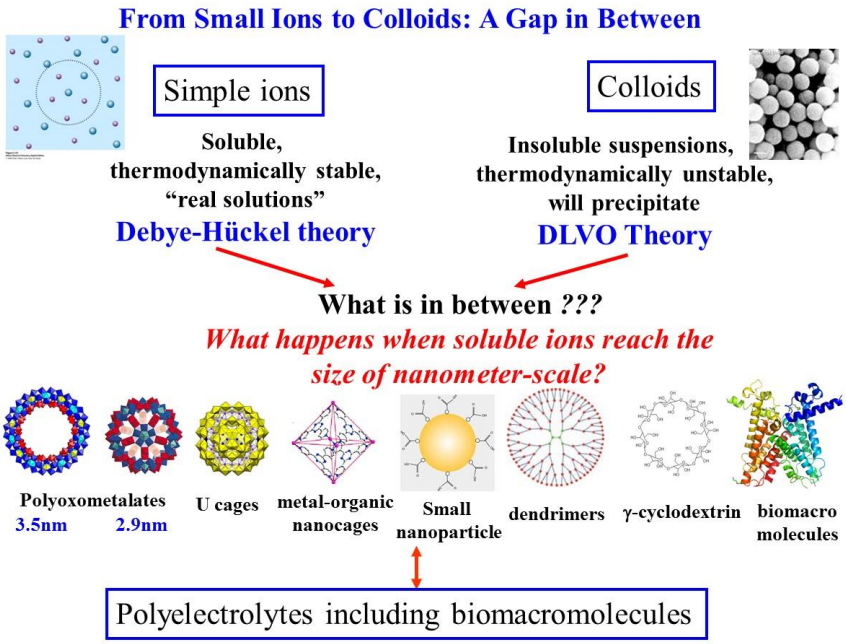
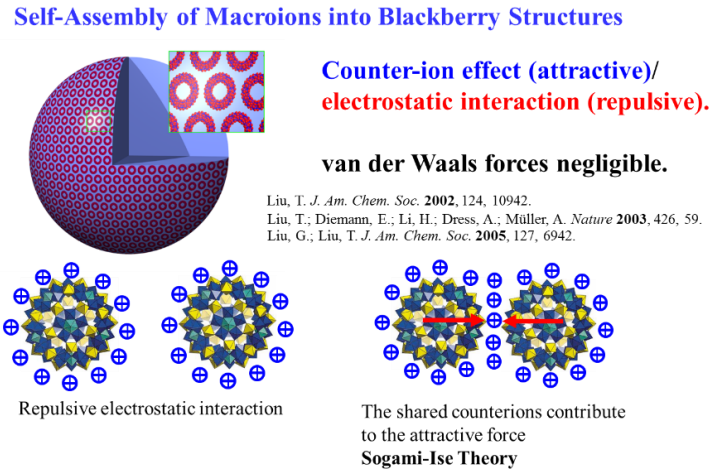
A summary of what we are doing now (only published results)

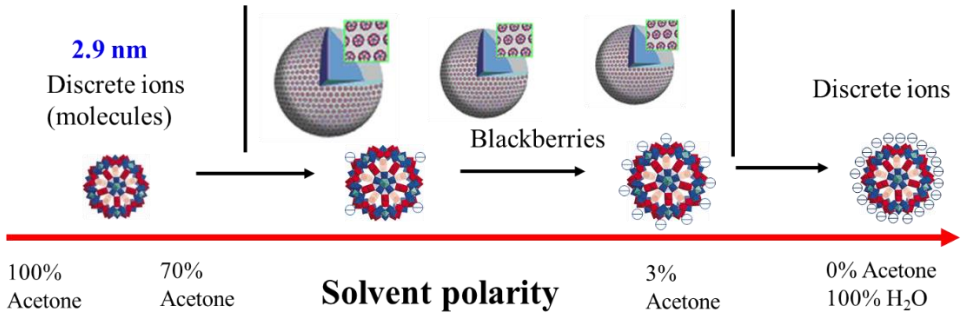
1. Hydrophilic Inorganic Macroions – Between Simple Ions and Colloids



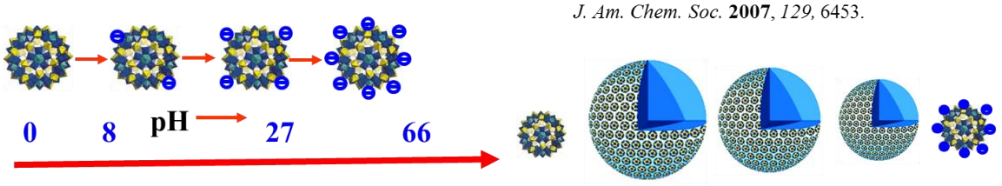
Instead of only existing as discrete macroions in dilute solution, they tend to form single-layered, spherical "blackberry" supramolecular structures (general case) or others if charge distribution changes.



Blackberry structure formation – large ions, moderate charges.
Blackberry size – macroionic charge density, solvent polarity, extra salts.



Kistler, M.; Bhatt, A.; Liu, G.; Casa, D.; Liu, T. *J. Am. Chem. Soc.* **2007**, *129*, 6453.



Liu, T.; Imber, B.; Diemann, E.; Liu, G.; Cokleski, K.; Li, H.; Chen, Z.; Müller, A. *J. Am. Chem. Soc.* **2006**, 128, 15914.

$$R \approx \frac{-2.7\times10^{-3}u}{\varepsilon_R \Psi^2}$$

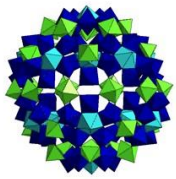
u: monomer interaction energy;
ε_R: solvent dielectric constant;
ψ: Zeta potential.

Verhoeff, A. A. *et al. Phys. Rev. Lett.* **2007**, *99*, 066104.

Key questions:

1. Driving forces for the self-assembly: not due to van der Waals forces, hydrophobic interaction or chemical interaction.
   Counter-ion-mediated attractions and hydrogen bonding are important.
2. Controlling and adjusting the blackberry size.
3. Macroion-cation interaction, counterion distribution and counterion replacement.
4. The roles of co-ions and the structure of water layers.

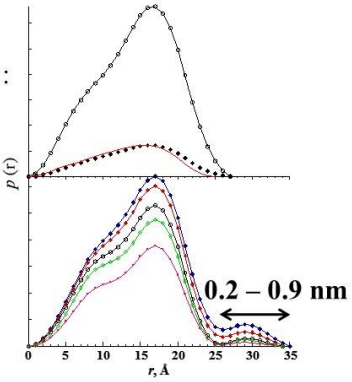
Small Angle X-ray Scattering at Argonne National Laboratory

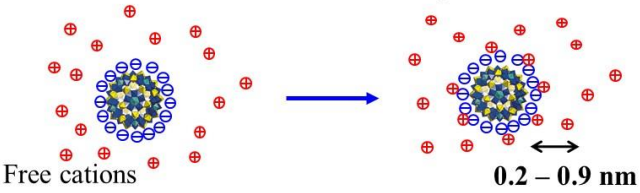


Single $\{Mo_{72}V_{30}\}$ cluster – 2.5-nm hollow sphere

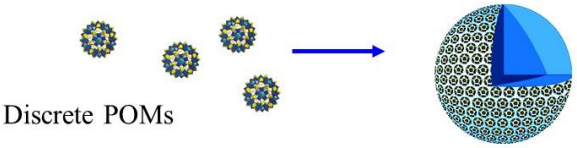
Macroions – uniform, spherical;
exist as discrete clusters in dilute aqueous solution;
Counterions – enough (metal) cations for providing signal.

0.05 mg/mL $\{Mo_{72}V_{30}\}$:
cations are all free.





Counter-ion association
(not only ion-pairing)

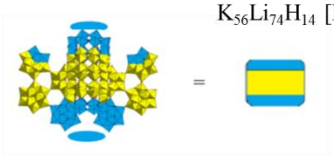


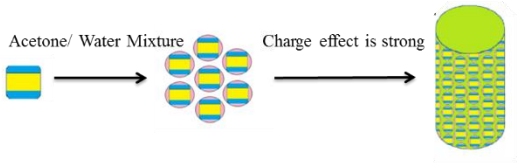
Blackberry formation

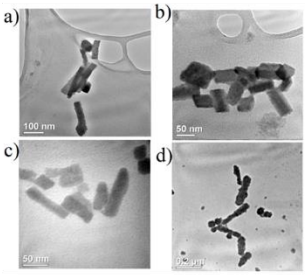
Pigga, J. M.; Kistler, M. L.; Shew, C.-Y.; Antonio, M.; Liu, T.
Angew. Chem. Int. Ed. **2009**, *48*, 6538.

Macroions with Anisotropic Charge Distribution

$K_{56}Li_{74}H_{14}$ $[Mn^{III}_{40}P_{32}W^{VI}_{224}O_{888}]$ .ca.$680H_2O$

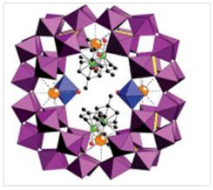


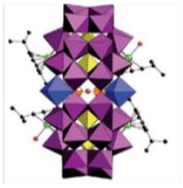




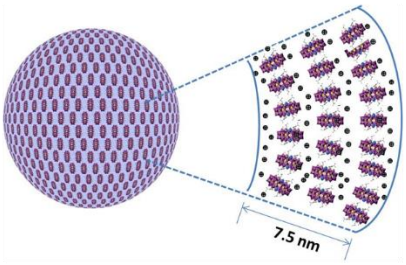
Haso, F.; Fang, X.; Yin, P.; Li, D.; Ross, J. L.; Liu, T. *Chem. Comm.* **2013,** 49, 609.

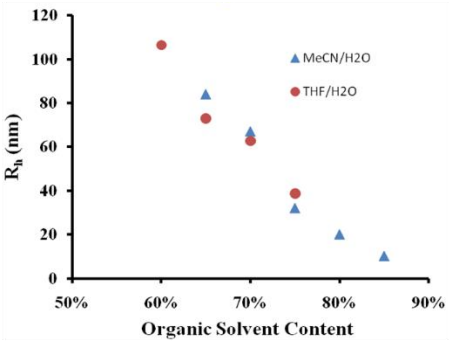
Limited Hydrophobic Interaction Change the Trend





$[\{K(H_2O)\}_3\{Ru(\text{-cymene})(H_2O)\}_4P_8W_{49}O_{186}(H_2O)_2]^{27-}$



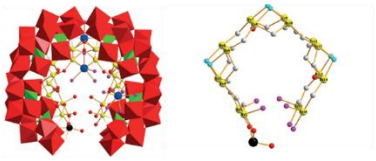


The size vs. solvent polarity trend is opposite to the known charge regulated process.

The central p-cemene group offers directional hydrophobic interaction?

Zhang, J.; Liu, T.; Mal, S. S.; Kortz, U. *Eur. J. Inorg. Chem.* **2010**, *3195.*

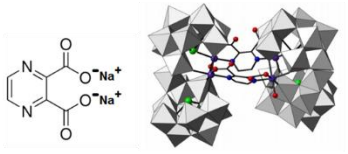
Directional H-bonds can also be Involved



"Horseshoe" from Kortz:
$K_9LiNa[P_8W_{49}O_{189}Fe_{16}O_2(OH)_{23}(H_2O)_9Gd_4(H_2O)_{20}]\cdot 50H_2O$

Charge = -11; size = 2.2 nm.

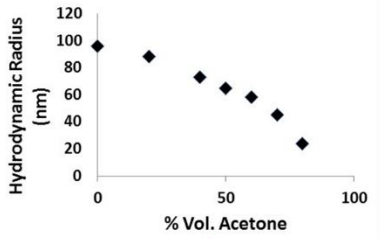
OH groups (grey) and water (purple) in internal cavity for hydrogen bonding.

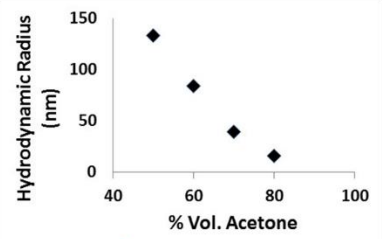


Sample from Gutiérrez-Zorrilla:
Two 2,3-pyrazinedicarboxylate ligands as bridges

Size: ~ 2.1 nm; charge: 24-; counterion: Na^+

COO- groups provides strong hydrogen bonding.

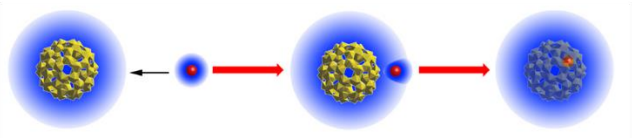




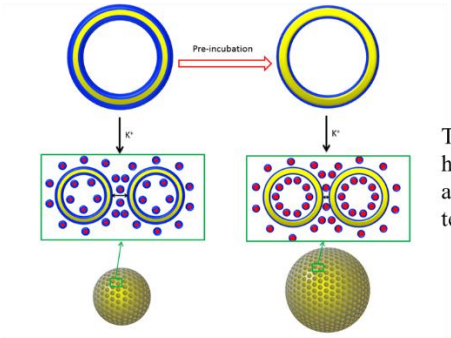
T. ↑ hydrogen bonding ↓, interaction between macroions ↓, blackberry structure size ↓.

Chemistry Select **2016**, 1, 4345-4349.

Cation Transport Over the Surface Pores on Clusters



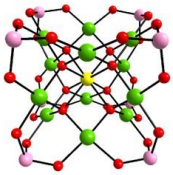
Only Na^+ and K^+ can selectively pass through the pores.
Hydration shell matters! (Main source of entropy gain during binding)



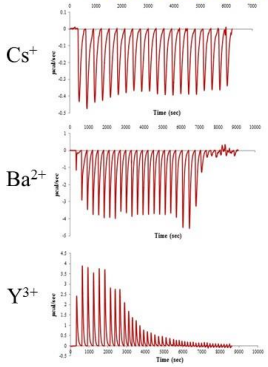
The ion selectivity is tunable via changing the hydration shell thickness, which can be easily achieved by controlling the incubation temperature.

Gao, Y.; Haso, F. ; Szymanowski, J. E.; Zhou, J.; Hu, L.; Burns, P. C.; Liu, T. *Chem. Eur. J.* **2015,** 21, 18785-18790.
Gao, Y.; Szymanowski, J. E.; Sun, X.; Burns, P. C.; Liu, T. *Angew. Chem. Int. Ed.* **2016**, 55, 6887-6891.

Water Layer Change During Macroion-Counterion Interaction – Three Scenarios



$[MO_8Pd^{II}_{12}(SeO_3)_8]^{6-}$

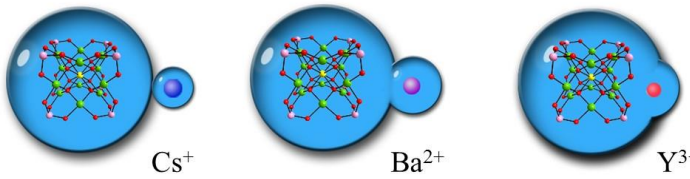


ITC:

No obvious interaction.
No self-assembly.

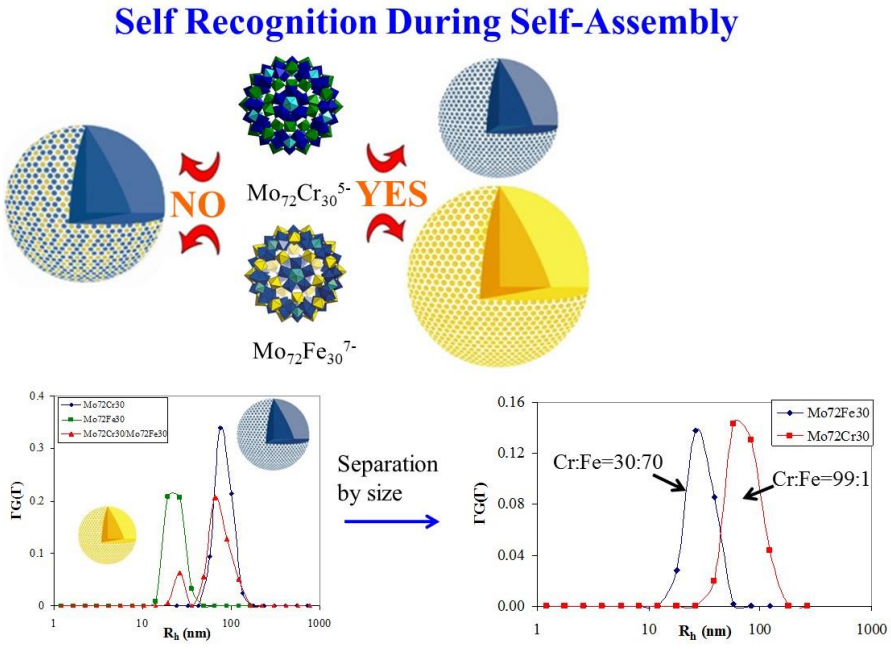
Water layers partially broken.
Strong counterion association.
Blackberry structure formation.

Water layers broken.
Ion fusion with a new water layer.
No self-assembly – single ion-pair.



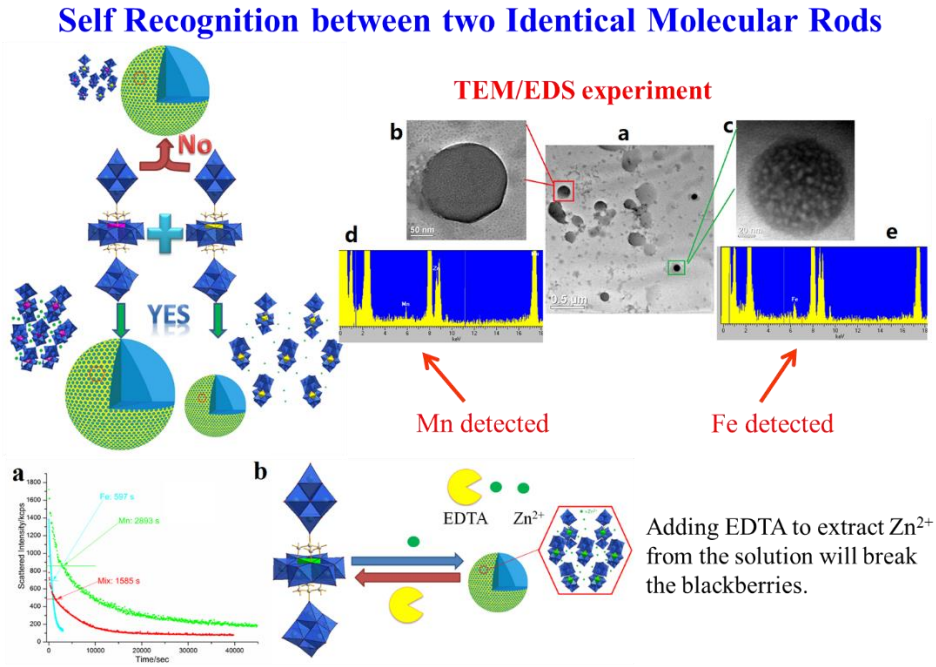
Collaborated with Ulrich Kortz

2. Self-recognition – simple macromolecules demonstrating the level of intelligence similar to biomacromolecules



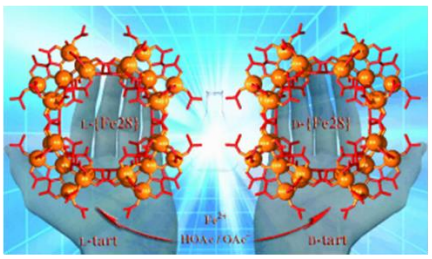
Liu, T.; Langston, M. L. K.; Li, D.; Pigga, J. M.; Pichon, C.; Todea, A.; Muller, A. *Science* **2011**, 331, 1590.

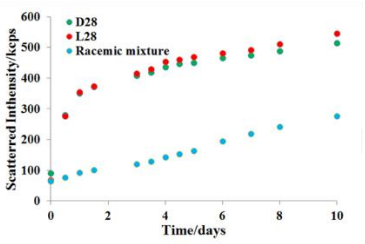
Self-recognition is discovered in macroionic solutions during their self-assembly. More impressively, the chiral recognition and chiral selection can be easily achieved when the long-range electrostatic interaction dominates the assembly.

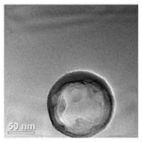


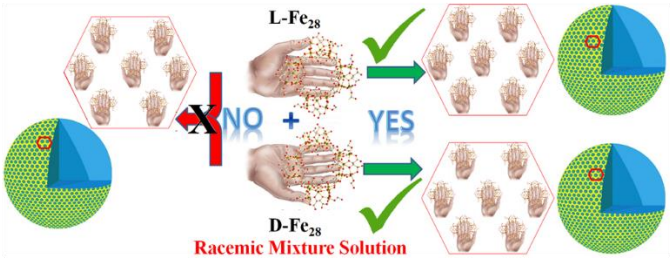
Yin, P.; Zhang, J.; Li, T.; Zuo, X.; Hao, J.; Warner, A. M.; Chattopadhyay, S.; Shibata, T.; Wei, Y.; Liu, T. *J. Am. Chem. Soc.* **2013**, 135, 4529.

Self-Recognition between Chiral Enantiomers







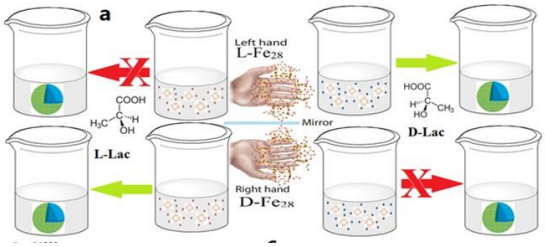


The two enantiomers can strictly self-recognize with each other during assembly.

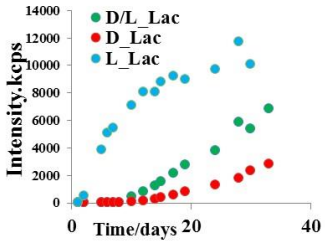
Yin, P.; Zhang, Z.-M.; Lv, H.; Li, T.; Haso, F.; Hu, L.; Zhang, B.; Bacsa, J.; Wei, Y.; Gao, Y.; Hou, Y.; Li, Y.-G.; Hill, C. L.; Wang, E.-B.; Liu, T. *Nature Comm*. **2015**, 6, 6475.

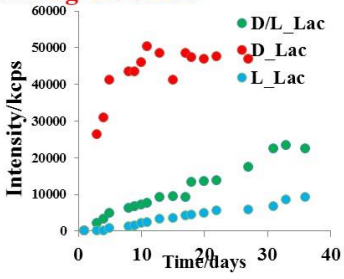
Chiral Selection – the Role of Co-anions

Small extra anions are expected to be unimportant in macroanionic solution...



The presence of chiral lactic acid co-anions amazingly signifies the self-assembly of one Fe_{28} enantiomer while depressing the other.

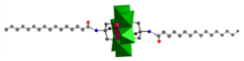




Yin, P.; *et al*. *Nature Comm*. **2015**, 6, 6475.

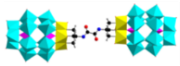
3. Inorganic-Organic Hybrid Materials

Competition Between Two Types of Attractions



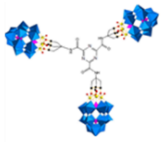
Surfactant

Zhang, J.; Song, Y.-F.; Cronin, L. Liu, T. *J. Am. Chem. Soc*. **2008**, 130, 14408.



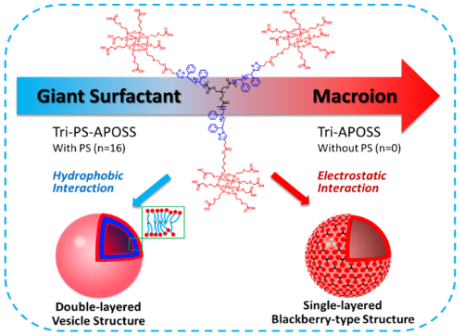
Single-layer surfactant vesicle or blackberry structure

Pradeep, C. P.; Misdrahi, M. F. ; Li, F. Y.; Zhang, J.; Xu, L.; Long, D.-L.; Liu, T.; Cronin, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 8309.



Blackberry structure

Zhang, B., Pradeep, C.P, Cronin ,L., Liu, T., *Chem. Comm.* **2015**, 51, 8630 – 8633.

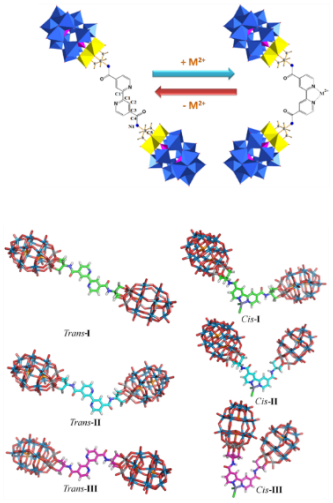


For tri-armed hybrids, the length of the organic linker matters!

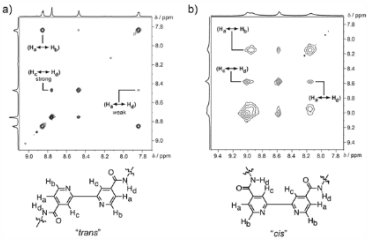
Chu, Y., Zhang, W., Lu, X., Mu, G., Li, Y., Cheng, S.Z.D, Liu, T. *Chem. Comm.* **2016**, 52, 8687 – 8690.

With the addition of hydrophobic interaction and/or other attractive forces, the inorganic-organic hybrid materials will demonstrate various features, from basic self-assembly similar to amphiphilic surfactants to luminescence…

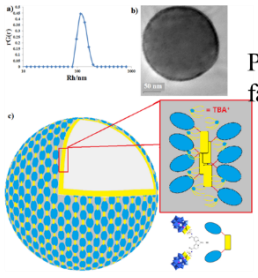
Response to External Stimulus – Changing the Packing Parameter



Possible conformations from simulation



^{1}H-^{1}H NOESY NMR spectra confirms *trans*-III to *cis*-II transition with Zn^{2+}

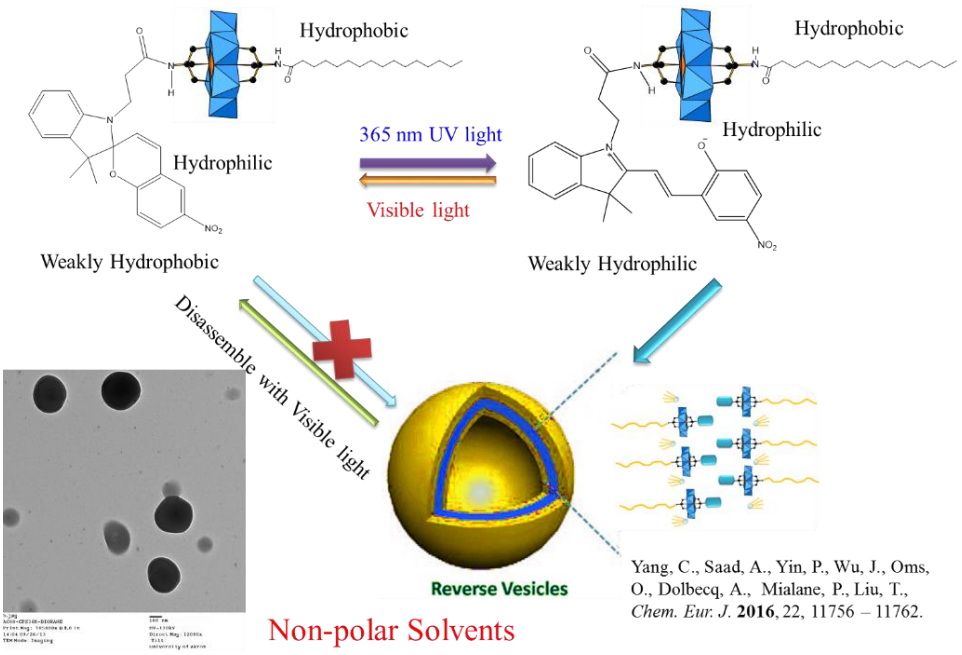


Packing parameter of *cis*-II favors vesicle formation.

Reversible assembly and disassembly of the vesicles.

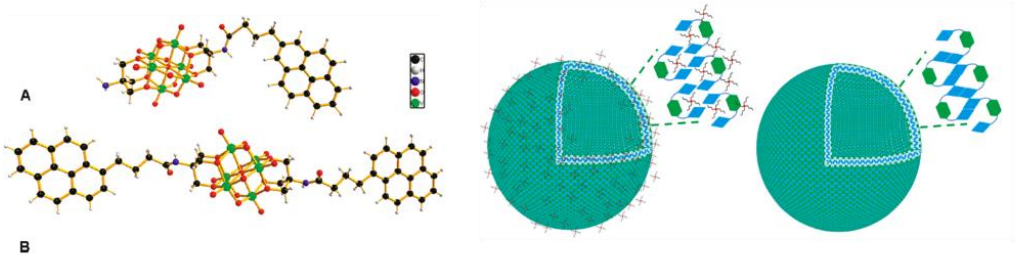
Yin, P.; Li, T.; Forgan, R. S.; Lydon, C.; Zuo, X.; Zheng, Z.; Lee, B.; Cronin, L.; Liu, T. *J. Am. Chem. Soc*. **2013**, 135, 13425 .

Polarity (Packing Parameter) Switch Controlled by UV/vis Light



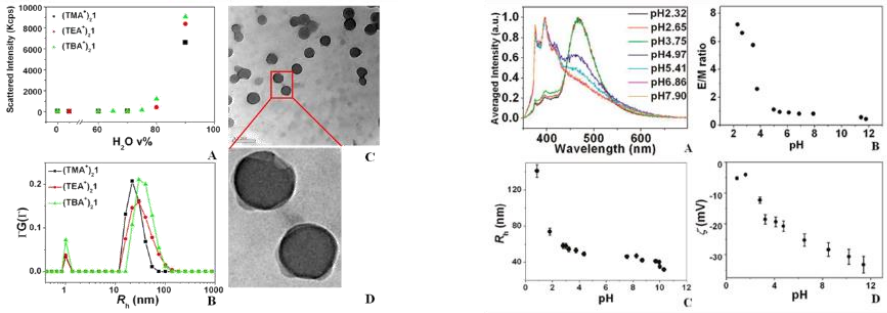
Yang, C., Saad, A., Yin, P., Wu, J., Oms, O., Dolbecq, A., Mialane, P., Liu, T., *Chem. Eur. J.* **2016**, 22, 11756 – 11762.

π-π Interaction Leads to pH- and Ionic-controlled Fluorescence



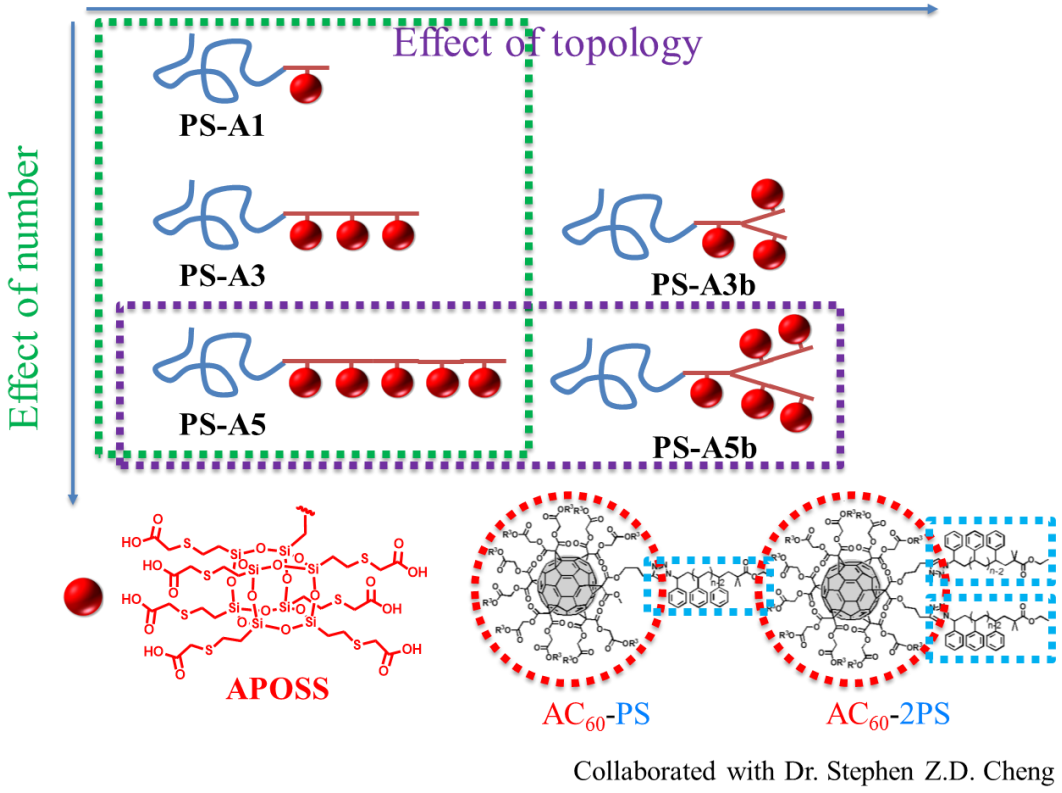
[a] Atoms are represented as follows: V (green), N (blue), O (red), C (black), H (white).

π-π interaction between pyrene groups



Li, D.; Song, J.; Yin, P.; Simotwo, S.; Bassler, A. J.; Aung, Y.; Roberts, J.; Hardcastle, K. I.; Hill, C. L.; Liu, T. *J. Am. Chem. Soc.* **2011**, 133, 14010.

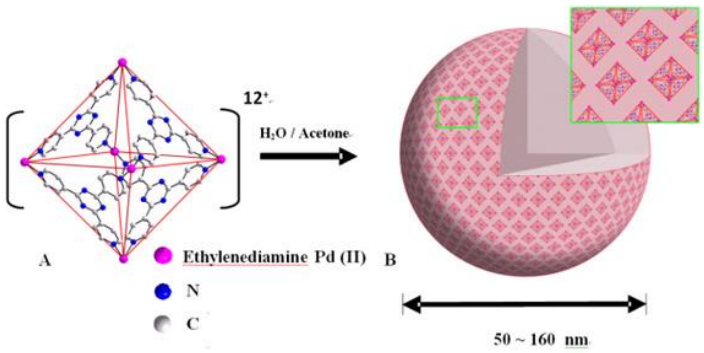
Hybrids Involving Multiple POSS, POM or C_{60} Groups with Proper Surface Functionalization



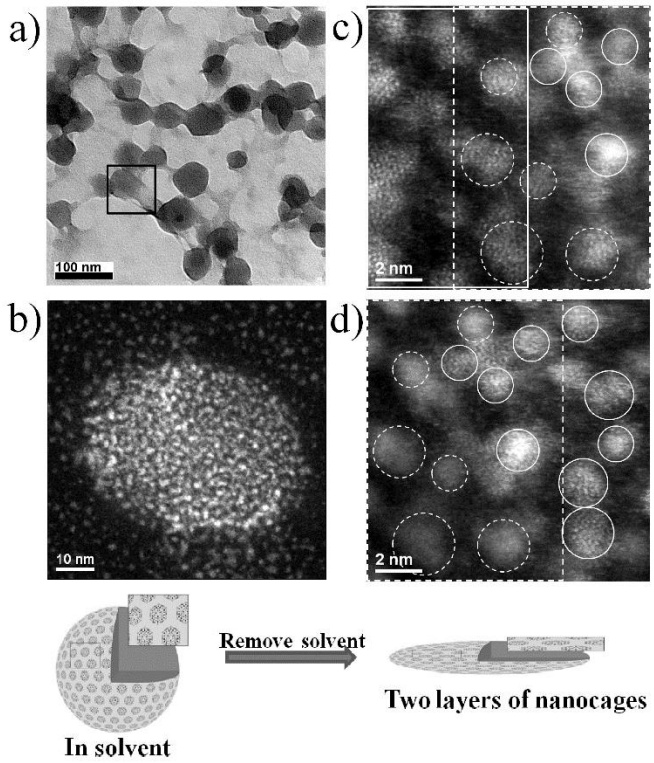
Collaborated with Dr. Stephen Z.D. Cheng

4. Metal-organic Nanocages and Cyclodrexins

The well-defined metal-organic nanocages are another type of valuable macorionic systems with many tunable features, loading/unloading properties and beyond.

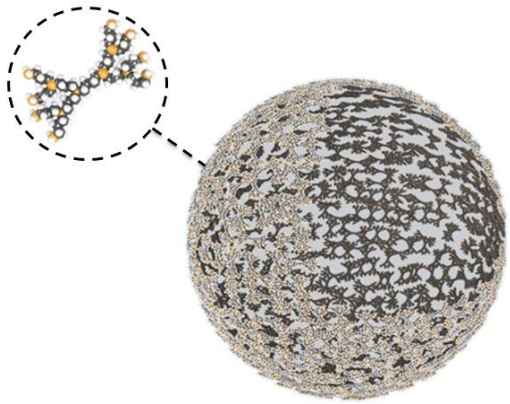


Li, D.; Zhang, J.; Landskron, K.; Liu, T. *J. Am. Chem. Soc*. **2008**, 130, 4226.



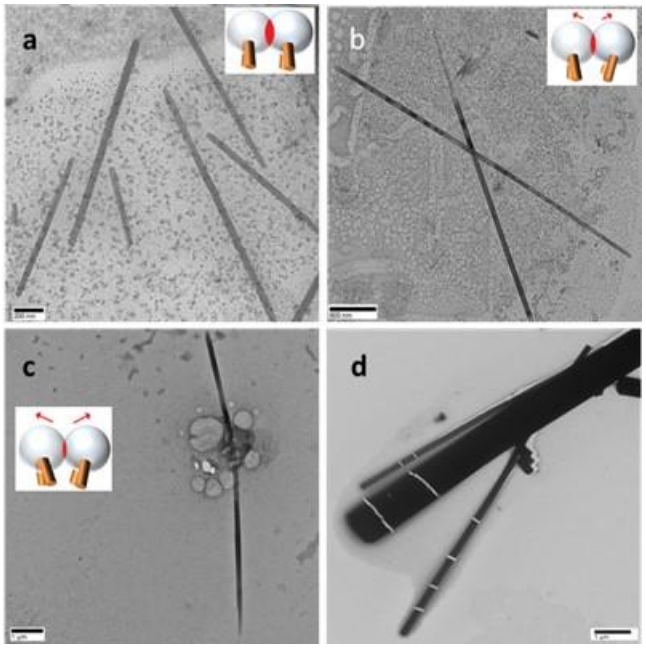
Li, D.; Zhou, W.; Landskron, K.; Sato, S.; Kiely, C. J.; Fujita, M.; Liu, T. *Angew. Chem. Int. Ed.* **2011**, 50, 5182.

5. Dentrimers and dentrimer-based complexes



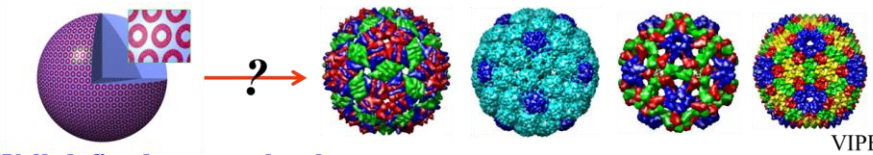
Dendrimers also form blackberry-type structures.

Eghtesadi, S.A.; Haso, F.; Kashfipour, M. A.; Lillard, R. S.; Liu, T. *Chem. Eur. J.* **2015**, 21, 18623 – 18630.



Zwitterionic dendrimer-surfactant form dynamic tubular structures with many varieties.

6. The Role of electrostatic interaction on the virus capsid formation
(collaborated with Dr. Yinan Wei, University of Kentucky)



VIPERdb

Well-defined supramolecular structure

Spherical, single-layer, relatively monodispersed.

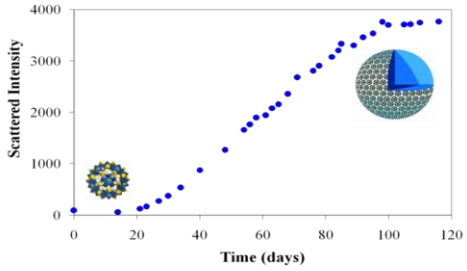
Average sizes does not change with initial concentration and temperature.

Do not further grow once reached the optimized size.

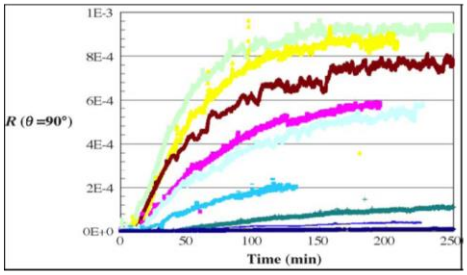
Similar mechanisms of formation

A speed-limiting stage – oligmer formation.

A lag phase: the delay time shows temperature and concentration dependence.

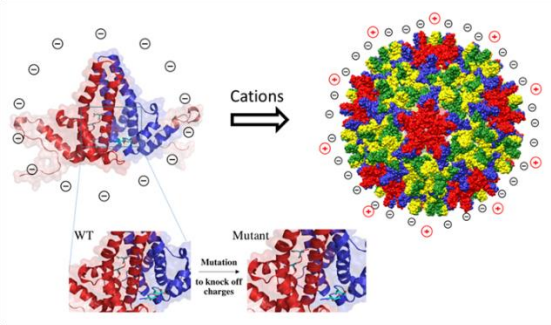


Zhang, J.; Li, D.; Liu, G.; Glover, J.; Liu, T. *J. Am. Chem. Soc.* **2009**, 131, 42.



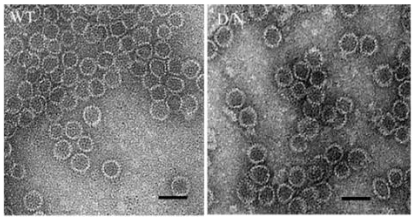
Casini, G. L.; Graham, D.; Heine, D.; Garcea, R. L.; Wu, D. T. *Virology 2004, 325, 320*

The role of electrostatic interaction in viral capsid assembly



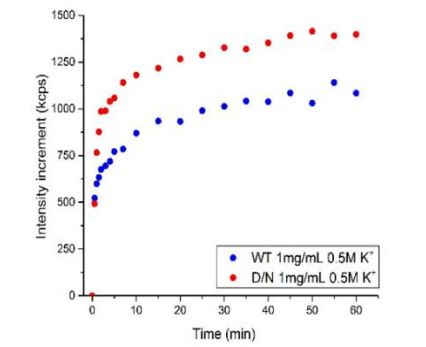
Hepatitis B virus (HBV) capsid:
120 dimers (*T*=4 symmetry, D=36nm, major);
90 dimers (*T*=3 symmetry, D=32nm, minor);
In vitro capsid formation triggered by cations (e.g. K^+, Ca^{2+}).

Reduce four charges on HBV capsid protein:
-14.4 to -10.4 at pH7.5.
No impact on protein structural conformation;
Avoid salt bridge and dimer-dimer contacts.



Scale bar 50nm

➢ WT and mutant capsids are of the same size.



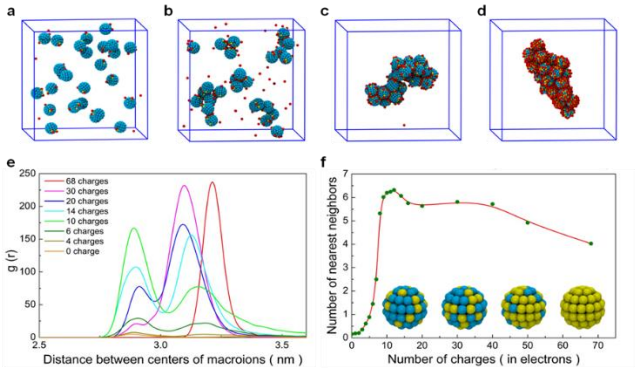
➢D/N capsids are more easy to assemble;
➢Less charges on D/N provide less repulsion than WT.

7. Course-grain simulations on the macroionic solutions – countereion mediated attraction and symmetry breaking! (with Professor Mesfin Tsige)

Course-grain simulations provide complete consistent results to the earlier experiments on the driving force, size change and the mechanism of the blackberry structure formation. In addition, an important symmetry breaking process is finally elucidated.

Course Grain Simulation – Effect of Macroionic Charge

2.5-nm size hollow clusters carrying 2, 6, 16 and 30 charges, respectively.



When they are charged – strong attraction after sometime.
When they are uncharged – stay as single clusters.
→ Counterions are critical for the self-assembly of macroions.

No charge or too many charges – weaker net attraction.
When charge >7, more charges, longer cluster-cluster distance.
→ Blackberry structure size can be tuned by macorionic charge density.

Liu, Z.; Liu, T.; Tsige, M. *Sci. Rep.* **2016**, *6*, 26595.