



CCP-SAS meeting.

19<sup>th</sup> June 2017

# Zebedde: Solvated polymer model construction for comparison with SAS data

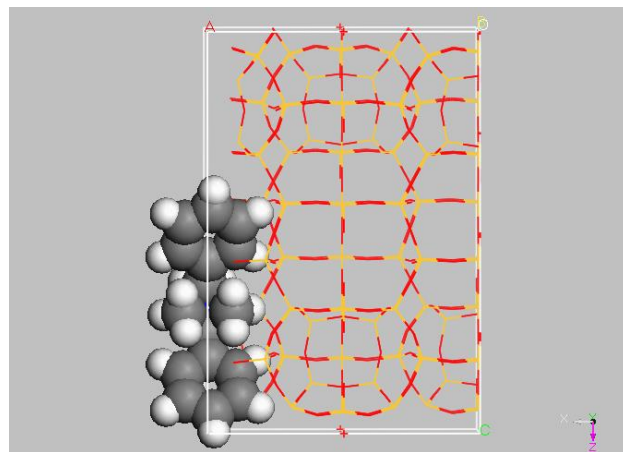
Alison Paul, Jamie Platts  
and David J. Willock

School of Chemistry, Cardiff University

# Template design

- Design : molecules are constructed from a data base of fragments with fragment additions being assessed by a cost function. (ZEBEDDE<sup>1</sup>).

Fragments: methane, ethane, propane, cyclohexane, phenyl, 5-rings *etc.*



- The cost function is the steric match between the template and the target zeolite. This was originally a simple sum of close contact distances but now the interaction system energy.
- Structures of promising candidates are geometry optimised.

1. D.W.Lewis, D.J.Willock, C.R.A.Catlow, G.J.Hutchings and J.M.Thomas, *Nature*, **382**, N<sup>o</sup> 6592, 604, (1996).

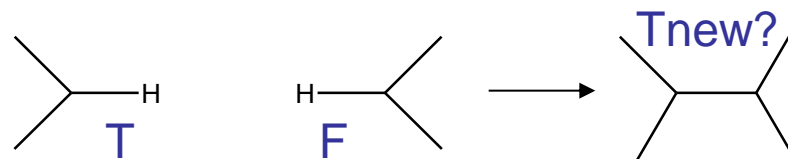
Under the control of the cost function new potential templates are grown within the target framework by randomly selected actions:

- **Shake**: The template is displaced along a random vector with respect to the host.
- **Rock**: The template is randomly rotated as a rigid body.
- **Bond twist**: A randomly selected bond joining fragments in the template is rotated.

- 
- **Build**: A new fragment is randomly selected from a library and is added to the existing template.

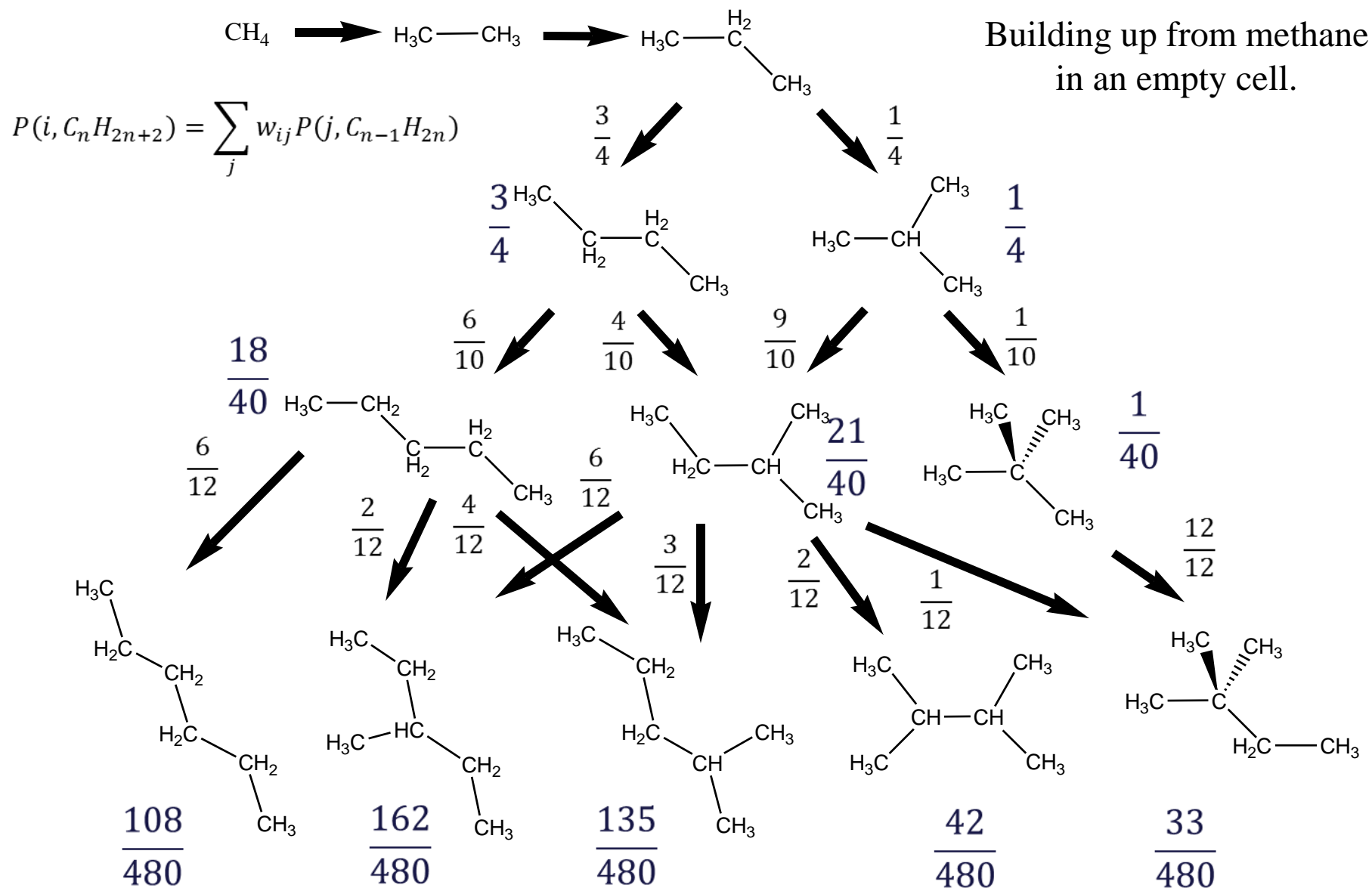
Test only after further “moves”.

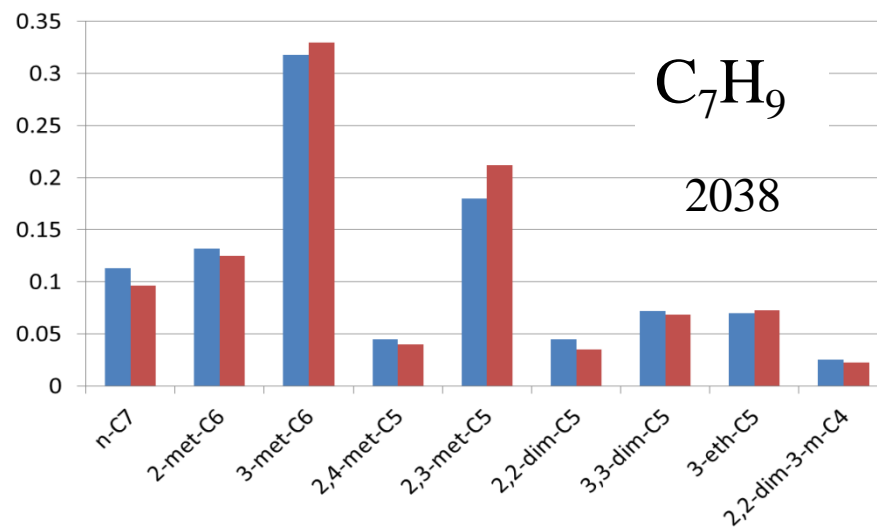
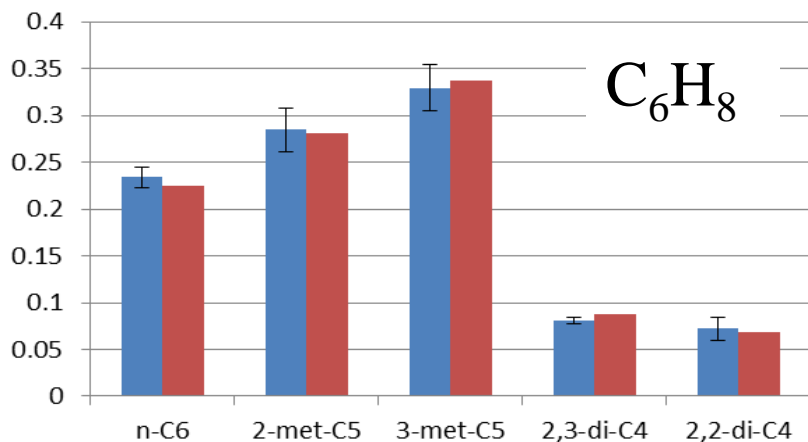
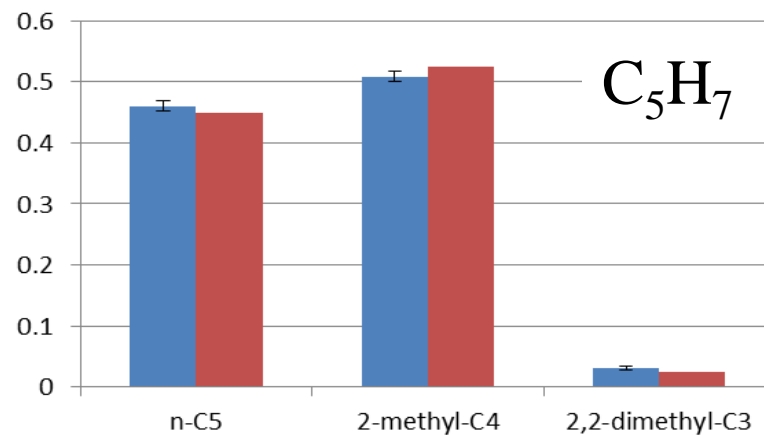
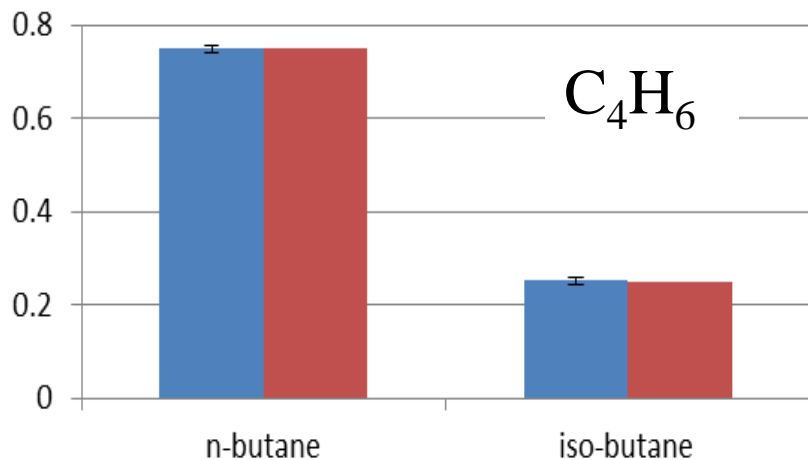
“test probability~0.5%”



- **Ring formation**: Atoms which are  $n^{\text{th}}$  order neighbours and are within a cutoff distance are joined, forming a ring.

# Test of random sampling

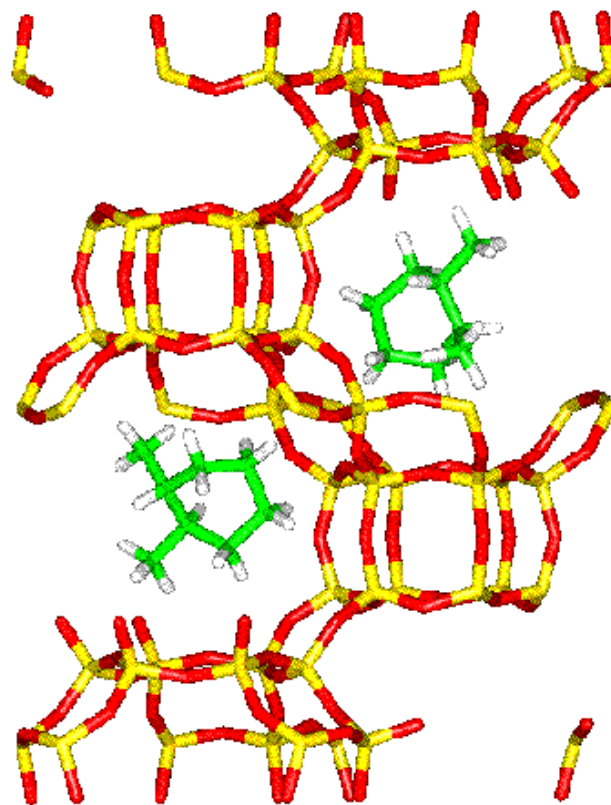
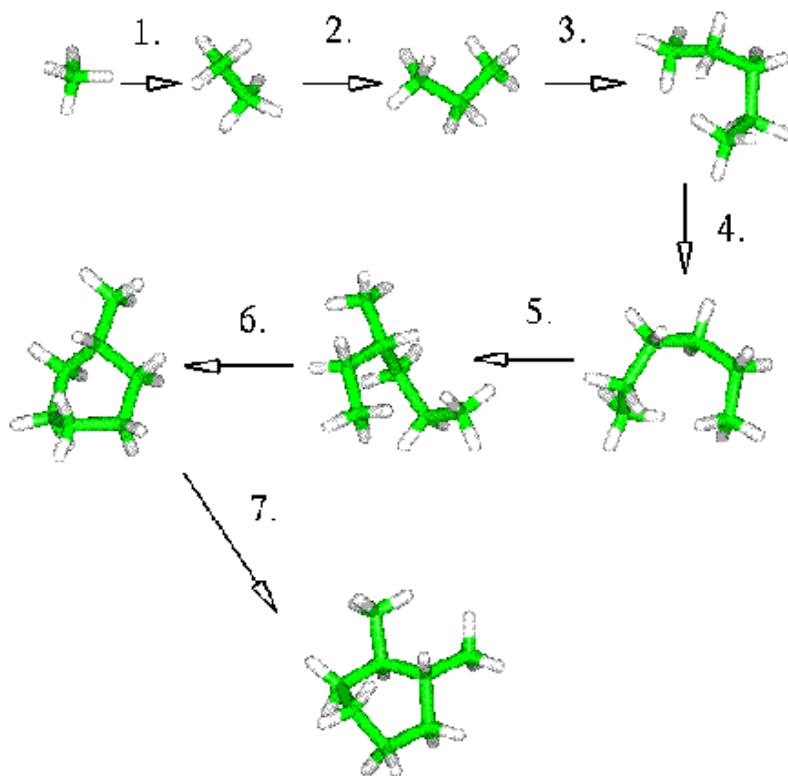




7118 sampled molecules in 5 batches, error bars from batch-batch standard deviation.

Blue : Zebedde samples, Red: expected.

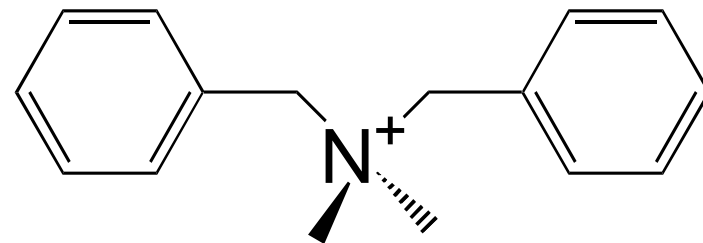
# Template design



D.W.Lewis, D.J.Willock, C.R.A.Catlow, G.J.Hutchings and J.M.Thomas,  
*Nature*, **382**, N<sup>o</sup> 6592, 604, (1996).

D.W.Lewis, G.Sankar, J.Wyles, D.J.Willock, C.R.A.Catlow & J.M.Thomas.  
*Angew.Chem.Int.*, **36**, 2675, (1997)

# Known template for EU-1

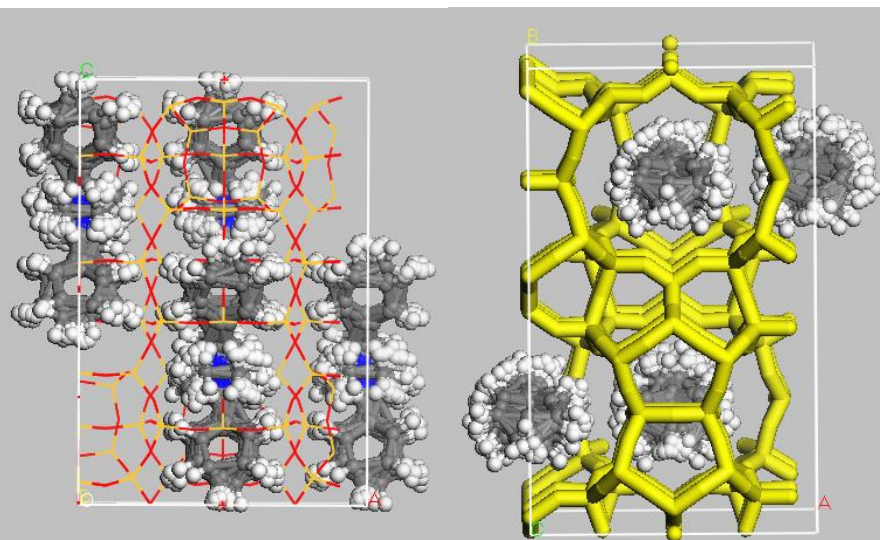
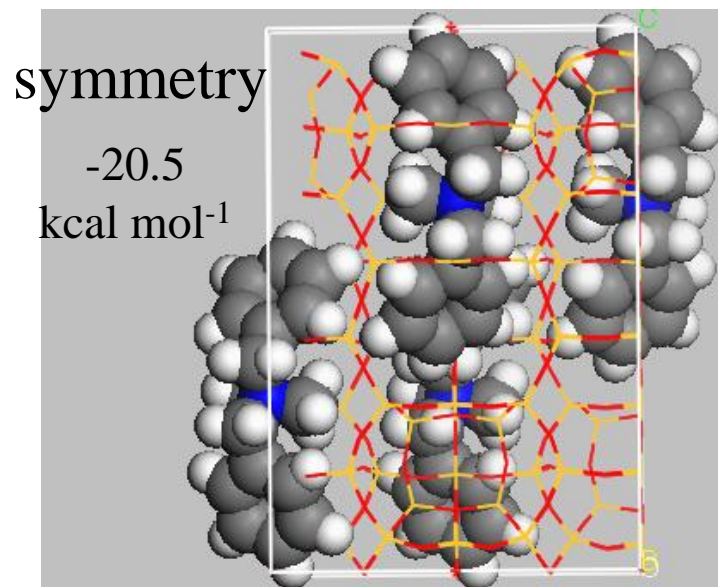
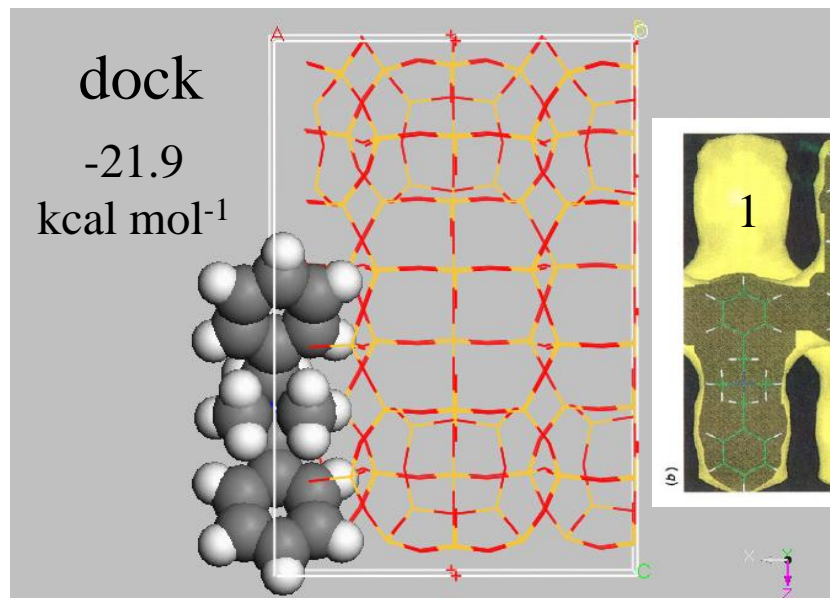


Docking known template:

Dibenzyldimethylammonium

Rigid molecule with shape complementary to side pocket.

Interaction between templates destabilises the packing by around  $1.4 \text{ kcal mol}^{-1}$



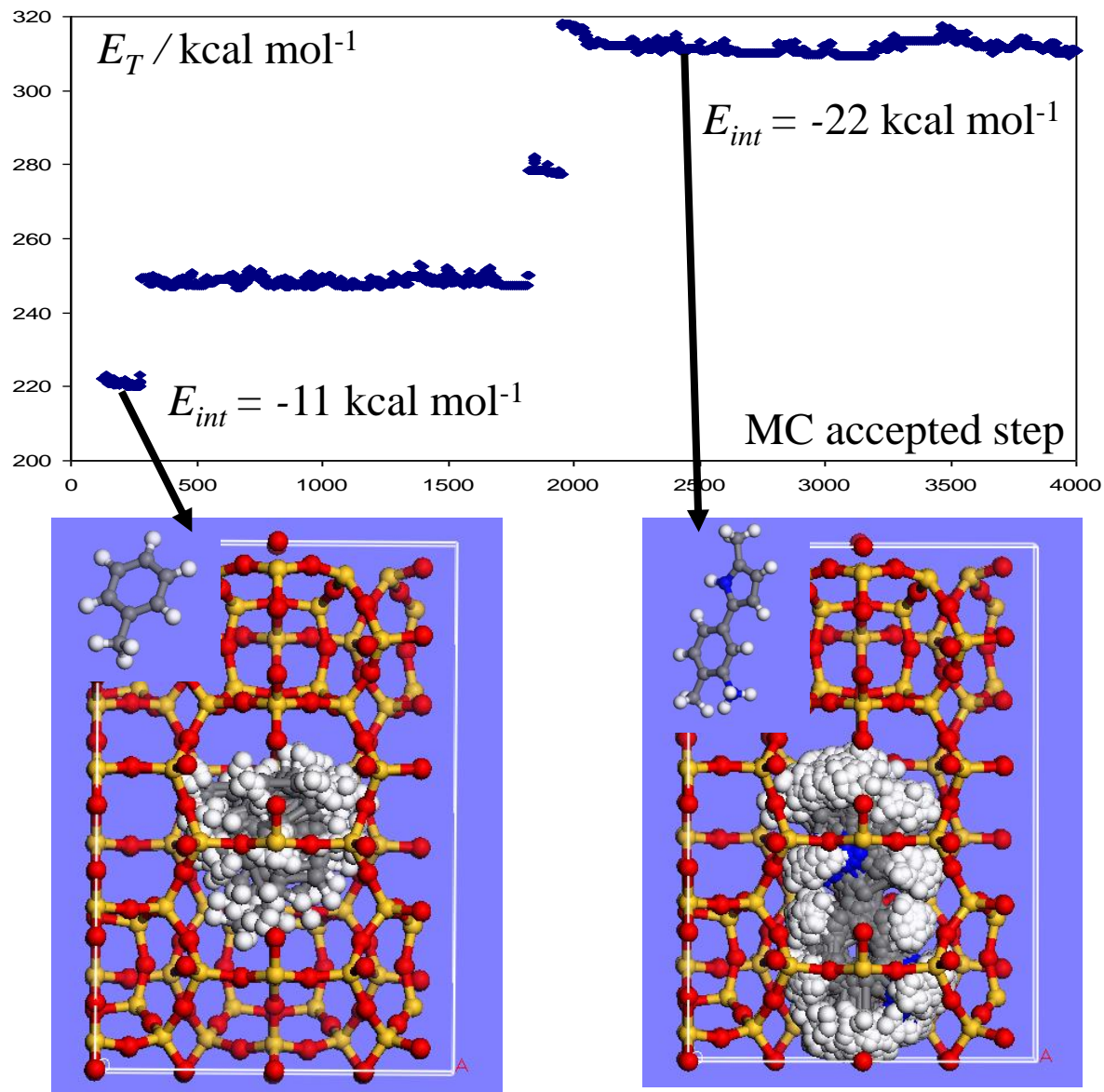
1. Cox and co-workers, *Farad Trans*, **92**, 2065, (1996).



## Energy terms

During a building run the total energy of the system tends to jump when new fragments are added.

So MC test for build events uses only the interaction component of the energy.





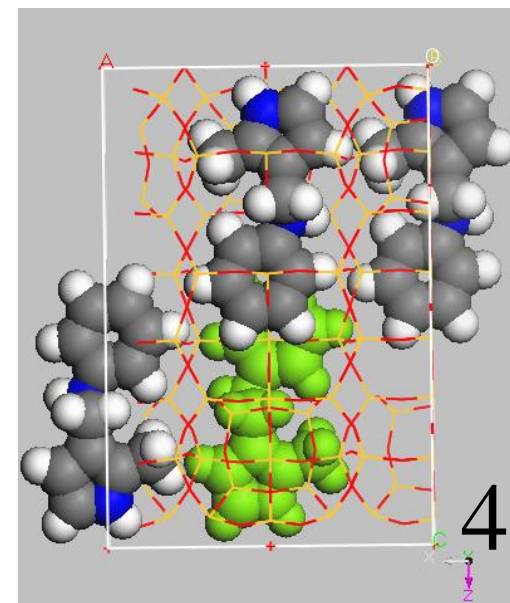
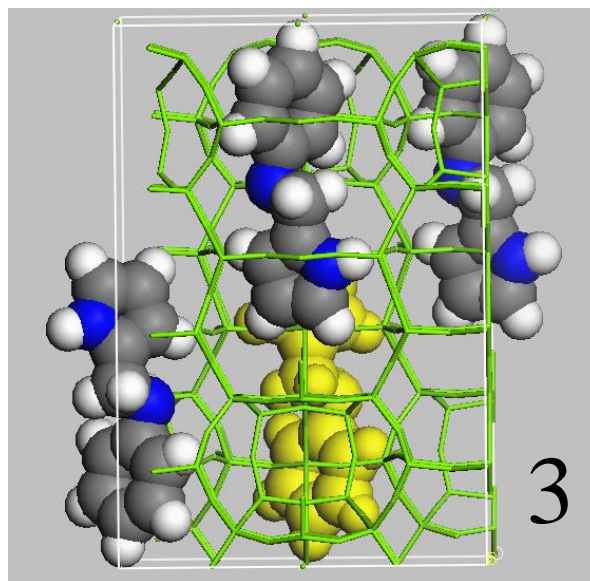
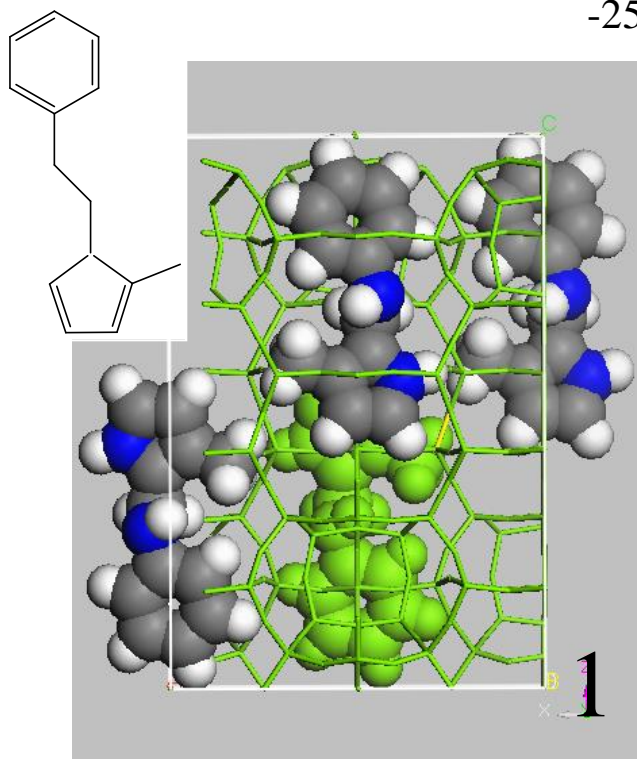
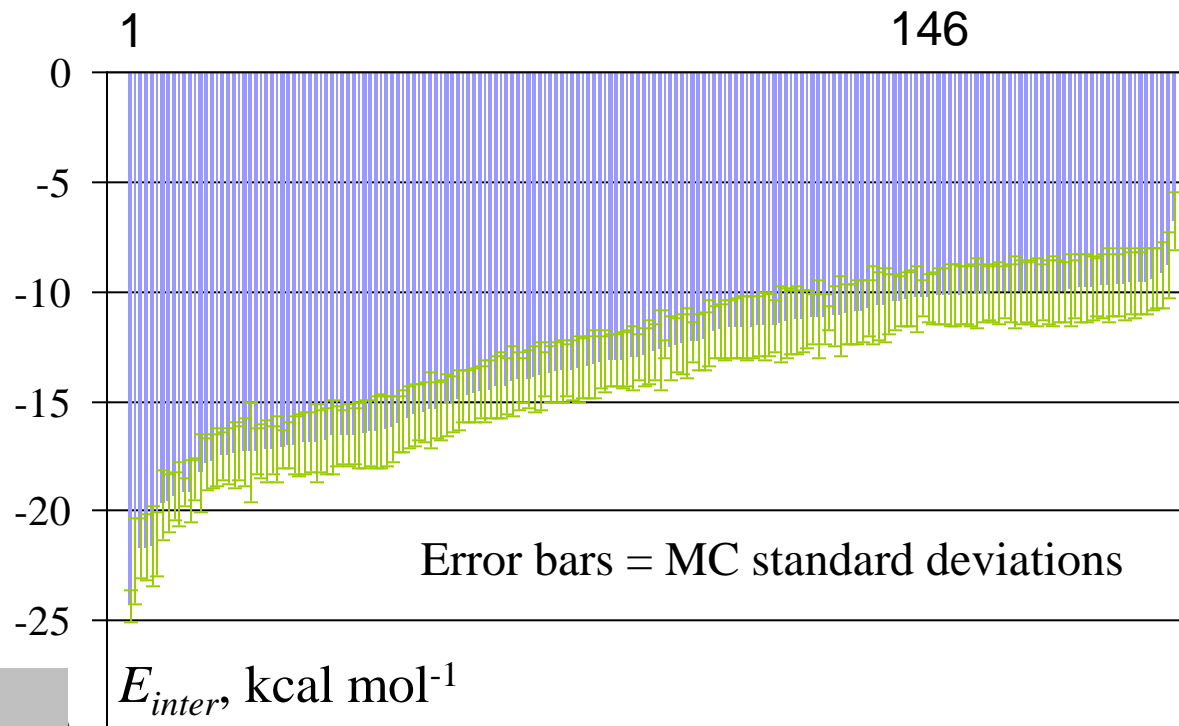
Combination of seeds &  
builds generates many  
structures:

50 seedings with  $\text{HC}_6\text{D}_5$

$5 \times 10^4$  MC trials,

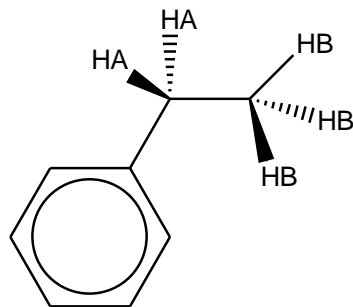
Gave 146 structures.

Ranked by interaction  
energy opposite.



## Test Case: Styrene

Density known to be around  $1 \text{ g cm}^{-3}$



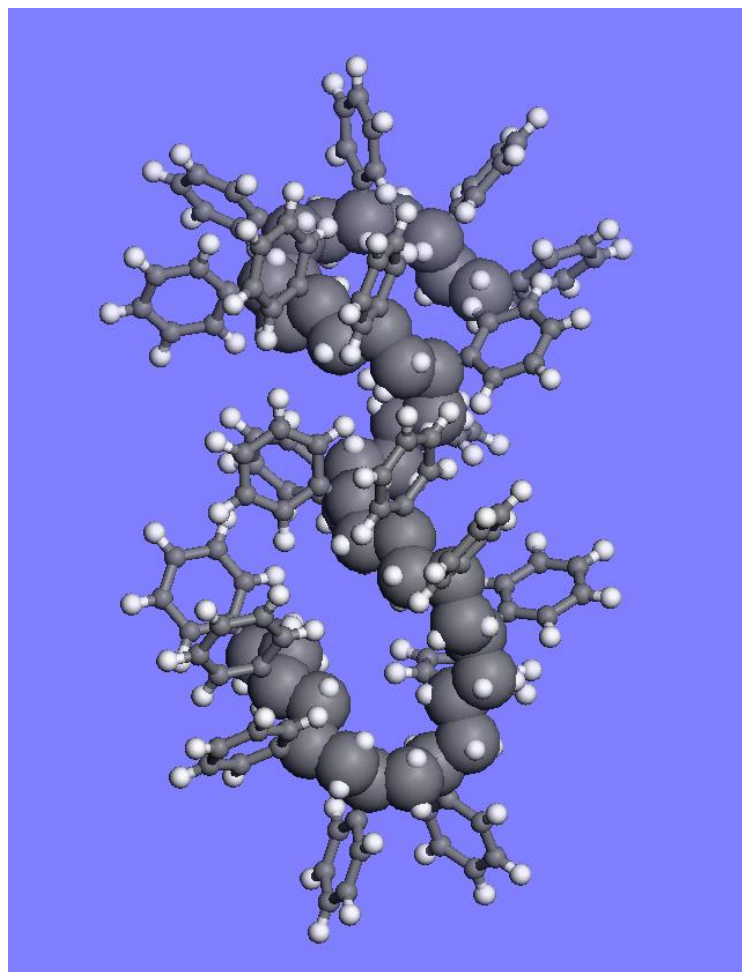
HA and HB defined to give chain growth.

Phenyl H atoms labelled H simply ignored.

Structure forms twisting chain with helical portions.

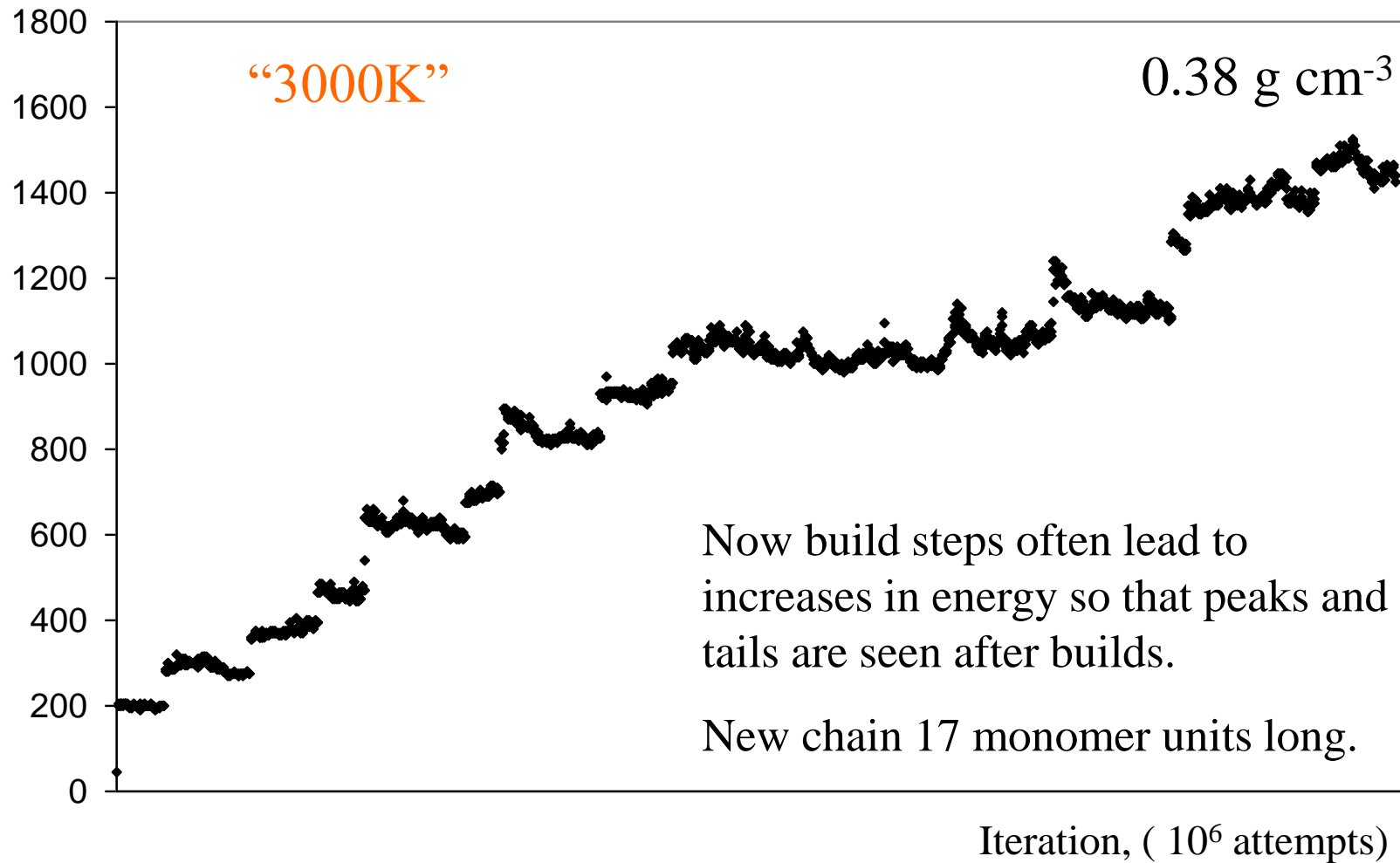
35 monomer units in  $30 \text{ \AA}$  Cube

However, density is low,  $0.23 \text{ g cm}^{-3}$ .



## Growth of third chain

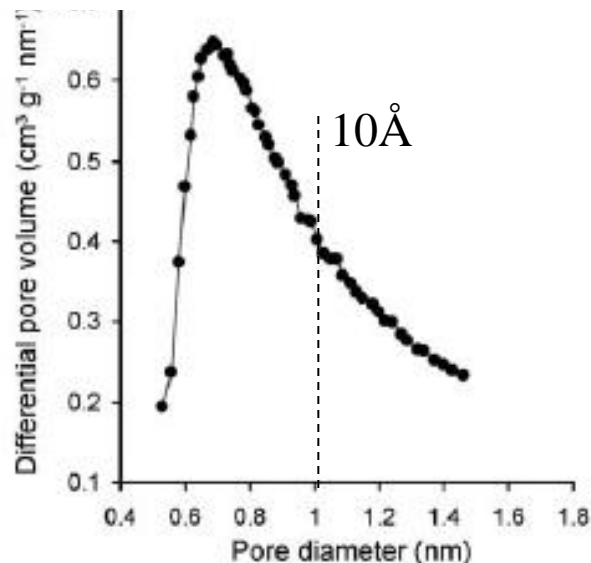
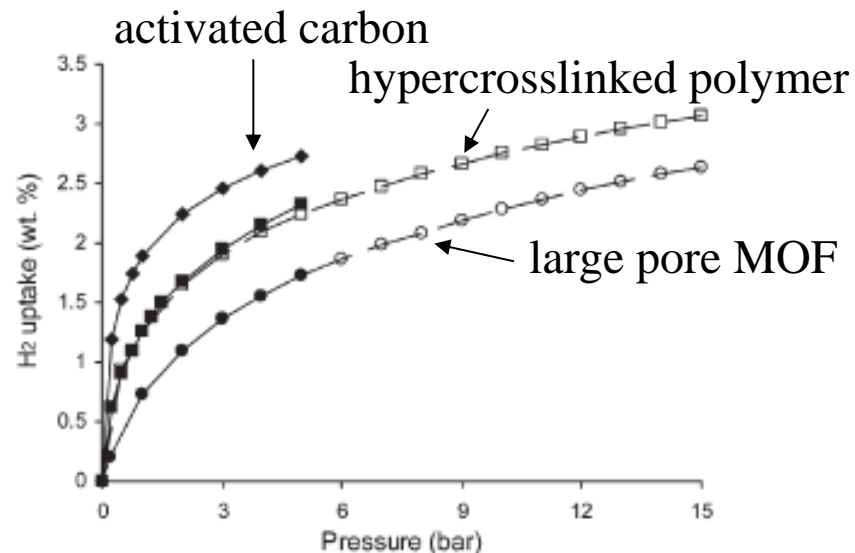
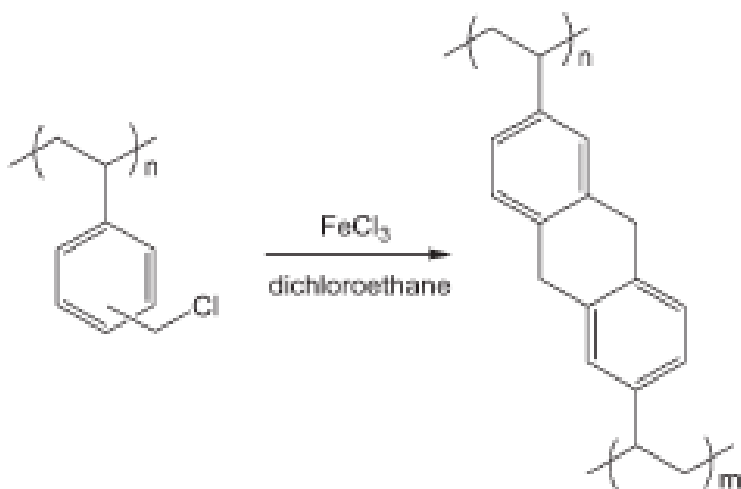
Total Energy/ kcal mol<sup>-1</sup>



# Polymer networks for H<sub>2</sub> storage applications

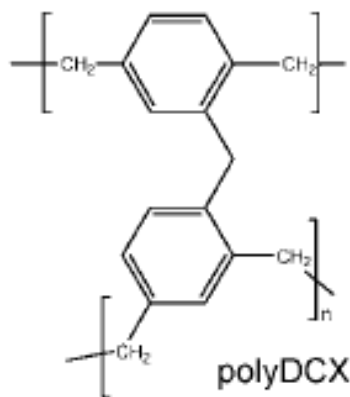
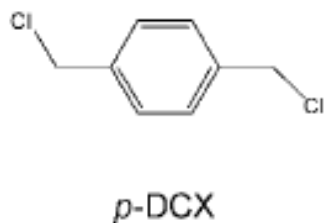
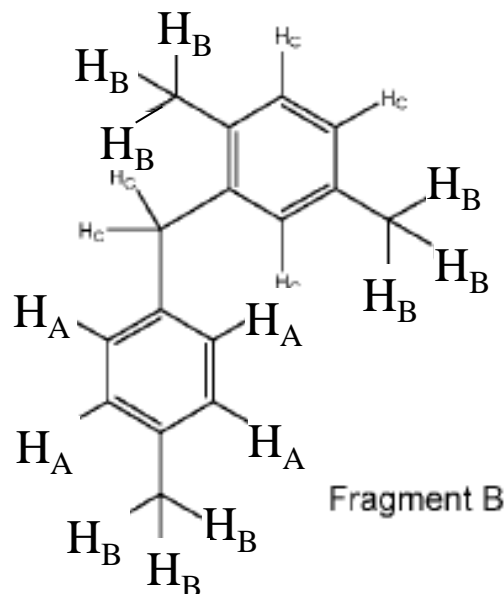
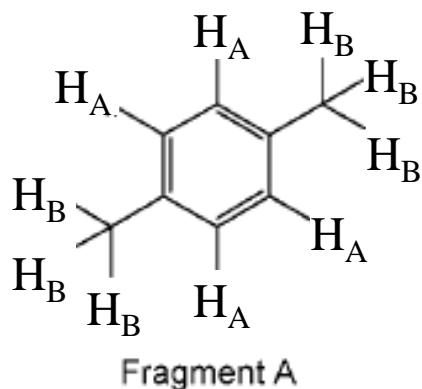
Use of H<sub>2</sub> in fuel cell powered vehicles will require on board storage of the fuel.

US Department of Energy has set a target of 6.5 wt.% sorption by mass for a usable H<sub>2</sub> storage device.



Jun-Young Lee, Colin D. Wood, Darren Bradshaw, Matthew J. Rosseinsky and Andrew I. Cooper, *Chem. Commun.*, 2006, 2670–2672

# Amorphous Microporous Polymer Network



Self condensation of  
poly-dichloroxylylene (*p*-DCX).

NMR suggests very few tetra-  
substituted phenyl rings.

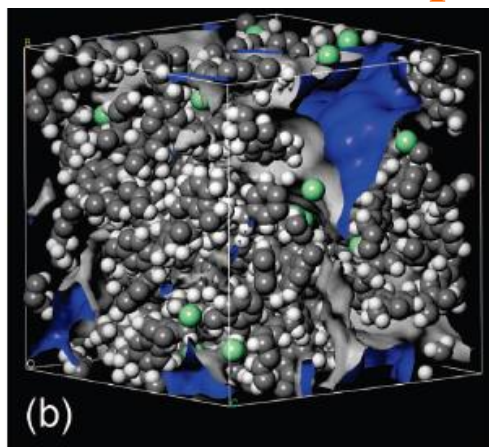
Build rule:

C-H<sub>A</sub> can join to C-H<sub>B</sub> only.

Once new bond formed H atoms  
in ring and methyl involved are  
deactivated.



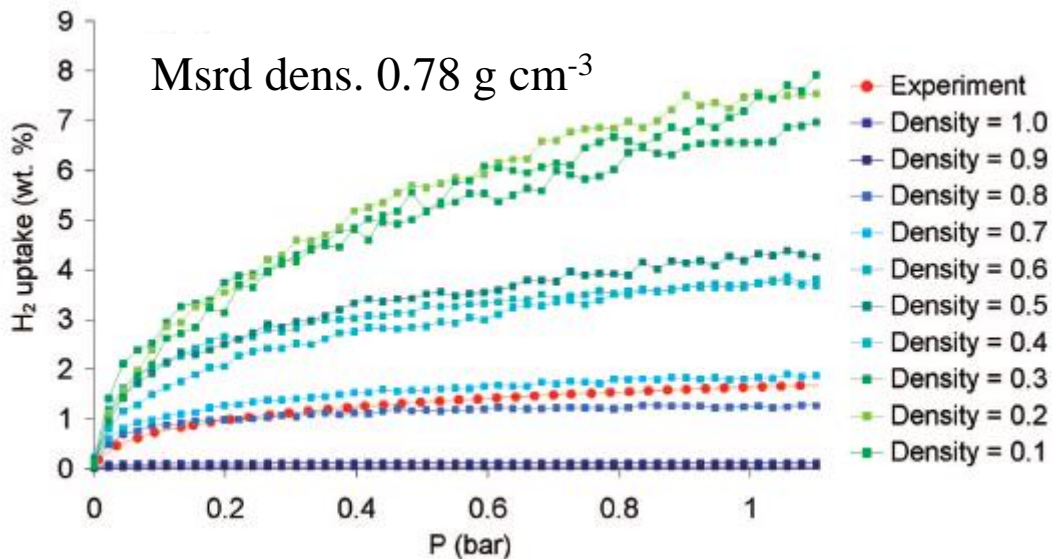
# Amorphous Microporous Polymer Network



Solvent  
accessible  
surface

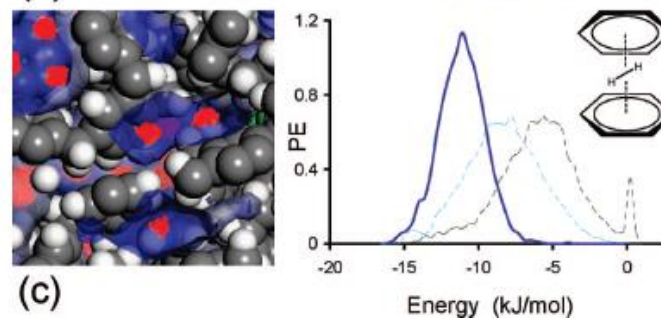
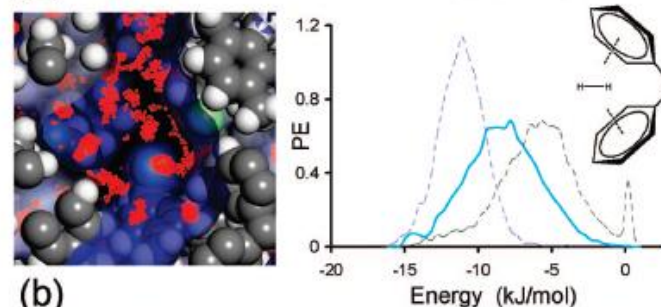
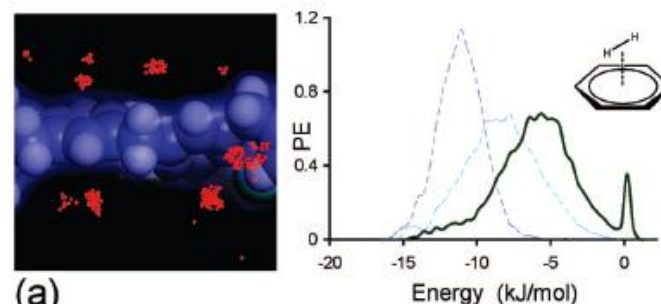
H<sub>2</sub> uptake modelling

Msrd dens. 0.78 g cm<sup>-3</sup>



H<sub>2</sub> ... benzene this method -1.8 kJ mol<sup>-1</sup>

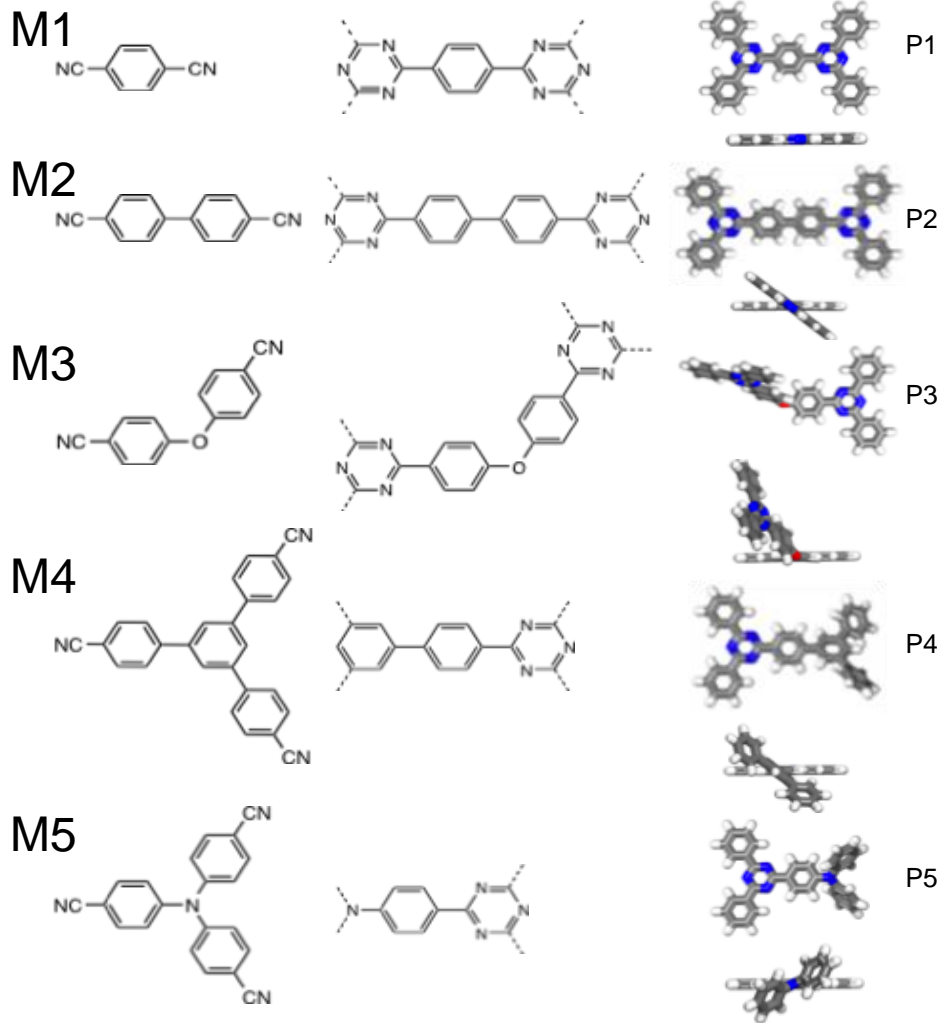
<sup>1</sup>Correlated QM, -3.8 to -5.0 kJ mol<sup>-1</sup>



A. Trewin, D. J. Willock and A. L. Cooper, *J. Phys. Chem. C*, 112, 20549, (2008)

1. Lochan *et al.*, PCCP, 8, 1357, (2006), Hubner & Kloppe, *J. Phys. Chem. A*, 111, 2426, (2007).

# Node-struts: Covalent Triazine-based Frameworks (CTFs)



Triazine will polymerise with molecules containing cyano groups in the presence of strong acids.

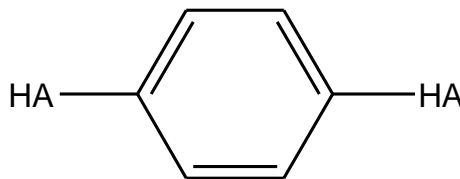
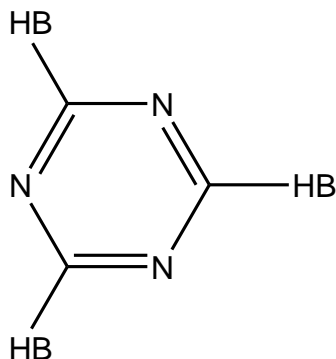


Microwave heating is thought to increase the reversibility of bond formation and so allow access to the thermodynamic product.

A. I. Cooper and co-workers, *Advanced Materials*, **24**, 2357, (2012).



## Simulation protocol:



Zebedde run: (24 hrs)

$5 \times 10^6$  move/modification attempts.

prob. test 0.5 %

rock step  $30^\circ$

Build 50, Shake/Rock/Twist 100.

PCFF forcefield.

3 - 18 seed molecules,

50 Å cubic simulation repeat unit.

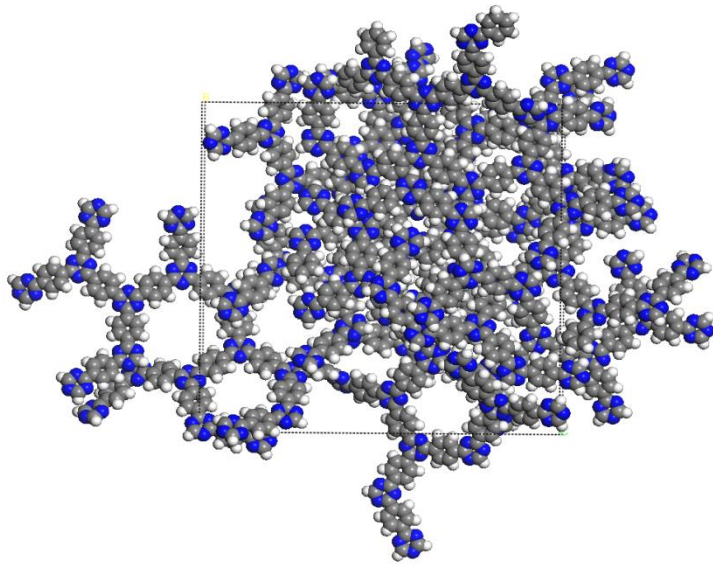
output: Insight car file converted to dl\_poly CONFIG & FIELD files using [dlpoly\\_prep](#).

dl\_poly run: NVE ensemble, 300K, 50 ps equil. + 1 ns production dynamics. (8 hrs)

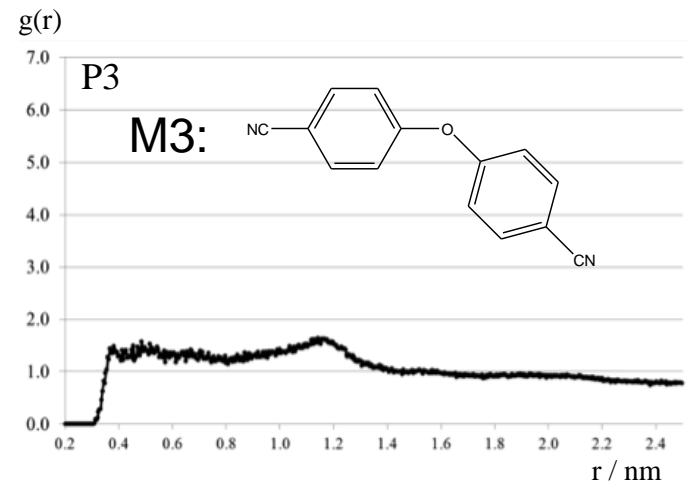
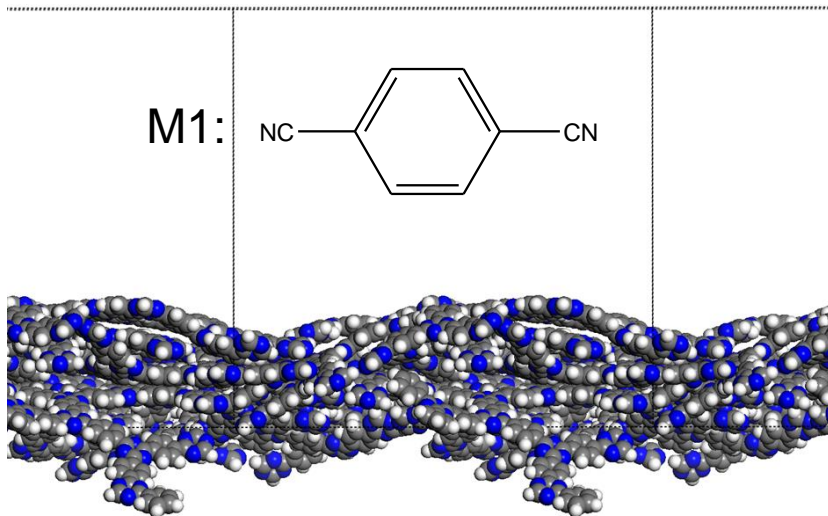
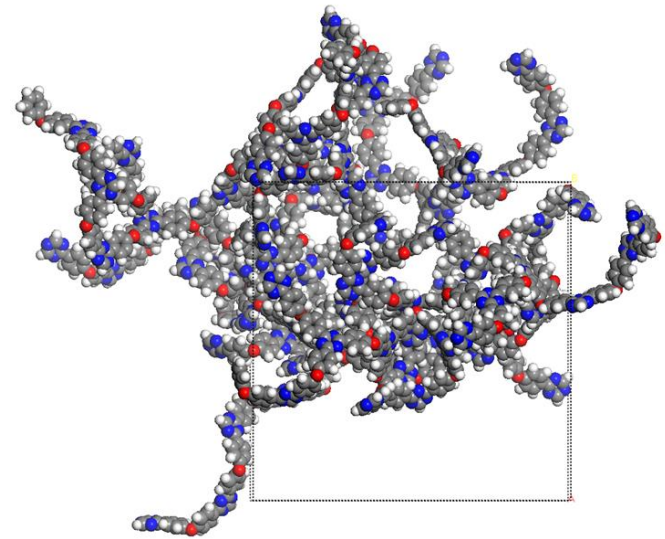
Typical system size produced: 105 triazines, 28 kDa ( 3 networks ).

C. Reece, D.J. Willock and A. Trewin,  
*Phys. Chem. Chem. Phys.*, **17** (2), 817–823, (2015).

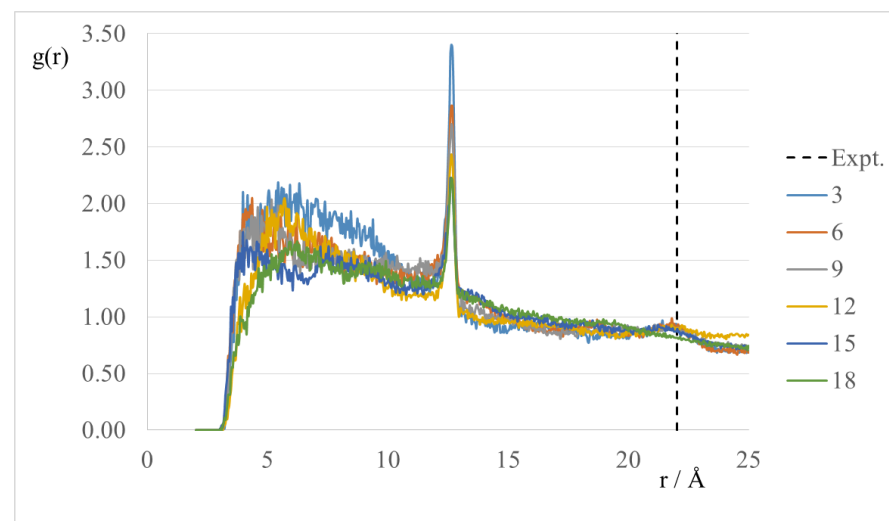
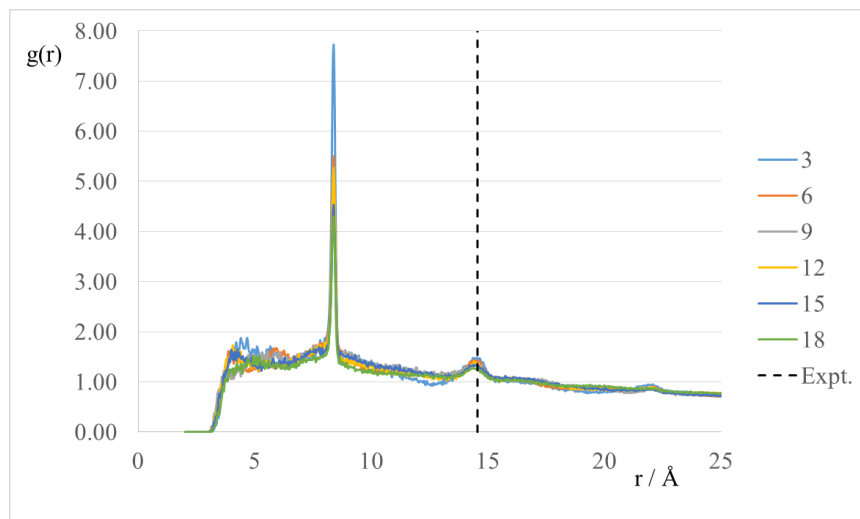
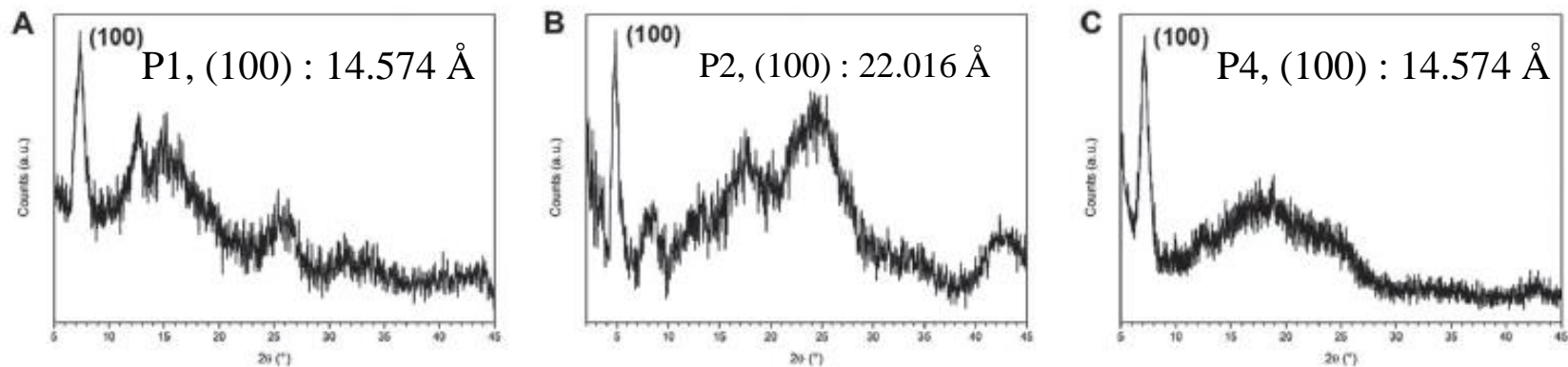
P1 Forms planar sheets with hexagonal ordering:



P3 Forms 3-D network:



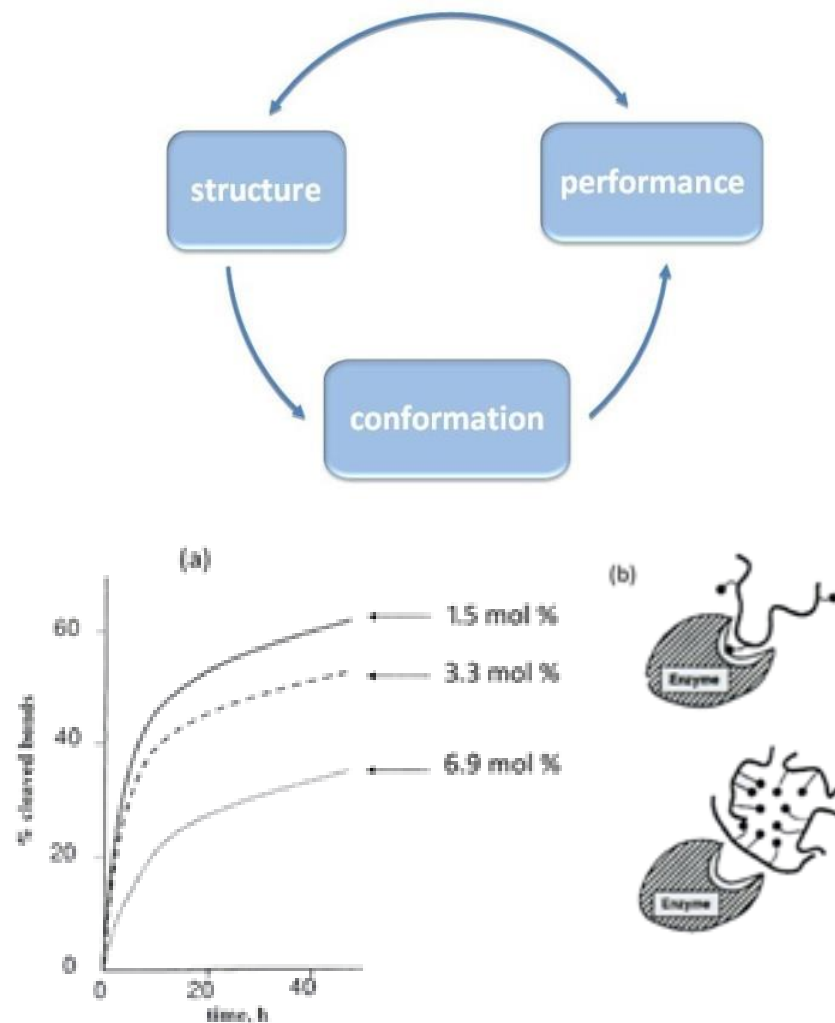
P1, P2 & P4 show some degree of order, P3 and P5 less so:



PXRD: A. I. Cooper and co-workers, *Advanced Materials*, **24**, 2357, (2012).

# Polymer-drug conjugates

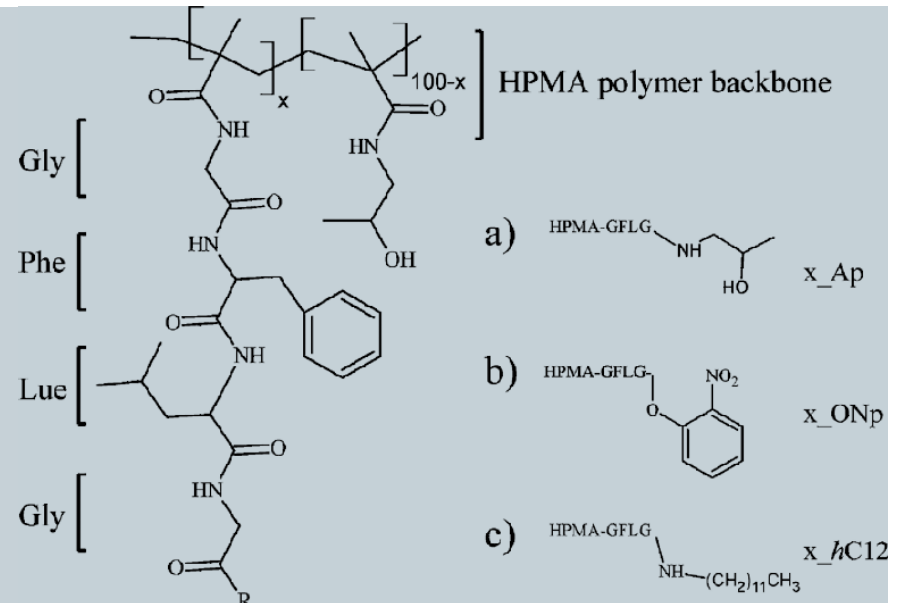
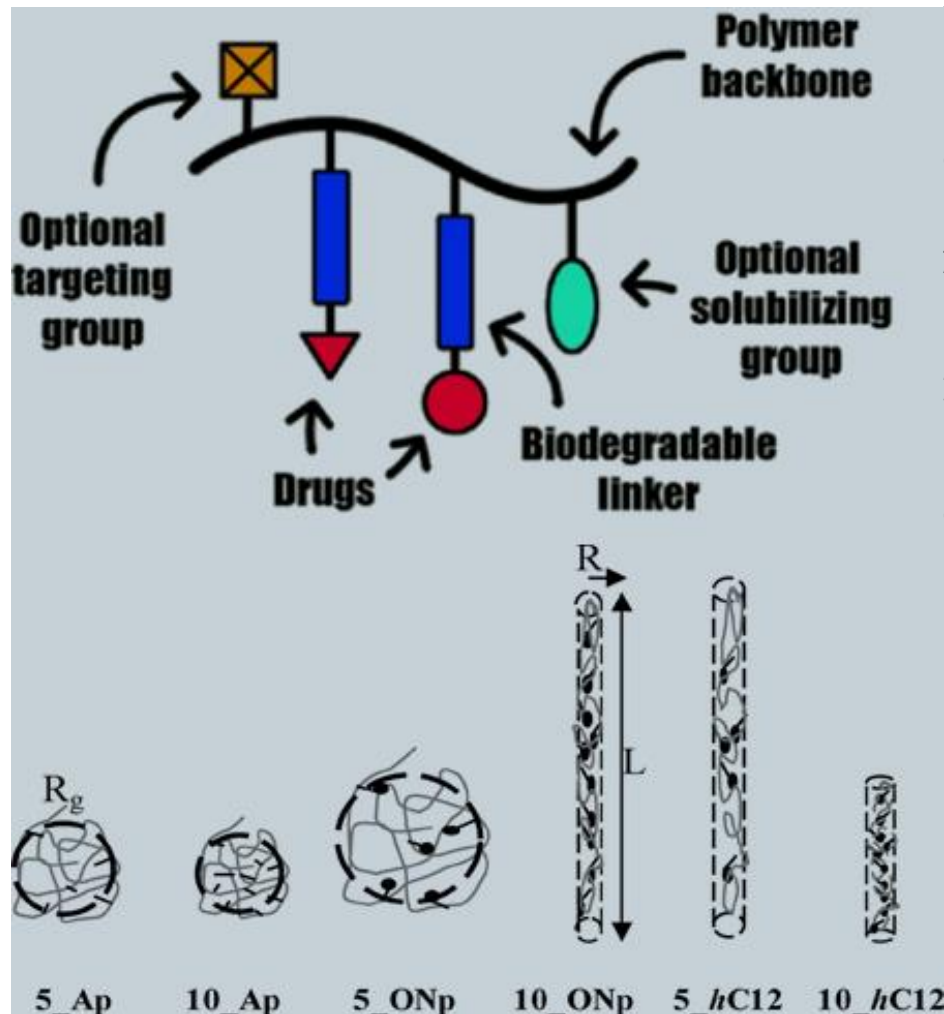
- The conformation that polymer-drug conjugates adopt in solution has a significant effect on their performance as drug delivery systems[1]
- Various combinations of polymer-drug conjugates have been investigated by SANS(Small Angle Neutron Scattering).
- Combining of molecular modelling techniques with experimental methods data analysis can provide reliable model for polymer-drug conjugate characterisation[2]



[1] *Biomacromolecules* **11**, 1978–1982 , (2010).

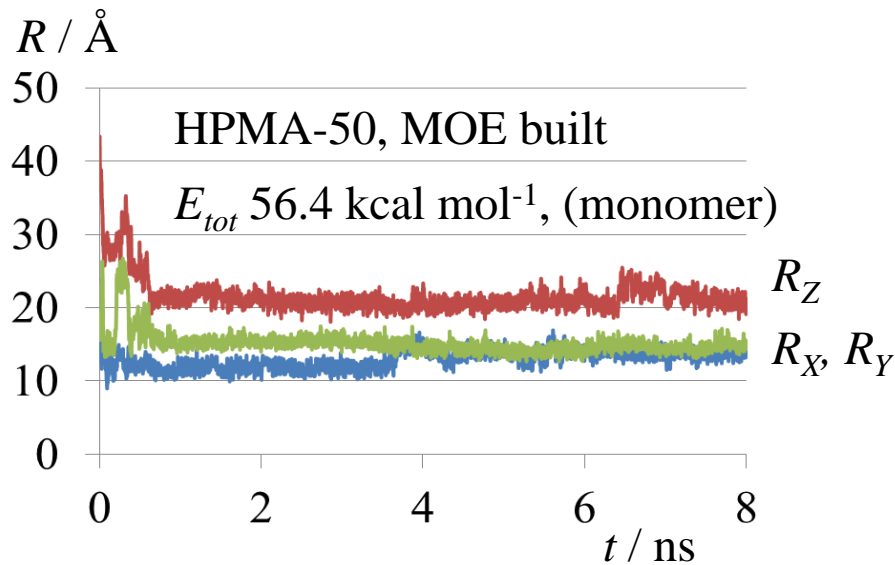
[2] *J Comput Aided Mol Des.*, **26**, 15–26., (2012).

# N-(2-hydroxypropyl) methacrylamide HPMA



- well characterised
- non toxic
- water soluble
- biodegradable
- must have binding sites for desired drug to be attached

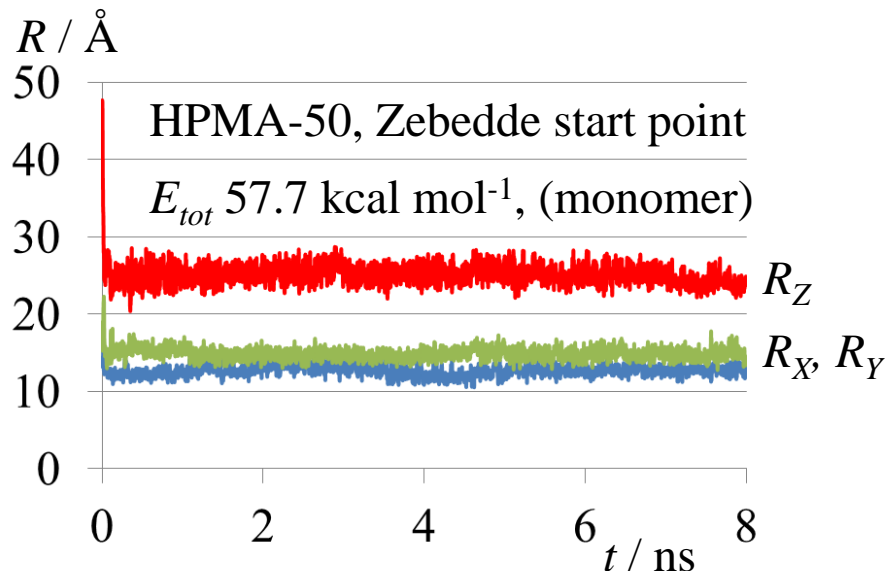
## HPMA-50 comparison of starting points



MD runs comparing elongated (MOE) and Zebedde generated start points.

NVT ensemble, 310 K,  
AMBER99 forcefield  
Reaction field implicit water ( $\epsilon = 80.1$ ).

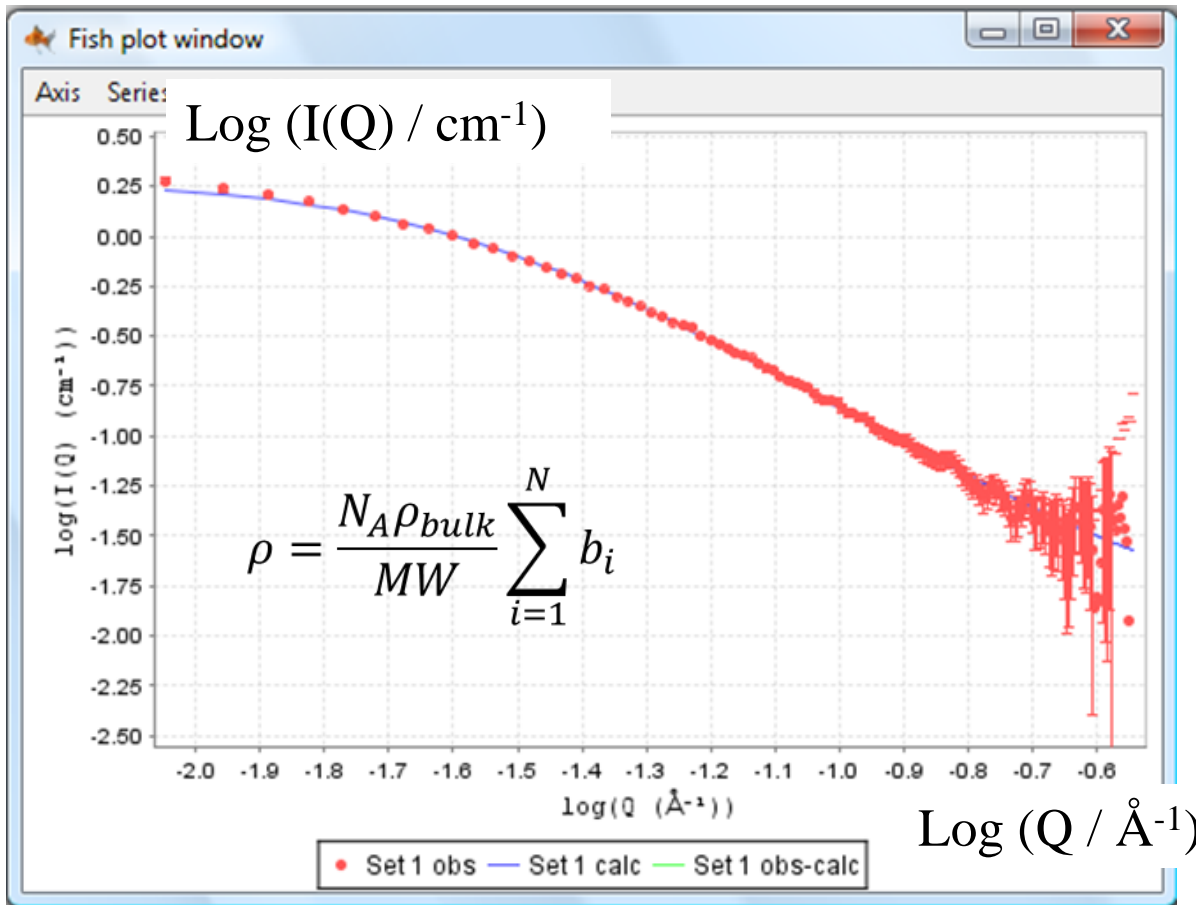
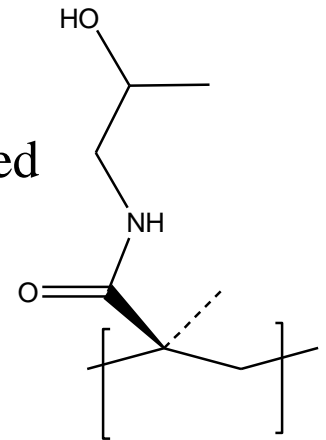
MOE start point eventually gives more spherical polymer shape.



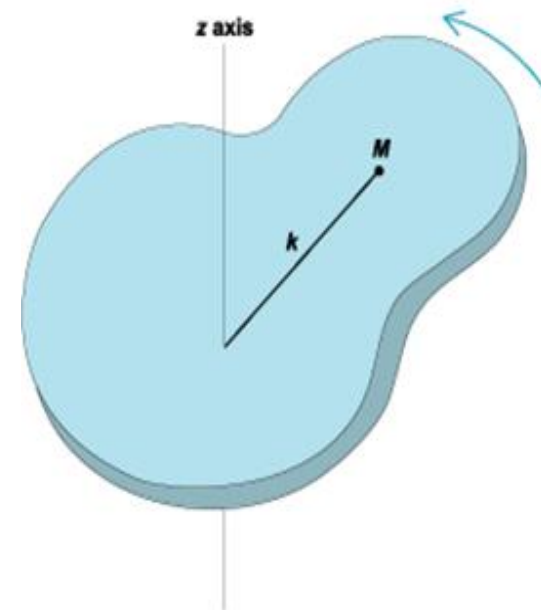
Zebedde start point rapidly achieves constant shape parameters.

# SANS data

- N-(2-hydroxypropyl) methacrylamide (HPMA) is a polymer used as carrier in drug delivery systems.
- MD compared with small angle neutron scattering (SANS) data.



$$R_g = \left( \frac{\sum_i \|\mathbf{r}_i\|^2 m_i}{\sum_i m_i} \right)^{\frac{1}{2}}$$

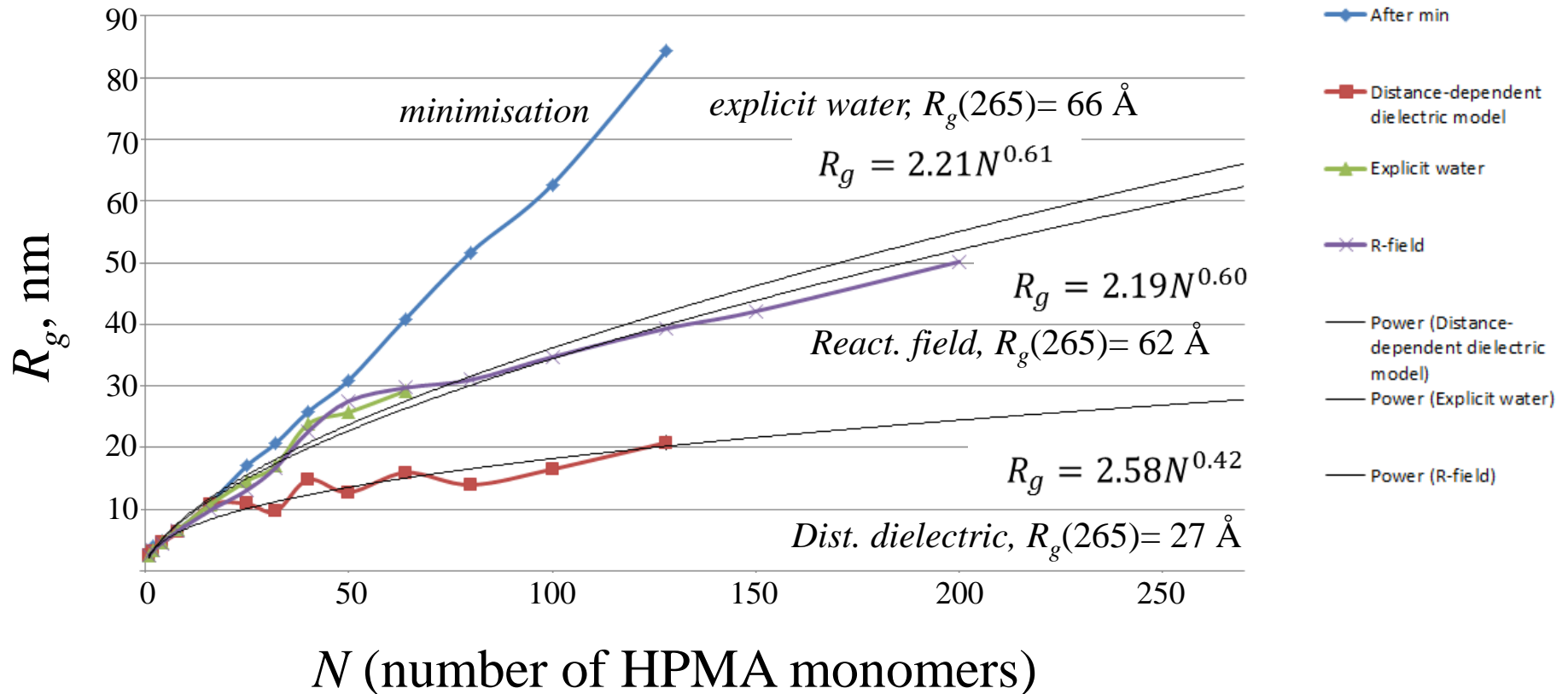




# Flory power law approximation

Flory used self avoiding random walks to show that a polymer conformation should be expected to lead to a radius of gyration that depends on monomer number via a power law:

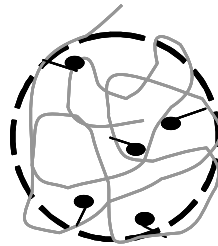
$$R_g = R_0 N^\nu \quad \text{With } \nu = 0.6 \text{ for a "good" solvent}$$



SANS: HPMa-265,  $R_g = 75 \pm 3 \text{ Å}$

# Shape Information: Moments of inertia

Ellipsoid  
dimensions:  
 $R_X / R_Z = 0.36$   
 $R_Y / R_Z = 0.43$   
 $R_Z / R_Z = 1.00$



$R_X / R_Z = 0.02$   
 $R_Y / R_Z = 0.02$   
 $R_Z / R_Z = 1.00$

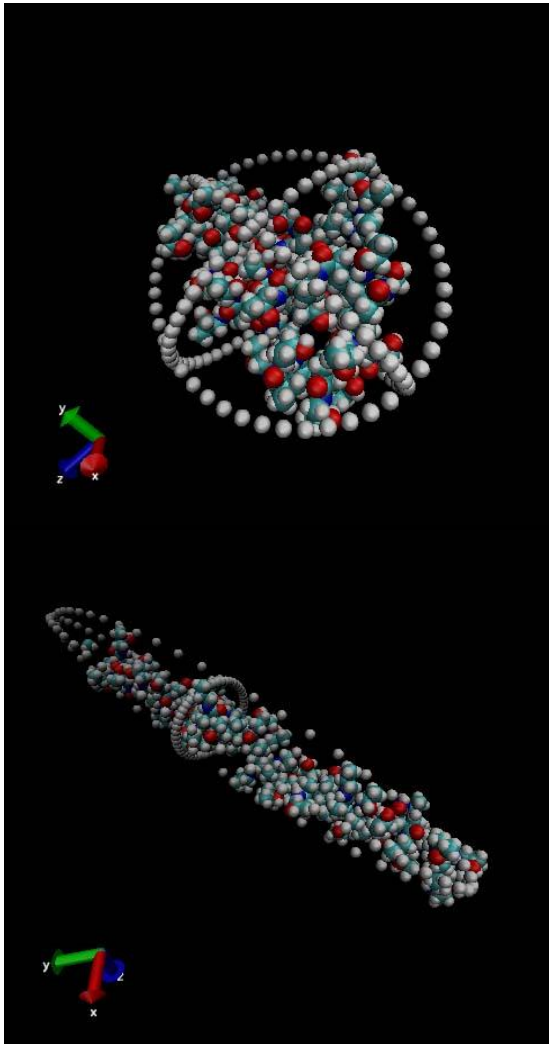


Neutron scattering is controlled by the scattering length density:

$$\rho = \frac{N_A \rho_{bulk}}{MW} \sum_{i=1}^N b_i$$

To describe the observed “shape” we can use the scattering factors,  $b_i$ , in place of mass in the moment of inertia matrix.

This allows us to define a set of axes and determine the dimensions of an ellipsoid that represents the shape using the furthest atom distance in each direction at each frame of the MD trajectory.



## Comparison with SANS data

Conjugate	Vol. Calc. / $10^5 \text{ \AA}^3$	Vol. SANS / $10^5 \text{ \AA}^3$	$V_{\text{calc}}/V_{\text{SANS}}$	Aspect ratio calc.	Aspect ratio SANS
HPMA-C6-F-10	1.275	1.024	0.803	2.56	4.83
HPMA-C8-OH-10	1.232	1.024	0.831	1.95	4.83
HPMA-C6-OH-10	1.122	1.125	1.003	1.70	4.38
HPMA-C6-10	1.052	2.658	1.975	1.43	3.48
HPMA-C12-5	1.196	7.654	6.397	1.54	7.80

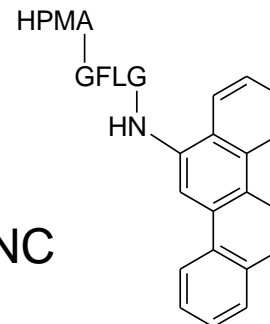
The volume from the MD ellipsoids and cylinders fitted to SANS measurements show reasonable agreement for first three cases.

For HPMA-C6-10 and HPMA-C12-5 cases data suggests that there is agglomeration of polymer in the experimental case.

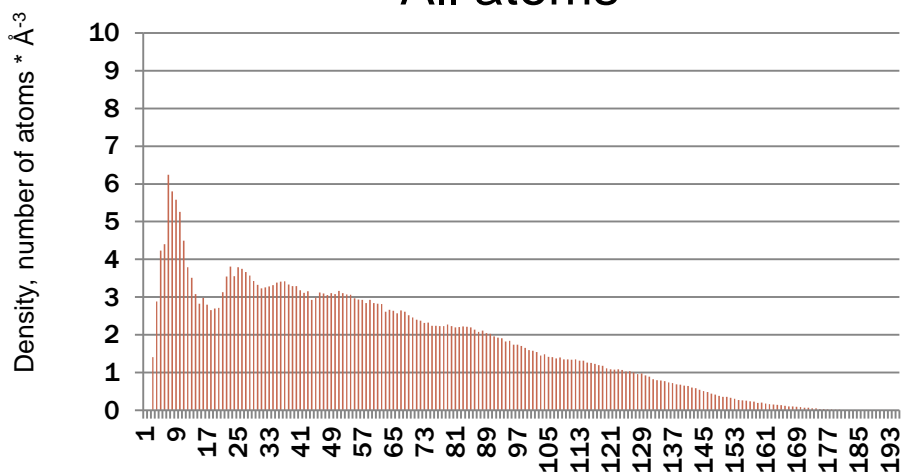
Aspect ratios for single chains show more elongated structures than would be expected from the simulations.

# Composition profiles

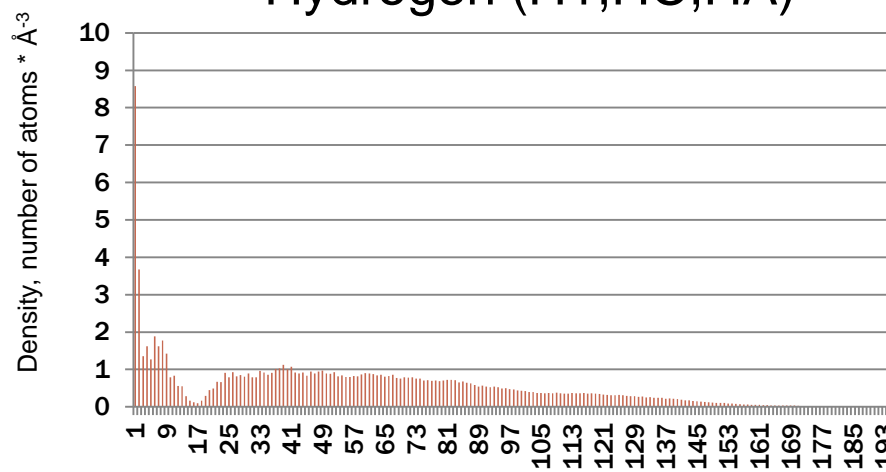
Density profiles for HPMA-ANC



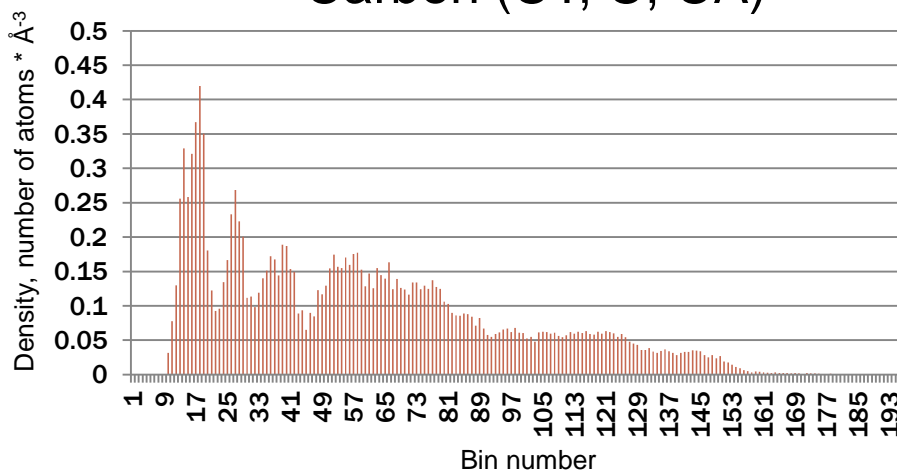
All atoms



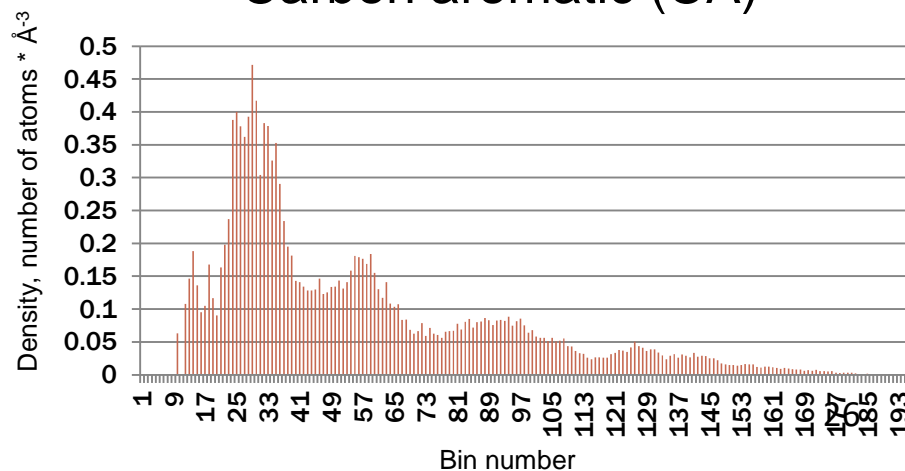
Hydrogen (H1,HC,HA)



Carbon (CT, C, CA)



Carbon aromatic (CA)





# Acknowledgements

## Cardiff

Glib Meleshko\*  
Niamh W. Hickey  
Filippo Marozzelli  
Adam Thetford

Alison Paul  
Jamie Platts  
Graham Hutchings

## Machines

“Mott”, RAL  
Merlin and Raven via the Cardiff ARCCA division.  
HECToR and ARCHER through the Materials Consortium.

## Liverpool

Abbie Trewin  
Andy Cooper

Kim Jelfs

## UCL

Dewi W. Lewis,  
A.J.W. Lobo

## Bath

Andrew M<sup>c</sup>Cluskey

## Funds

EPSRC  
JM  
SASOL

