ADVANCED MANUFACTURING & GRAPHENE

FFG Workshop

Chiral resolution of drug molecules by functionalized, single-atom-thick membranes

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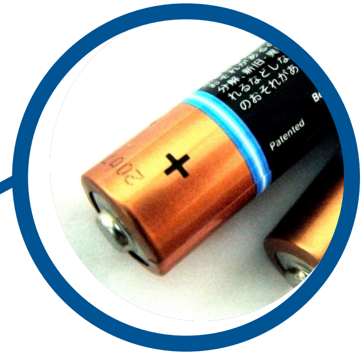
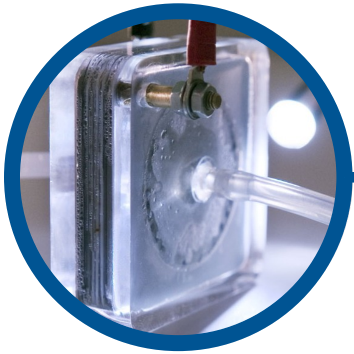
TU Graz
Graz University of Technology

Nanomaterials and their applications



The scope:

- Batteries
- **Drug delivery and pharmaceutics**
- Fuel cells
- Environmental chemistry
- Sustainable energy production
- Petroleum industries

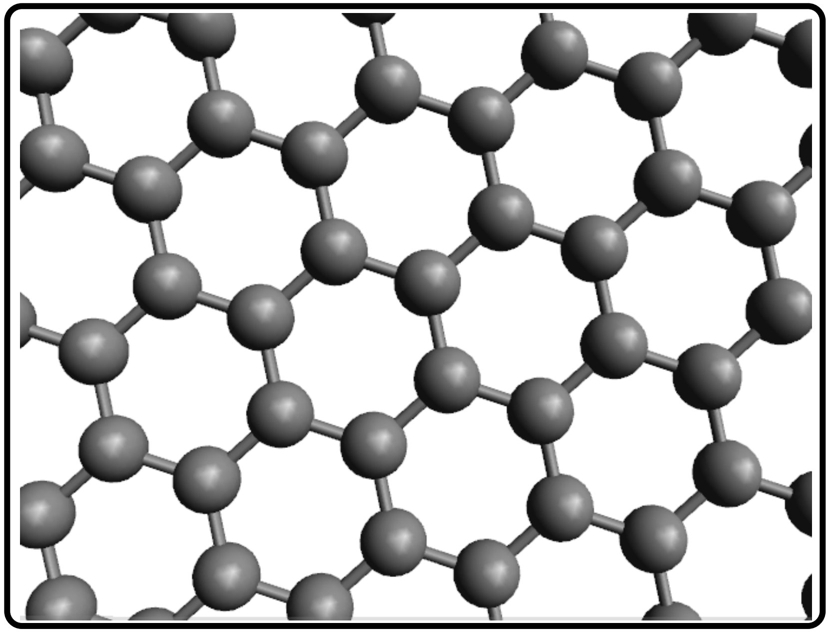


Gas separation: Beyond molecular sieving

First free-standing sheet of graphene isolated in 2004

Very robust, chemically inert, essentially two-dimensional and impermeable even to He

The perfect molecular sieve if the pore size can be adjusted



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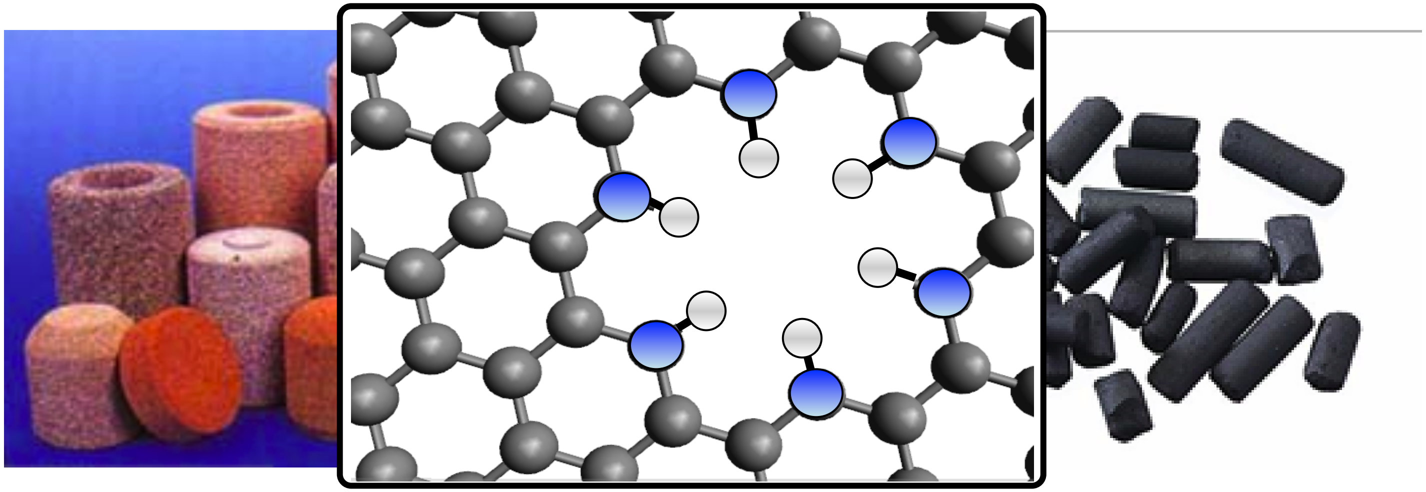
What makes graphene so special?

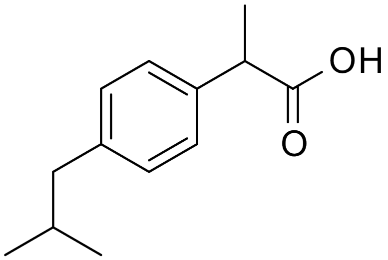


Flux through a membrane of thickness d and permeability L:

$$\boxed{J = \Delta p\, L/d}$$

Chiral resolution

- Currently, about 40% of the drugs in use are chiral



Ibuprofen

- What is the best approach to chiral drug design? Enantioselective synthesis
  - Typically via chiral coordination complexes, either direct or via chiral auxiliaries

- What is a common alternative? Chiral separation
  - Gas Chromatography
  - High Performance Liquid Chromatography (HPLC)
  - Capillary Electrophoresis

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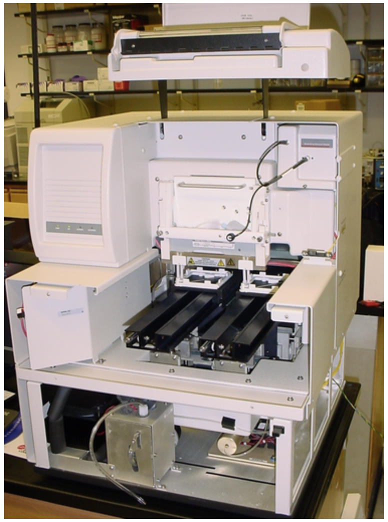
Chiral resolution

◆ Chromatographic methods have dominated, especially HPLC

- Preparative-scale capable
- Expensive equipment
- Consumes large amounts of buffer solutions
- Slow and labor intensive

◆ How does it compare to Capillary Electrophoresis?

- CE is less laborious
- Has a reduced environmental impact
- Limited throughput, not suitable for upscaling



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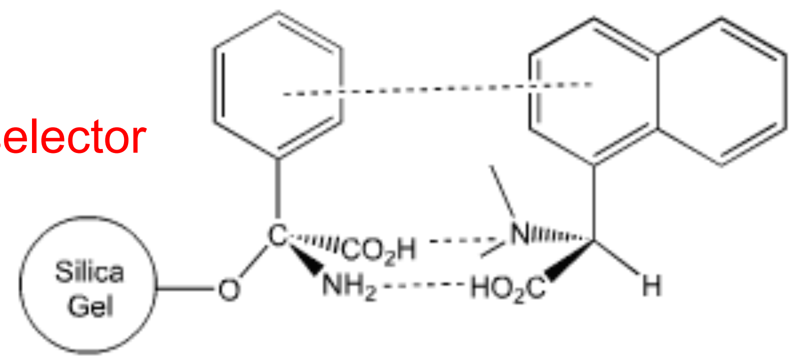
Chiral resolution

◆ The principle

- Both common techniques are based on a stereoselective interaction between the reactant and a chiral selector.

- Typical setup in chromatography: Two phases, one mobile, one stationary:

Stationary selector



Mobile reactant

- Leads to:
  - different retention times in chromatography
  - different effective mobility in electrophoresis

Chiral resolution

- The consequence:
  - It's all about perfect pairing between reactant and selector
  - Hundreds of selectors known and used, none works for all
  - Expertise, experience and testing are necessary

ChirBase

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Chiral resolution

◆ All chiral separation methods discussed so far have on problem in common:

Multiple microscopic interactions are necessary in order to obtain a reasonable macroscopic effect.

◆ What is desired?

Not multiple, but a single microscopic interaction should identify and separate a chiral molecule from its enantiomer.

◆ A possible realization: Nanoporous, functionalized sheets of graphene

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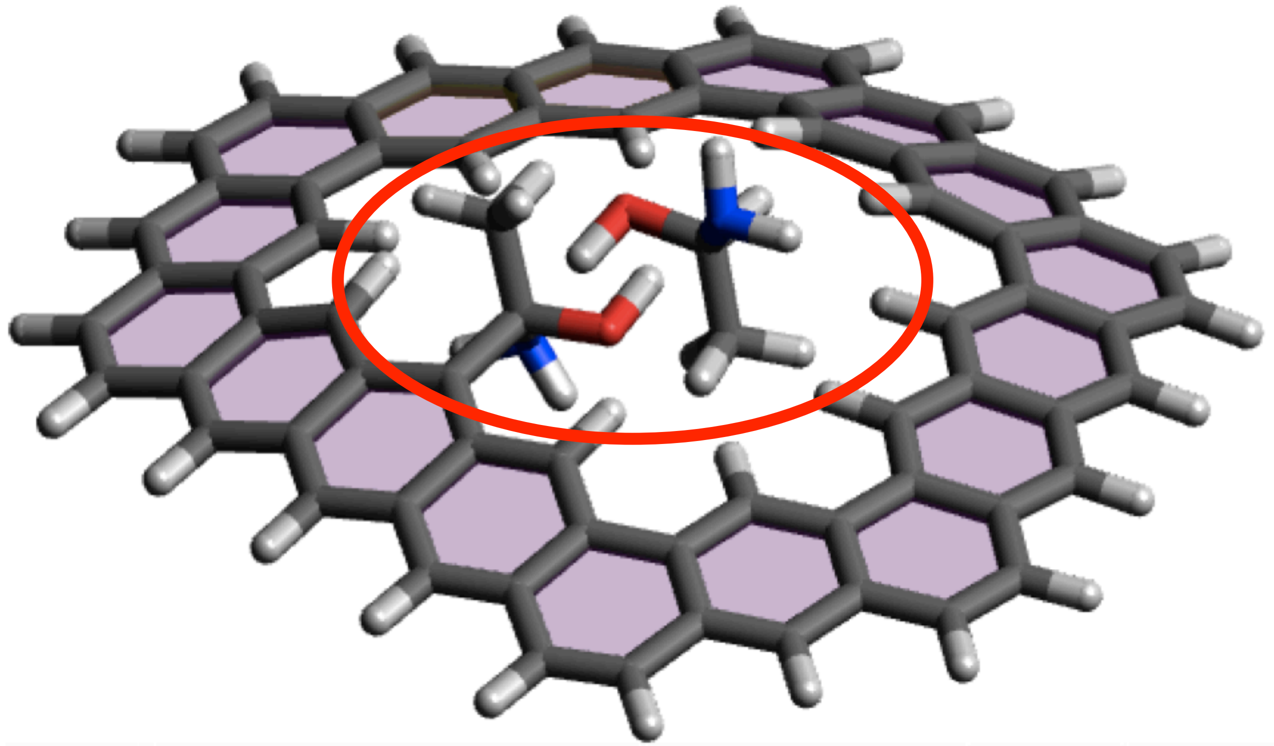
Chiral resolution via nanoporous graphene

- Our finite pore model of a nanoporous graphene sheet[1]



- Method: Density functional theory (B97-D), aug-cc-pVDZ basis set

1) AW Hauser, N Mardirossian, JA Panetier, M Head-Gordon, AT Bell , P Schwerdtfeger: Angewandte Chemie, DOI: 10.1002/anie.201406608 (2014)

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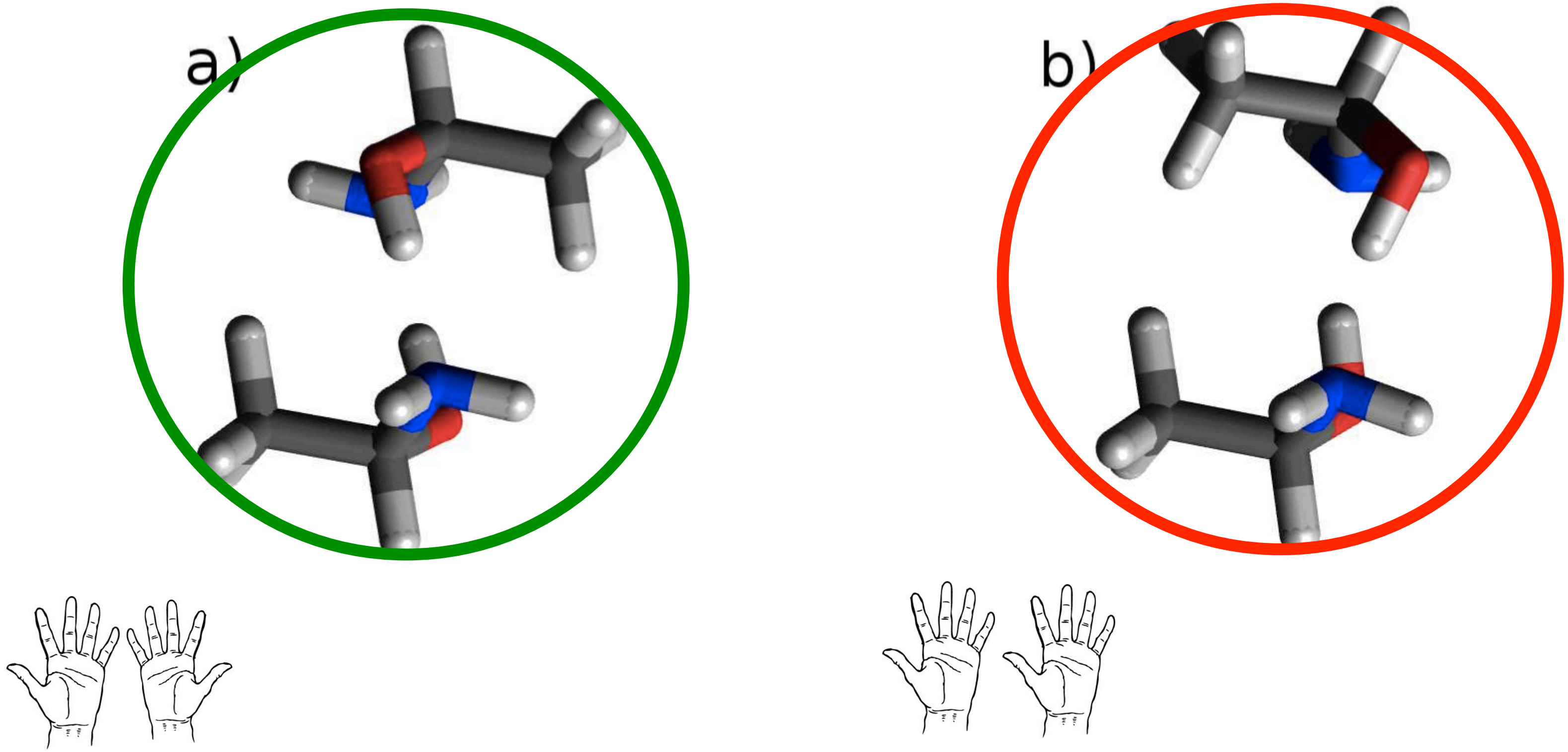
Chiral resolution via nanoporous graphene

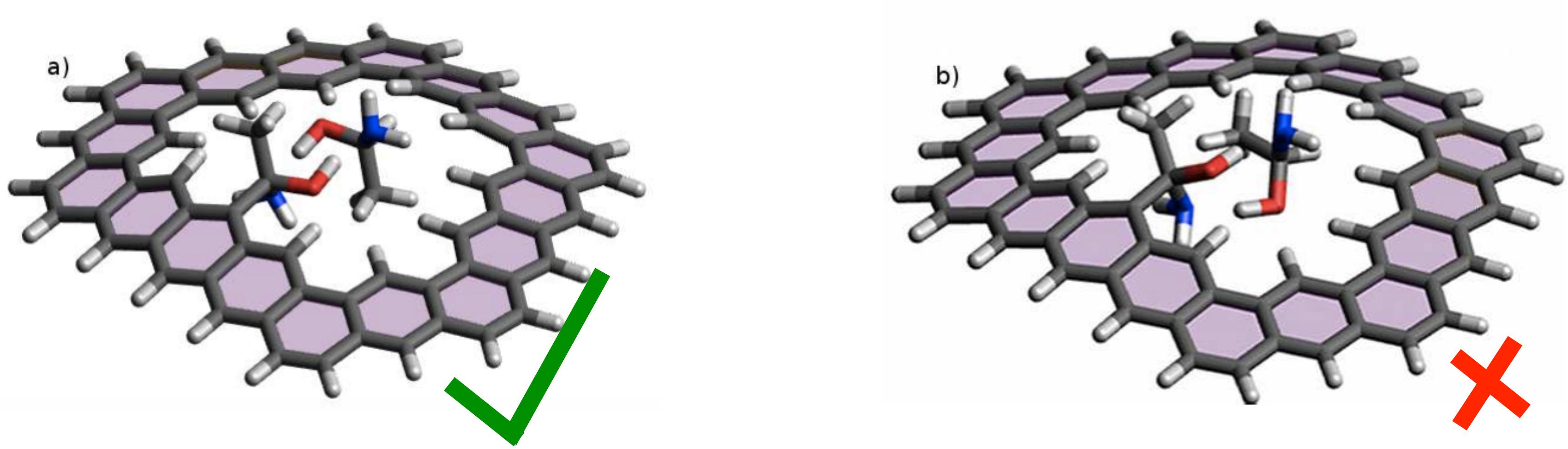
- The principle of the separation mechanism:



Dimer complexes have different size

Chiral resolution via nanoporous graphene

◆ The geometries of the rate-determining transition states:



Only one complex fits easily through the pore,
the 'bouncer' takes care

nature chemistry
RESEARCH HIGHLIGHTS
Nature Chemistry **6**, 754 (2014)

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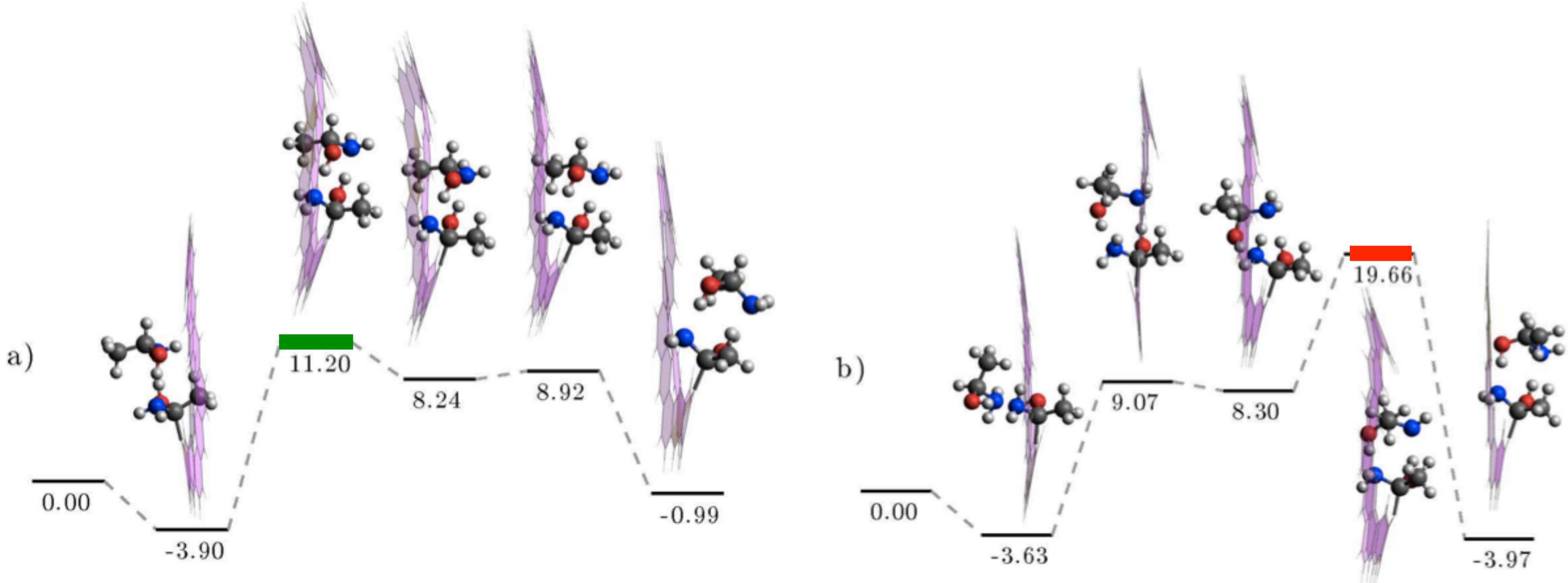
Chiral resolution via nanoporous graphene

◆ The two reaction pathways (Gibbs energies at room temperature):



The highest barrier differs by 9.5 kcal/mol,
Leading to a selectivity of about 3.8 x10^4

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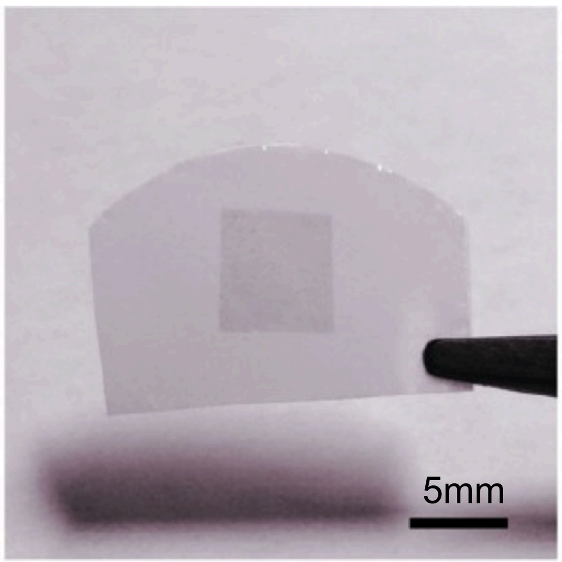
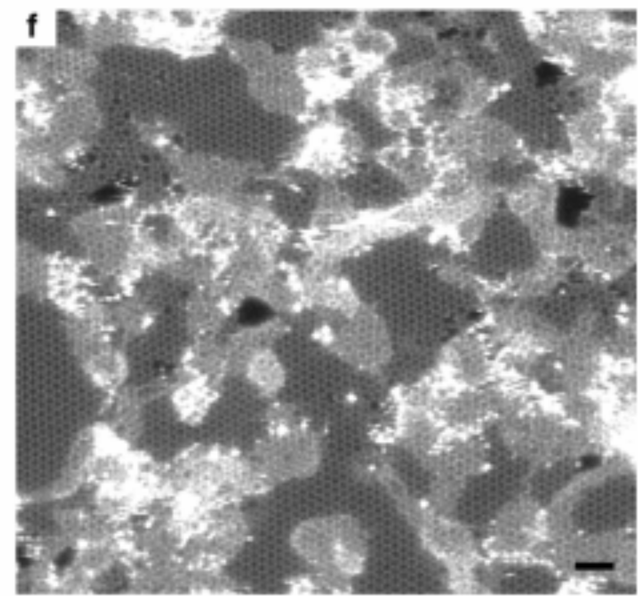
The problem with graphene...



1

Graphene composite material: nanoporous graphene on polycarbonate membrane

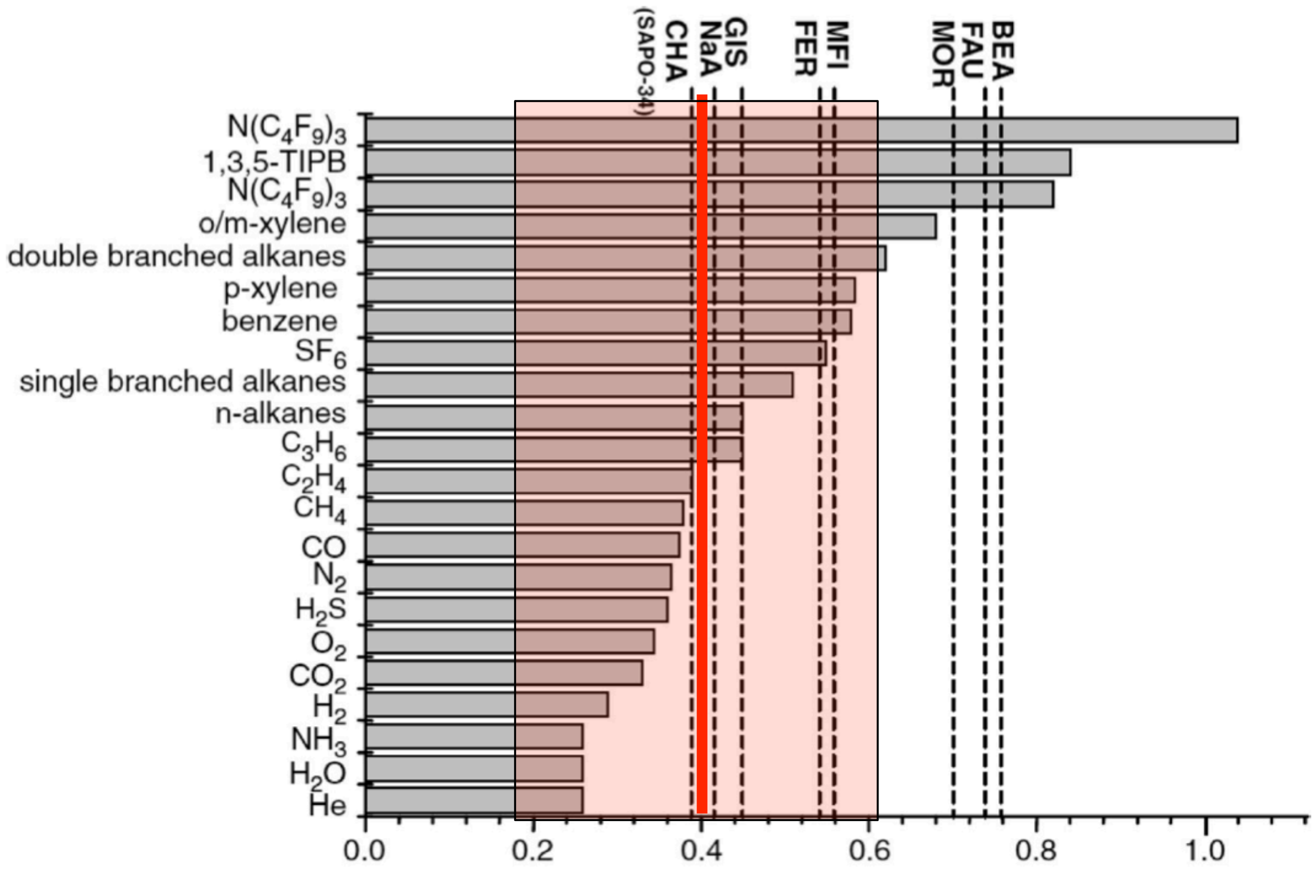


2

Nanoporous graphene, obtained via ion bombardment and etching with potassium permanganate: Sizes around 0.4 ± 0.2 nm

1) Karnik et al., ACS Nano 2012, 6, 10130–10138
2) Karnik et al., Nano Letters 2014, 14, 1234-1241

The problem with graphene...



1) McLeary et al., Microporous Mesoporous Mater. 2006, 90, 198-220

Acknowledgments

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