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Supramolecular Polymers – we've Come Full Circle

Takuzo Aida^[a, b] and E.W. Meijer^[c, d]

- About a century ago, Dr. Staudinger substantiated the existence of ultralong molecules and won the long-term debate against the colloidal theory to establish polymer science.
- Supramolecular polymerization, is a modernized version of the colloidal approach to polymeric materials. Supramolecular polymers attract attention not only because they are 100% recyclable but also they can be designed to be eco-friendly, self-healable, responsive, and adaptive .
- In 1988, Aida et al. reported the prototype of supramolecular polymerization using an amphiphilic porphyrin with water-soluble oligoether side chains as the monomer and have made fundamental contributions to this field.

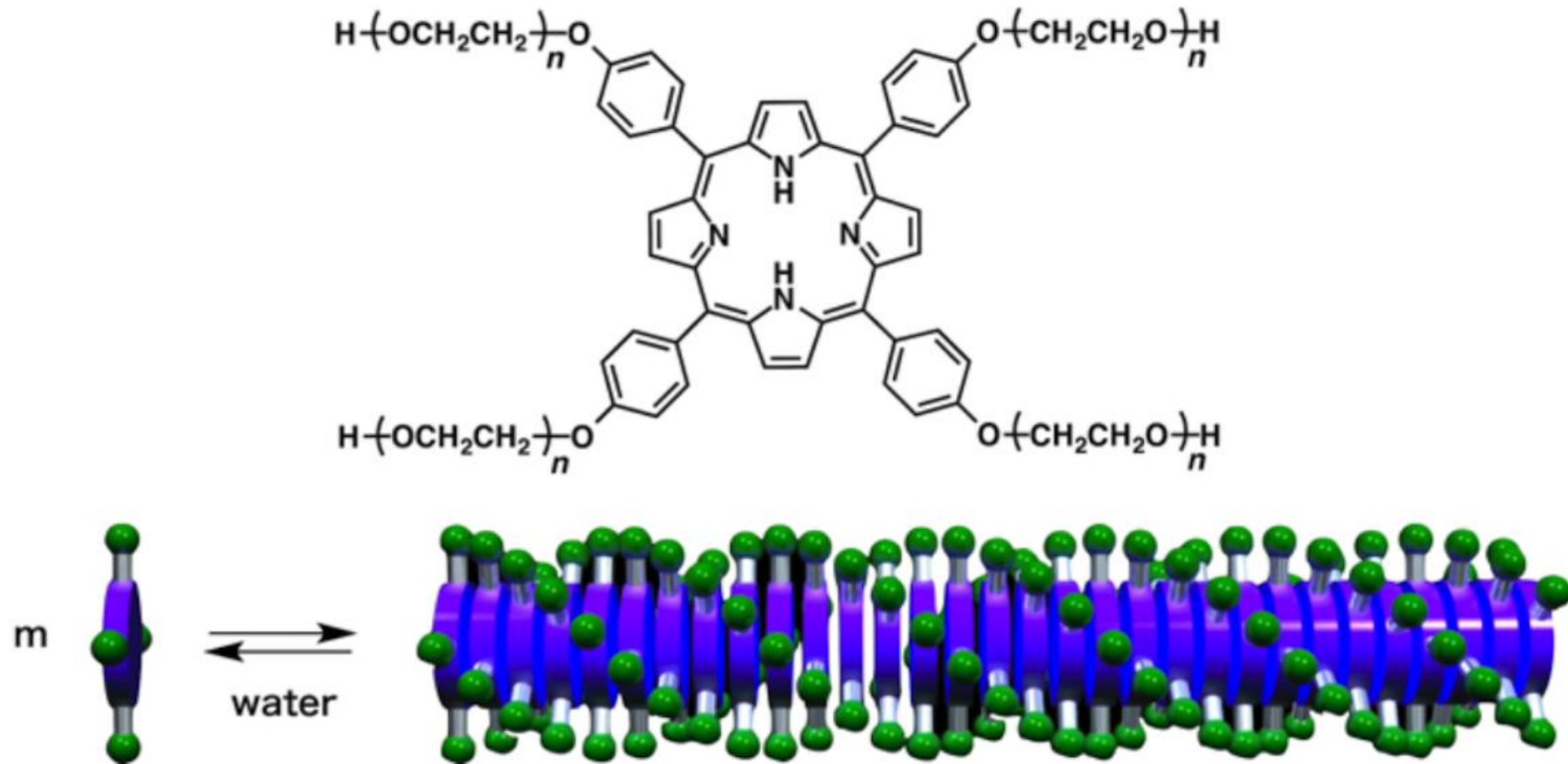
The first work of T. Aida

The recent developments for one-dimensional aggregates or supramolecular polymers started in 1988, when T. Aida published the concept of cofacial assembly of amphiphilic porphyrins into one-dimensional architectures (Figure 2).

At that time, this discovery was not connected to any form of supramolecular polymers but was rather discussed within the field of amphiphiles by analogy to the formation of cylindrical micelles.

Cylindrical micelles were considered too labile to generate materials, and this perception did not change even when much more stable polymersomes were introduced in 1995.

Aida: supramolecular polymerization in water of PEG-functionalized porphyrin



The work of Wuest, Lehn and Griffin

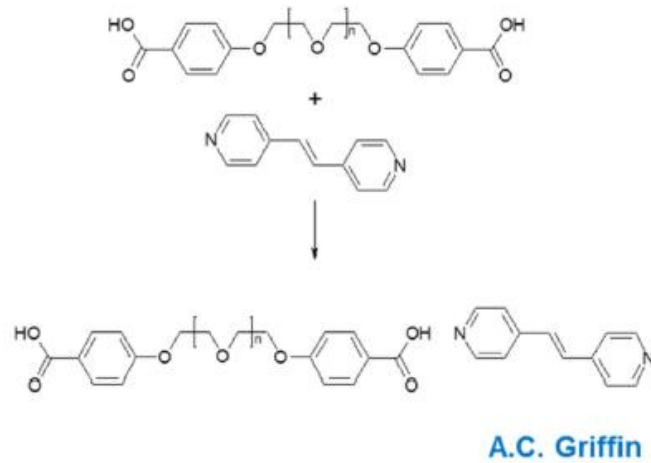
Independently and in the same year 1988, one-dimensional aggregates based on hydrogen bonds in the crystalline state were introduced by Wuest and coworkers. They used an array of double hydrogen-bonded monomers that formed polymeric arrays in the crystal, provided that the units were designed for linear arrays, otherwise cyclic structures were obtained.

Lehn moved to the liquid crystalline phase using a triple-hydrogen bonded strategy in 1990. Here, his group synthesized two complementary monomeric units (A-A and B-B), assembled them into a $(A-A : B-B)_n$ polymeric structure, and observed chiral fiber-like architectures with electron microscopy.

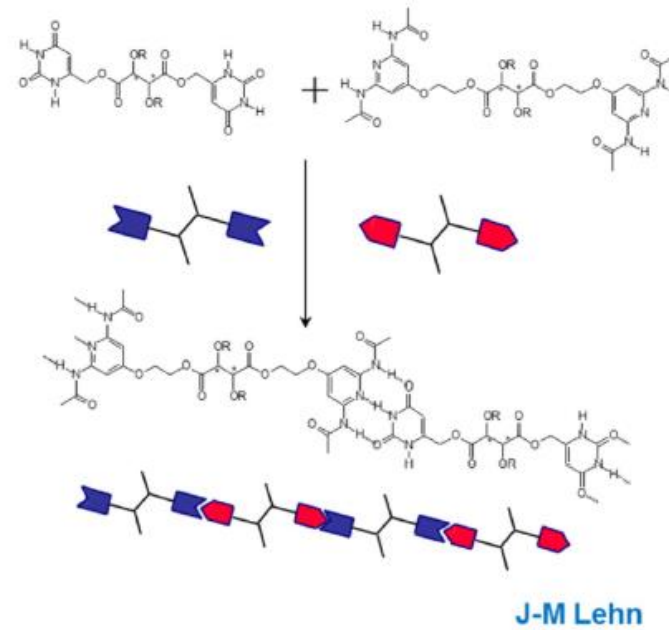
In 1994, Lee and Griffin moved to amorphous materials using a single hydrogen bond between a carboxylic acid and a pyridine again in A-A and B-B arrangements. In this case, the supramolecular complexes could be drawn into fibers displaying some mechanical properties, probably due to the ionic character of the bond between an acid and pyridine.

Hydrogen-bonded polymers by Wuest, Griffin, Lehn

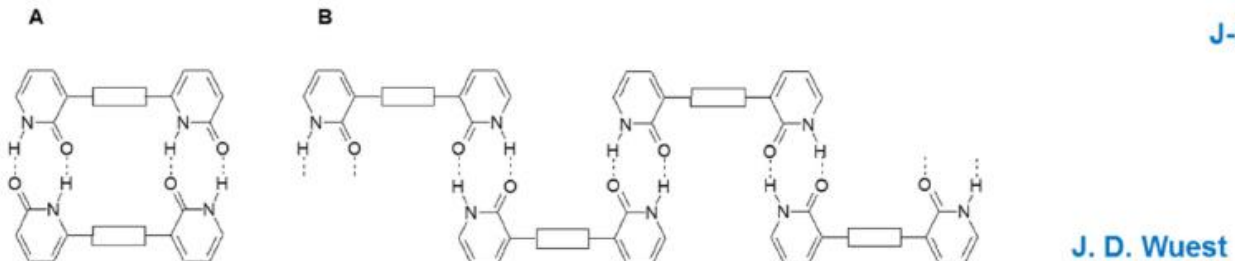
Single Hydrogen Bonds :



Triple Hydrogen Bonds :



Double Hydrogen Bonds :



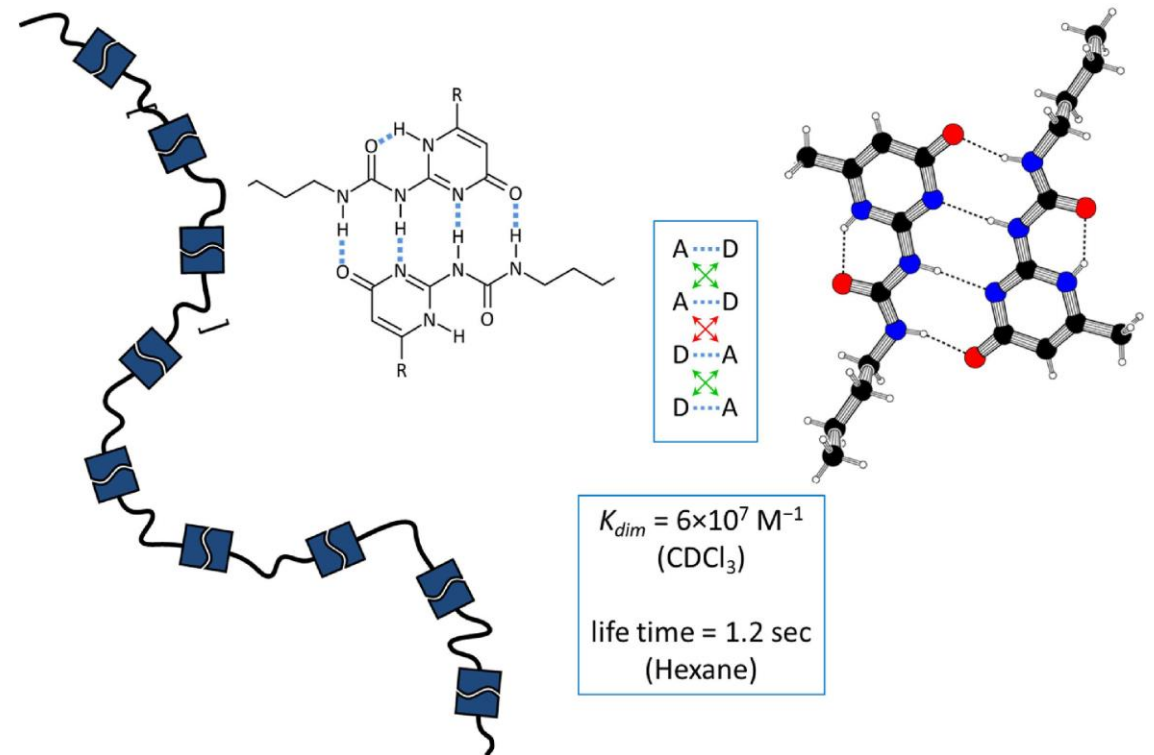
The problem of mechanical strength

Despite their beauty in representing the birth of supramolecular polymers, the association constants between the repeating building blocks are actually too low to furnish high virtual molecular weights of the polymers in solution, melt and amorphous states. Hence, the idea to make mechanically strong polymeric materials by 1D association of small molecules remained within the realm of fantasy.

The First Mechanically Robust Supramolecular Polymeric Materials

That all changed in 1997 when the ureidopyrimidinone (UPy) self-complementary quadruple hydrogen bonding unit was introduced to this field.

Meijer and Sijbesma, developed the ureidopyrimidinone (UPy) motif and investigated its mode of action in detail



The Upy supramolecular polymer

The molecule is very easy to synthesize in one step from commercially available precursor molecules or in three steps from methyl acetate.

At that time, it represented the first example of a (self-complementary) quadruple hydrogen bonding unit

A combination of techniques, including magnetization-transfer NMR studies, yielded a dimerization constant of $K_{dim}=10^7-10^8 \text{ M}^{-1}$ and a life time of 0.1–1.0 second, both properties depending on the dielectric constant of the solvent. This UPy-group when attached to both sides of a spacer furnished thermodynamically stable supramolecular polymers with macroscopic properties that were traditionally only reserved for covalent macromolecules

Films and fibers could be prepared and these materials possess in many ways the bulk properties of macromolecular materials.

The Upy-motif and supramolecular polymers

Through the years the use of the UPy-motif expanded and a large number of different spacers, oligomers and even macromolecules were decorated with the UPy-motif. 1D supramolecular polymers and 3D polymer networks are obtained with the UPy-unit at the end of the chain. Strong supramolecular aggregation is obtained when the UPy-unit is incorporated in the main chain and versatile thermoplastic elastomers are obtained. Similar ideas were used to make highly elastic supramolecular hydrogels.

The successful combination of interactions yielded supramolecular thermoplastic elastomers that are used as temporary biomaterials for regenerative medicine.

Supramolecular polymers are defined as polymeric arrays of monomeric units that are brought together by reversible and highly directional secondary interactions, resulting in polymeric properties in dilute and concentrated solutions, as well as in the bulk. The monomeric units of the supramolecular polymers themselves do not possess a repetition of chemical fragments. The directionality and strength of the supramolecular bonding are important features of systems that can be regarded as polymers and that behave according to well-established theories of polymer physics

Indeed, it was from 1997 onwards that the field of supramolecular polymers as materials witnessed an unexpected expansion following the early examples described above. Seminal contributions were made by Zimmerman, Leibler, Craig, Bouteiller, Zhang, Binder and Long, just to name a few.

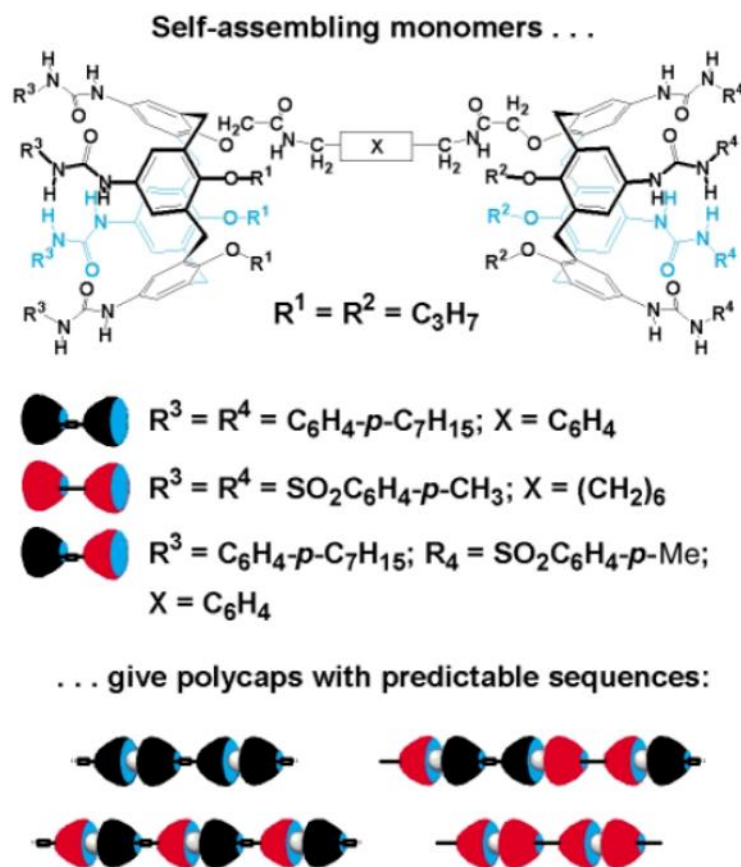


Fig. 5 Heterodimerization preferences lead to predictable polymer sequences from either complementary or self-complementary subunits.

Almost simultaneously with the first UPy-based polymers, Rebek published the strong association between urea substituted calix(4)arenes to design 'polycaps' (polymeric capsules) formed from monomers that contain two covalently linked calix(4)arene tetra-ureas. In chloroform, the polymers are formed reversibly, as was shown by depolymerization upon the addition of mono-functional chain-cappers.

History of Polymer Science

1920 Concept of Macromolecules (Staudinger)

Full of Innovations

- 1929 Step-Growth & Chain-Growth Polymerizations (Carothers/Flory)
- 1935 Invention of Nylon (Carothers)
- 1953 Olefin Polymerization Catalysts (Ziegler/Natta)
- 1954
- 1956 Living Polymerization (Szwarc)
- 1974 Behaviors of Polymers in Solution (Flory)
- 1991 Soft Matters (Pierre-Gilles de Gennes)
- 2000 Electroconductive Polymers (Shirakawa, Heeger, MacDiarmid)

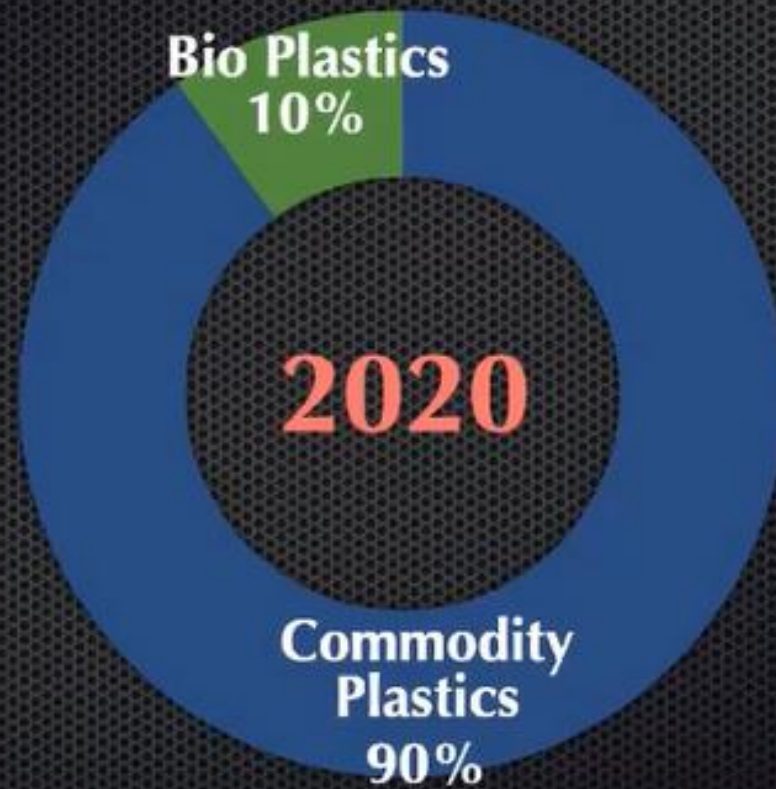
ACS SPRING 2021

MACROMOLECULAR CHEMISTRY: THE SECOND CENTURY

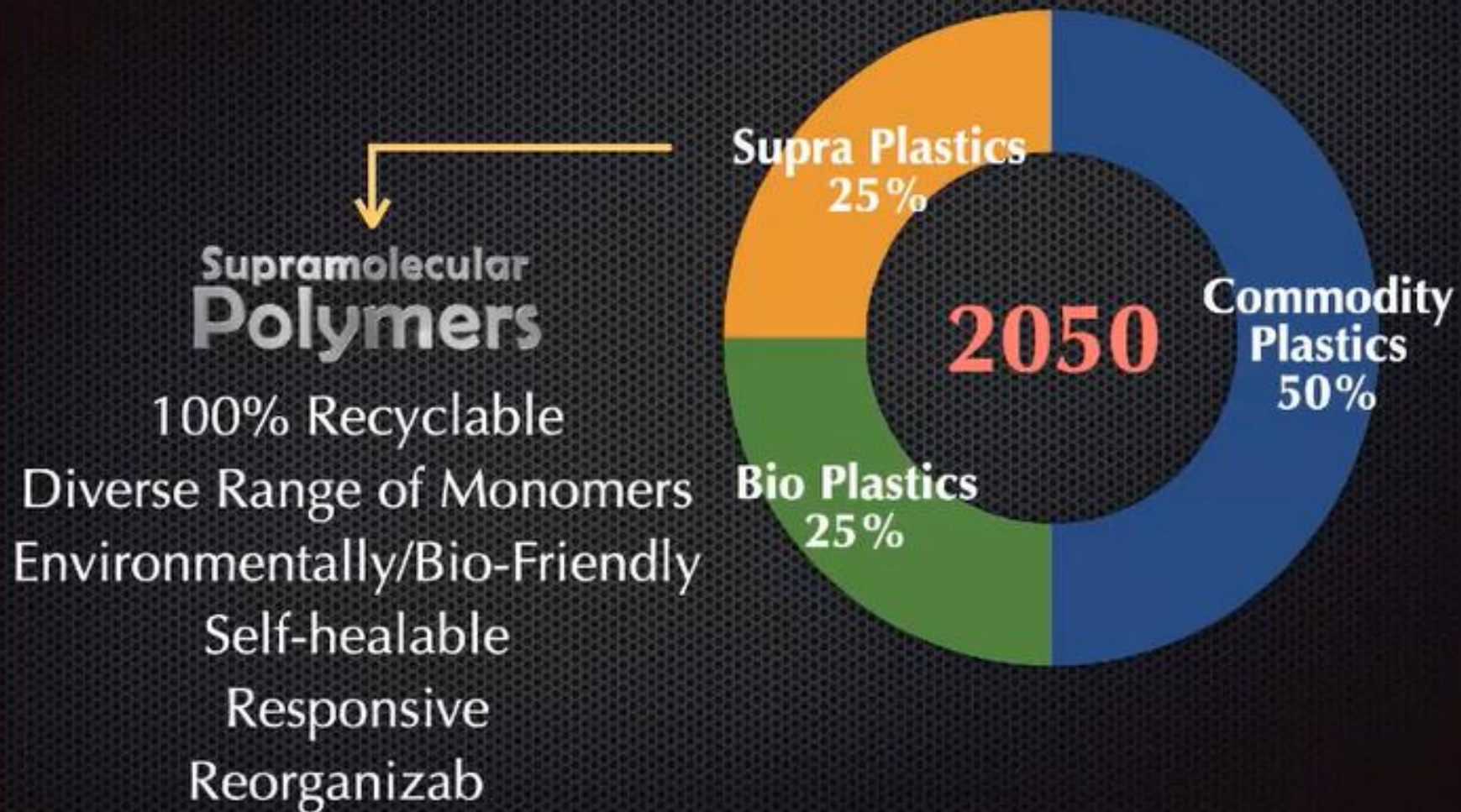


MEETINGS & EVENTS

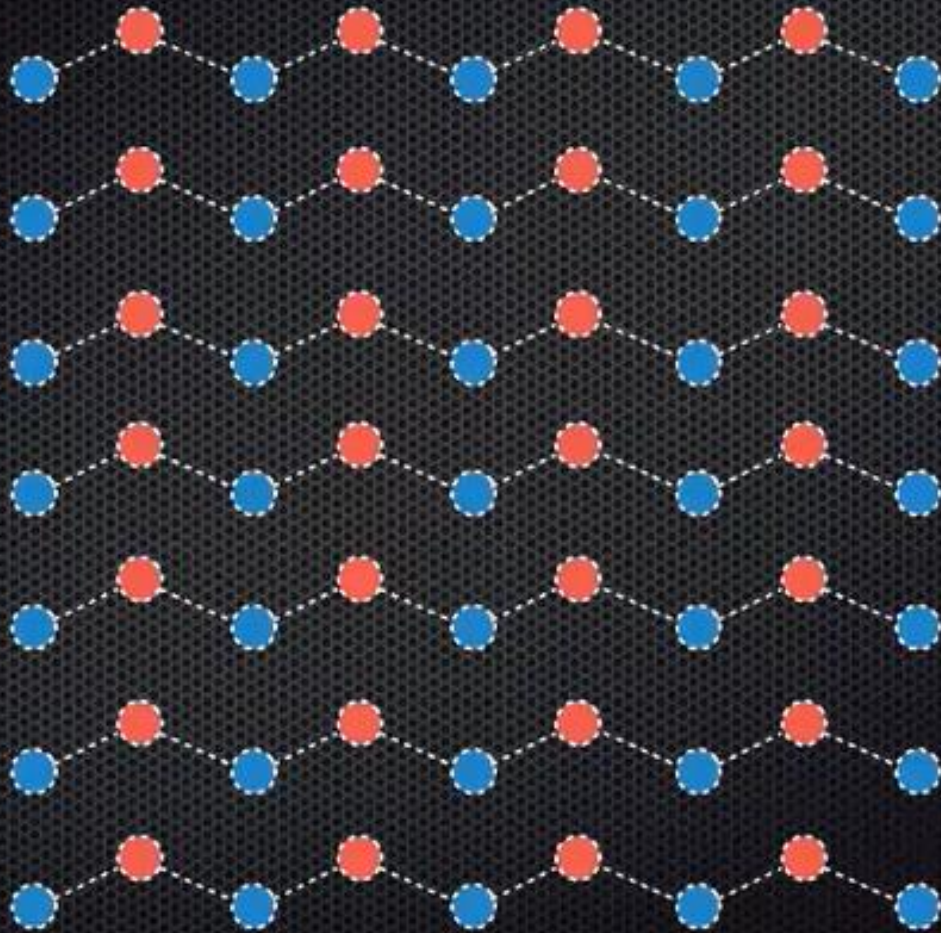
None of us would be happy to die with plastics!



None of us would be happy to die with plastics!
However, none of us can survive without plastics!



Noncovalent Bonding



We've Come Full Circle

A Long-term Debate until 1920

Macromolecule or ~~Colloidal Assembly?~~

1920

**Polymer
Science**



Covalent Polymers

|| Modernized

**Supramolecular
Polymers**

1D (2D) Supramolecular Polymerization

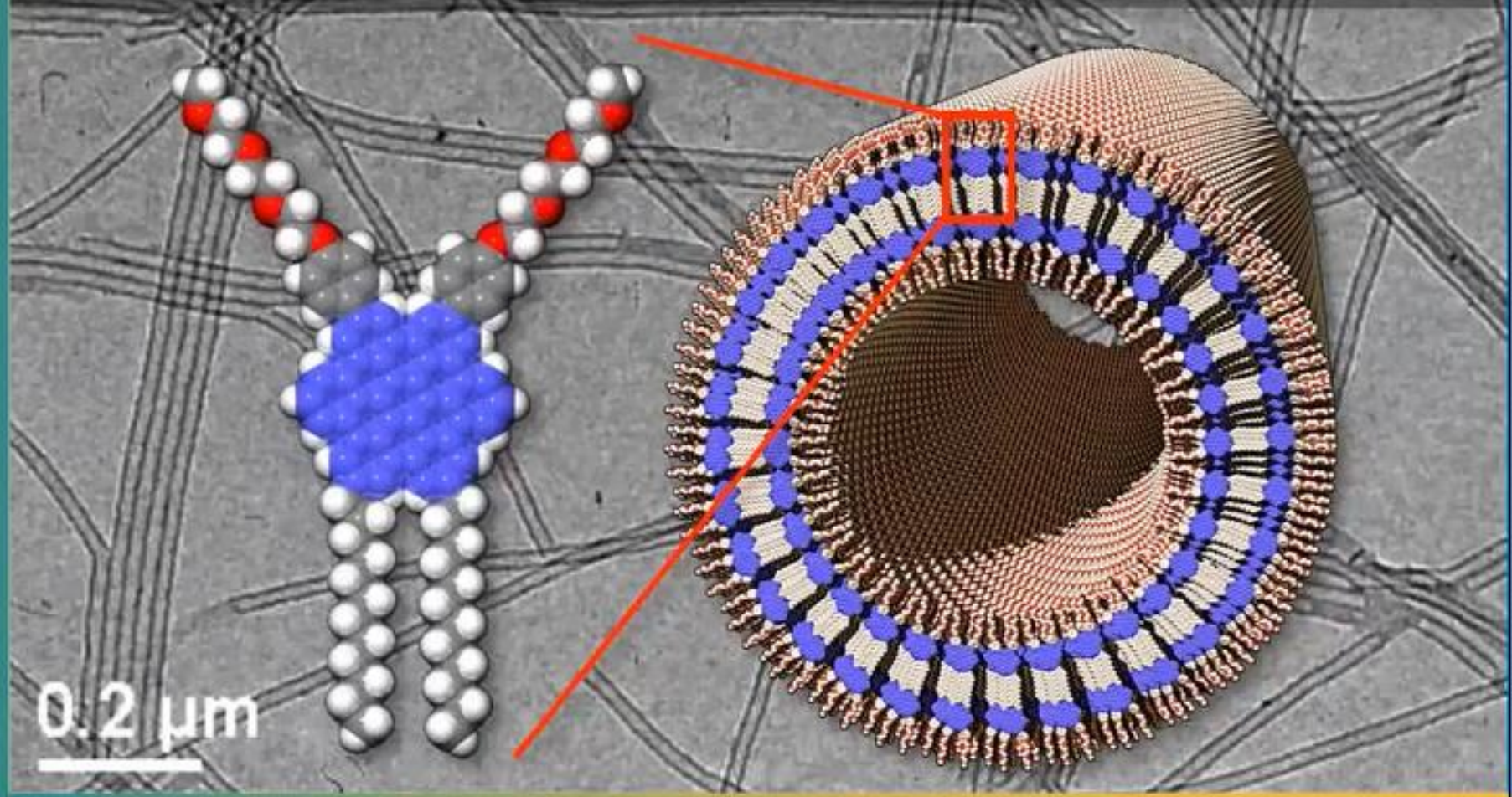
Hill, Fukushima & Jin *et al.*, *Science* **2004**, 304, 1481 (Graphite Nanotube)

Jin & Fukushima *et al.*, *PNAS* **2005**, 102, 10801 (One-handed Helical Graphite Nanotube)

Yamamoto *et al.*, *Science* **2006**, 314, 1761 (Photoconductive Graphite Nanotube)

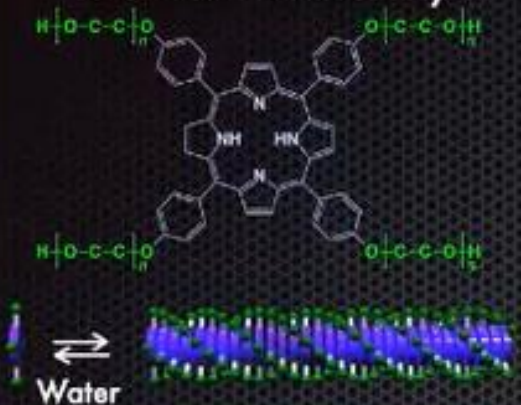
Jin & Yamamoto, *PNAS* **2009** (Photovoltaic Graphite Nanotube)

Wei & Fukushima, *Science* **2011** (Linear Heterojunction Graphite Nanotube)



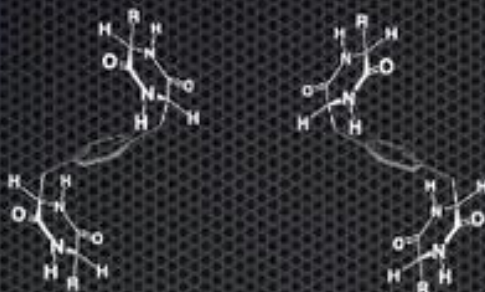
Supramolecular Polymerization (SP) at Aida Group since 1988

Elaborate Colloidal Approach
to SP for 1D Assembly



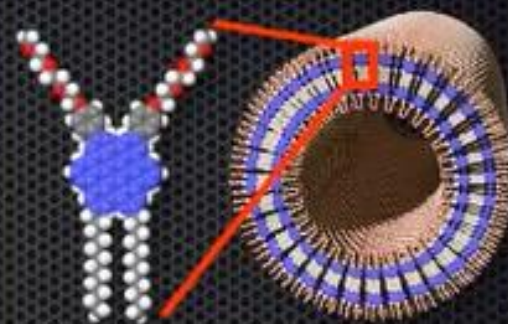
Aida et al., CHEMCOMM 1988

Homochiral SP
to Allow Optical Resolution
by Achiral GPC



Ishida et al., JACS 2002

SP of Molecular Graphene
to Form Conductive NPs



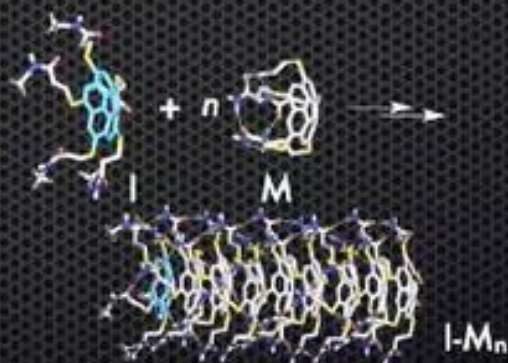
Fukushima et al., Science 2004
Yamamoto et al., Science 2006
Zhang et al., Science 2011

Solid-State SP to Form
Ferroelectric Columnar LC



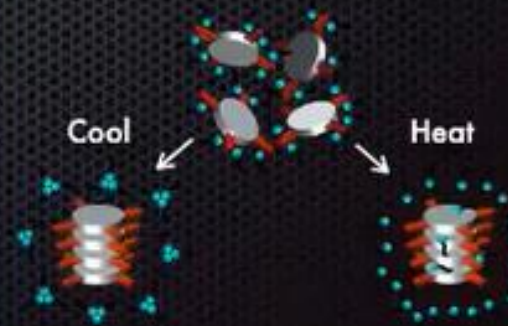
Miyajima et al., Science 2012
Alok et al., Nat. Chem. 2015

Living Chain-Growth SP



Kang et al., Science 2015

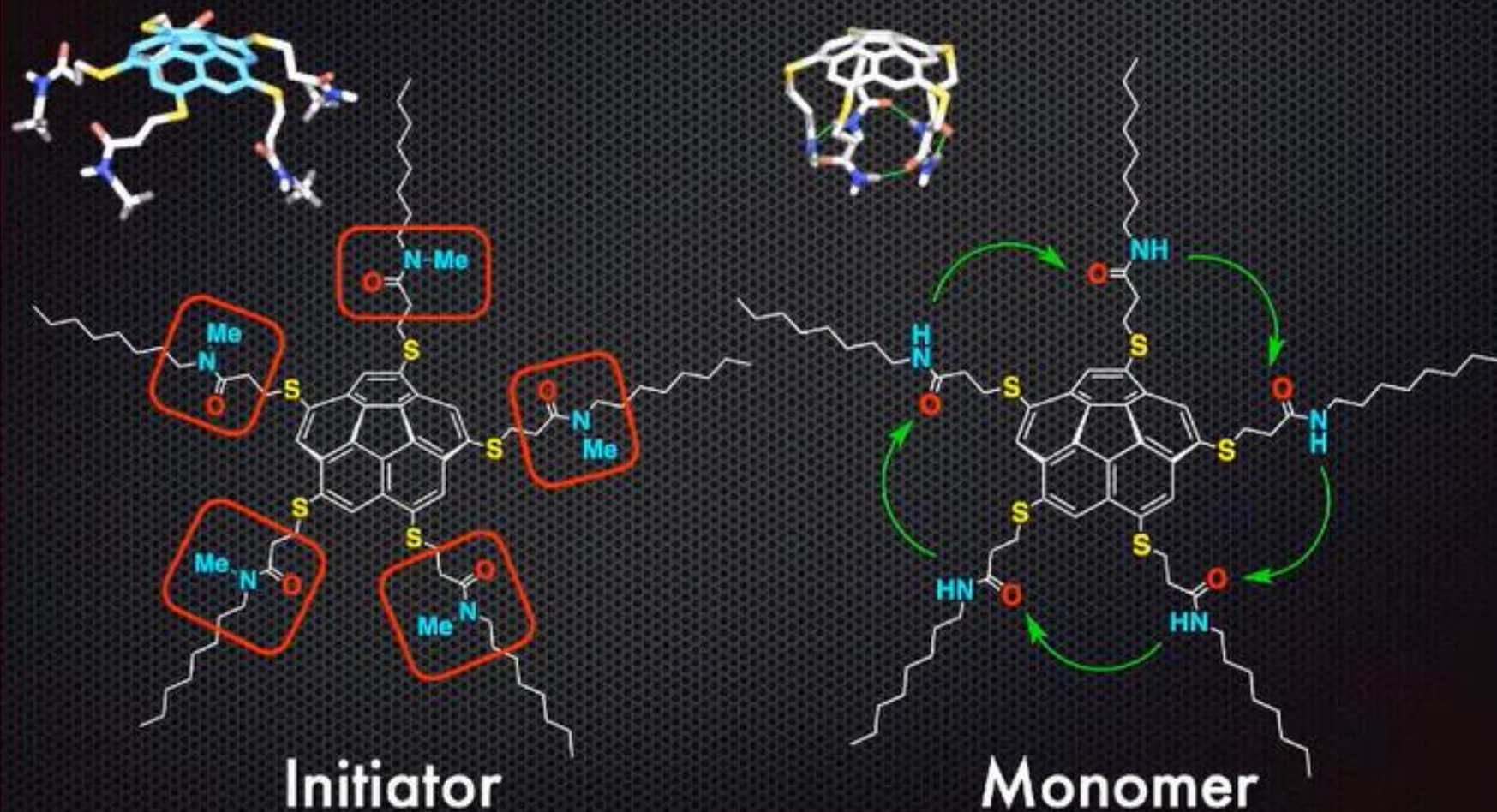
Thermally Bisignate SP
with H-Bond Scavenger



Rao et al., Nat. Chem. 2017

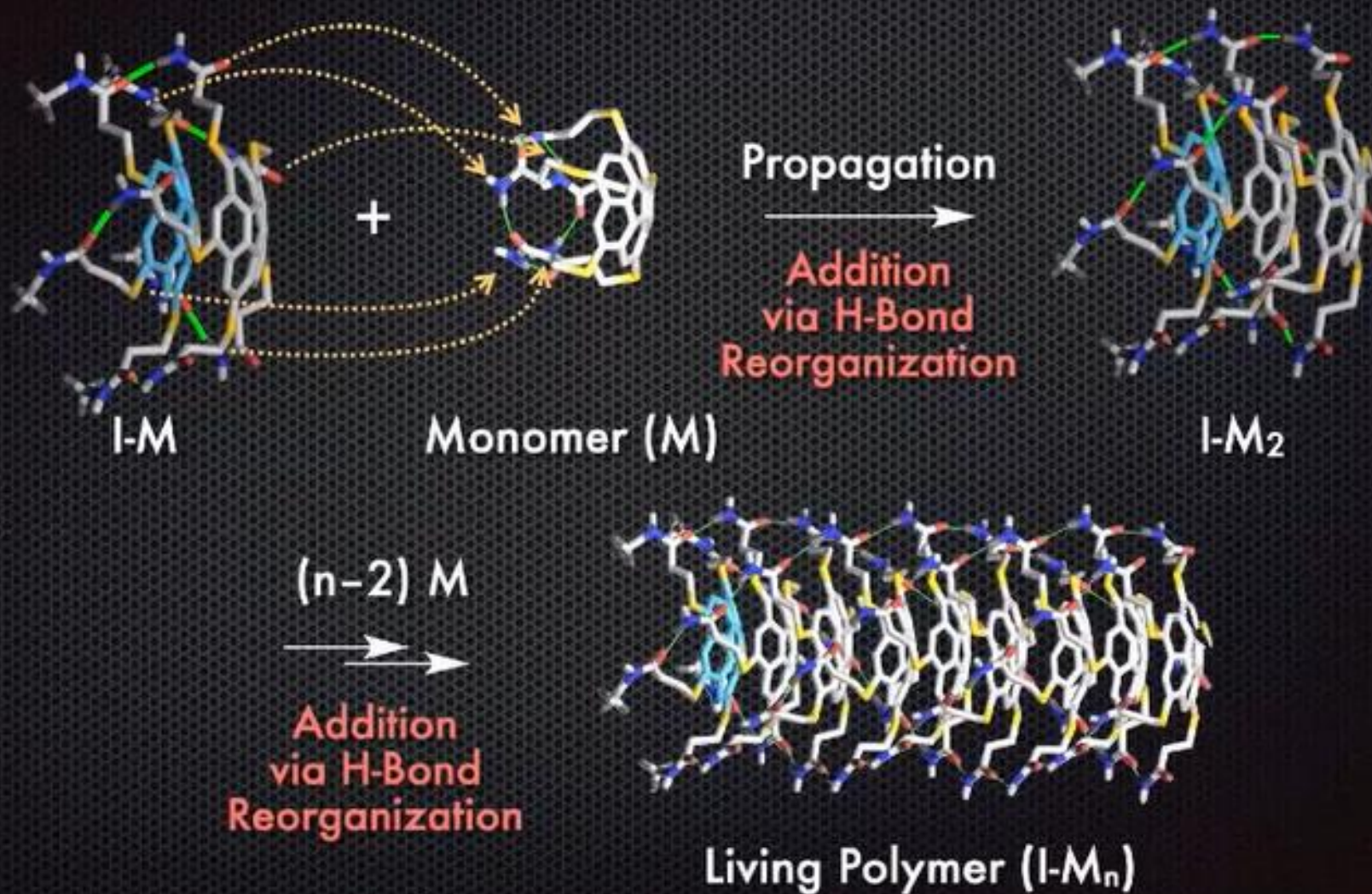
Ring-Opening Supramolecular Polymerization

Kang et al., *Science* **2015**, 347, 646–651.

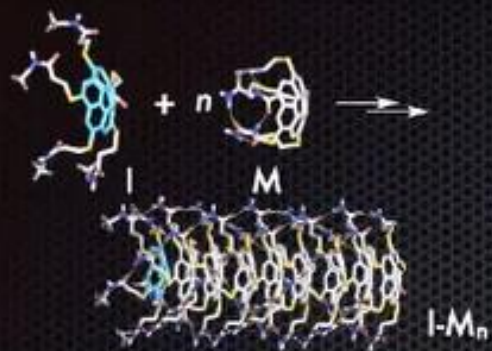


Ring-Opening Supramolecular Polymerization

Kang et al., *Science* **2015**, 347, 646–651.

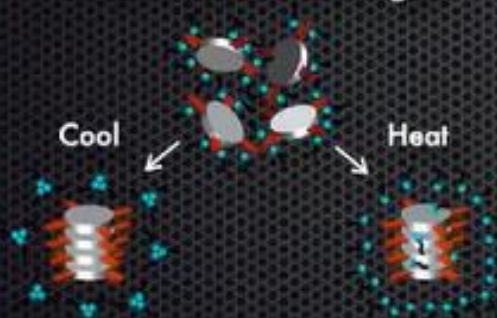


Living Chain-Growth Supramolecular Polymerization

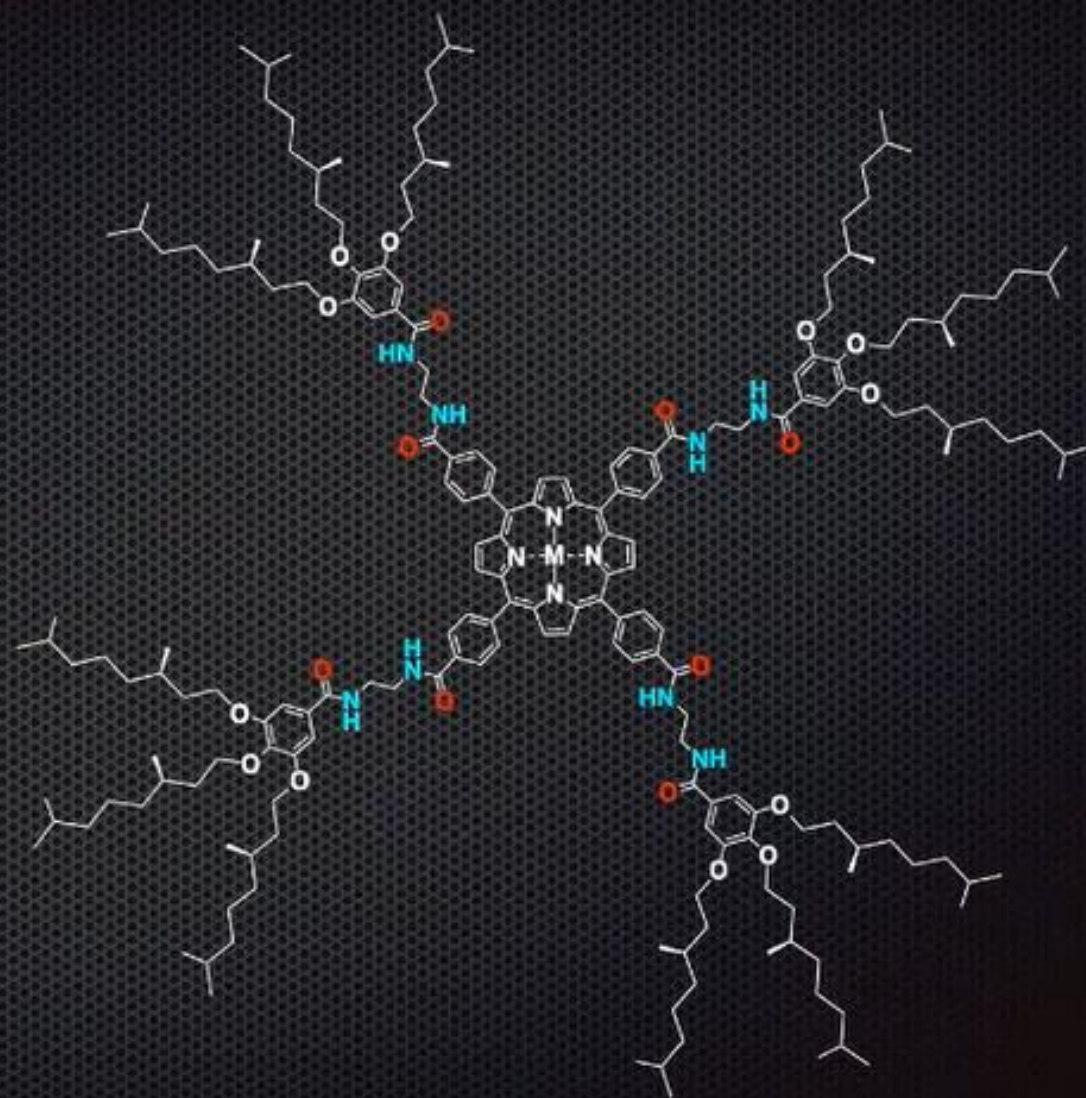


Kang et al., *Science* **2015**

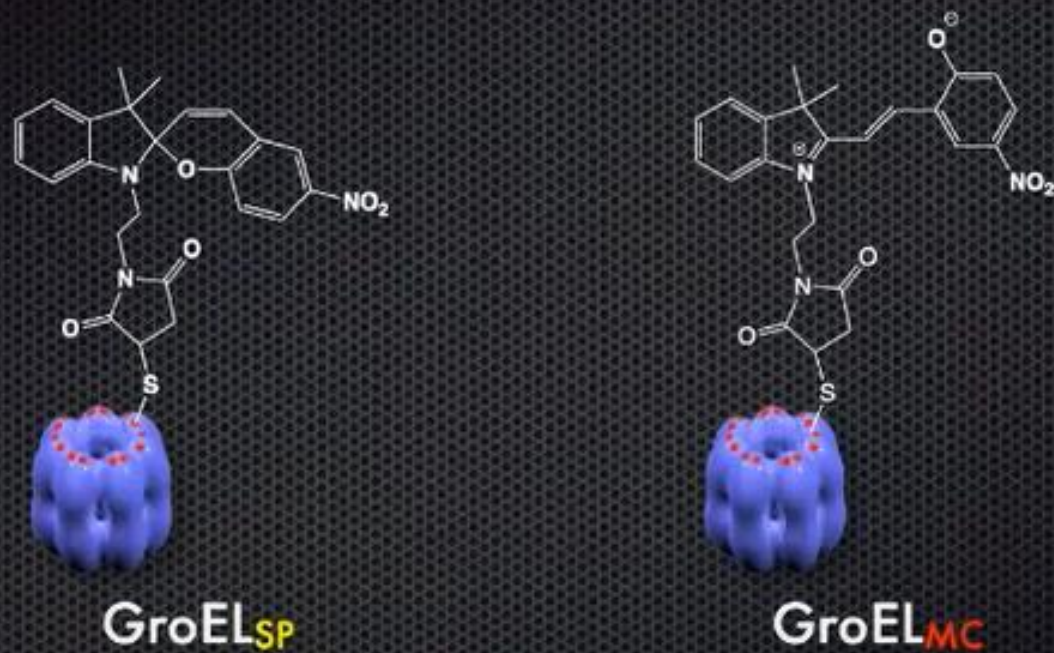
Thermally Bisignate Supramolecular Polymerization with H-Bond Scavenger



Rao et al., *Nat. Chem.* **2017**

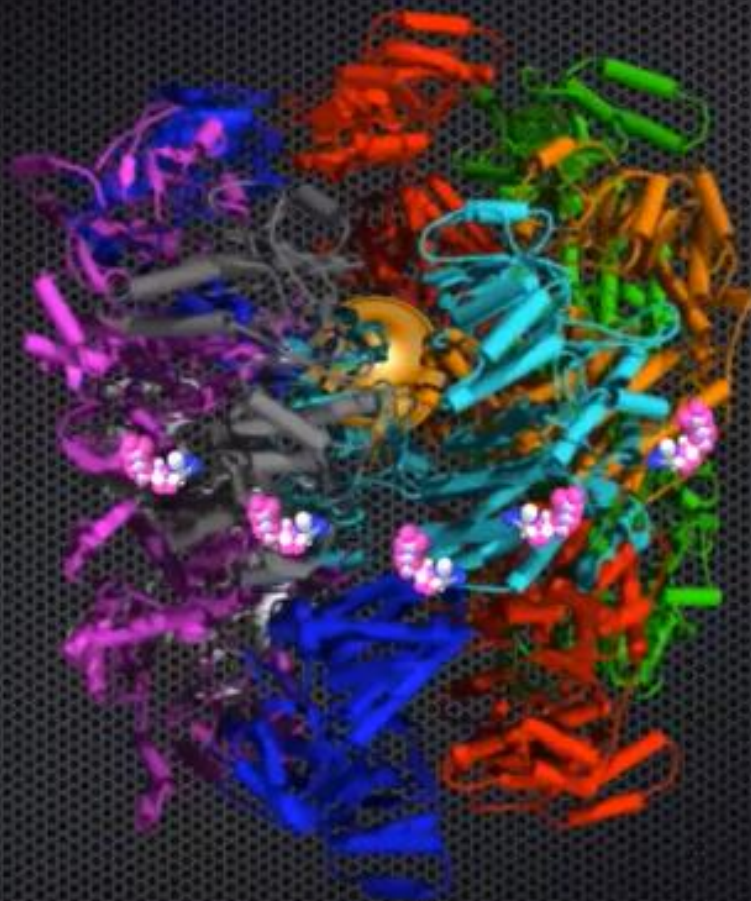


Spiropyran (SP) – Merocyanin (MC)



Spontaneous Ring-Opening in Buffer

Trapping of Artificial Guests & ATP-Triggered Release



Ishii, Kinbara, Aida *et al.*, *Nature* **2003**, 423, 628–632.

Biomolecular Robotics for Drug Delivery

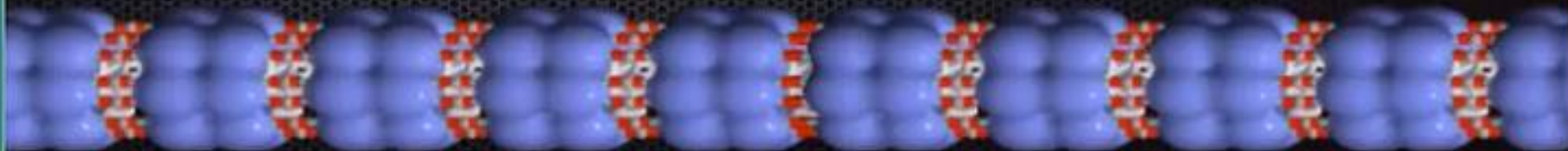
Carrier: Chaperonin Nanotube (NT)
Protein-based 1D Carrier

Stimulus: ATP (Endogenous Signal)

[Intracellular ATP] = 1–10 mM

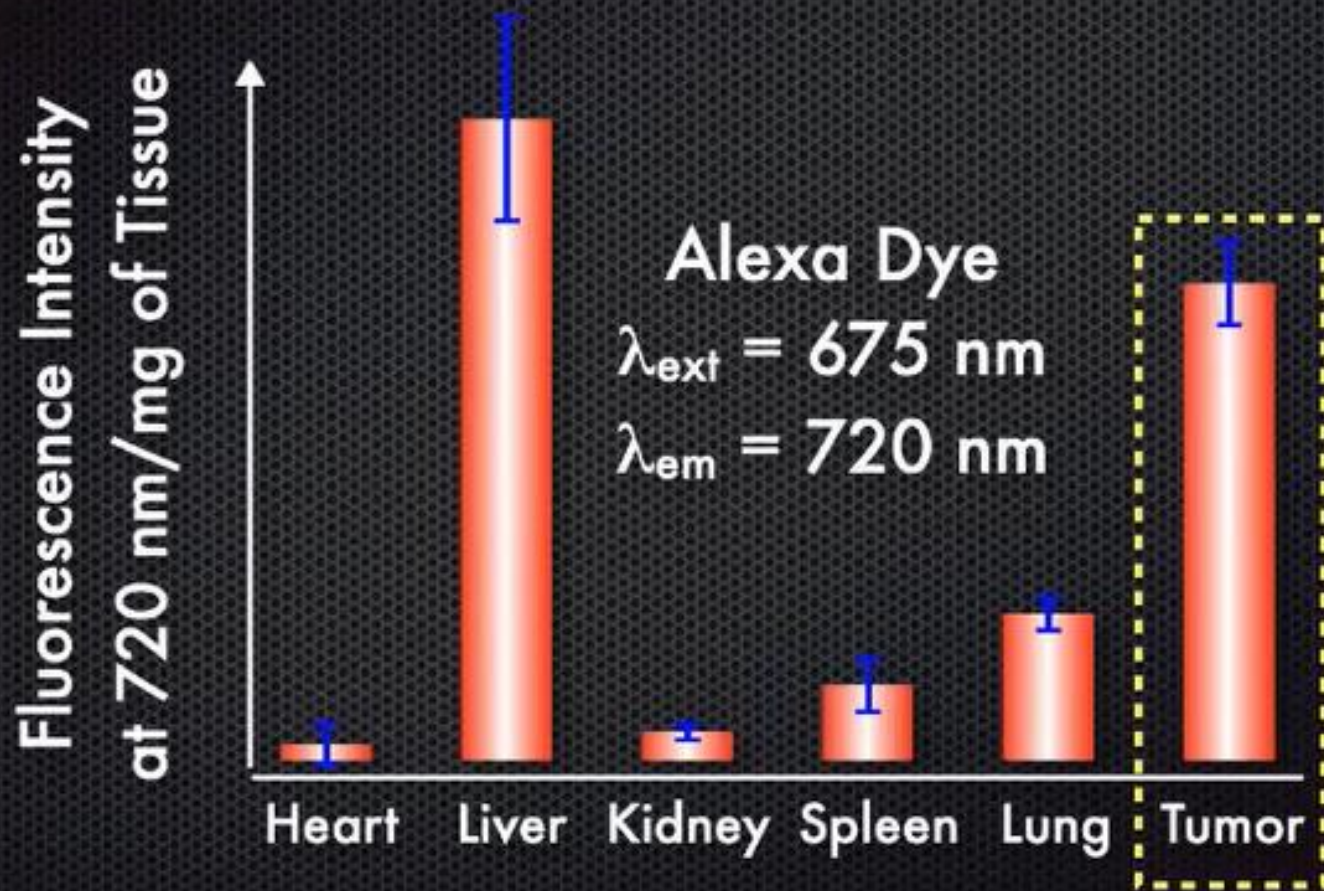
[Extracellular ATP] = 0.1 μ M

[ATP] at Inflammatory Sites (Tumor Tissues) = 1 mM



Bio-distribution of BANT_{MCD} -AlexaLA_{denat} in Tumor-carrying Mice

Biswas et al., *Nature Chem.* **2013**, 5, 613.



One day after Intravenous Injection ($n = 3$): **Kataoka Lab**

Nature **2010**, 463, 339.
Nature Comm. **2013**, 4, 2029.
Nature Mat. **2015**, 14, 1002.

JACS **2013**, 135, 15650.
Nature **2015**, 517, 68.
Nature Comm. **2016**, 7, 12559.

Aqua Material

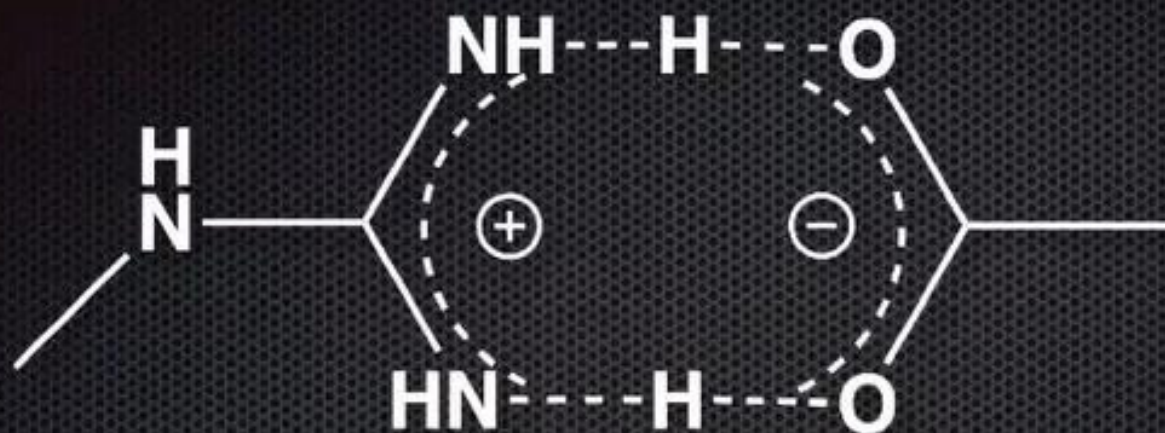
Water Content: 98%

Organic Content: 0.1% (1 ton/1 kg)

Clay Nanosheets (Clay NS): 1.9%

Self-standing & Moldable into Any Shape
(Unprecedented)

Electrostatic & H-Bonding Interactions



Molecular Glue Project

Okuro and Aida *et al.*

JACS **2009**, *131*, 1626–1627. *Nature* **2010**, *463*, 339–343.

ACIE **2010**, *49*, 3030–3033. *JACS* **2012**, *134*, 15273–15276.

JACS **2013**, *135*, 4684–4687. *Chem. Sci.* **2015**, *6*, 2802–2805.

JACS **2015**, *137*, 15608–15611. *ACIE* **2016**, *55*, 193–198.

JACS **2017**, *139*, 10072–10078. *Chem. Soc. Rev.* **2017**, *46*, 6480–6491.

JACS **2018**, *140*, 2687–2692. *JACS* **2019**, *141*, 2862–2866.

JACS **2019**, *141*, 8035–8040. *JACS* **2020**, *142*, 8080–8084.

Inorganic/Organic Supramolecular Copolymerization in Water

Aqua Material



Laponite
XLG

1.9%

+



Molecular
Glue

0.1%



Water



Wang *et al.*, *Nature* **2010**, 463, 339.

Nature **2010**, 463, 339.

Nature Comm. **2013**, 4, 2029.

Nature Mat. **2015**, 14, 1002.

JACS **2013**, 135, 15650.

Nature **2015**, 517, 68.

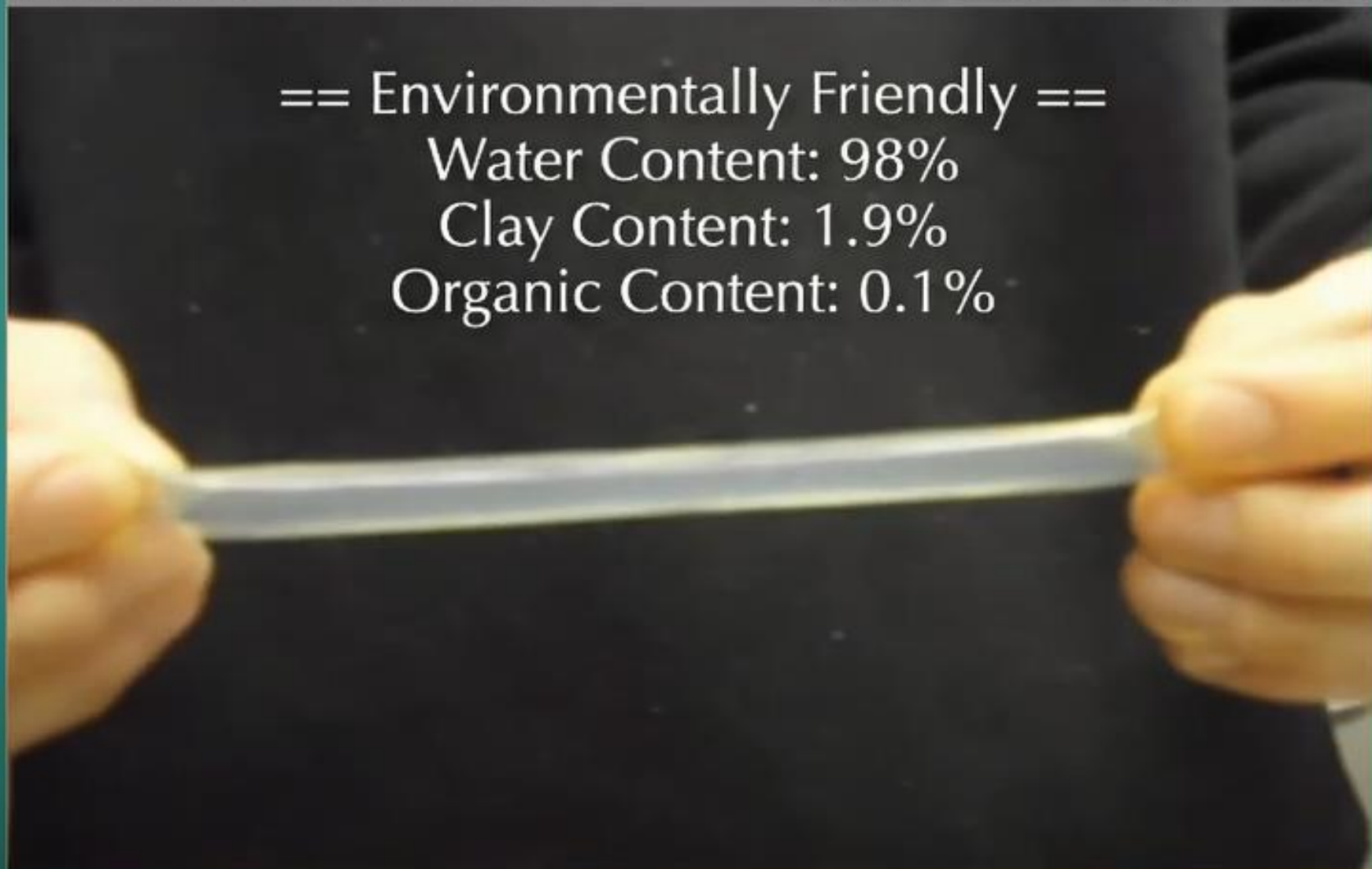
Nature Comm. **2016**, 7, 12559.

== Environmentally Friendly ==

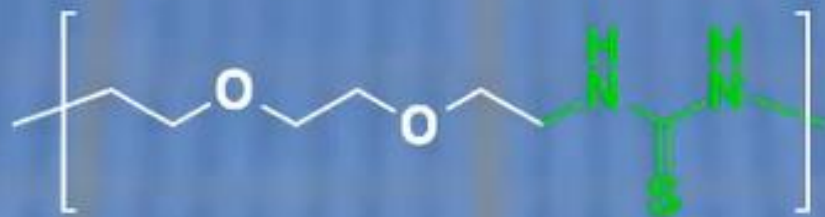
Water Content: 98%

Clay Content: 1.9%

Organic Content: 0.1%

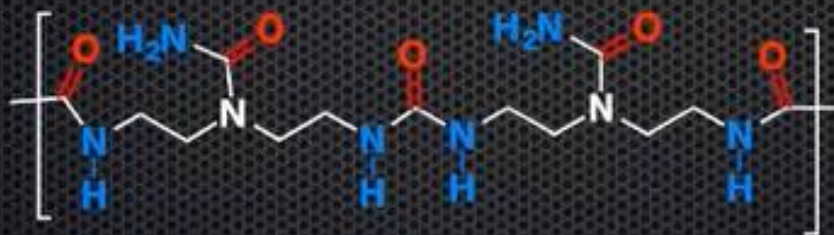
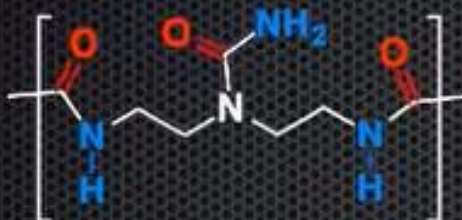
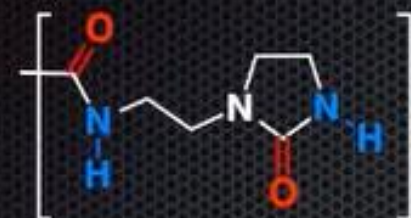


Self-Healable Polymer Glass



Y. Yanagisawa, Y. Nan, K. Okuro, T. Aida
Science **2018**, 359, 72–76

Supramolecular Healable Materials



Poly(amide/urea) + Dodecane
Leibler et al., *Nature* **2008**, 451, 977.

$E = 0.05 \text{ MPa}$

List of Representative Healable Materials

Journal	Year	Author	Matrix	E (MPa)	σ_{break} (MPa)	Healing Temp (°C)
Science	2018	Our Work	Poly(ether thiourea)	1400	45	24
Nat. Chem.	2016	Z. Bao	PDMS Crosslinked by Coordination Complex	0.5	0.25	20
Adv. Mater.	2012	A. Takahara	Polymer Crosslinked by Thiuram Disulfide	0.6	0.4	20
Nature	2008	L. Leibler	Poly(amide/urea)	0.5	3.5	20
Nat. Chem.	2012	Z. Guan	Brush Polymer with Amide Brushes	38	3.8	25
ACIE	2015	W. Binder	Polymer Blend of Triblock Copolymers	12	0.27	30
Adv. Mater.	2016	Z. Bao	PDMS Crosslinked by Boroxine Bonds	180	8	60
Nat. Commun.	2014	J. Cheng	Polymer Crosslinked by Hindered Ureas	1.2	0.9	60
JACS	2012	S. Rowan	Polymer Composite	260	—	85
Science	2002	F. Wudl	Polymer Crosslinked by Dieles-Alder Reaction	3100	68	120

The Debut of Thiourea in Materials Science

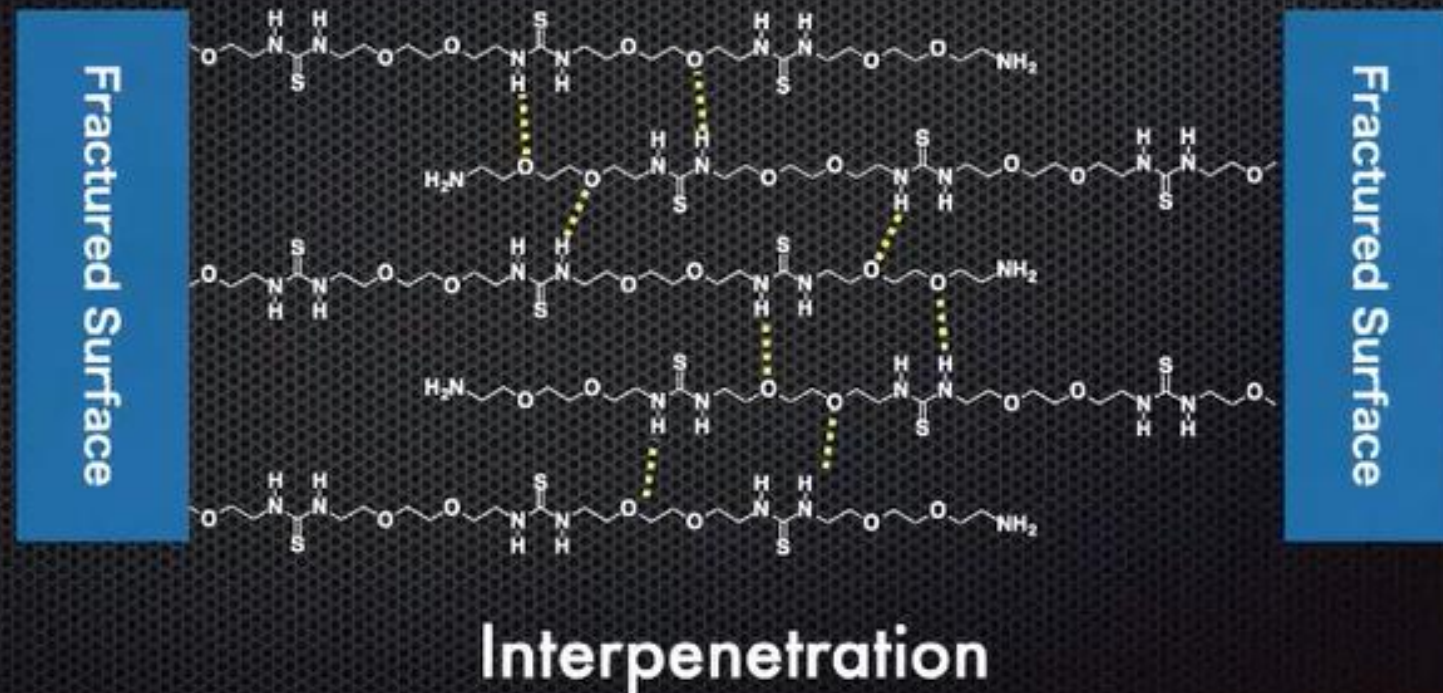


Highly Dense but Irregular H-Bonding Arrays



Swapping of H-Bonded Pairs Allows for Healing

"Thiourea and ether are miscible"
thereby lowering the activation energy for swapping



Why Supramolecular Polymers for the Second Century?

100% Recyclable
Diverse Range of Monomers
Environmentally/Bio-Friendly
Self-healable
Responsive
Reorganizable
Adaptive

T. Aida & E. W. Meijer, *Rosarium Philosophorum* **2020**.

E. W. Meijer & T. Aida *et al.*, *Prog. Polym. Sci.* **2020**.