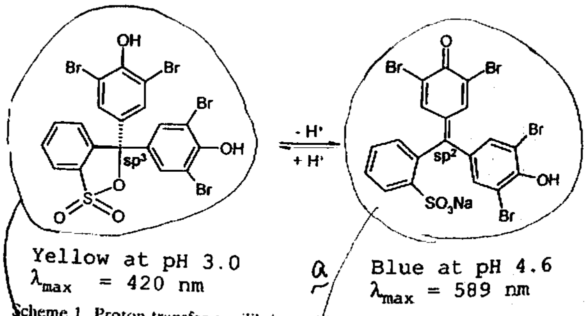
1: X = OH, hydrogelator



intermediate ? aggregation of gelator → ANS binding

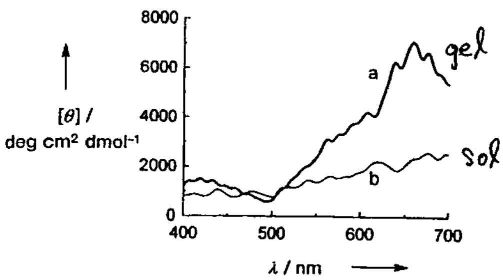
gel state

Figure 3. Time dependence of the ANS fluorescence during gelation of 1 in 20% AcOH/H$_2$O at 26°C. The final concentrations of 1 and ANS were 5.25 mM and 10 μM, respectively. I_{475} = emission intensity at 475 nm relative to that of 10 μM of ANS alone in 20% AcOH/H$_2$O. The structure of ANS is shown.



a

Scheme 1. Proton-transfer equilibrium of bromophenol blue.

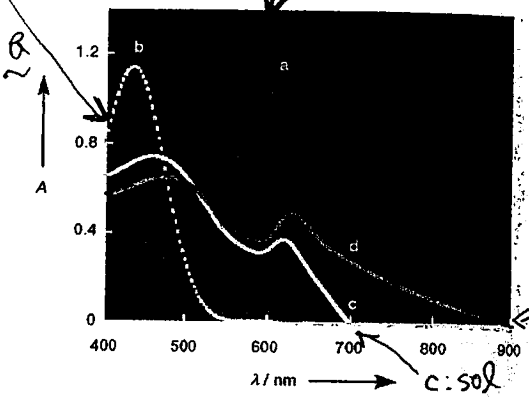


gel

sol

Figure 5. Induced circular dichroism of bromophenol blue in the a) gel state at 20°C and b) sol state at 70°C. Concentrations of bromophenol blue and the gelator 1 are 0.37 mM and 7.50 mM, respectively. [θ] = Molar ellipticity.

b



d: gel

c: sol

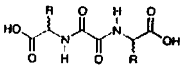
Figure 4. Absorption spectra (26°C) of the sodium salt of bromophenol blue (0.37 mM): a) in neutral water, b) in 25% AcOH/H$_2$O, c) in the presence of 1 (5.25 mM) in 25% AcOH/H$_2$O (before forming a gel) and d) after forming a gel. The sample colors closely resemble the colors used in the plots. A = absorbance.

◎ other examples (amide · urea type)

A Novel Type of Small Organic Gelators: Bis(Amino Acid) Oxalyl Amides

Milan Jokić, Janja Makarević and Mladen Žinić* J. Chem. Soc. Chem. Commun. 1995, 1723

Laboratory for Supramolecular and Nucleoside Chemistry, Department of Organic and Biochemistry, Rudjer Bošković Institute, POBox 1016, 01 Zagreb, Croatia

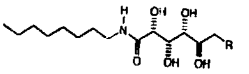


		R
(*S,S*)-, *meso*,	1	CH$_2$CHMe$_2$
(*R,R*)-and (±)-	2	Ph
(*S,S*)-	3	CH$_2$Ph
(*S,S*)-	4	CHMe$_2$

Organogels from Carbohydrate Amphiphiles

Rudi J. H. Hafkamp, Martinus C. Feiters,* and Roeland J. M. Nolte*

Department of Organic Chemistry, NSR Centre, University of Nijmegen, Toernooiveld, NL-6525 ED Nijmegen, The Netherlands



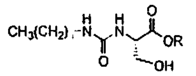
J. Org. Chem. 1999, *64*, 412–426

Low molecular weight organogelators for water

Guijun Wang and Andrew D. Hamilton*

Department of Chemistry, Yale University, New Haven, CT 06520, USA. E-mail: andrew.hamilton@yale.edu; Fax: 203 432 3221; Tel: 203432 5570

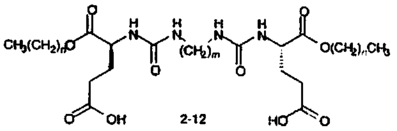
CHEM. COMMUN., 2003, 310–311



7-19

Effective Gelation of Water Using a Series of Bis-urea Dicarboxylic Acids**

Lara A. Estroff and Andrew D. Hamilton*

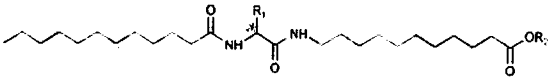


2-12

Angew. Chem. Int. Ed. **2000**, *39*, 3447

11-Aminoundecanoic acid: a versatile unit for the generation of low molecular weight gelators for water and organic solvents

Anthony D'Aléo,[a] Jean-Luc Pozzo,[a] Frédéric Fages†,*[a] Marc Schmutz,[b] Gudrun Mieden-Gundert,[c] Fritz Vögtle,*[c] Vesna Caplar[d] and Mladen Zinic*[d]



R$_1$ = (CH$_3$)$_2$CH R$_2$ = H
R$_2$ = Na
R$_1$ = Phenyl R$_2$ = H
R$_2$ = Na

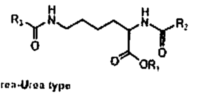
190 Chem. Commun., 2004, 190–191

Effects of Hydrogen Bonding and van der Waals Interactions on Organogelation Using Designed Low-Molecular-Weight Gelators and Gel Formation at Room Temperature

Masahiro Suzuki,*† Yasushi Nakajima,‡ Mariko Yumoto,‡ Mutsumi Kimura,† Hirofusa Shirai,‡ and Kenji Hanabusa†

Graduate School of Science and Technology and Department of Functional Polymer Science, Shinshu University, Ueda, Nagano 386-8567, Japan

Langmuir 2003, *19*, 8622–8624



Urea-Urea type
1: R$_1$ = CH$_3$, R$_2$ = R$_3$ = NHC$_6$H$_{13}$
2: R$_1$ = CH$_3$, R$_2$ = R$_3$ = NHC$_8$H$_{17}$
3: R$_1$ = CH$_3$, R$_2$ = R$_3$ = NHC$_{12}$H$_{25}$
Amide-Urea type
4: R$_1$ = C$_2$H$_5$, R$_2$ = C$_{11}$H$_{23}$, R$_3$ = NHC$_6$H$_{13}$
5: R$_1$ = C$_2$H$_5$, R$_2$ = C$_{11}$H$_{23}$, R$_3$ = NHC$_{12}$H$_{25}$
6: R$_1$ = C$_2$H$_5$, R$_2$ = C$_{11}$H$_{23}$, R$_3$ = NHC$_{18}$H$_{37}$
Amido-Amide type
7: R$_1$ = C$_2$H$_5$, R$_2$ = R$_3$ = C$_{11}$H$_{23}$

2.2 Sugar-Containing Compounds

ORGANIC LETTERS
2002
Vol. 4, No. 9
1423–1426

Molecular Design of “Super” Hydrogelators: Understanding the Gelation Process of Azobenzene-Based Sugar Derivatives in Water

Hideki Kobayashi,[†] Arianna Friggeri,[‡] Kazuya Koumoto,[†] Masato Amaike,[†] Seiji Shinkai,*[,†] and David N. Reinhoudt*[,‡]

Table 2. Gelation Capability and Sol−Gel Phase Transition Temperatures for **1** (3 wt %) in DMSO/H_2O Mixtures (G, Transparent Gel; S, Solution after Cooling)

gel → sol

DMSO:H_2O	1	T_{gel} (°C)
0:100	G	184
20:80	G	167
40:60	G	153
50:50	G	115
60:40	G	73
80:20	S	
100: 0	S	

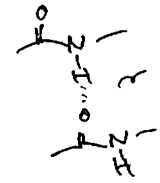
↑ stable

- gel is destabilized by DMSO
- aromatic π-π stacking of azobenzene moiety → driving force for gelation?
- intergelator hydrogen bond?

ATR-IR spectra of sol-gel phase (amide $\nu_{C=O}$)

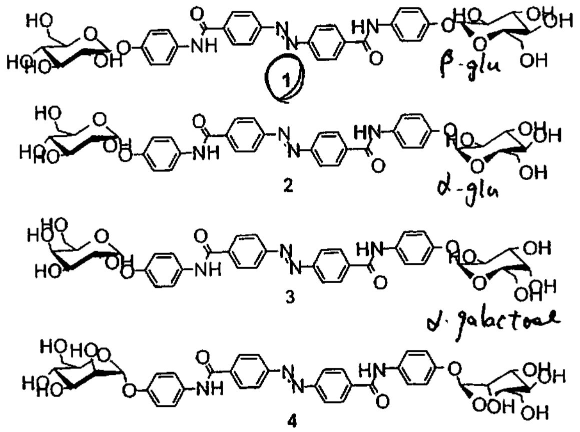
	DMSO : H_2O	$\nu_{C=O}$
(sol)	100 : 0	1662 cm^{-1}
	80 : 20	1647
	60 : 40	1638
(gel)	0 : 100	1641

→ some interaction? or hydrogen bond.



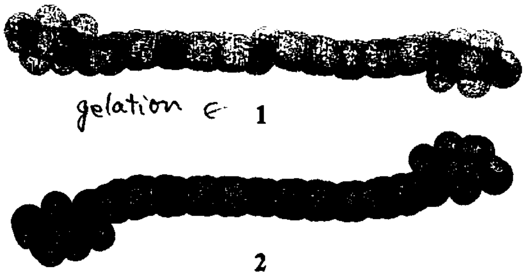
[redacted]

Scheme 1. Structures of Sugar-Based Gelators



only 1 acts as aqueous gelator!!

Scheme 2. Energy-Minimized Structures of **1** and **2** (Side View)

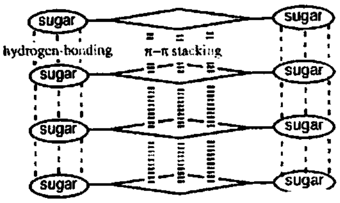


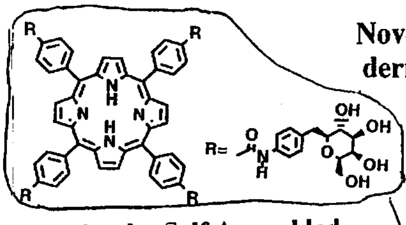
other examples containing sugar

Rational Design of a Sugar-Appended Porphyrin Gelator That Is Forced To Assemble into a One-Dimensional Aggregate

OL. 2001. 3. 3631

Shun-ichi Tamaru, Michihiko Nakamura, Masayuki Takeuchi, and Seiji Shinkai*



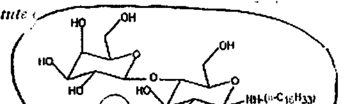


Pronounced Hydrogel Formation by the Self-Assembled Aggregates of *N*-Alkyl Disaccharide Amphiphiles

Santanu Bhattacharya* and S. N. Ghanashyam Acharya

Department of Organic Chemistry, Indian Institute

Chem. Mater. **1999,** *11,* 3504−3511

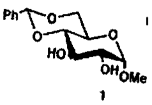


An Attempt to Predict the Gelation Ability of Hydrogen-bond-based Gelators Utilizing a Glycoside Library

Roman Luboradzki,[a,†] Oliver Gronwald,[b] Masato Ikeda,[a] Seiji Shinkai[a,*] and David N. Reinhoudt[c]

Tetrahedron 56 (2000) 9595–9599

soln. in water



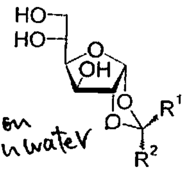
1

Novel class of saccharide-based organogelators: glucofuranose derivatives as one of the smallest and highly efficient gelators

Roman Luboradzki[a,*] and Zbigniew Pakulski[b,*]

Tetrahedron. 2004. 60. 4613

[a]*Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*



2: $R^1, R^2 = CH_3$
3: $R^1, R^2 = CH_2CH_3$
4: $R^1 = CH_3, R^2 = CH_2CH_3$
5: $R^1 = CH_3, R^2 = (CH_2)_2CH_3$
6: $R^1 = CH_3, R^2 = (CH_2)_3CH_3$

→ hydrogelator: hydrophobic effect seems to be important

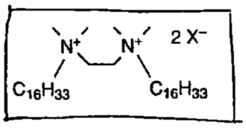
2-3 other gelators.

a) cation-anion interaction

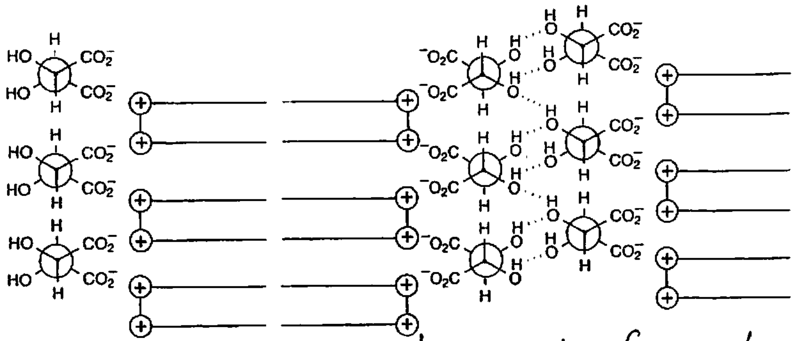
Angew. Chem. Int. Ed. 1998.37.2689

Gemini Surfactants as New, Low Molecular Weight Gelators of Organic Solvents and Water**

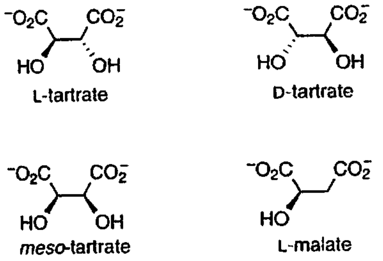
Reiko Oda, Ivan Huc,* and Sauveur J. Candau



1 : $2X^-$ = L-tartrate } gelator
2 : $2X^-$ = D-tartrate
3 : $2X^-$ = *meso*-tartrate } not gelate
4 : $2X^-$ = L-malate



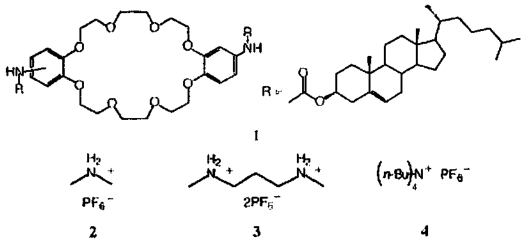
proposed structure for the aggregates of 2 in solvents.



b) host-guest chemistry

Novel host–guest organogels as stabilized by the formation of crown–ammonium pseudo-rotaxane complexes

Shin-ichiro Kawano, Norifumi Fujita and Seiji Shinkai*



1+2 or 1+4 → precipitation in Benzene. tol. p-Xylene

1+3 → gelation in Benzene. tol. p-Xylene

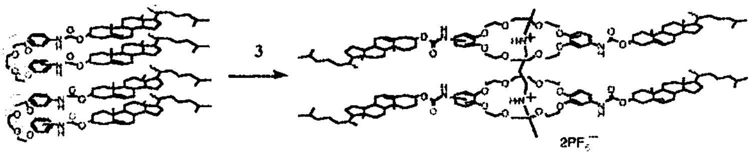
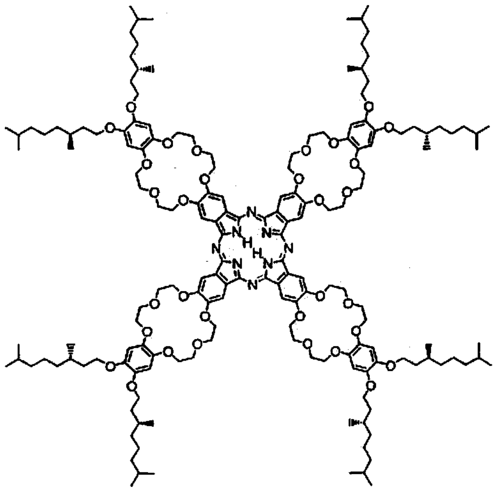
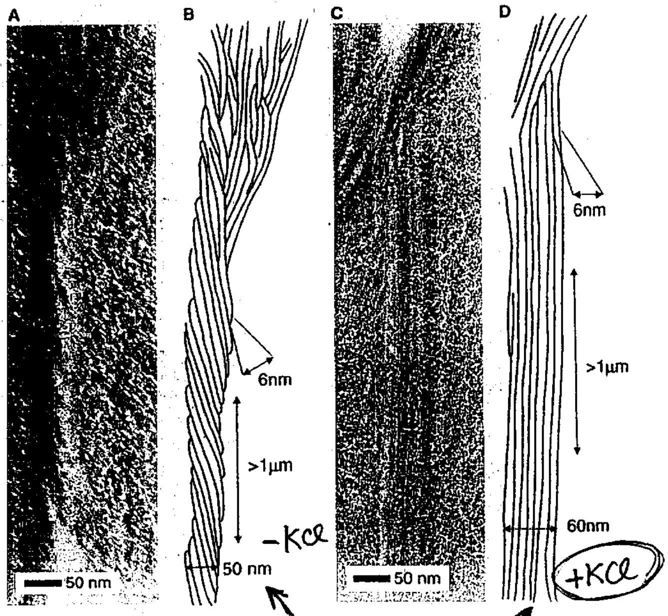


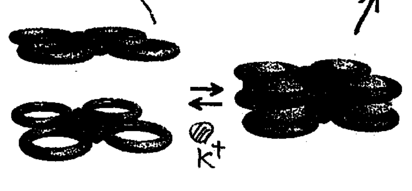
Fig. 2 Conformational change induced by complexation of 3 proposed on the basis of the spectral results.
↳ NMR study.

Self-Assembly of Disk-Shaped Molecules to Coiled-Coil Aggregates with Tunable Helicity

H. Engelkamp, S. Middelbeek, R. J. M. Nolte*







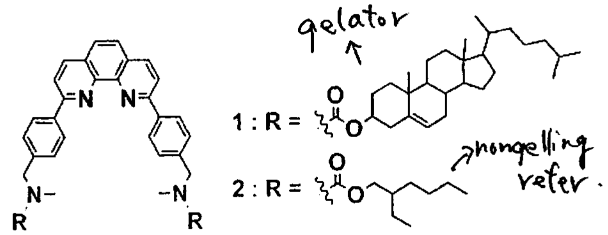
chiral transfer
↓
Helix

3. Application

Org. Biomol. Chem., 2003, 1, 895–899

Proton-sensitive fluorescent organogels†

Kazunori Sugiyasu,[a] Norifumi Fujita,[a] Masayuki Takeuchi,[a] Sunao Yamada[b] and Seiji Shinkai*[a]



Scheme 1 Structure of cholesterol-based 1,10-phenanthroline gelator (1) and its nongelling reference compound (2): 2-carbon in the 2-ethylhexyl group is racemic.

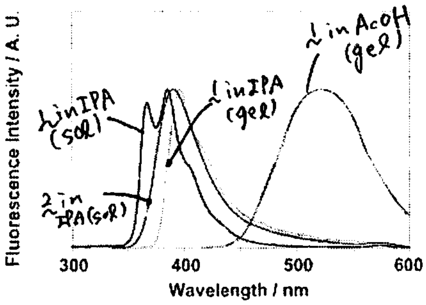


Fig. 2 Fluorescence spectra of monomeric 1 (1.6 × 10^{-5} mol dm^{-3}) in 1-propanol (black), 1 (0.3 wt%: 2.4 mmol dm^{-3}) in gelated 1-propanol (green), 2 (2.4 mmol dm^{-3}) in 1-propanol (blue) and 1 (8.0 mmol dm^{-3}) in gelated acetic acid (red).

$$\underset{\sim}{1} \xrightleftharpoons{H^+} \underset{\sim}{1}\cdot H^+$$

Em. ~380nm　　Em. 520nm

↓

gel / sol phase shows the same wavelength

soln. condition

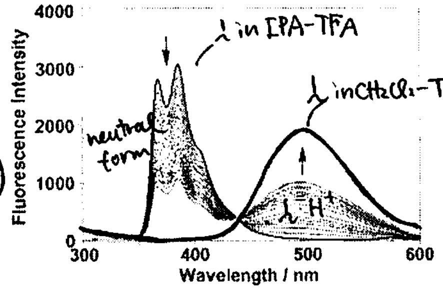


Fig. 4 Fluorescence spectral change in monomeric 1 (1.6 × 10^{-5} mol dm^{-3}) induced by TFA addition: 1-propanol, 25 °C, [TFA] = 0–15 mmol dm^{-3} (blue to green), λ_{ex} = 285 nm. The red line indicates a fluorescence spectrum of 1 (1.6 × 10^{-5} mol dm^{-3}) in CH$_2$Cl$_2$ at 25 °C: [TFA] = 1.3 mmol dm^{-3}, λ_{ex} = 294 nm (an isosbestic point in the UV/VIS absorption spectra in CH$_2$Cl$_2$).

difference in protic / aprotic solvents

in CH$_2$Cl$_2$

$$\underset{\sim}{1} \overset{H^+}{\underset{\leftarrow}{\longrightarrow}} \underset{\sim}{1}\cdot H^+$$

in IPA

$$\underset{\sim}{1} \xrightleftharpoons[IPA]{H^+} \underset{\sim}{1}\cdot H^+$$

(IPA works as proton acceptor
(fully protonation of 1 is difficult.

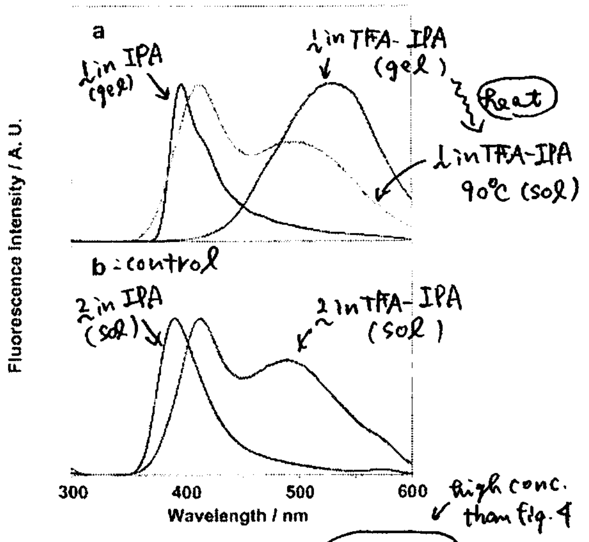


Fig. 6 Fluorescence spectra of (a) 1 (0.3 wt%: 2.4 mmol dm^{-3}) in the gel phase at 25 °C without TFA (blue), in the gel phase at 25 °C with TFA (2.0 equivalents) (red) and in the sol phase at 90 °C with TFA (2.0 equivalents) (green); (b) 2 (2.4 mmol dm^{-3}) in the sol phase at 25 °C without TFA (blue) and with TFA (2.0 equivalents) (red).

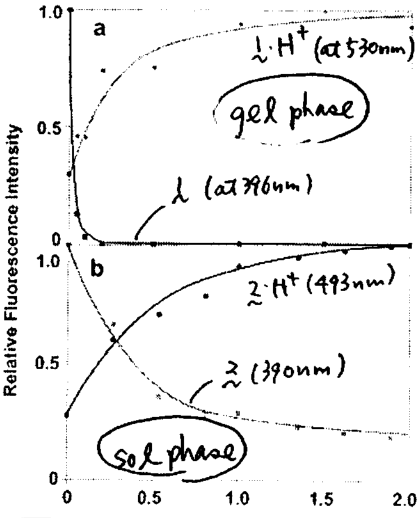


fig. 7.

energy transfer occurs?

$$\underset{\sim}{1}^* + \underset{\sim}{1}\cdot H^+ \underset{\text{in gel phase}}{\longrightarrow} \underset{\sim}{1} + (\underset{\sim}{1}\cdot H^+)^*$$

(due to crystal-like structure?)

⇒ Fluorescence spectra.
proton. temp. sensitive
(functionalized gel?)

*Possibility of the gel as new materials.

☑ "intelligent" materials.

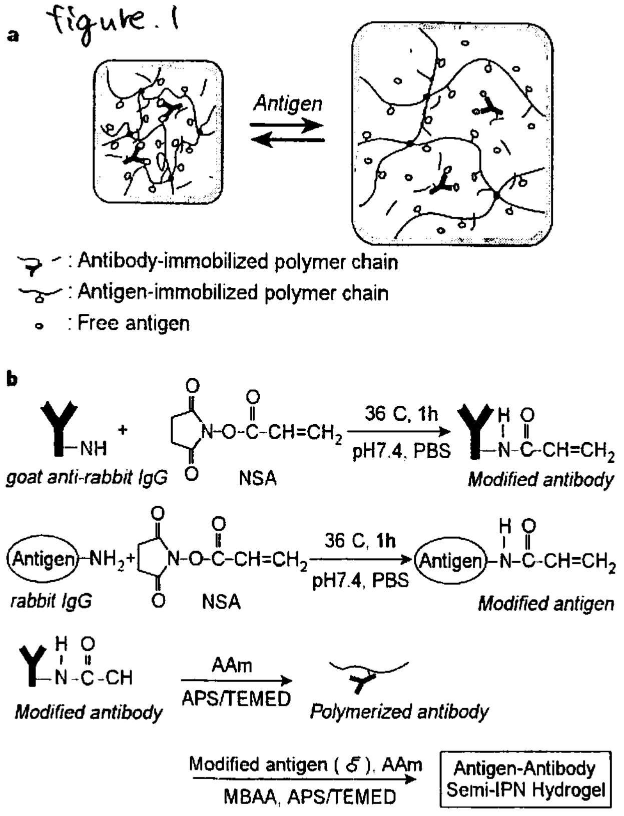
A reversibly antigen-responsive hydrogel

Takashi Miyata, Noriko Asami & Tadashi Uragami

Chemical Branch, Faculty of Engineering and High Technology Research Center, Kansai University, Suita, Osaka, 564-8680, Japan

Nature. 1999. 399. 766

figure. 1



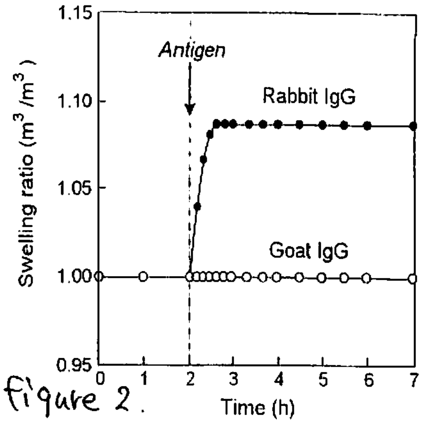


figure 2.

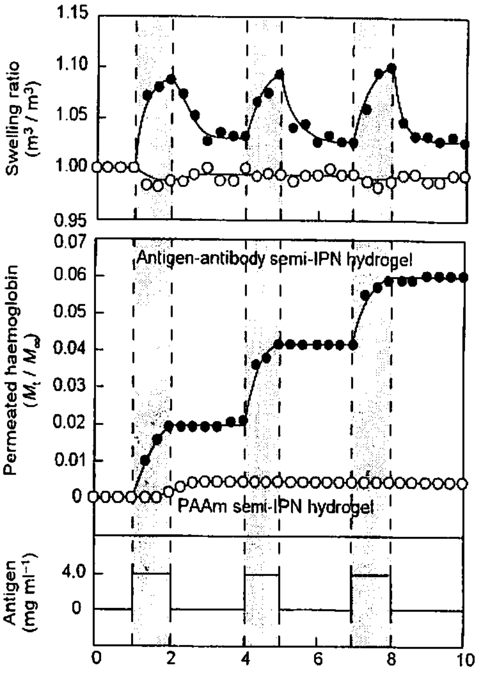


figure. 3

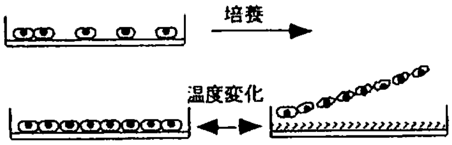
Makromol. Chem., Rapid Commun. 11, 571–576 (1990)

Thermo-responsive polymeric surfaces; control of attachment and detachment of cultured cells

Noriko Yamada, Teruo Okano, Hideaki Sakai, Fumiko Karikusa[a], Yoshio Sawasaki[a], Yasuhisa Sakurai*

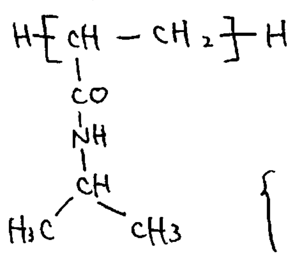
Institute of Biochemical Engineering, Tokyo Women's Medical College, 8 Kawada, Shinjuku, Tokyo 162

→ for tissue engineering application



図Ⅲ-2-5 PIPAAm固定化細胞培養皿からの細胞の回収

PNIPAAm : Poly (N-isopropylacrylamide)



LCST (lower critical solution temperature) : ~32°C

below 32°C : hydrophilic nature, cells are recovered from the dishes.
above 32°C : hydrophobic, work as "usual" cell culture

usually… cells are recovered from the cell culture by treatment with protease (e.g. trypsin)

also LPA assay.

8/9

* entrapment of enzyme into hydrogel

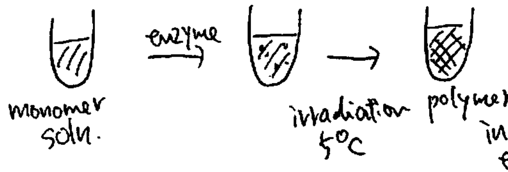
Journal of Molecular Catalysis B: Enzymatic 1 (1995) L1–L6

Effect of heat treatment on enzymes entrapped into polymer gels

enzyme : glucoamylase

Minoru Kumakura

Department of Bioscience, The Nishi-Tokyo University, Uenohara, Kitatsuru, Yamanashi 409-01, Japan



heat treatment resulted in rearrangement of entrapped enzyme?

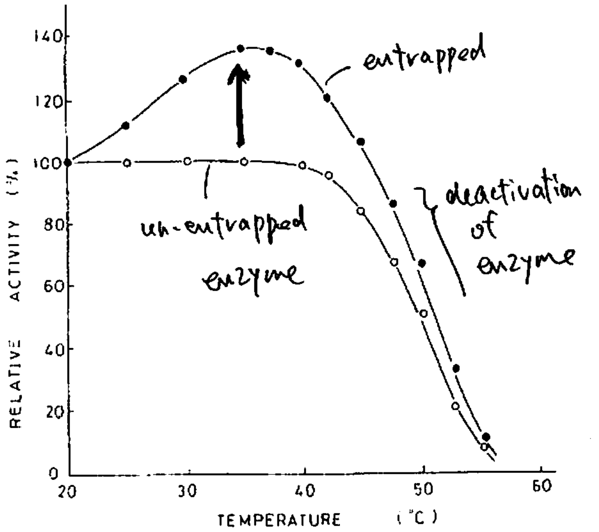
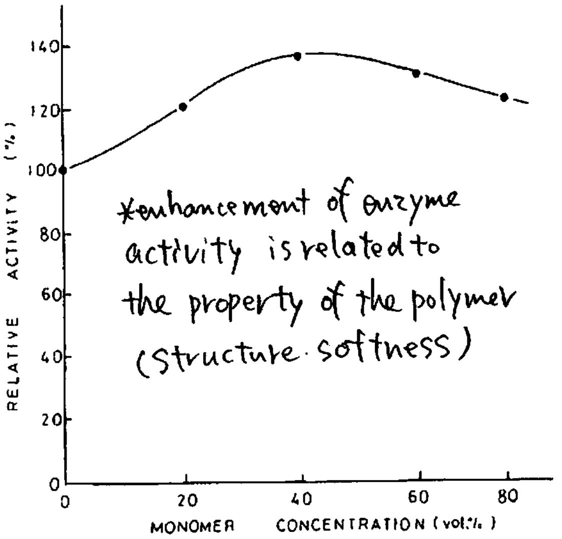


Fig. 1. Relationship between relative activity and treatment temperature of the un- and entrapped enzymes irradiated with a low energy electron beam. Irradiation temperature: 5°C. Monomer: A 14G (concentration: 40%). O: un-entrapped enzymes; ●: entrapped enzymes.



*enhancement of enzyme activity is related to the property of the polymer (structure·softness)

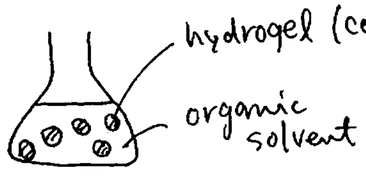
Fig. 6. Relationship between relative enzyme activity of entrapped enzymes and monomer concentration after irradiation with a low energy electron beam. Irradiation temperature: 5°C. Monomer: A 14G (concentration: 40%). Heat treatment (40°C).

Enzymatic catalysis in gel-stabilized two-phase systems: improvement of the solvent phase

Bastien Doumèche[a], Matthias Heinemann[b], Jochen Büchs[b], Winfried Hartmeier[a], Marion B. Ansorge-Schumacher[a,]*

[a] *Department of Biotechnology, Aachen University of Technology (RWTH), D-52056 Aachen, Germany*
[b] *Department of Biochemical Engineering, Aachen University of Technology (RWTH), D-52056 Aachen, Germany*

Journal of Molecular Catalysis B: Enzymatic 18 (2002) 19–27



enzymes are usually not stable in organic solvent (and also two-phase system)

↓

entrapment of enzyme into hydrogel
- stability ↑
- reusable (solid catalyst)

entrapment of enzyme (lipase)

sodium alginate, lipase } + CaCl2 → gel