Post-it™ Fax Note 7671	Date Oct. 11 # of pages ▸ 21
To Prof. Sunney Chan	From Stephanie
Co./Dept. Caltech	Co. Academia Sinica
Phone #	Phone # 886-2-27880472
Fax # 626-578-0471	Fax # 886-2-27853208

PHYSICAL CHEMISTRY

= Physical Description of Chemical Systems, or

Description of Chemical Systems explicitly in terms of the laws of physics

CHEMICAL SYSTEMS

Gases

- Molecular beams
- Rarefied gases
- Gases at low pressures
- Real gases

Liquids

- Pure liquids
- Ideal solutions
- Non-ideal solutions
- Simple electrolyte solutions
- Polyelectrolyte solutions
  - e.g., DNA, protein

Solids

- **Pure metals**
- **Crystalline inorganic or organic compounds**
- **Solid solutions**
- **Powders**
- **Alloys**
- **Composites**
- **Supramolecular assemblies**
- **Nanostructures**
- **Glasses**
- **Liquid crystals**
- **Protein crystals**

Surfaces

- **Thin films**
  (supported on solid; between two immiscible liquids)

Biophysical Chemistry

A DNA or RNA solution

A protein solution

A DNA or RNA crystal

A protein crystal

Protein-DNA or RNA complexes of well-defined stoichiometry

Protein-protein complexes

Enzyme-inhibitor complexes

Enzyme kinetics

Phospholipid membranes

Proteins in bilayer membranes

Cell membranes

Organelles and whole cells

Single DNA, RNA, or protein Molecule

Biological Structure

Primary Sequence

DNA: sequence of nucleic acid bases (A, G, C,T)

e.g., ATATGCGC or GCGCATAT

RNA: sequence of nucleic acid bases (A, G, C, U, and minor bases)

Protein: sequence of amino acids

Non-polar:	**A, V, L, I, F, W, M, P**
Polar:	**G, S, T, C, Y, N, Q**
Acidic:	**D, E**
Basic:	**K, R, H**

Primary sequence gives

CHEMICAL STRUCTURE!

Secondary Structure

DNA: alpha helix (right hand; left hand)

RNA: alpha helix; loops

Proteins: double-helix; beta-sheets; loops; Random coils

Tertiary Structure

DNA: double-helix; triple-helix; aptamers

RNA: cloverleaf fold; other

Protein: three-dimensional fold

Quaternary Structure

3-D structure = location of every atom of macromolecule in three-dimensional space

Structural Biology

In chemistry,

the chemical formula gives the number of each element in the molecule;

the structure of a molecule is defined by the detailed arrangement of the atoms in three-dimensional space; and

the properties of the molecule are determined by its molecular structure.

Similarly, in biology

The three-dimensional fold of a macromolecule in the cell determines its properties and its biological function. Thus,

STRUCTURE AND FUNCTION!

Intermolecular Forces /Intermolecular Interactions

Intermolecular forces or intermolecular interactions are important in chemistry. Otherwise, there would be

- no exchange of energy between molecules in the gas phase during collisions;
- no formation of van der Waal molecules, such as A.HCl, $(H_2O)_n$;
- no formation of condensed phases, i.e., liquids and solids
- no chemical reactions

Orders of magnitude:

Weak:	<<	k_BT
Intermediate:		k_BT
Strong:	>>	k_BT

k_BT = thermal energy per molecule

k_B = 1.38×10^{-16} ergs/K

and k_BT = 1×10^{-21} calories

or 4.2×10^{-21} joules

or 2.5×10^{-2} eV

at room temperature, namely 300 K.

Intermolecular forces

Electrostatic in nature

Strong:

Exchange forces arising from overlap of electron charge clouds

Ion-monopole ion-monopole interactions

Hydrogen-bonding

Hydrophobic interactions

Intermediate:

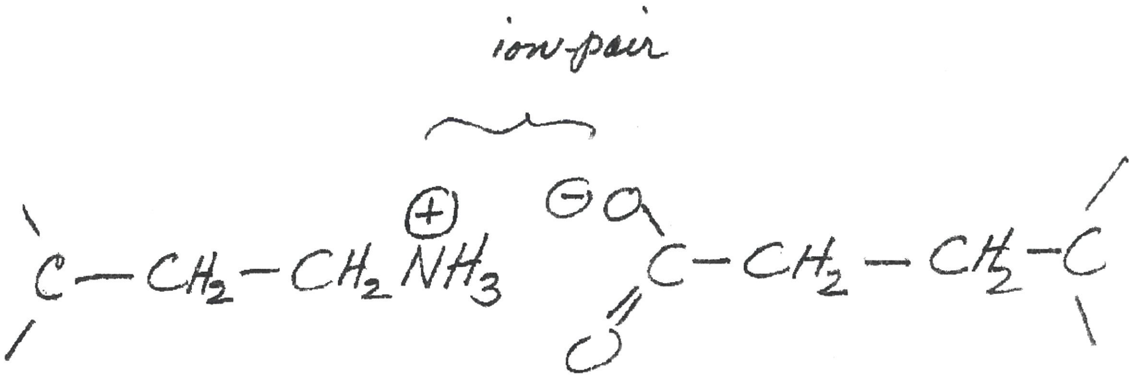
Electric dipole-dipole interactions

Weak:

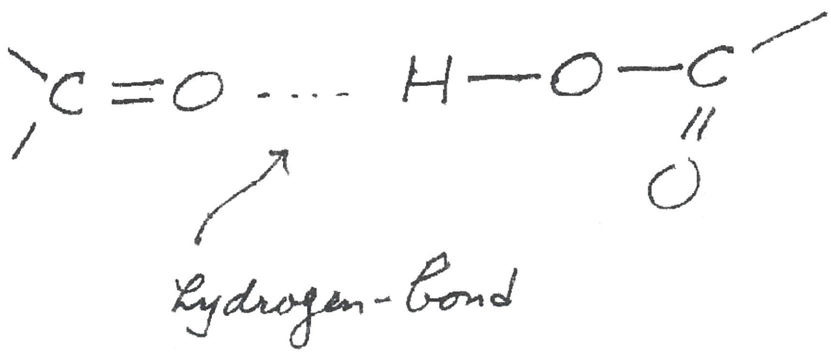
Electric-dipole induced-dipole interactions

Spontaneous-dipole induced-dipole interactions

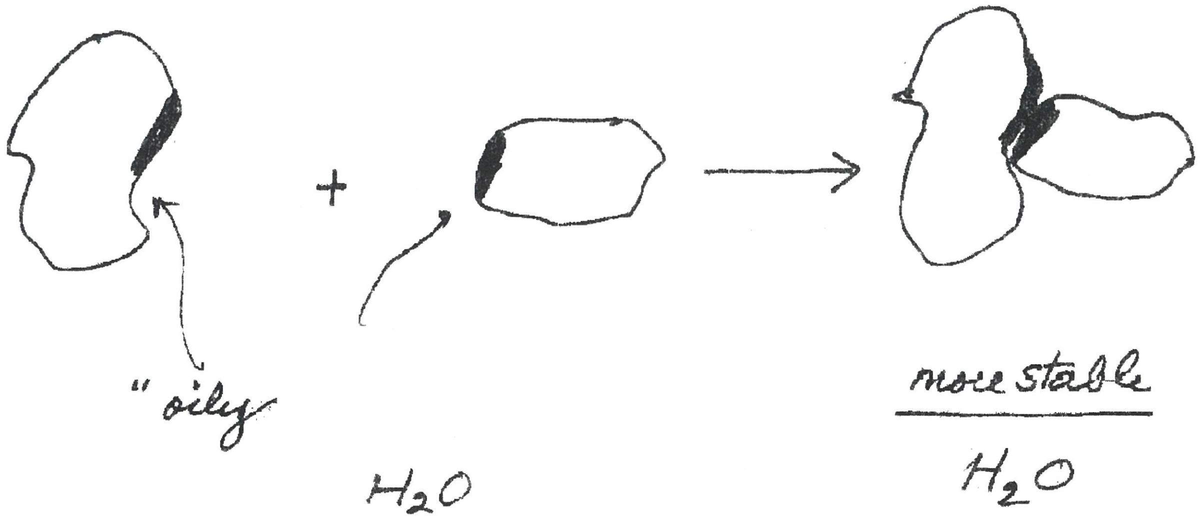
Monopole-monopole interaction



Hydrogen-bonding interaction

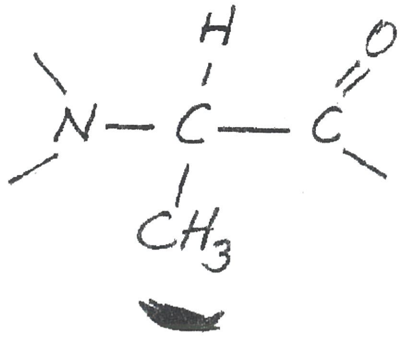


Hydrophobic interaction

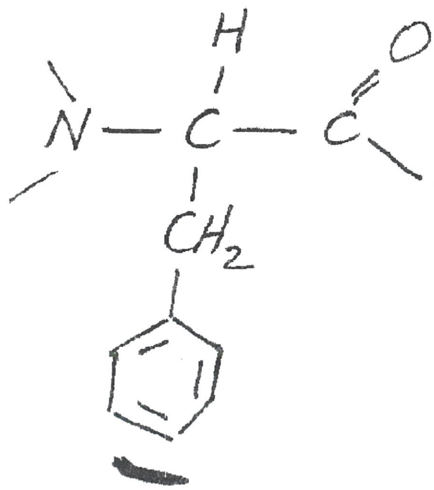


Amino acids with hydrophobic side-chains:

A, V, L, I, F, W, M



(A)



(F)

Consequences of Intermolecular Interactions

Σ interactions = Binding strength

Define

Kequilibrium constant

If A + B $\rightleftharpoons$ Complex,

Then,

$$K = [\text{Complex}] / [A] \quad [B]$$

where [ ] denotes concentration of species at chemical equilibrium.

K large, strong interaction

K small, weak interaction

Antibody-antigen interactions:

$$K = 10^{8} - 10^{12}$$

Drug-Receptor Interactions:

$$K = 10^{6} - 10^{10}$$

Enzyme-substrate/inhibitor interactions

$$K = 10^{3} - 10^{6}$$

Importance of Biological Interactions

Self-assembly of biological molecules

bilayer membranes

cytosketal system (microtubules and microfilaments)

muscle fibers

Recognition

Antigen-antibody interaction

Enzyme-substrate/inhibitor interaction

Hormone-receptor interaction

Drug-receptor interaction

Chemistry

Signaling

Energy transduction

Transport

Catalysis

Biological interactions are neither too strong or too weak!

If too weak, the interaction is not specific enough;

If too strong, it would require too much energy to break apart and recover original components after the biological event is accomplished.

So, biological macromolecules are characterized by a high degree of molecular motions:

Fast local motion of side-chains (often referred to as molecular motility; timescales of picoseconds to nanoseconds)

Slow collective motions of domains (timescales of milliseconds to microseconds)

Conformational transitions (timescales of milliseconds to seconds)

Important issues in Biophysical Chemistry

1) Three-dimensional structures of proteins, DNA's and RNA's.

2) The folding of a heteropolymer (RNA folding
   and protein folding)
   a) three-dimensional fold at native state;
   b) density of conformational states at various energies;
   c) pathway(s) and kinetics of folding in solution;
   d) biological folding in the cell.

3) Macromolecular dynamics
   a) breathing motions
   b) collective fluctuations
   c) conformational transitions

4) Prediction of protein structure and function

5) Relating molecular structure and dynamics to biological function in general

6) Signal transduction

7) Self-assembly and organization of biological macromolecules

8) Macromolecular recognition

9) Mechanism of energy transfer and energy transduction

- **a) transfer of light excitation**
- **b) electron transfer**
- **c) light driven ion and proton pumps**
- **d) electron driven ion and proton pumps**
- **e) conversion of redox energy and protonomotive force to synthesis of ATP**
- **f) coupling of ATP hydrolysis to activate biochemical processes**

g) membrane-protein associated signal transduction linked to control of cellular differentiation and development

10) Mechanisms of solute transport across cellular membranes

10) Development of methods for macromolecular structural determination in solid state and in solution

12) Development of methods for determining the molecular weight, size, and shape of macromolecules

13) Imaging of specific macromolecules in cells

14) Imaging of single macromolecules

15) Single molecule spectroscopy

Important new areas in biophysical chemistry

Proteomics

Bioinformatics

Structure determination of supramolecules including protein-protein complexes, protein-nucleic acid complexes, structures of complex RNA's and protein RNA structures; structures of organelles such as Golgi apparatus, lysosomes, etc.

Signaling and signal transduction

Imaging of single molecules

Pathways of in-vitro protein- and RNA folding and biological folding