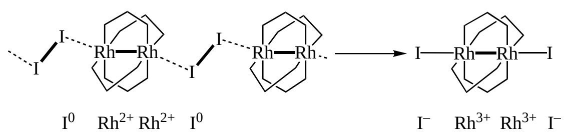
mode of molecular diiodine to a transition metal atom found in **1**.

Another interesting synthetic aspect of this result is the resistance of the dirhodium trifluoroacetate unit toward oxidation by I_2 at temperatures above 150 °C. Analogous reactions with different concentrations of Br_2 and $PhI \cdot Cl_2$ (as a dichlorine source) have been attempted over a wide range of temperatures (100–180 °C), but no crystalline products were formed under the conditions used. These reactions most probably resulted in the oxidation of $[Rh_2(O_2CCF_3)_4]$ and formation of nonvolatile materials. The oxidation of dirhodium carboxylates by Br_2 is known to take place in solutions at ambient temperatures.[8] The unique halo-metal complex **1** represents a model for probable intermediates during the early stages of oxidative addition reactions by halides (Scheme 1).



Scheme 1. Schematic representation of oxidative addition reactions of halides with $[Rh_2(O_2CCF_3)_4]$, with **1** as a model for probable intermediates.

Experimental Section

All experimental manipulations involving the synthesis of the starting materials were carried out under dry, oxygen-free argon by employing Schlenk techniques. The unligated form of $[Rh_2(O_2CCF_3)_4]$ was obtained using literature procedures.[9] The EI/DP mass spectra were acquired using a VG Analytical 70S high-resolution, double focusing, sectored (EB) mass spectrometer.

The title compound **1** was prepared by heating a mixture of $[Rh_2(O_2CCF_3)_4]$ (65 mg, 0.10 mmol) and freshly sublimed I_2 (20 mg, 0.08 mmol) at 150–160 °C for 5–6 days in a sealed evacuated Pyrex ampoule. Dark (red-violet on grinding) crystals of **1** were collected in the "cold" zone of the tube where the temperature was set about 5 °C lower; yield: 34 mg (29.2 %). MS (300 °C): m/z (%): 657 (38, $[Rh_2(O_2CCF_3)_4]^+$), 544 (47, $[Rh_2(O_2CCF_3)_3]^+$), 431 (65, $[Rh_2(O_2CCF_3)_2]^+$), 318 (9, $[Rh_2(O_2CCF_3)]^+$), 127 (100, $[I]^+$)

The use of FeI_2 as a slow release source of I_2, and lower concentrations of molecular I_2 produced no crystalline iodine-containing products.

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[1] a) F. A. Cotton, R. A. Walton, *Multiple Bonds Between Metal Atoms*, 2nd Ed., Oxford University Press, Oxford, **1993**, pp. 432–443; b) T. R. Felthouse, *Prog. Inorg. Chem.* **1982**, *29*, 73–166.

[2] a) F. A. Cotton, E. V. Dikarev, S.-E. Stiriba, *Organometallics* **1999**, *18*, 2724–2726; b) F. A. Cotton, E. V. Dikarev, M. A. Petrukhina, *J. Organomet. Chem.* **2000**, *596*, 130–135; c) F. A. Cotton, E. V. Dikarev, M. A. Petrukhina, S.-E. Stiriba, *Organometallics* **2000**, *19*, 1402–1405.

[3] Crystallographic data for **1** ($C_8F_{12}I_4O_8Rh_2$): $M_r = 1165.50$, red-violet block, $0.45 \times 0.25 \times 0.18$ mm, triclinic, space group $P\bar{1}$, $a = 10.4259(3)$, $b = 10.671(1)$, $c = 11.924(3)$ Å, $\alpha = 80.35(3)$, $\beta = 89.82(1)$, $\gamma = 68.80(1)^\circ$, $V = 1216.9(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 3.181$ g cm^{-3}, $\mu = 6.553$ mm^{-1}, $2\theta_{max} = 50.14^\circ$, Nonius FAST area detector system, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = -60$ °C, 8002 reflections measured, data corrected for Lorentz and polarization effects, absorption correction (transmission coefficients 0.109–0.286), direct method solution (SHELXTL V.5), full-matrix refinement on F^2 (SHELXL-93), $R1$ (on F_o) = 0.040, $wR2$ (on F_o^2) = 0.1121 for 316 parameters and 37 restraints, 4061 independent reflections, $R1$ (on F_o) = 0.0381, $wR2$ (on F_o^2) = 0.1094 for 3874 reflections with $I > 2\sigma(I)$, highest residual peak 1.51 e$^-$ Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no.CCDC-138682 (entries carrying the suffix *x* represent disordered atoms). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[4] I. L. Karle, *Chem. Phys.* **1955**, *23*, 1739.

[5] a) F. Calderazzo, R. Poli, P. F. Zanazzi, *Gazz. Chim. Ital.* **1988**, *118*, 595–601; b) R. Ambrosetti, W. Baratta, D. B. Dell'Amico, F. Calderazzo, F. Marchetti, *Gazz. Chim. Ital.* **1990**, *120*, 511–525; c) K.-F. Tebbe, A. Gräfe-Kavoosian, B. Freckmann, *Z. Naturforsch. B* **1996**, *51*, 999–1006.

[6] a) M. F. Belicchi, G. G. Fava, C. Pelizzi, *Acta Crystallogr. Sect. B* **1981**, *37*, 924–926; b) L. R. Gray, D. J. Gulliver, W. Levason, M. Webster, *Inorg. Chem.* **1983**, *22*, 2362–2366; c) R. D. Bailey, L. L Hook, W. T. Pennington, *Chem. Commun.* **1998**, 1181–1182; d) P. H. Svensson, L. Kloo, *Inorg. Chem.* **1999**, *38*, 3390–3393.

[7] a) J. A. M. van Beek, G. van Koten, W. J. J. Smeets, A. L. Spek, *J. Am. Chem. Soc.* **1986**, *108*, 5010–5011; b) J. A. M. van Beek, G. van Koten, G. P. C. M. Dekker, E. Wissing, M. C. Zouberg, C. H. Stam, *J. Organomet. Chem.* **1990**, *394*, 659–678.

[8] M. A. Golubnichaya, E. M. Trishkina, G. N. Kuznetsova, A. V. Rotov, I. B. Baranovskii, *Russ. J. Inorg. Chem.* **1989**, *34*, 1493–1494.

[9] F. A. Cotton, E. V. Dikarev, X. Feng, *Inorg. Chim. Acta* **1995**, *237*, 19–26.

Thermosensitive, Reversibly Cross-Linking Gels with a Shape "Memory"

Babinder K. Samra, Igor Yu. Galaev, and
Bo Mattiasson*

Smart polymers/gels are materials that undergo a sharp and reversible change in their microstructure when subjected to an external stimulus such as temperature, pH, ionic strength, solvent composition. When triggered, this change can be seen on a macroscopic level either as phase separation, or else in the case of gels, an order-of-magnitude volume change.[1] The ability of smart materials to change their physical properties according to their environment makes them desirable for a multitude of applications, including drug delivery devices,[2] supports for biocatalysts,[3, 4] bioseparations,[5] and biosensors. The external trigger for a thermosensitive polymer is temperature. The polymer is soluble in water at temperatures below the lower critical solution temperature (LCST) as a result of a thermodynamic balance of the four fundamental forces between the polymeric material and the water.[6]

The polymer-enriched phase formed above the LCST could be either in the form of a compact polymer precipitate or as a physically cross-linked gel. The latter occurs with linear polymer chains where there is an increased physical interaction between neighboring chains.[7, 8] This type of self-

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assembling behavior occurs as a consequence of multi-point contacts, mainly by hydrophobic interaction and hydrogen bonding.[9]

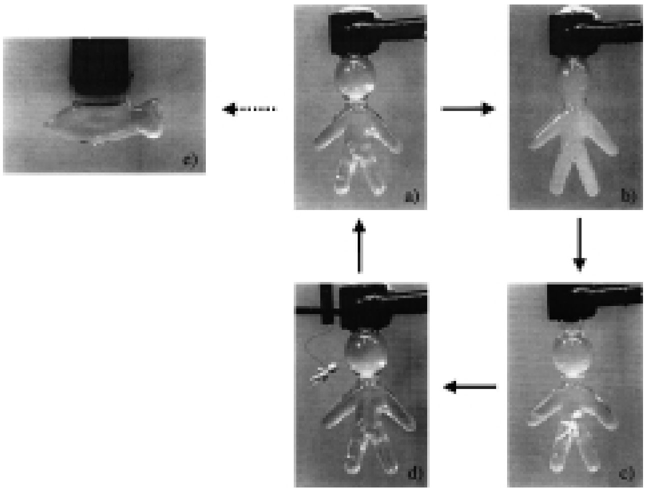
Herein we discuss the properties of a thermosensitive, three-component copolymer that undergoes phase separation to form either a compact polymer precipitate or a physically cross-linked gel, depending on the relative composition of the components used. Moreover, an additional feature is that the physically cross-linked gel formed collapses with a further increase in temperature to result in shrunken, shape-remembered gel formation (see Scheme 1).

The polymers were synthesised and their composition determined as follows. The monomer *N*-isopropylacrylamide (NIPAAM; Aldrich, Germany) was recrystallized twice from cyclohexane prior to use, while styrene (Aldrich, Germany) and 2-hydroxyethylmethacrylate (HEMA; Aldrich, Germany) were passed twice through an alumina (ICN; high resolution aluminium oxide, W200 neutral, particle size 18–32 µm) column using a volume ratio of approximately 3:1 alumina:monomer to remove *tert*-butylcatechol and hydroquinone monomethyl ether, respectively. NIPAAM styrene and *N*-acryloxysuccinimide (NASI; Acros, Belgium: used as supplied) or HEMA were dissolved in argon-degassed THF (analysis grade) and 0.2 mol% 2,2′-azobisisobutyronitrile (AIBN; Fluka, Germany: recrystallized from methanol, twice) relative to NIPAAM, was added to a reaction tube, which was sealed and subsequently heated at about 80 °C overnight. The reaction mixture was cooled and poured onto diethyl ether to precipitate the polymer. The polymer was filtered off, redissolved in THF, and precipitated again in diethyl ether to remove any oligomers. The polymer was air dried at room temperature and analyzed by NMR spectroscopy to determine the relative monomer composition. The relative compositions of the copolymers were calculated on the basis of the integrations for the protons from the pendant groups of the different monomer moieties (see Table 1).

Table 1. Relative molar ratio of monomers in the copolymers.

Polymer	Poly(styrene$_x$-NASI$_y$-NIPAAM$_z$)[a]			Comments[b]
	x	*y*	*z*	
a	10	–	90	17.0 °C
b	11	–	89	16.5 °C
c	12	–	88	15.5 °C
d	13	–	87	11.5 °C
e	14	–	86	11.5 °C
f	15	–	85	0
1	19	40	41	0
2	20	35	45	0
3	35	25	40	0
4	13	44	43	–
5	14	37	49	–
6	15	25	60	–
7	16	39	45	–
8	20	22	58	+
9	22	23	55	+
10	23	21	56	+
11	19	29	52	+++
12	19	30	51	+++
13	19	31	50	+++
14	19	32	49	+++
15	19	33	48	+++
16	22	29	49	+++

[a] The relative compositions of the copolymers were calculated from the integrations for the protons from the pendant groups of the different monomer moieties: ^{1}H NMR (500 MHz, [D$_8$]THF, 25 °C, TMS): $\delta = 1.2$ (NIPAAM 6H; $(CH_3)_2$), 2.9 (NASI 4H; $NC(O)(CH_2)_2C(O)$), 7.2 (styrene 5H; $C(CH_2)_5$). The combined signal of the above mentioned protons was taken as 100 mol% of the polymer with the accuracy of determination of the single component to be within 2–3 mol%. [b] 0: aqueous insoluble copolymer, –: forms a flocculated precipitate, +: forms a weak gel which decomposes into a flocculated precipitate on further heating, +++: forms a gel which shrinks on further heating preserving the shape of the vessel.



Scheme 1. Formation (a and b) and form-remembered shrinkage (c) of the poly(styrene$_{19}$-NASI$_{31}$-NIPAAM$_{50}$) physically cross-linked gel on increasing the temperature of an aqueous solution of the polymer. The shrunken gel is mechanically strong enough to be transported to another vessel (d). e) Resolubilization of the shrunken gel in cold water and recasting in another shape.

Copolymers of styrene and NIPAAM (Table 1, polymers a–f) have higher LCST values relative to a NIPAAM homopolymer, which has a LCST of 32 °C.[10] The LCST was reduced to a minimum of 11.5 °C by the incorporation of 14 mol% styrene. A higher styrene content rendered the polymer insoluble in aqueous media. Conversely, NASI-NIPAAM copolymers had increased LCST values relative to poly(NIPAAM) (data not shown). However, the resulting gel formed from a three-component polymer demonstrated properties quite distinct from the usual behavior exhibited by thermosensitive gels. A narrow composition range of the three components resulted in the formation of shape-remembered gels (Scheme 1). The difference with this type of physical cross-linked hydrogel compared to a chemically cross-linked gel is that the former gel is formed thermoreversibly. At low temperatures the polymer remained in solution. As the temperature was increased, the polymer thermoprecipitated and the resulting gel had the appearance of a turbid, homogenous, viscous phase, which filled the volume of the vessel. The turbid gel collapsed and shrank with a further increase in temperature. A distinct phase separation was observed as the gel formed a dense white miniaturized version of the original polymer in the vessel, and the water was expelled as a separate phase. The collapsed gel cast was mechanically strong enough to be removed from the aqueous phase and transported into another vessel.

The polymer was resolubilized simply by cooling. The solubilized polymer could then be recast in another form, using a different shaped vessel (Scheme 1). This behavior was exhibited by polymers 8–16 (Table 1) in which the styrene content was around 20 mol % and the NASI around 30 mol %. The polymers outside this relatively narrow composition range (Figure 1) behaved in a more conventional manner, forming either a compact polymer precipitate, such as polymers 4–7 (Table 1), or being insoluble, such as polymers 1–3. The insolubility of poly(styrene$_{35}$-NASI$_{25}$-NIPAAM$_{40}$) was the result of a high styrene content. This result was expected owing to the high hydrophobicity of the styrene component. However, for the other two polymers in this group, poly(styrene$_{19}$-NASI$_{40}$-NIPAAM$_{41}$) and poly(styrene$_{20}$-NASI$_{35}$-NIPAAM$_{45}$), it appears the same insolubility effect was also observed with a high NASI content.

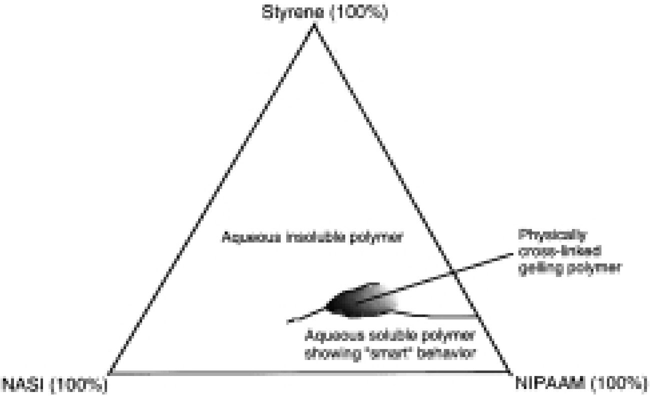


Figure 1. Effect of poly(styrene$_x$-NASI$_y$-NIPAAM$_z$) composition on the behavior of the polymer in aqueous solutions in response to increasing temperature.

The requirements for the formation of thermosensitive, physically cross-linked gels are for the polymeric chain to be composed of "blocks" of copolymers of differing hydrophobicity.[10] The hydrophobic segments form self-aggregating temporary cross-links, whilst the hydrophilic components allow the copolymer to remain in solution. As the degree of blocking in the synthesized polymers is unknown, the explanation for the behavior of the gel could be that the mixture of copolymers of various composition has been created with ongoing conversion. The more hydrophobic copolymers in the mixture may be responsible for the cross-linking effects, whilst the more hydrophilic ones give rise to swelling.

The degree of maximal shrinkage attained within the concentration range (0.1–1.0% (w/w)) and volume (3 mL) tested, was the same for all the different polymer concentrations. Below 0.1 % (w/w), the shrunken gel did not properly conserve the shape. At 2.0% (w/w), the shrunken gel was not floating, as with the lower concentrations, but was splattered on the bottom of the vessel, presumably because of the increased density of the collapsed gel. The lowest concentration where the polymers of type poly(styrene$_x$-NASI$_y$-NIPAAM$_z$) could form thermoreversible gels was found to be 0.1 % (w/w), which is much lower than is usually observed for other types of synthetic, thermoreversibly gelating polymers. For example, poly(ethylene glycol-*b*-(DL-lactic acid-*co*-glycolic acid)-*b*-ethylene oxide)[8] or poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene)[10] form gels at polymer concentrations above 15 % (w/w) with increasing temperatures. Natural polymers, such as methylcellulose, form thermoreversibly gels at lower concentrations of 0.5 % (w/w),[7] which is comparable to that of poly(styrene$_x$-NASI$_y$-NIPAAM$_z$)-type polymers.

The degree of shrinkage (the ratio of the volumes of swollen and shrunken state of the gel) of the gels formed by polymers of the type poly(styrene$_x$-NASI$_y$-NIPAAM$_z$) increased with the duration of heating to a maximum of about 150 after 16 h (Figure 2). As the degree of shrinkage increased, more water was expelled from the cross-linked polymer network, and the gel became increasingly impermeable to water. At this stage the gel proved extremely difficult to resolubilize by simple cooling, and required mechanical grinding before resolubilization occurred. Otherwise, the precipitated cross-linked gel was extremely stable and could be stored in water at ambient temperature indefinitely.

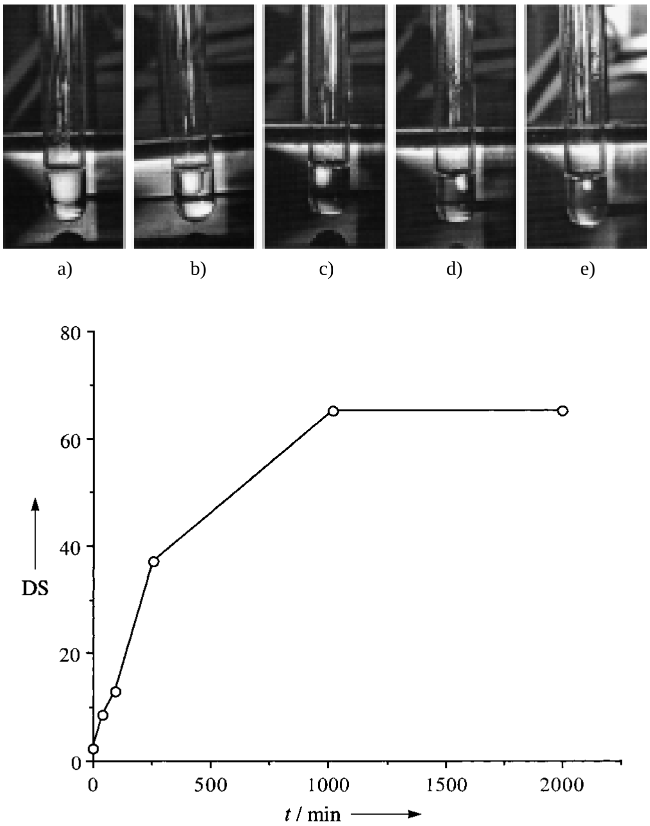

a) b) c) d) e)

Figure 2. Time dependence of the shrinking of a physically cross-linked gel formed by poly(styrene$_{19}$-NASI$_{31}$-NIPAAM$_{50}$) at 43 °C at a) 0, b) 40, c) 90, d) 260, and e) 1000 min. The graph presents the dependence of the degree of shrinkage (DS) versus time.

The narrowest diameter vessel where the shape of the shrunken polymer gel was conserved was found to be 2 mm. The precipitated gel shape was not observed below this thickness. It is believed that as the thickness decreases the convection flows and surface forces in the water become too strong for the formation of very thin polymer threads.

The preliminary, investigative work described here shows the synthesis of a novel, multifunctional copolymer with an unusual combination of properties, the full potential of which are beyond the scope of this article. However, this polymer demonstrates a range of different features, and is envisaged to have potential use for the development of new drug-delivery systems, biocatalysts, and biosensors.

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---

[1] I. Yu. Galaev, B. Mattiasson, *Enzyme Microb. Technol.* **1993**, *15*, 354–366.

[2] S. Miyazaki, F. Suisha, N. Kawasaki, M. Shirakawa, K. Yamatoya, D. Attwood, *J. Controlled Release* **1998**, *56*, 75–83.

[3] Y. Ito, N. Sugimura, H. K. Oh, Y. Imanishi, *Nat. Biotechnol.* **1999**, *17*, 73–75.

[4] H. Lee, T. G. Park, *Biotechnol. Prog*. **1998**, *14*, 508–516.

[5] Using Stimuli-Responsive Polymers in Bioseparation (Ed.: I. Yu. Galaev), *Bioseparation Special Issue* **1999**, *7*, 175–280.

[6] E. Kokufuta, *Responsive gels: Volume transitions II* (Ed.: K. Dusek) Springer, Berlin, **1993**, pp. 158–176.

[7] K. Kobayashi, C. Huang, T. P. Lodge, *Macromolecules* **1999**, *32*, 7070–7077.

[8] B. Jeong, Y. H. Bae, S. W. Kim, *Macromolecules* **1999**, *32*, 7064–7069.

[9] H. Hachisako, R Murakami, *Recent Res. Develop. Pure Appl. Chem.* **1998**, *2*, 547–561.

[10] L. E. Bromberg, *J. Phys. Chem.* **1998**, *102*, 1956–1963.

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