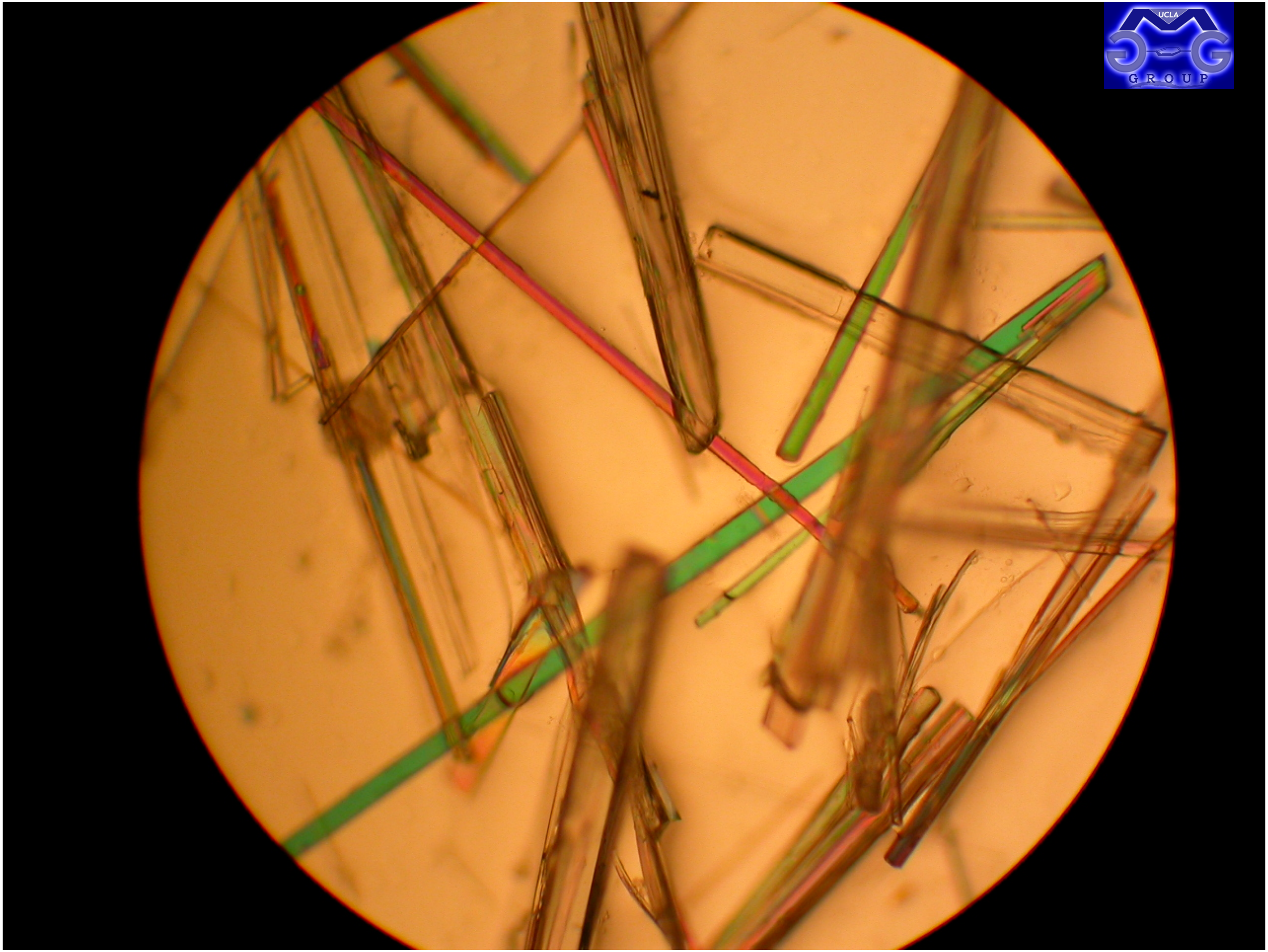
UCLA
GROUP

University of California, Los Angeles

ARTIFICIAL MOLECULAR MACHINES

M. A. Garcia-Garibay
Department of Chemistry and Biochemistry

Artificial Molecular Machinery

Goal: To set a general context to guide our synthetic efforts as materials chemists

PART 1: General concepts: What are molecular machines? What can they do? What forces to consider?

PART 2: A bit of history

PART 3: Increasing complexity: From simple molecules to comples nano- and macroscopic materials (*our work on CRYSTALLINE MOLECULAR MACHINES*)

WHAT IS A MACHINE?

"An assemblage of parts that transmits forces, motion, or energy from one to another in a predetermined manner"

Merriam-Webster English Dictionary

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Merriam-Webster English Dictionary

Macroscopic machines

(pulleys, levers, inclined planes, wedges, wheels, screws)

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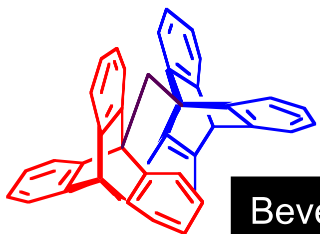
Merriam-Webster English Dictionary

Macroscopic machines

(pulleys, levers, inclined planes, wedges, wheels, screws)

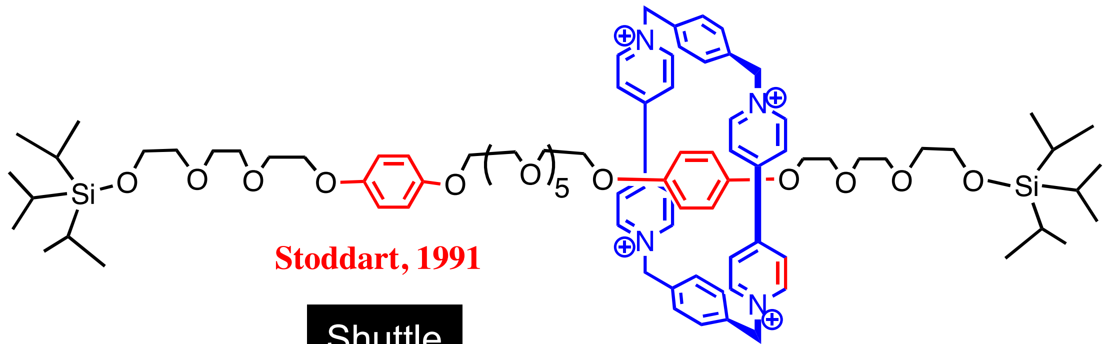
Organic Chemists' Views of Molecular Machinery

"An assemblage of atoms and molecules that transmits forces, motion, or energy from one to another in a predetermined manner"



Bevel Gear

Mislow, 1988

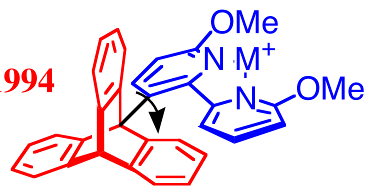


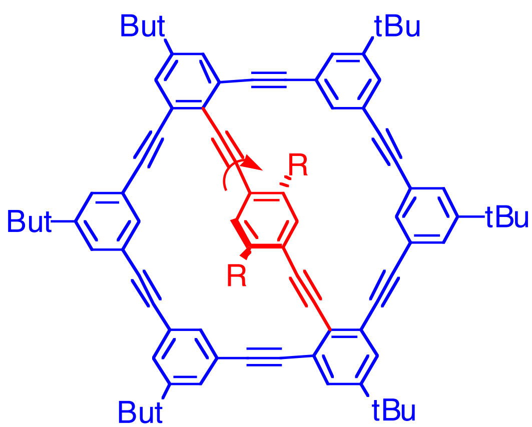
Stoddart, 1991

Shuttle

Kelly et al., 1994

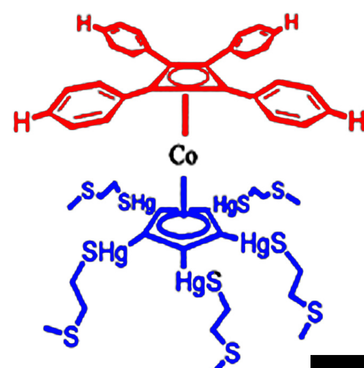
Brake





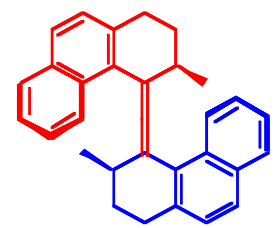
Moore, 1995

Turnstile



Rotor

Michl et al., 2001



Feringa et al., 1999

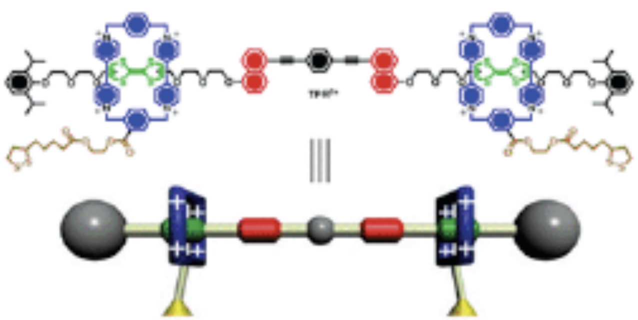
Motor

Balzani, Credi, Hawthorne, Raymo, Sauvage, Leigh, Zink, etc…

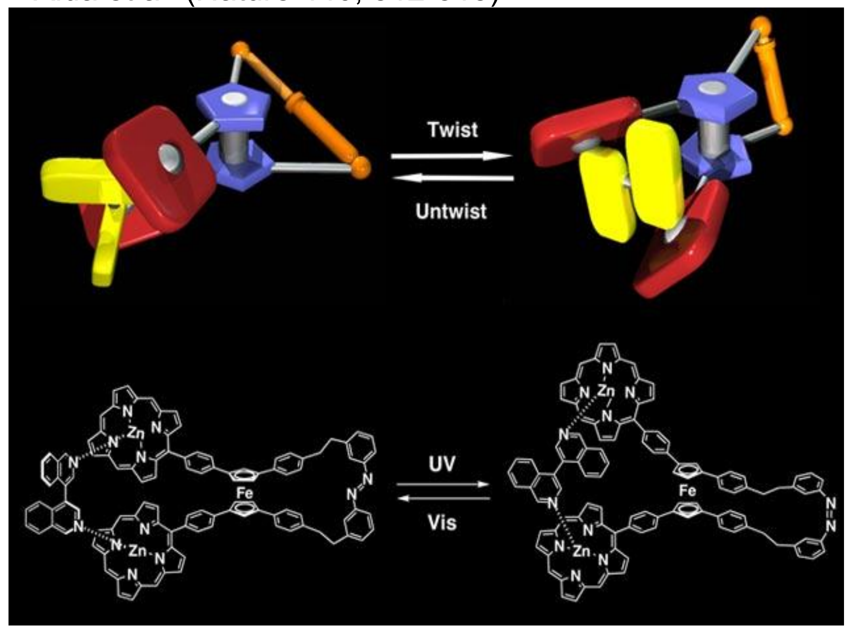
Organic Chemists' Views of Molecular Machinery

Recent Efforts : Increase structural complexity, add functionality, support it in membranes, surfaces or solids

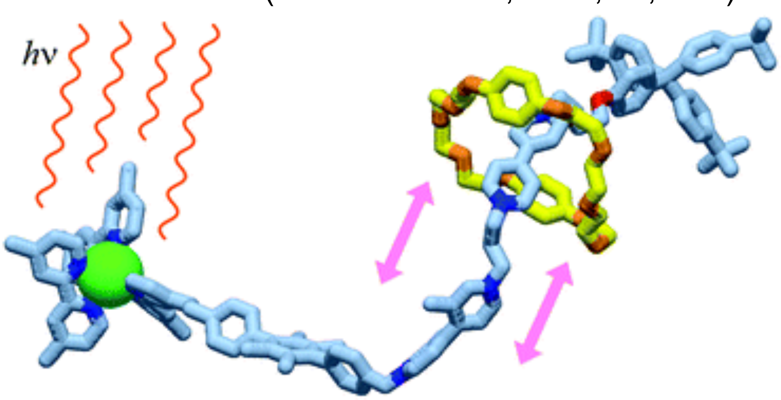
Stoddart



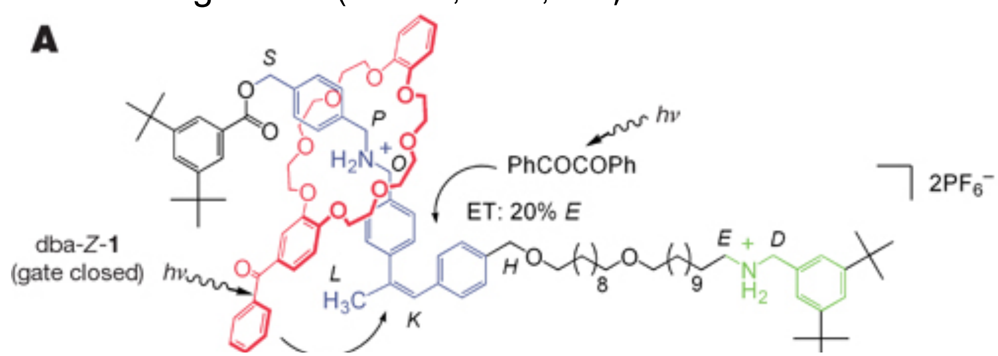
Aida et al. (Nature 440, 512-515)



Balzani et al. (Chem Soc. Rev., 2006, 35,1135)



Leigh et al. (Nature., 2007, 445, 523



Structural Hypothesis

Properties

Molecular Structure

Reactivity
accessible products (Ea's)
reaction trajectories

Physical Properties
color, emission, band structure, magnetism, morphology, solubility, aggregation, etc.

Dynamics
normal modes
lattice vibrations
librations (segmental motions)

Organic Synthesis

Garcia-Garibay, M. A., Statistical Entropy and Information in Crystals and Enzymes, *Curr. Opinion in Solid State and Material Science* **1998**, *3/4*, 399-406.

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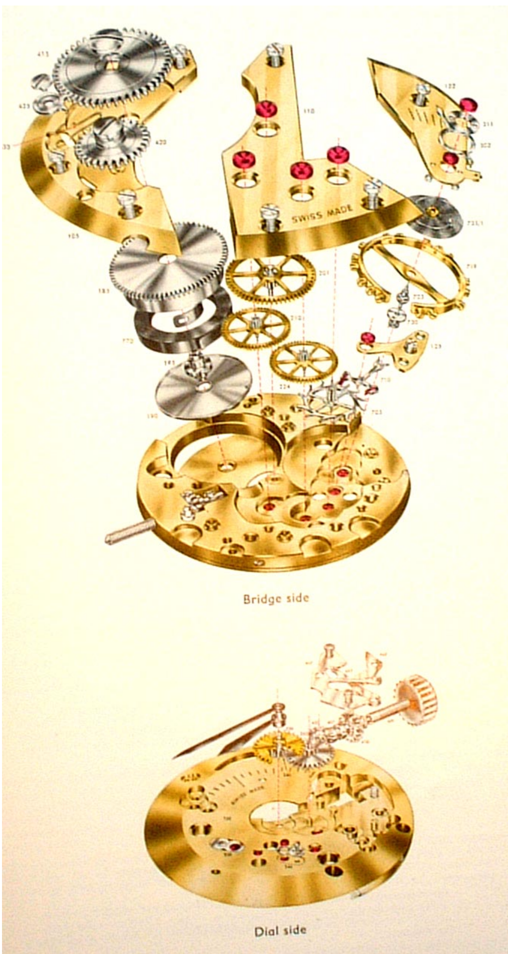
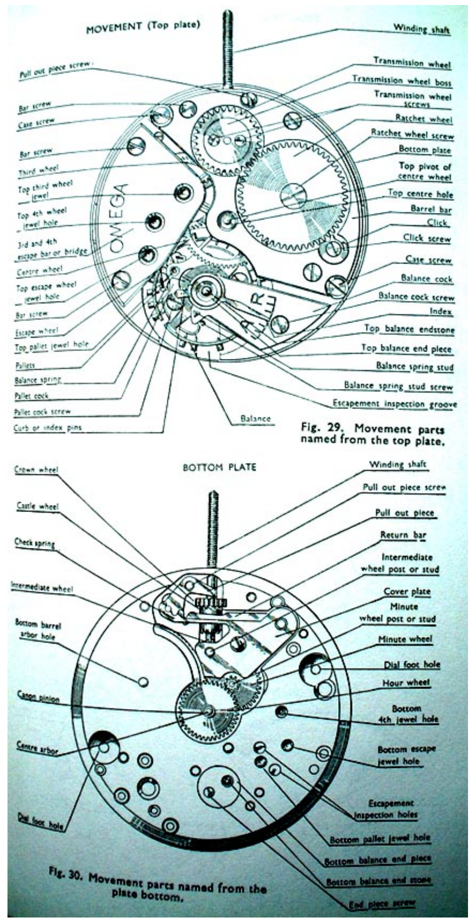
Blueprints = Structure and Dynamics Information

N-components
6N degrees of freedom

"Informed"
Assembly

1 Machine
6+1 degrees of freedom





In Molecules:
Structure <=> Energy
[free-energy surface]

Blueprints = Structure and Dynamics Information

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6N degrees of freedom

“Informed”
Assembly

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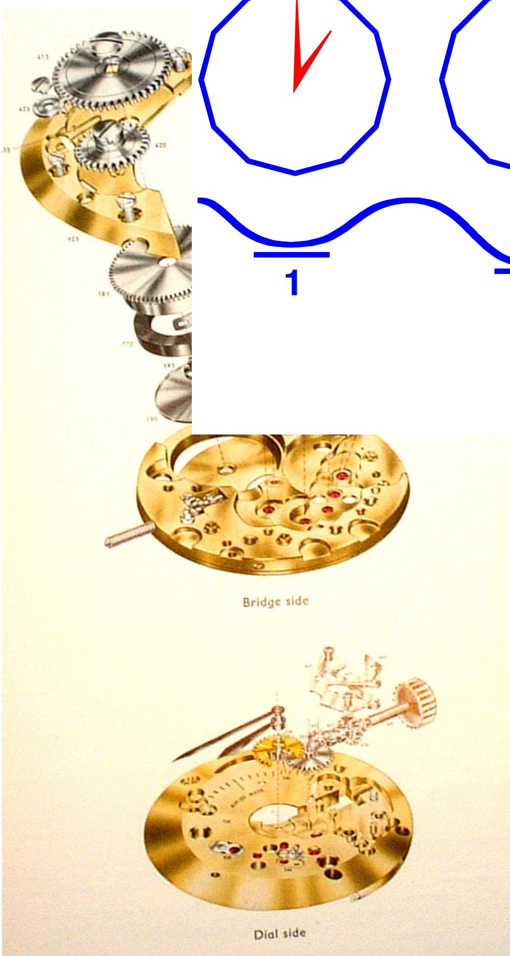
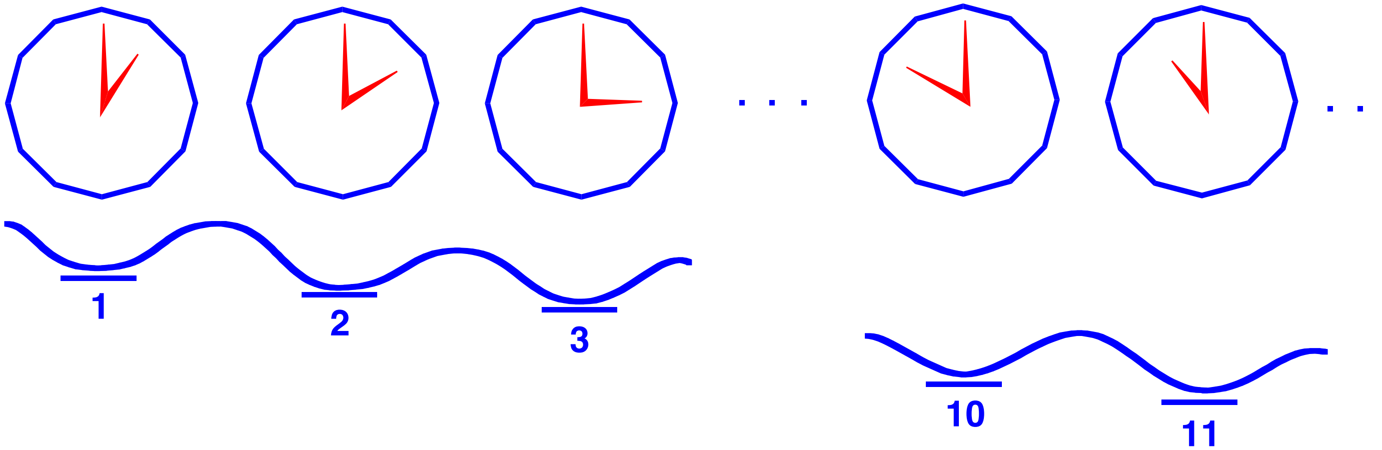
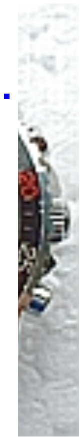
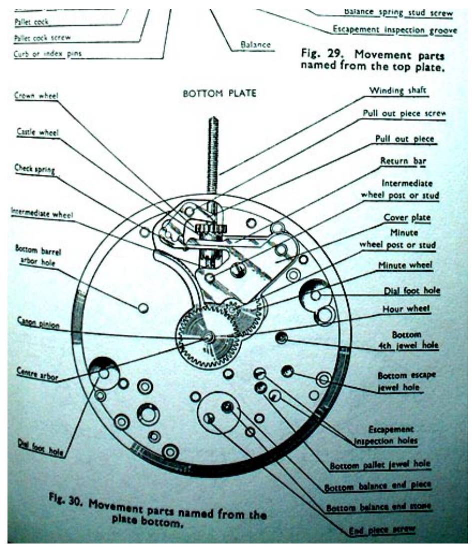
6+1 degrees of freedom









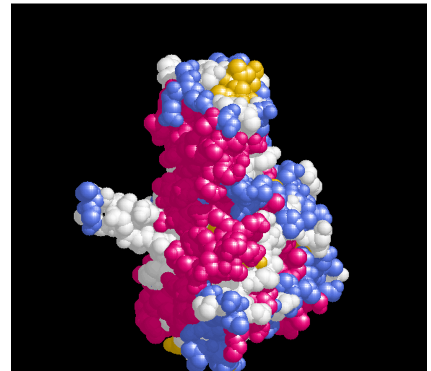
If each second is a different isomer …
control the dynamic of isomerization!

In Molecules:
Structure <=> Energy
[free-energy surface]

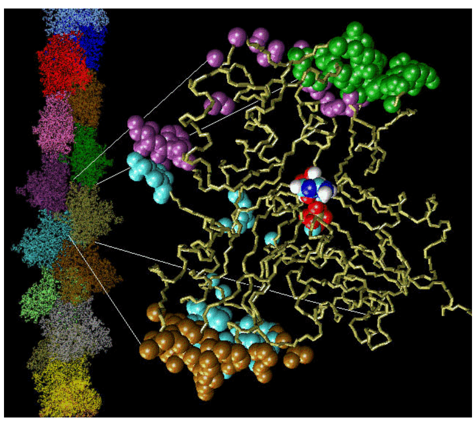
Nature's Strategy: From Atoms to Molecules to Supramolecular Aggregates to Biomolecular Machines

STRUCTURE
INFORMATION
FUNCTION

C, H, N, S → ***Aminoacids & polypeptides*** →

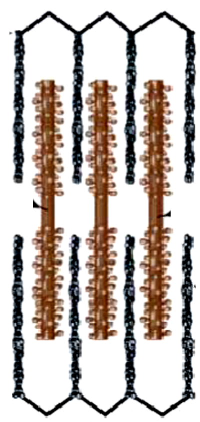


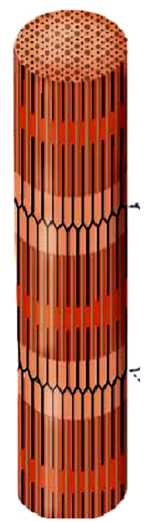
g-actin



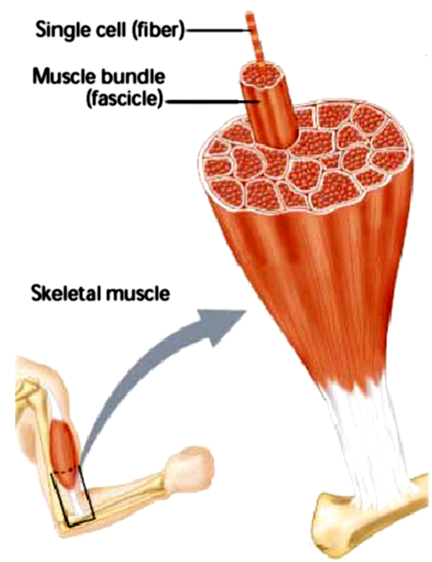
f-actin

sarcomers





fibers



Skeletal muscle

Garcia-Garibay, *Proc. Natl. Acad. of Sci.* **2005**, *102*, 10771-10776.
Khuong et al, *Acc. Chem. Res.* **2006**, *39*, 413-422.

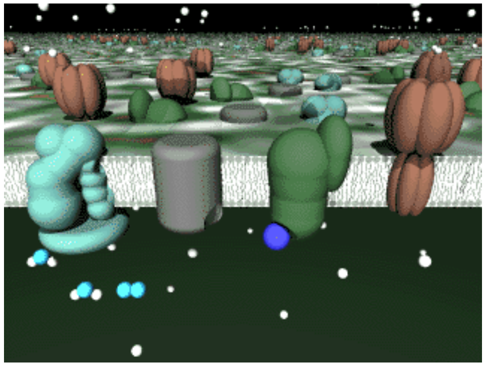
Molecular Machines : What can they really do?

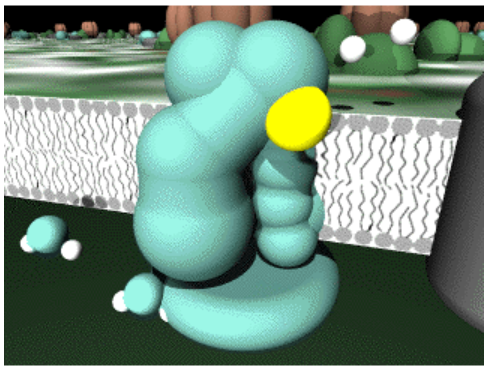
Energy Capture and transduction, Sensing, Locomotion, etc.

Molecular Machines : What can they really do?

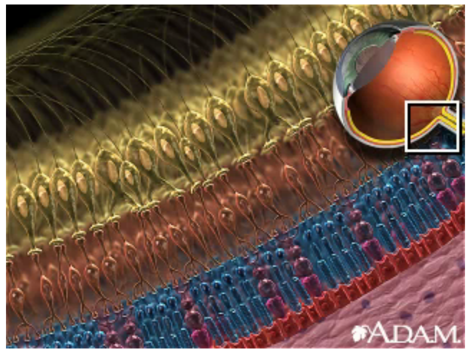
Energy Capture and transduction, Sensing, Locomotion, etc.

Photosynthesis

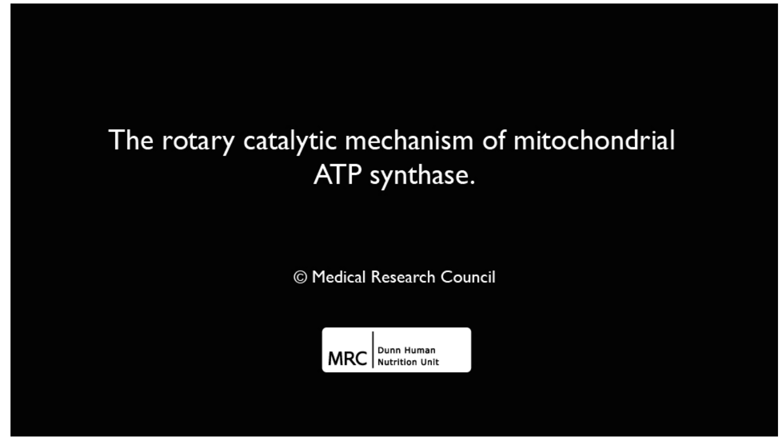




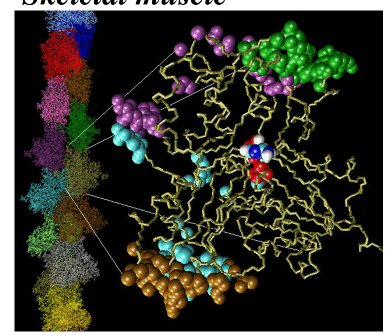
Vision

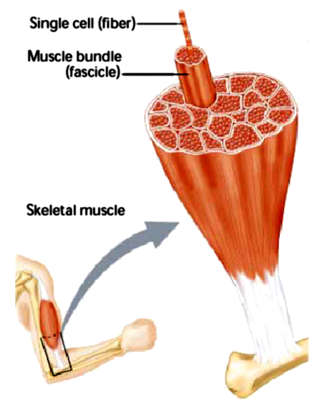


ATPase

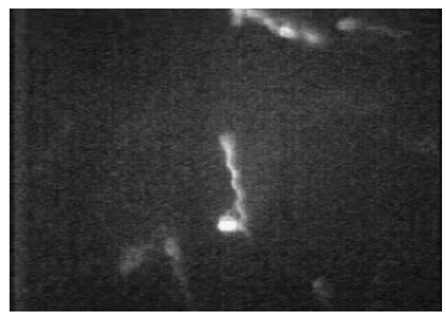


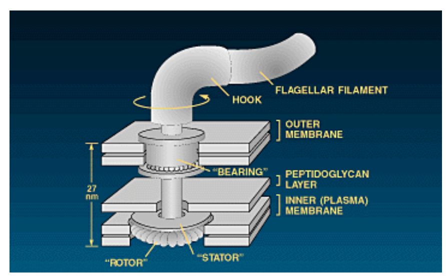
Skeletal muscle





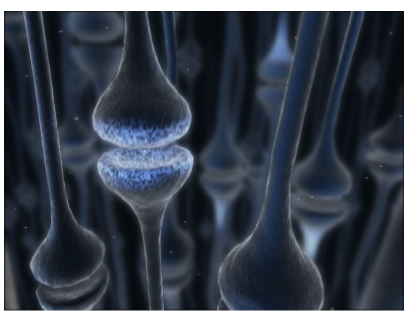
Bacterial flagellum

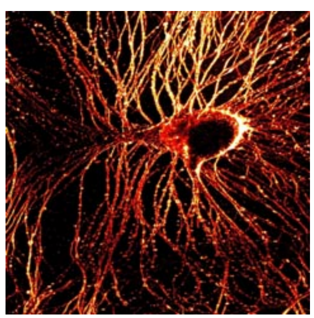




H.C. Berg, Rowland Institute

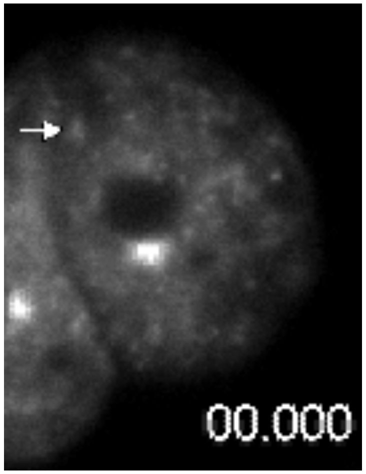
Neural Synapse

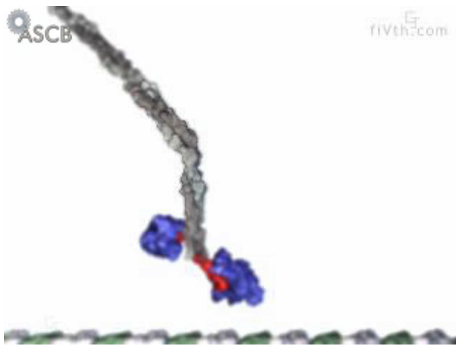




Molecular Machines : Autonomous and Collective

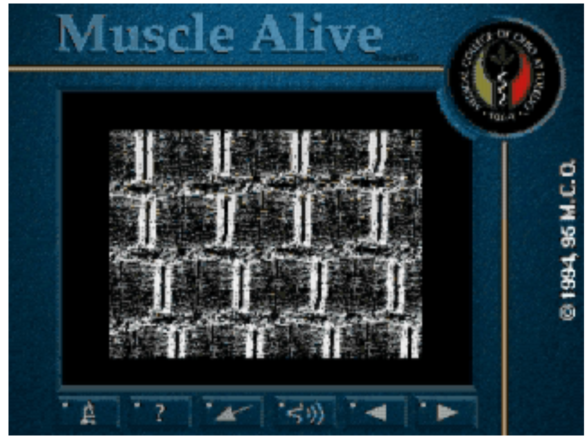
Kinesin and Dynein (microtubules)

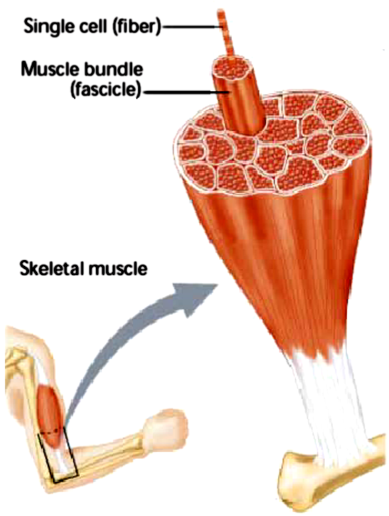




http://www.scripps.edu/cb/milligan/research/movies/kinesin_text.html

Skeletal muscle (myosin-actin)

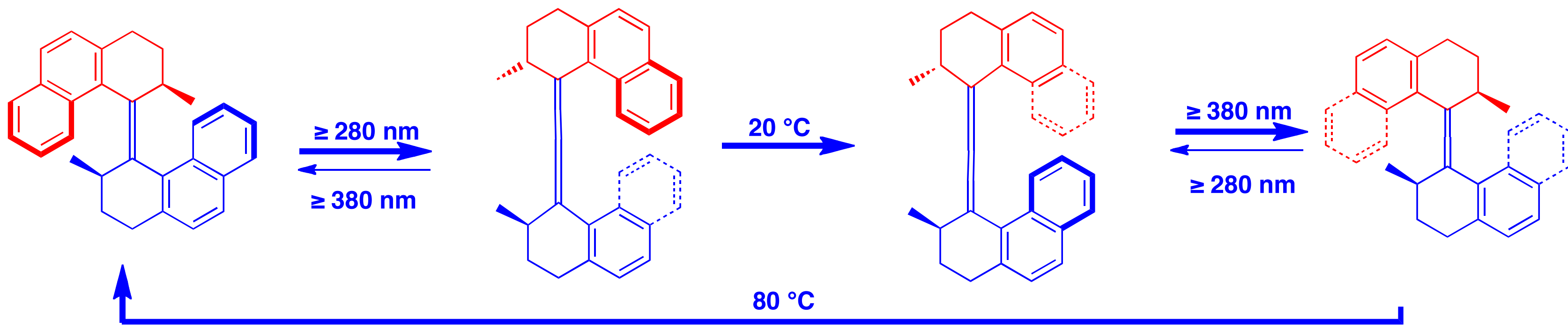




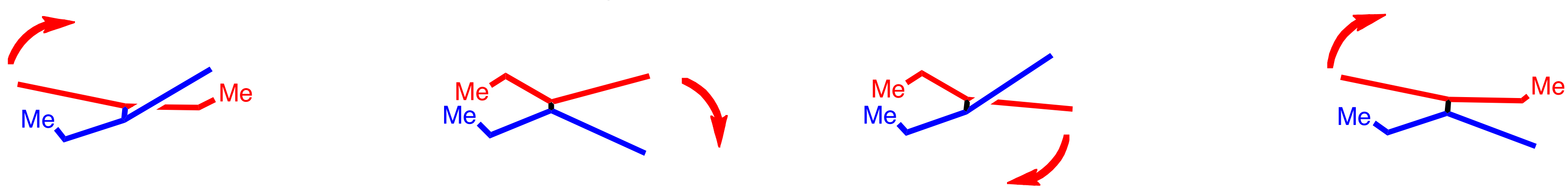
Autonomous Artificial Molecular Machines

A Unidirectional Motor: *Feringa et al., Nature, **1999**, 119, 7256*

Input: Photonic **Output: Mechanic** **+ HEAT!!**
(information: ORD, CD)



Projection down C=C bond



— ***Point chirality (R/S)***
— ***Geometric (Z/E) isomers***
— ***Axial chirality (M/P)***

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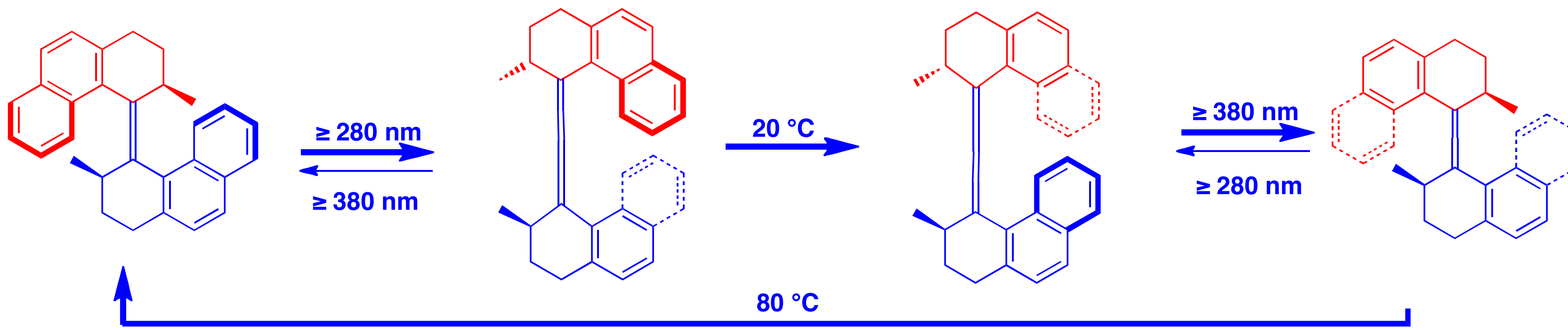
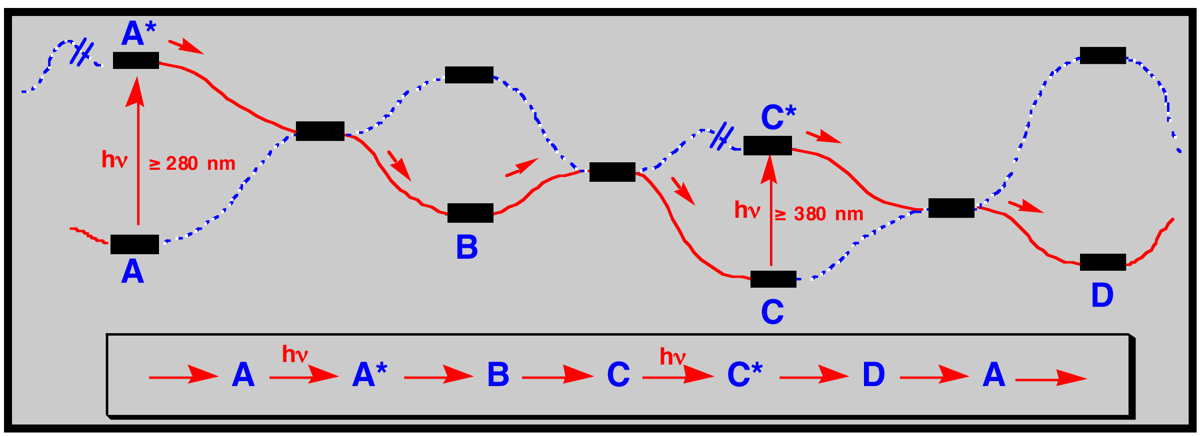


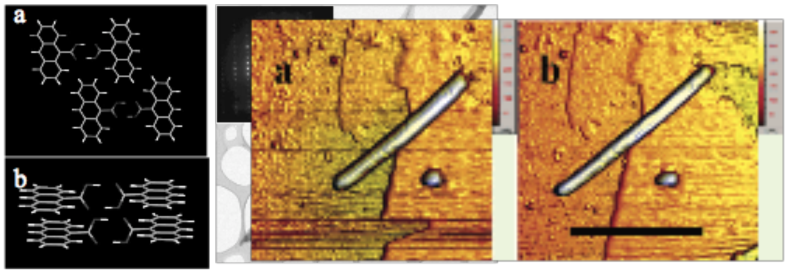


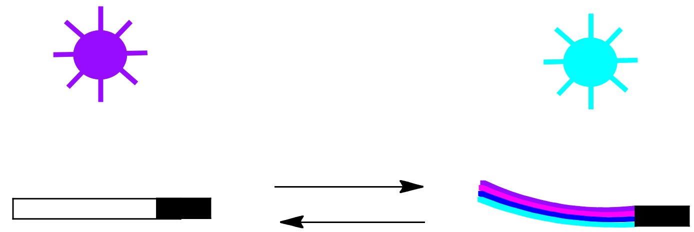
A biased (hν) Brownian Ratchet Potential

However,… tumbling molecules in solution, low efficiency, low addressability (λ), etc.

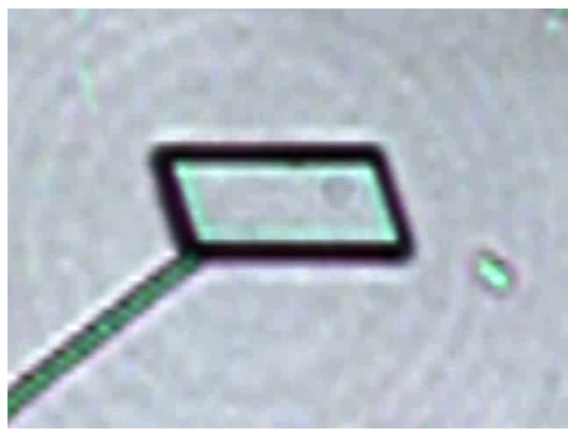
Collective Mechanochemical Responses in Molecular Micro- and Nanocrystals

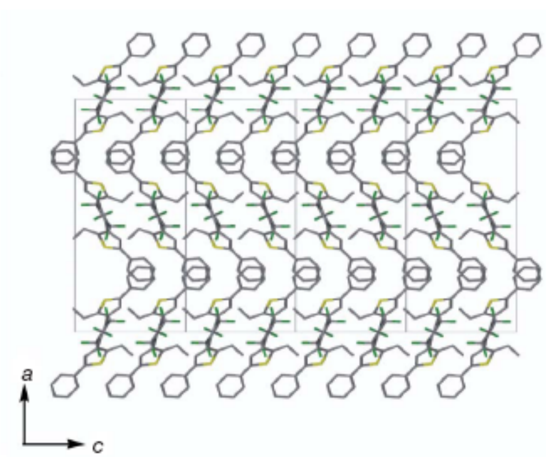
Bardeen, *Adv. Mat.*, **2007**, *19*, 1276

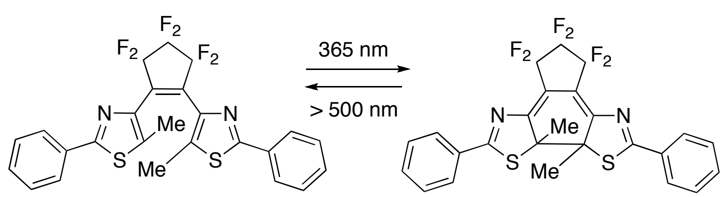


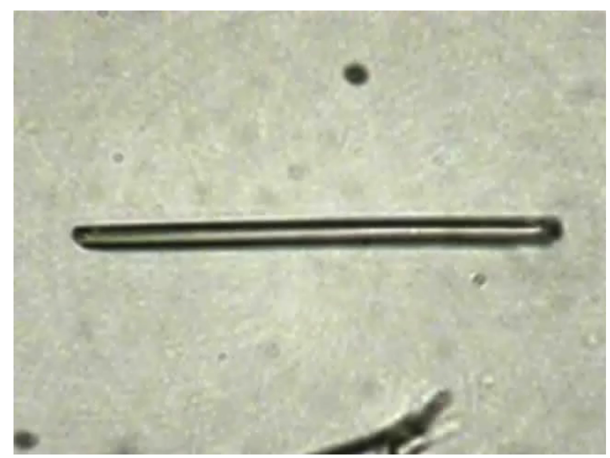


Irie, *Nature*, **2007**, *447*, 778







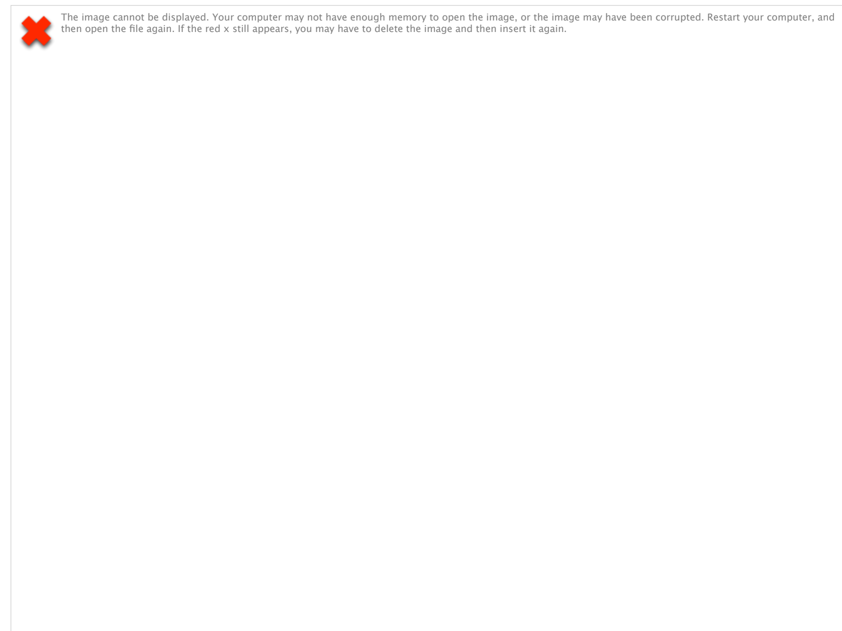


Collective Mechanochemical Responses in Other Complex Biomaterials and Polymers

A hummingbird: High frequency response of the keletal muscle

Charles W. Melton
http://www.nearfamous.com/Pages/HummingbirdVideo.html

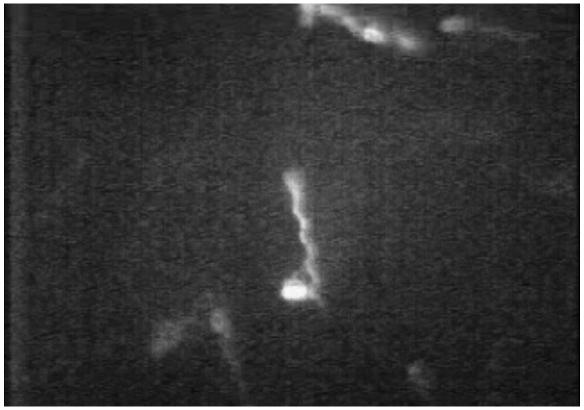
A High Frequency Polymeric Photodriven Oscillator

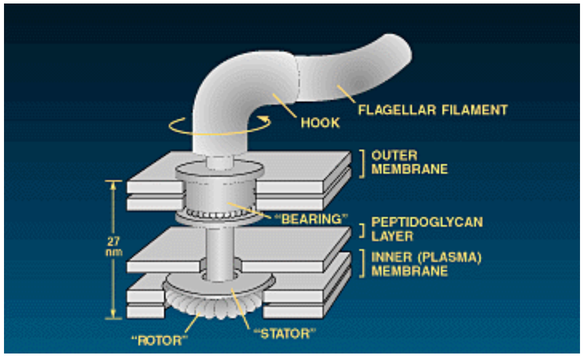


T. J. White, N. V. Tabiryan, S. V. Serak, U. A. Hrozhyk, V. P. Tondiglia, H. Koerner, R. A. Vaia, and T. J. Bunning, *Soft Matter* **2008**, *4*, 1796.

A step back….

What can we learn by reviewing the similarities and differences between macroscopic and molecular mechanics





Mechanics

***Kinematics**: the study of <u>motion</u> without regard to the forces or energies that may be involved*

***Statics**: the study of <u>forces</u> in the absence of changes in motion or energy*

***Dynamics**: the branch of mechanics that deals with both <u>motion and forces</u> together*

Types of motion:

—*Translational*
—*Rotational*
—*Oscillatory*
—*Brownian, Thermal*

Dynamics: The types, origins and effects of acting forces

Fundamental forces. From a macroscopic viewpoint, all the forces in the universe can be explained in terms of the following four fundamental interactions.

Gravity

The interaction between objects due to their mass. Weight is the name for the force of gravity.

Electromagnetism

The interaction between objects due to their charges (charge and spin).

Strong Nuclear Interaction

The interaction between subatomic particles with "color" (an abstract quantity that has nothing to do with human vision). This is the force that holds protons and neutrons together in the nucleus and holds quarks together in the protons and neutrons. It cannot be felt outside of the nucleus.

Weak Nuclear Interaction

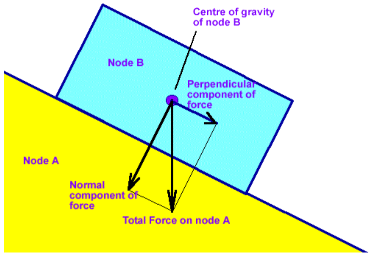
The interaction between subatomic particles with "flavor" (an abstract quantity that has nothing to do with human taste). This force, which is many times weaker than the strong nuclear interaction, is involved in certain forms of radioactive decay.

Dynamics: The types, origins and effects of acting forces

Forces associated with <u>macroscopic solid objects</u>

Normal

The force between two objects in contact that prevents them from occupying the same space. The normal force is directed perpendicular to the surface.



Friction

The force between objects in contact that resists their sliding across one another. Friction is directed opposite the direction of relative motion or the intended direction of motion of either of the surfaces.

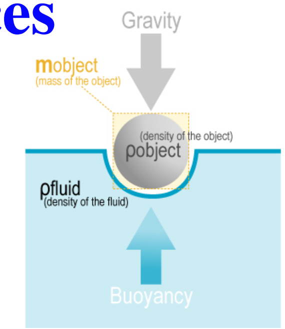
Tension

The force exerted by an object being pulled upon from opposite ends like a string, rope, cable, chain, etc. Tension is directed along the axis of the object.

Elasticity

The force exerted by an object under deformation (typically tension or compression) that will return to its original shape when released like a spring or elastic band. Elasticity, like tension, is directed along an axis (although there are exceptions to this rule).

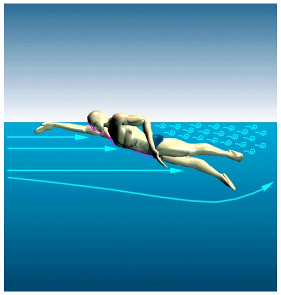
Dynamics: The types, origins and effects of acting forces



Forces associated with <u>fluids (liquids and gases)</u>

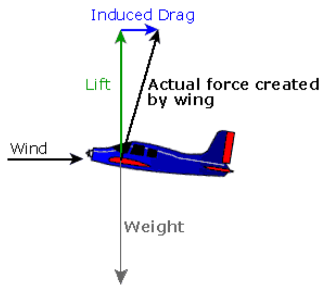
Buoyancy

The force exerted on an object immersed in a fluid. Buoyancy is usually directed upward (although there are exceptions to this rule).



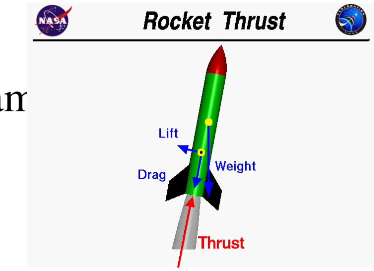
Drag

The force that resists the motion of an object through a fluid. Drag is directed opposite the direction of motion of the object relative to the fluid.



Lift

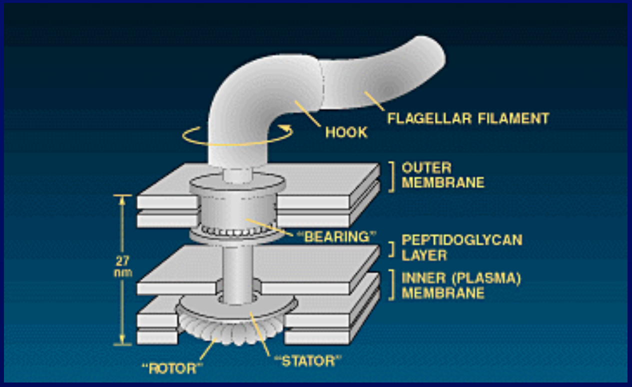
The force that a moving fluid exerts as it flows around an object; typically a wing or wing-like structure, but also golf balls and baseballs. Lift is generally directed perpendicular to the direction of fluid flow (although there are exceptions to this rule).



Thrust

The force that a fluid exerts when expelled by a propeller, turbine, rocket, squid, clam etc. Thrust is directed opposite the direction the fluid is expelled.

The machinery of life, David Goodsell, Springer 2009

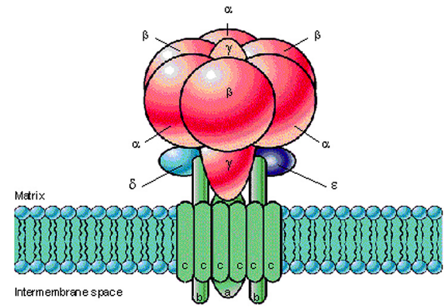


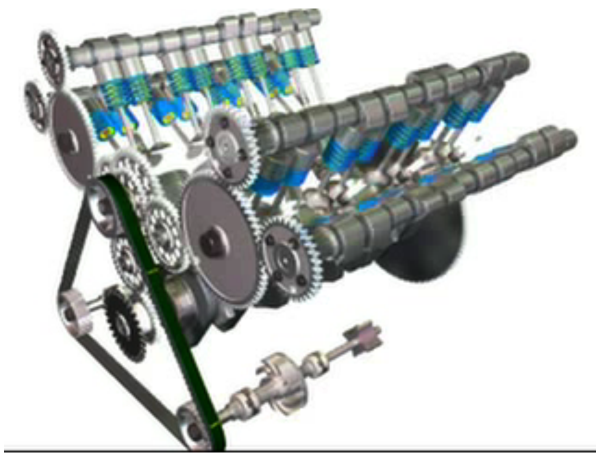
H.C. Berg, Rowland Institute

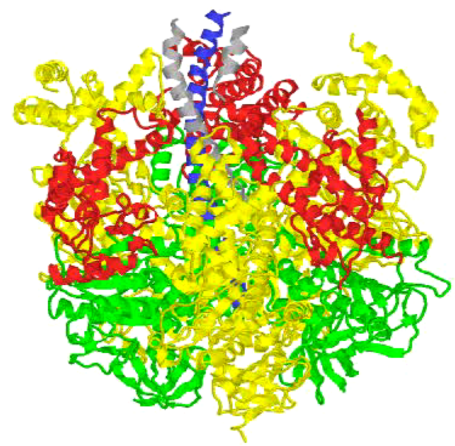
Forces Acting on Molecules

J. Howard, Mechanics of Motor Proteins and the Cytoskeleton, Sinauer Assoc. Inc., Sunderland MA, 2001

Newtonian, statistical and quantum mechanics







The behavior of macroscopic machines is deterministic and relatively reproducible, based on an interplay between forces, **inertia** and friction

The average behavior of a single molecule observed over a long period of time is the same as the behavior of a collection of molecules (*the ergodic hypothesis)*
*Small size, small Reynolds number ($R=av\delta/\eta$), **no inertia**, viscous forces rule!*

PART 2
A bit of history

Artificial Molecular Machinery : A Bit of History

There's Plenty of Room at the Bottom

An Invitation to Enter a New Field of Physics

by Richard P. Feynman

This transcript of the classic talk that Richard Feynman gave on December 29th 1959 at the annual meeting of the American Physical Society at the California Institute of Technology (Caltech) was first published in the February 1960 issue of Caltech's *Engineering and Science*, which owns the copyright. It has been made available on the web at http://www.zyvex.com/nanotech/feynman.html with their kind permission.

"I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle."… "What I want to talk about is the problem of manipulating and controlling things on a small scale…"

—How to write small
—Better electron microscopes
—The marvelous biological systems
—Miniaturization by evaporation
—Problems with lubrication
—A hundred tiny hands
—Rearranging atoms
—Atoms in a small world

Enzymes as molecular machines. Christen, P *Schweizerische medizinische Wochenschrift*, **1971**, *101*, 657-66.

On Binding Sites, Catalysis, Protein Conformation, Structure-Activity Relationships

Conformational dynamics of proteins and the simplest molecular " machines ". Shaitan K V; Rubin A B *Biofizika*, **1982**, *27*, 386-90.

A mathematical model is developed for conformational motions of proteins. The mechanism is shown to be by local jump diffusion via conformational substrates. A correlation between electron transport activity and protein conformation motions is discussed within the local jump mechanism.

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 9, pp. 5275–5278, September 1981
Chemistry

Molecular engineering: An approach to the development of general capabilities for molecular manipulation

(molecular machinery/protein design/synthetic chemistry/computation/tissue characterization)

K. ERIC DREXLER

Space Systems Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Communicated by Arthur Kantrowitz, June 4, 1981

— Feynman's 1959 talk… machines that make smaller machines that make smaller machines…

—"In this paper I will outline a path to this goal, a general molecular engineering technology" (a new *microtechnolgy*, no *nano* yet).

—Models : Enzymes complexes (ribosome)
—How: biotechnology (hijack bacteria)
—When: "imminent"

(Engineers need lower standards than those of scientists, errors are OK)

Engines of Creation

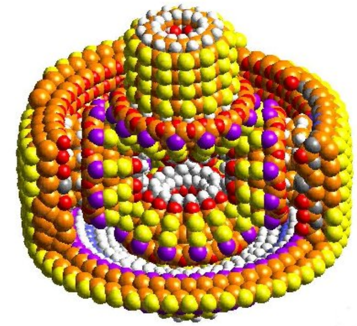
The Coming Era of Nanotechnology

K. Eric Drexler

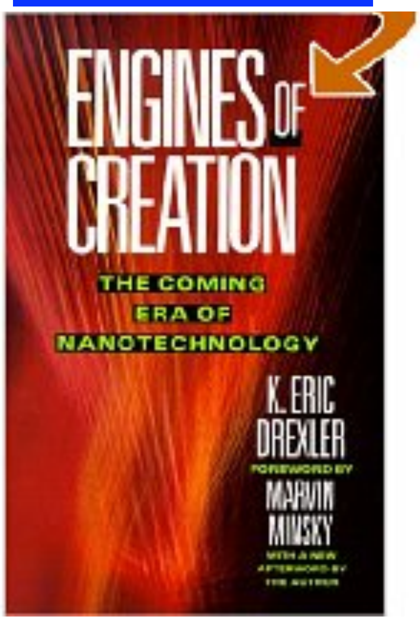
Anchor Books, 1986

Original web version prepared and links added by Russell Whitaker.

iMM
Institute for Molecular Manufacturing



1982—>1986



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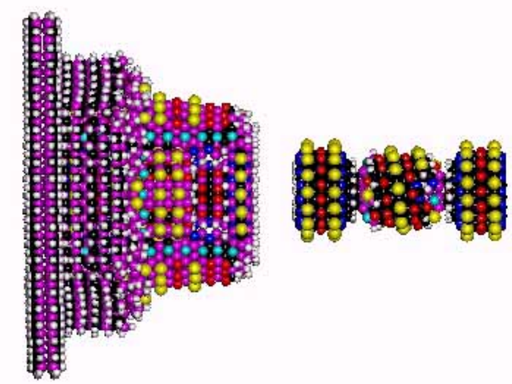

iMM
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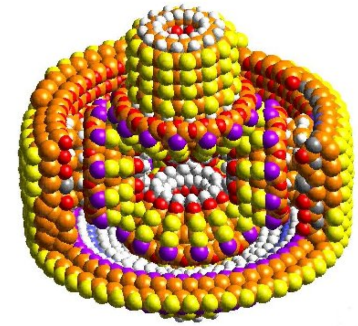
CHAPTER ELEVEN

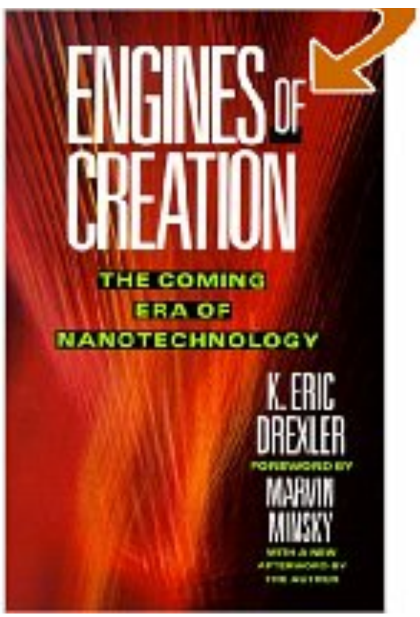
Engines of Destruction

"Nor do I doubt if the most formidable armies ever here upon earth is a sort of soldiers who for their smallness are not visible."

—Sir WILLIAM PERRY
on microbes, 1640



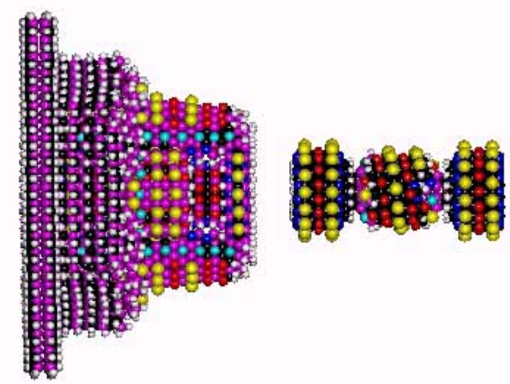
1986

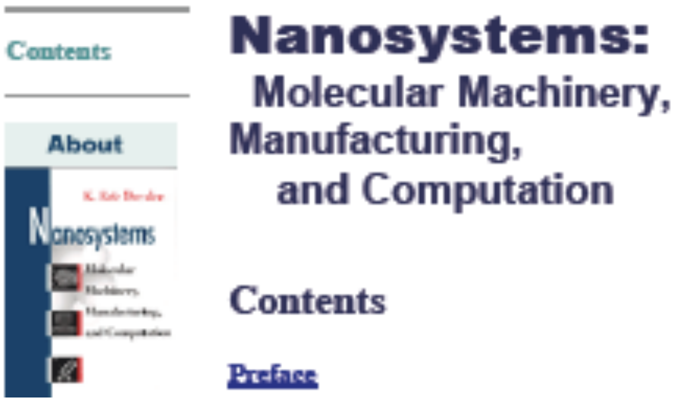


REPLICATING assemblers and thinking machines pose basic threats to people and to life on Earth. Today's organisms have abilities far from the limits of the possible, and our machines are evolving faster than we are. Within a few decades they seem likely to surpass us. Unless we learn to live with them in safety, our future will likely be both exciting and short. We cannot hope to foresee all the problems ahead, yet by paying attention to the big, basic issues, we can perhaps foresee the greatest challenges and get some idea of how to deal with them.

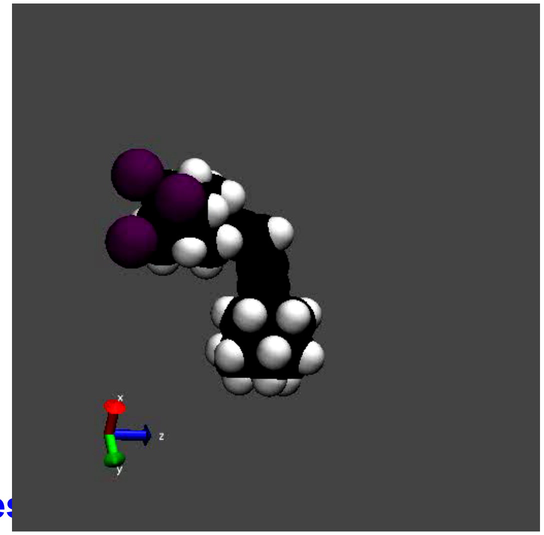
Entire books will no doubt be written on the coming social upheavals: What will happen to the global order when assemblers and automated engineering eliminate the need for most international trade? How will society change when individuals can live indefinitely? What will we do when replicating assemblers can make almost

353





K. E. Drexler 1992



iMM
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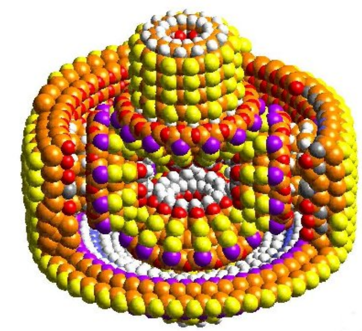
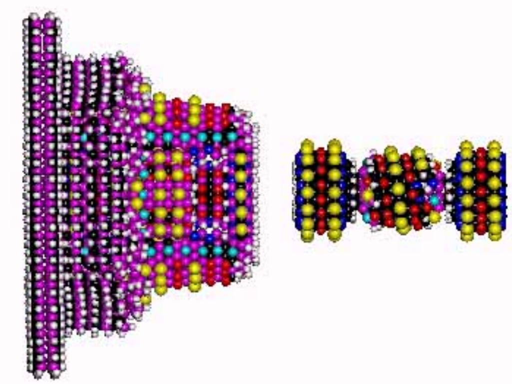


—Physical possibilities
—Challenges
—An example (molecular bearing)
—Solution Vs Mechanical Syntheses
—"Diamonoids" (no internal degrees of freedom)
— Assumptions

—Scaling laws (continuum)
—Potential Energy Surfaces
—Molecular Dynamics (entropy, "stiff molecules")
—Positional Uncertainty, σ^2=kT/ks, (ks= force constant)
—Transitions (between PES) = errors…
—thermal and photochemical
—TST and tunneling for Δ, ignore hν
—Energy dissipation (limit of operation rate)
—vibrations, phonons
—Mechanosynthesis



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Molecular Machinery, Manufacturing, and Computation

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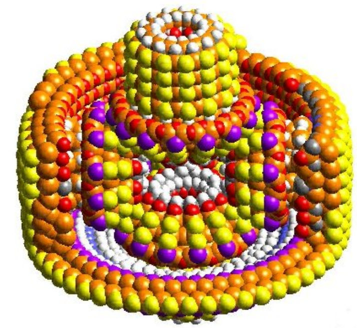
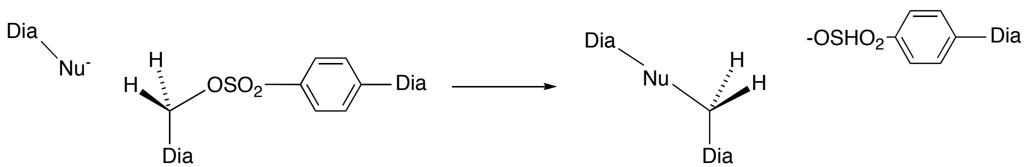
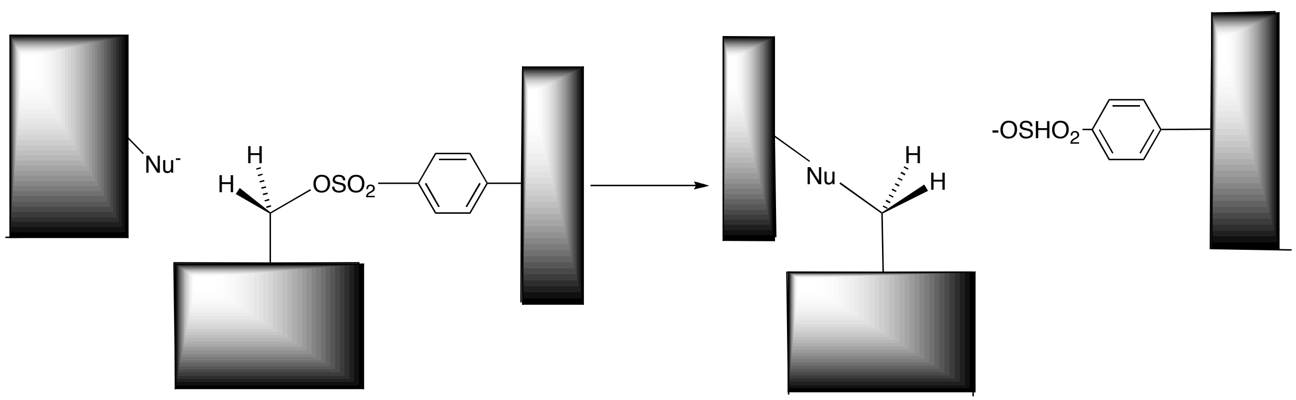
K. E. Drexler 1992

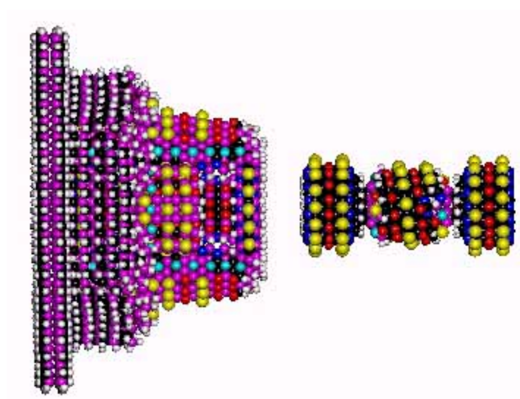
iMM Institute for Molecular Manufacturing



SOLUTION PHASE AND MECHANOSYNTHETIC CHEMISTRY







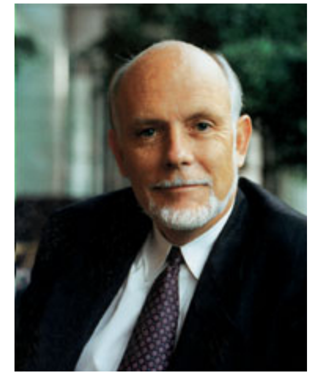
The debate…

"Engines of Creation: The Coming Era of Nanotechnology" 1986

CHEMICAL & Engineering News **December 1, 2003,** *81*, pp. 37-42

Are "molecular assemblers"--devices capable of positioning atoms and molecules for precisely defined reactions in almost any environment--physically possible?

MECHANOSYNTHETIC REACTIONS As conceived by Drexler, to deposit carbon, a device moves a vinylidenecarbene along a barrier-free path to insert into the strained alkene, twists 90ｼ to break a pi bond, and then pulls to cleave the remaining sigma bond. COURTESY OF K. ERIC DREXLER



Scientific American
September 2001

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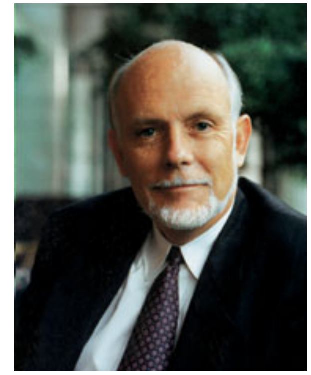

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1) Not possible, … fat, sticky fingers

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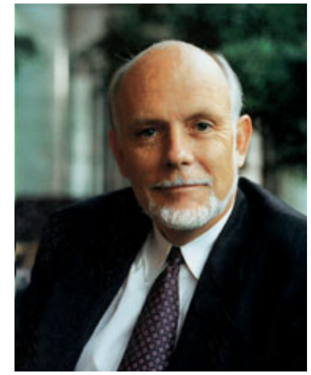

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2) Like enzymes and ribosomes, the proposed assemblers neither have nor need these "Smalley fingers." The task of positioning reactive molecules simply doesn't require them.

CHEMICAL
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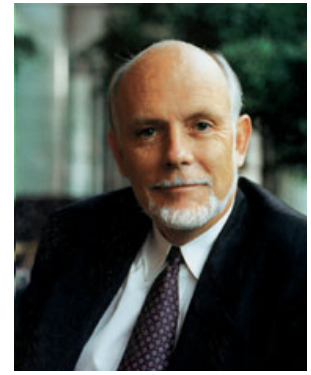

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3) But where does the enzyme or ribosome entity come from in your vision of a self-replicating nanobot?
…Is there a living cell somewhere inside the nanobot? There then must be liquid water present somewhere inside, .. Then cannot build anything that is chemically unstable in water.
…Biology can't make a crystal of silicon, or steel, or copper, or aluminum, or titanium, or virtually any of the key materials on which modern technology is built. Without such materials, how is this self replicating nanobot ever going to make a radio, or a laser, or an ultrafast memory, or virtually any other key component of modern technological society
….The central problem I see with the nanobot self-assembler is primarily chemistry.

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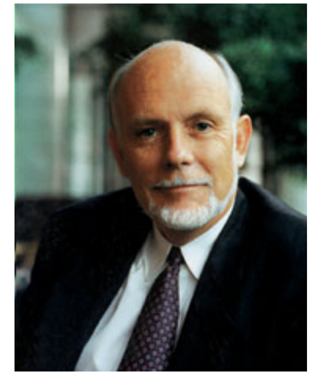

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…. The smallest devices position molecular parts to assemble structures through mechano synthesis- 'machinephase' chemistry.
…. Conveyors and positioners (not solvents and thermal motion) bring reactants together. The resulting positional control (not positional differences in reactivity) enables reliable site-specific reactions. Bound groups adjacent to reactive groups provide tailored environments that reproduce familiar effects of solvation and catalysis. Positional control enables a strong catalytic effect: It can align reactants for repeated collisions in optimal geometries at vibrational (greater than terahertz) frequencies.

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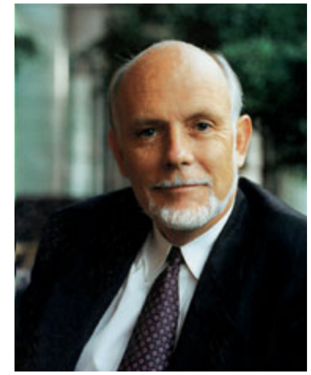

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4) "You do not get it, …"

Organic Chemists Enter the Realm of Molecular Machinery

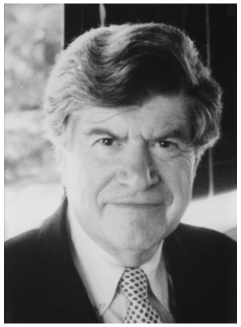
“A physicist may say anything he pleases, but a chemist must be at least partially sane." **Willard Gibbs****

“Chemistry has been termed by the physicist as the messy part of physics, but that is no reason why the physicists should be permitted to make a mess of chemistry when they invade it” **Frederick Soddy** **(NP 1921)**

“Organic chemistry is the chemistry of carbon compounds. Biochemistry is the study of carbon compounds that crawl” **?**

“I have always felt that I understood a phenomenon only to the extent that I could visualise it. Much of the charm organic chemical research has for me derives from structural formulae. When reading chemical journals, I look for formulae first”
Donald J. Cram **(NP 1986)**

Synthetic chemistry is one the most **tangibly rigorous** disciplines in the physical sciences. Your objective must be to designed, made, characterized, and (ideally) tested. **The standards of synthetic chemistry are ultimately determined by performance!**



Kurt Mislow was born in Berlin, Germany. He attended Tulane University (B.S. 1944) and obtained the Ph.D. degree with Linus Pauling at Cal Tech (1947). He then joined the New York University faculty, and in 1964 was appointed the first Hugh Scott Taylor Professor of Chemistry at Princeton University (1964).

Molecular Machinery in Organic Chemistry

Chemtracts—Organic Chemistry, **1989**, *2*, 151

—Molecular Models (iconic and analogic)

—Molecular Propellers and the Cogwheel Mechanism
-set theory to define number of isomers (states) and their connectivity (trajectories)

—Molecular Gears and Dynamic Gearing
-static and dynamic gearing
-bevel gears (and a chemical monkey wrench)

—Multiple Gears and Parity Rules

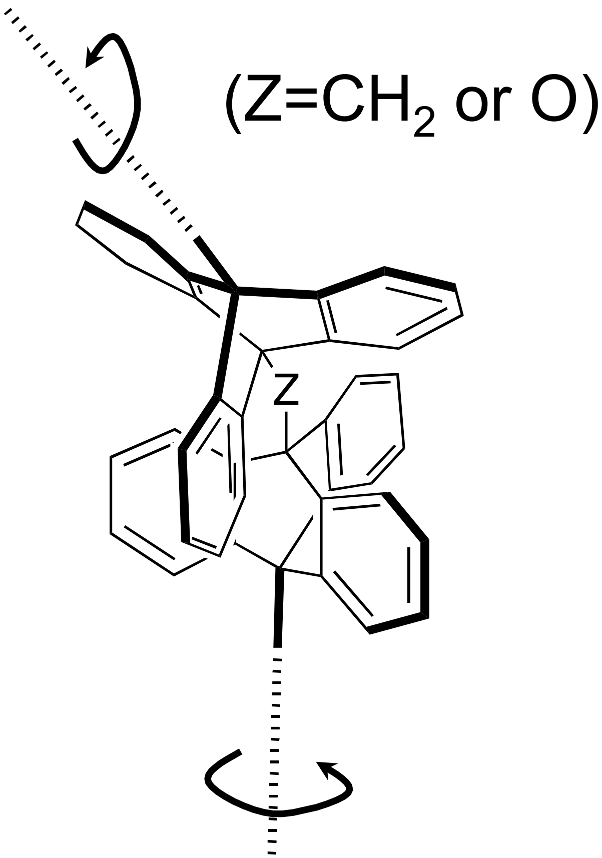
—"Despite profound dissimilarities (between molecular and macroscopic gear systems), some of them behave remarkably similar…"

***"MOLECULAR KINEMATICS"**

*Mislow's only publication with the word "machine" in the title. However, he published fifteen articles dating back to 1973 with the words "propeller" and "gear".

Gearing Motion: A molecular bevel gear

Bevel gears transfer rotary motion from one axis to another



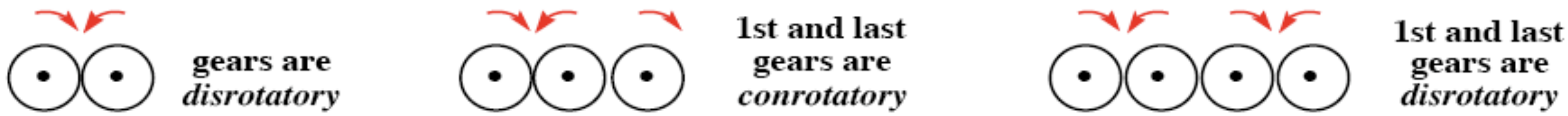
—Previously independent whole body translational and rotational degrees of freedom in the two triptycenes become one set for the new structure. Internal rotations with respect to the C-Z bonds are not independent and must be synchronous : Bevel gear action

—The new bonds bring about new stretching, bending and torsional modes.

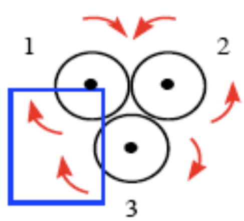
Iwamura, Mislow, *Acc. Chem. Res*. **1988**, *21*, 175

Linear Vs Cyclic Gear Trains

An unlimited number of gear wheels can interact with each other in a *linear* 'gear train'.

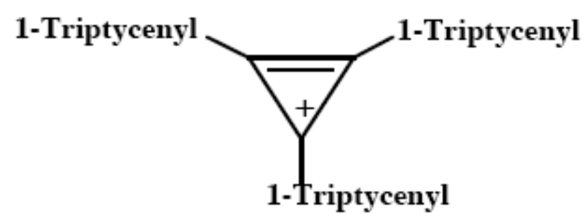


However, if the gear train is *cyclic*, then an *even parity* number of gear wheels must be present *or else free rotation will stop!*



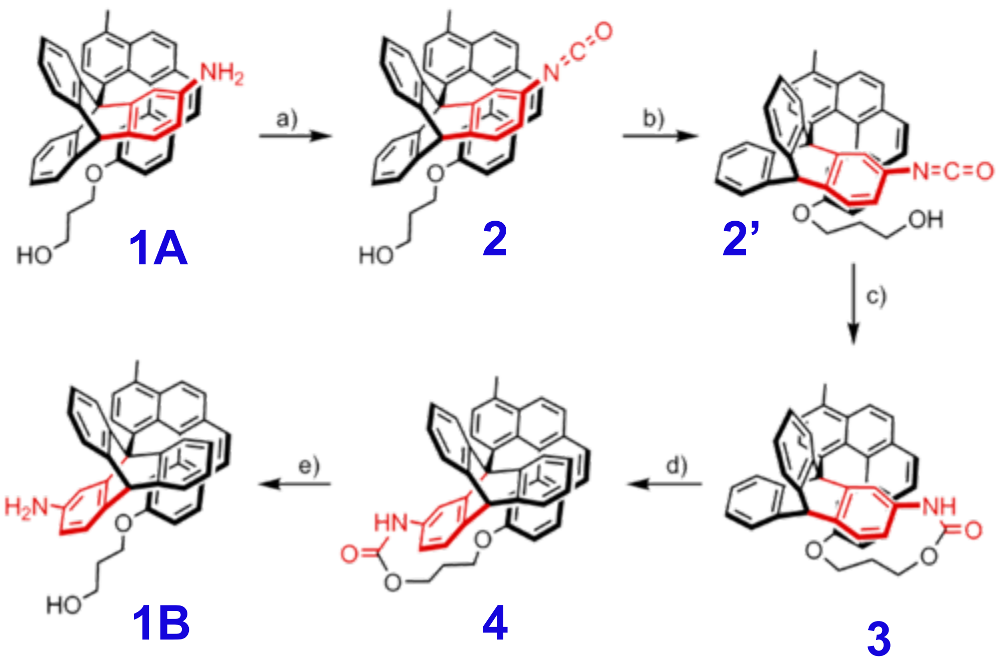
The gearing motion will stop since the 1st and last gears are *conrotatory* to each other rather than being *disrotatory*.

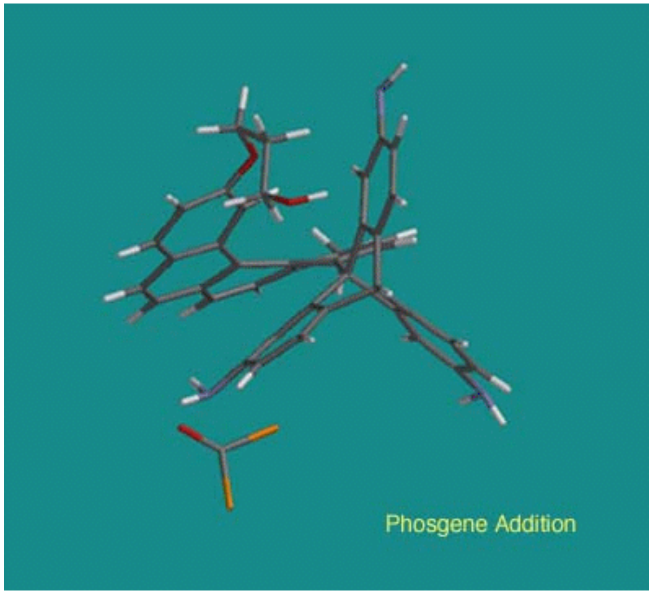
Mislow showed the cessation of rotational motion by synthesizing the rigid tris(9-triptycyl)-cyclopropenyl carbocation.

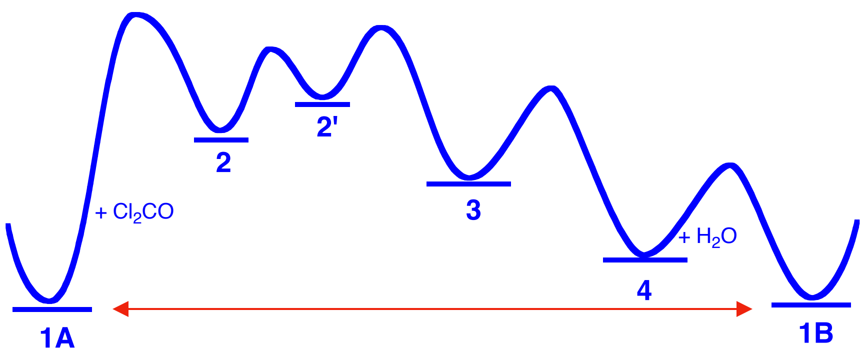


Selected Examples from the Literature

A chemically driven molecular motor







T.R. Kelly, *J. Am. Chem. Soc.*, **2007**, *129*, 376

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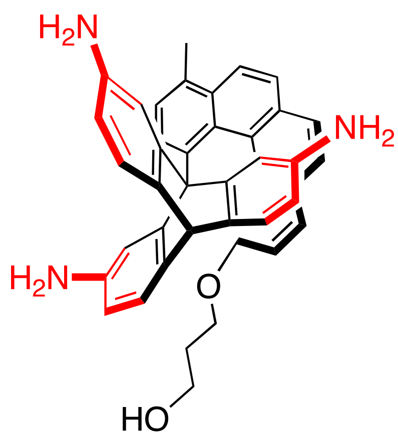
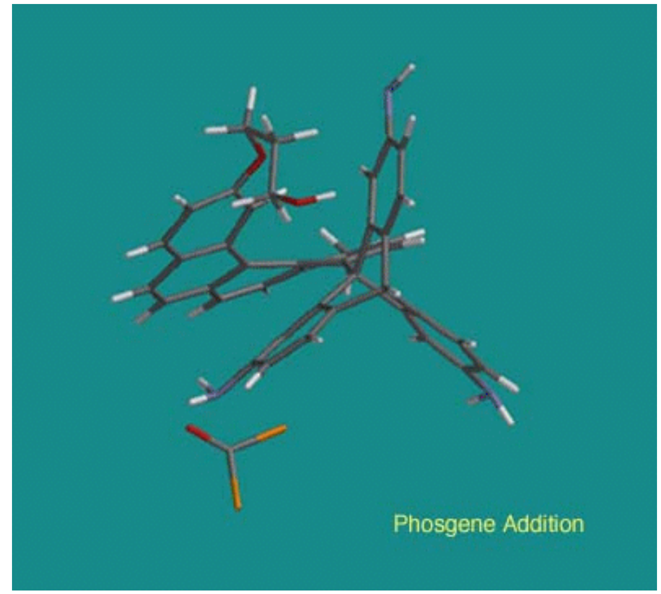
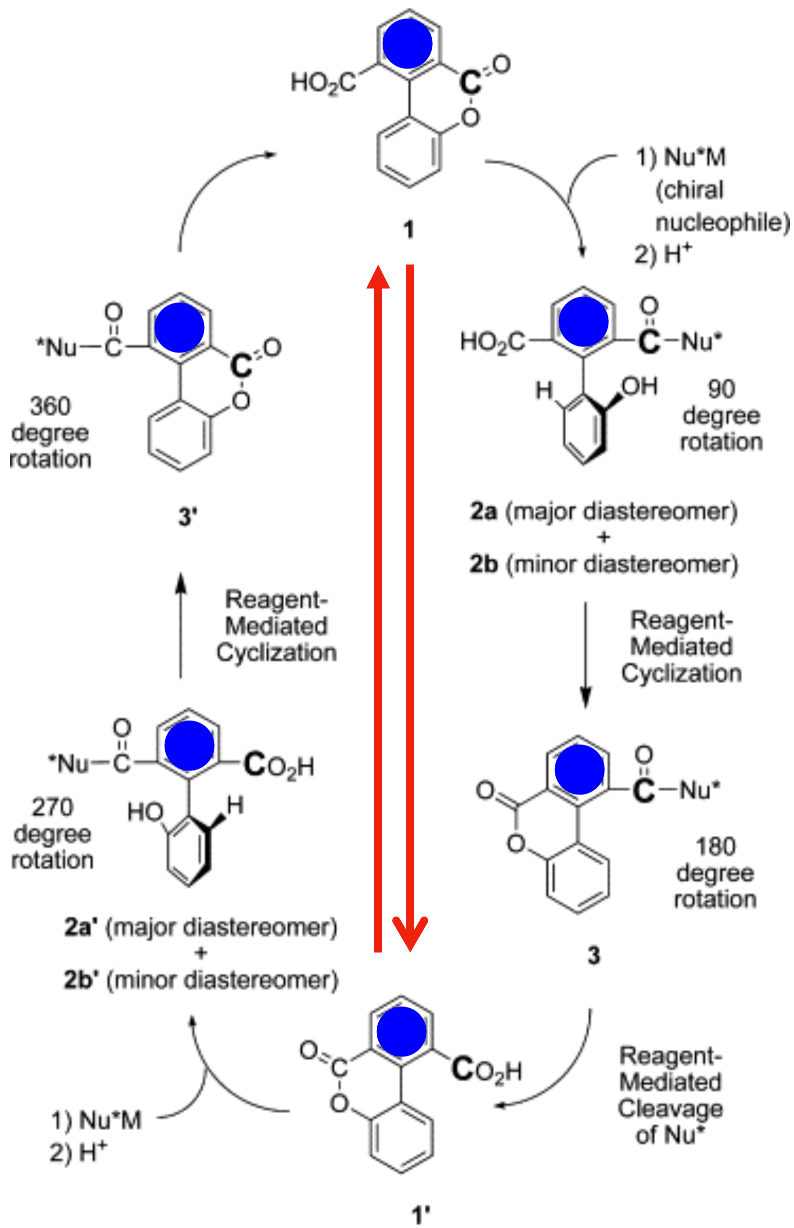


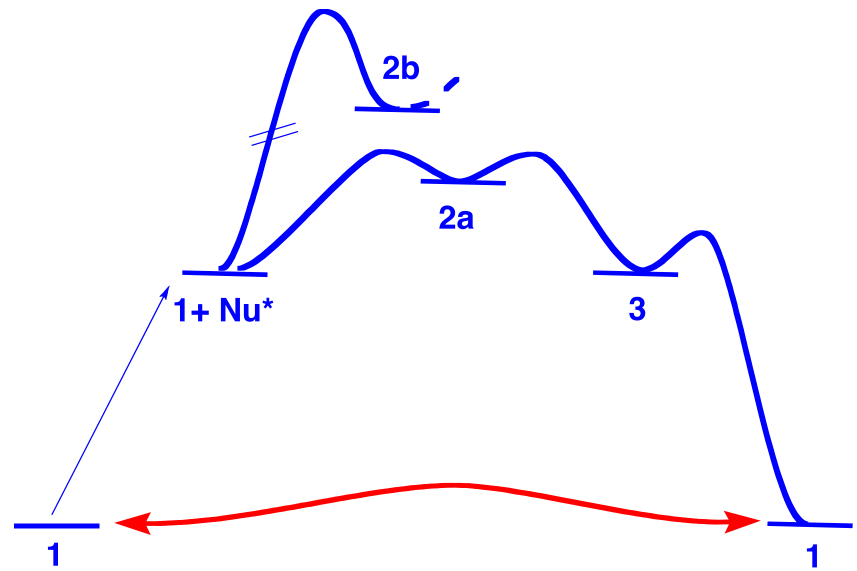


Challenge: Regioselectivity of the phosgene Addition Reaction

T.R. Kelly, J. Am. Chem. Soc., **2007**, *129*, 376

Selected Examples from the Literature

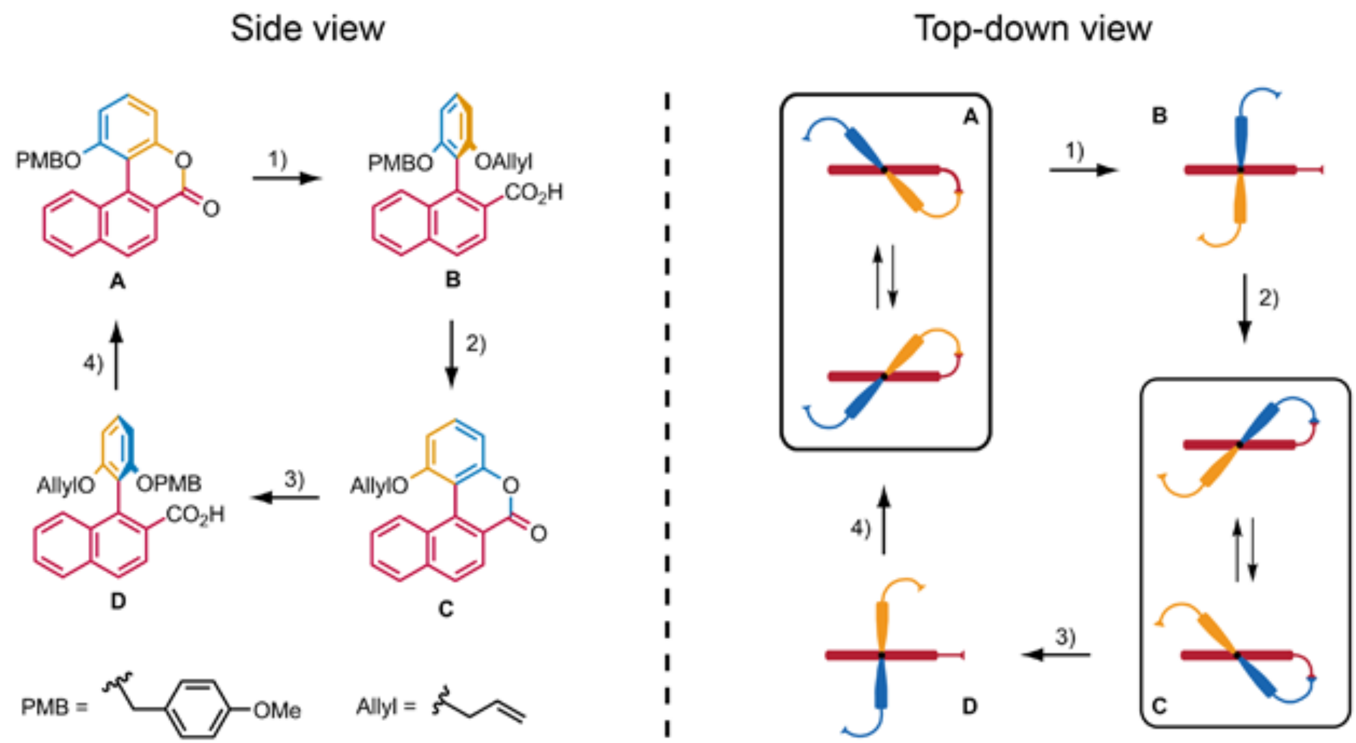




Challenge?

B. Branchaud, Tet. Lett. **2005**, *46*, 8359

Selected Examples from the Literature



Comments (room for improvement):

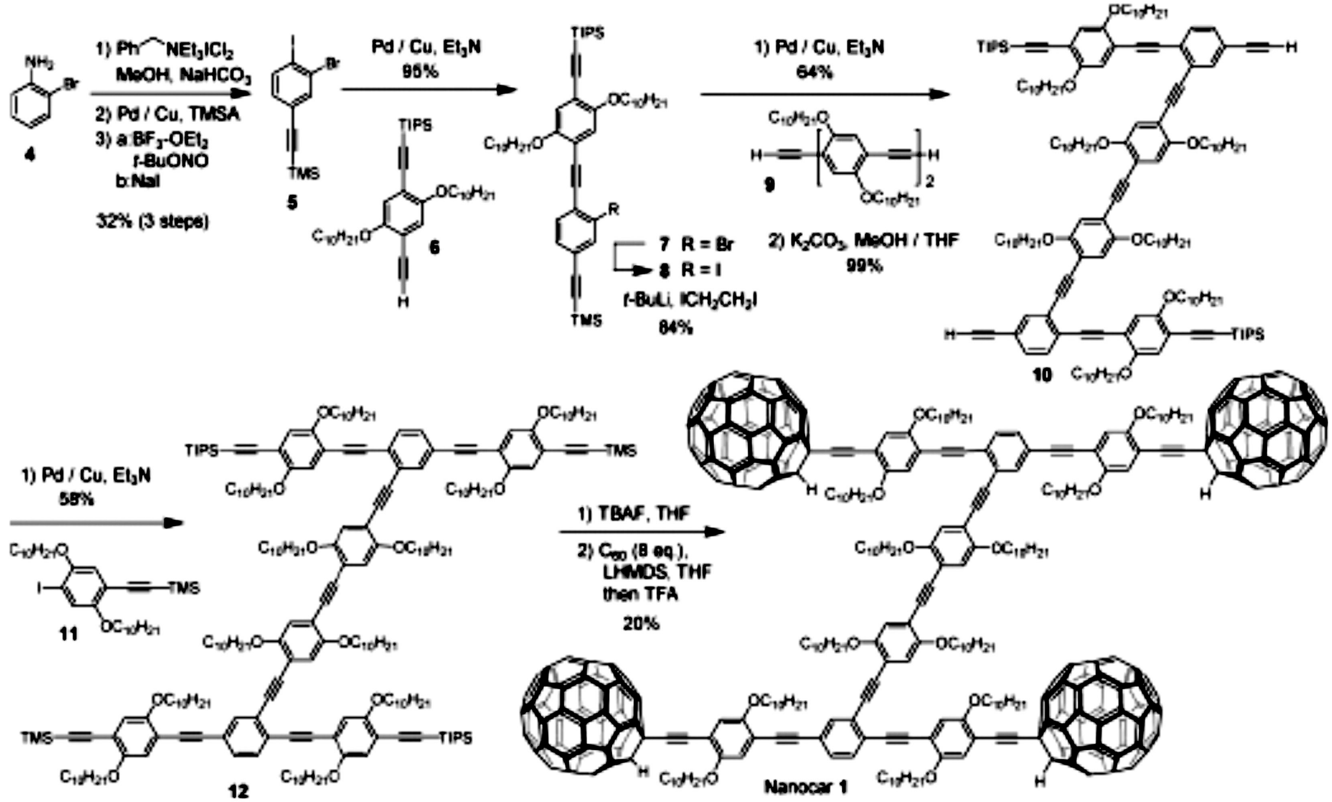
"Step 1, Reduction with (S)-2-methyl-CBS-oxazaborolidine and BH3 at 0°C for 25 min (92% yield of a diol. Mecules undergoing rotation 96.8 %. Alkylation with allyl bromide over 20 hours. Next, the alcohol moiety was oxidized to an aldehyde by CrO3·H2SO4·H2O in acetone for 2 hours, and then to an acid by $NaClO_2$ in the presence of 2-methyl-2-butene in AcOH, H2O, and THF over 1 hour to give 1b in 76% overall yield." ***(~23 h reaction, separation at each stage, 73% efficiency)***

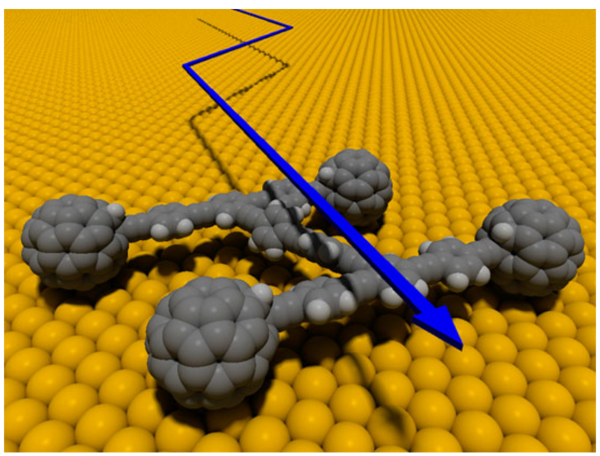
"Step 2, the PMB ether was cleaved by Ce(OTf)3 in MeNO2 in the presence of 1,3-dimethoxybenzene at 60°C for 25 min to give **1c** in 76% yield" ***(~25 min reaction, separation, 76% efficiency)***

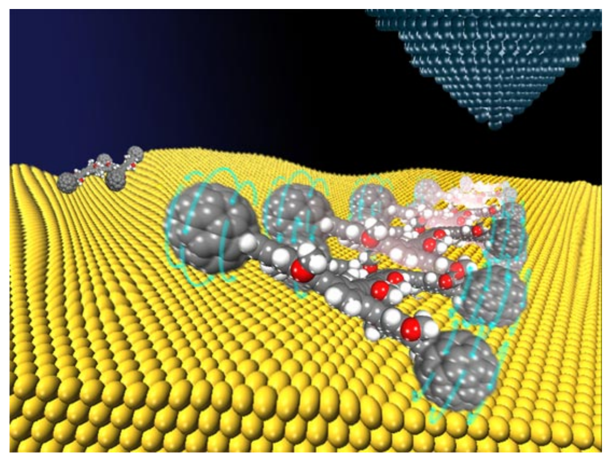
B. Feringa, Science **2005**, *310*, 80

Etc…

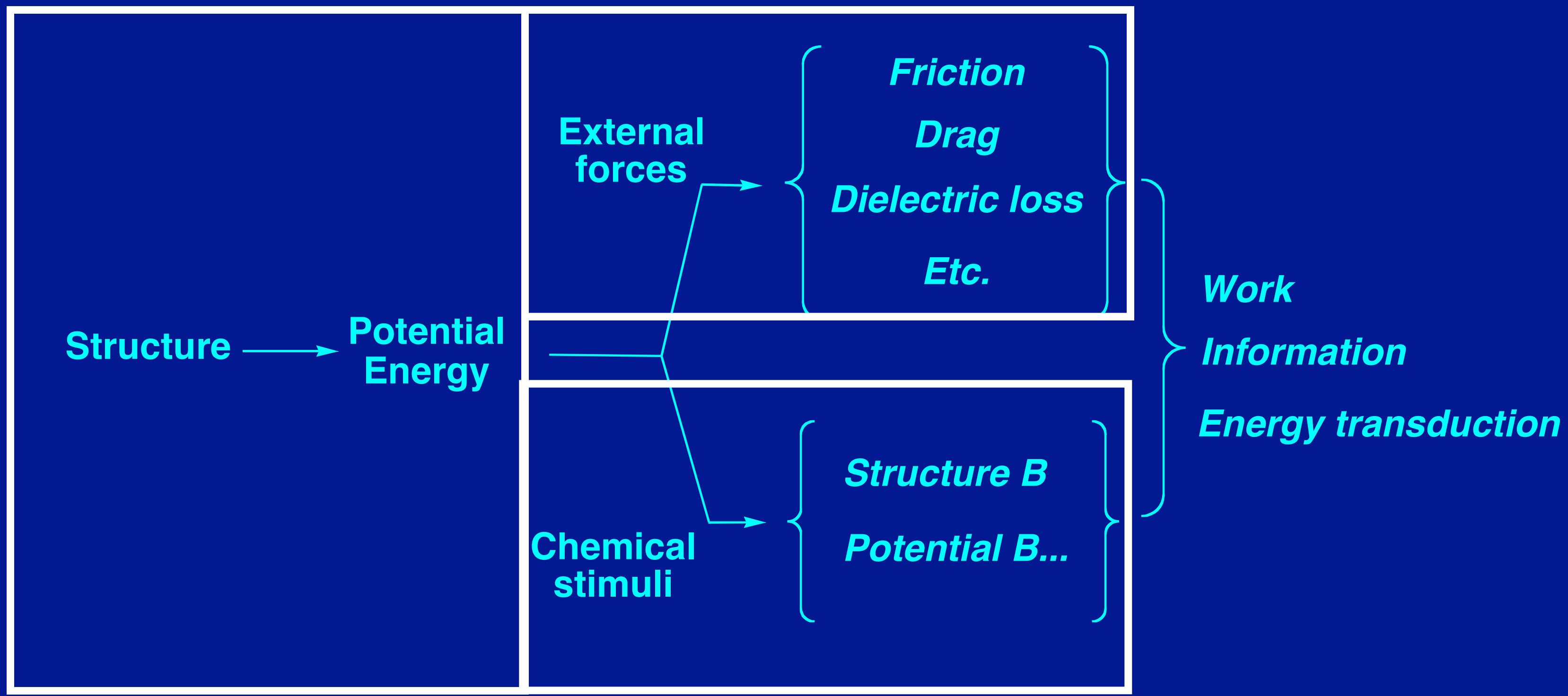
Selected Examples from the Literature







J. Tour, Rice University



From Structure to Function…

PART 3

From simple molecules to complex materials