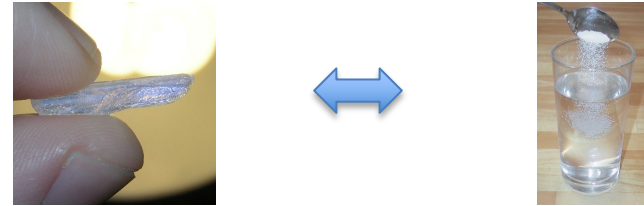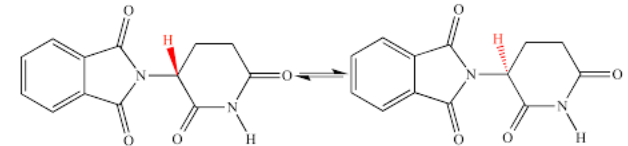# Drug Reactions and Transitions

- *Crystallization, Dissolution*

- Drug *Isomerization* to Active conformer
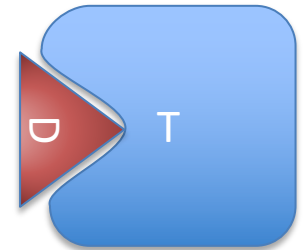
Thalidomide **R** ⟷ Thalidomide **S**

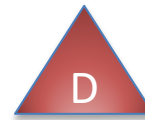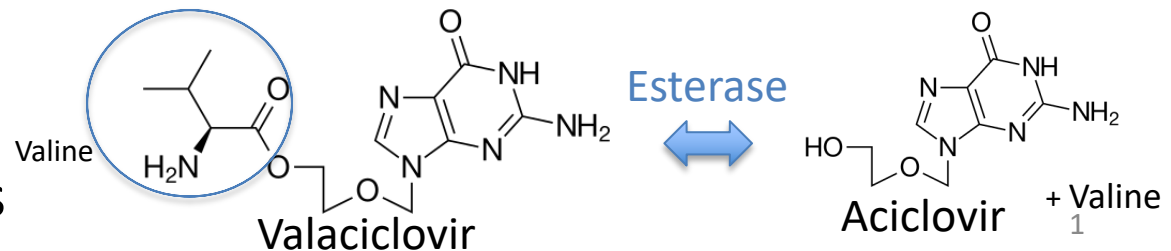- **D**rug *Binding* to its **T**arget

  D + T ⟷ DT

  vs *Dissociation*
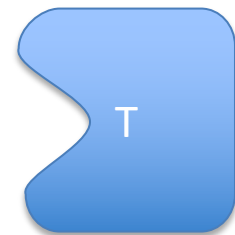
- *Chemical* Transformations

  reactants ⟷ products

- Many other examples

Valine

Valaciclovir

Esterase

Aciclovir   + Valine

1

Thermodynamics in Pharmacology
Drug Discovery and Properties
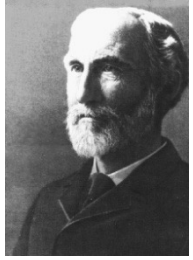
Most drugs act via **binding** specifically to a receptor. How do we find a **chemical structure** that binds to a receptor? What **concentration** is needed for a therapeutic effect?

$\Delta G_{binding}$: the median value for small drugs is ~ **-11 kcal/mole**. That corresponds to: $K_{dissociation}$ ~ **20 nM**. How is ΔG related to K?

$$\Delta G_{binding} = \Delta G_{complex} - (\Delta G_{ligand} + \Delta G_{target})$$

Imatinib (Gleevec)

What is **G and ΔG** ? How is it related to kinetic and potential energy of molecules? How to measure it?

Reactions and transitions, **Equilibria**, energies, concentrations,
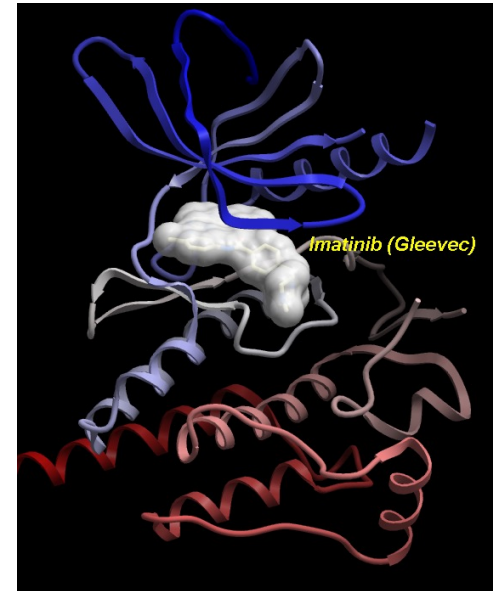
Thermodynamics. Part1. **Enthalpy**

- Drugs go through transitions and modifications, both physically and chemically.
- Transitions can reach EQUILIBRIUM in which the total free energy function **G** has the lowest value.
- **G** consists of **Enthalpic (H)** and Entropic terms
- Enthalpy, or **heat content**, grows with **T**
- The slope of **H** vs **T** curve is called **Heat Capacity**
- Properties of individual molecules are replaced by mean quantities for a very large number of molecules, called **Thermodynamic Variables**

Thermodynamics: System and variables

- Which quantities define a system? Concentrations of constituents, Energy functions (internal energy **U,** enthalpy **H**, free energy G), Temperature, Pressure, Volume, ..

SURROUNDINGS

P, V, T, ρ, U, H, G

SYSTEM

$c_1, c_2, c_3, n_1, ..$

BOUNDARY

- *Extensive* quantities are proportional to the amount of substance (e.g., V, number of moles, energy)

- *Intensive* quantities are independent of the amount of substance (e.g., density ρ , temperature T, pressure P, concentrations)

- Intensive quantities are either intrinsically intensive (e.g., pressure), or are the ratio of two extensive quantities (e.g., density = mass/volume).

- Power of theory: Thermodynamics predicts the state of a complex system via only small number of variables of state.
For example, to describe all properties of 1 g of water, only two variables of state are sufficient (e.g., **P** and **T**).

Type of system	Mass flow	Work	Heat
Open	✓	✓	✓
Closed	✗	✓	✓
Thermally isolated	✗	✓	✗
Mechanically isolated	✗	✗	✓
Isolated	✗	✗	✗

- **Equations of State:** relationship between variables (or quantities), e.g. **PV = n**R**T**

The First Law of Thermodynamics

- Conservation of Energy: "heat in" increases the energy, "work out" decreases the energy for closed systems
- Internal energy energy **U** consists of the kinetic energies and potential energies (e.g. molecular interactions) of all molecules in the system.

$$\Delta U = q - w$$

energy change   heat added   work done

The change in internal energy (ΔU) of all molecules in a closed system is equal to the heat added (q) to the system minus the work done by the system (w)
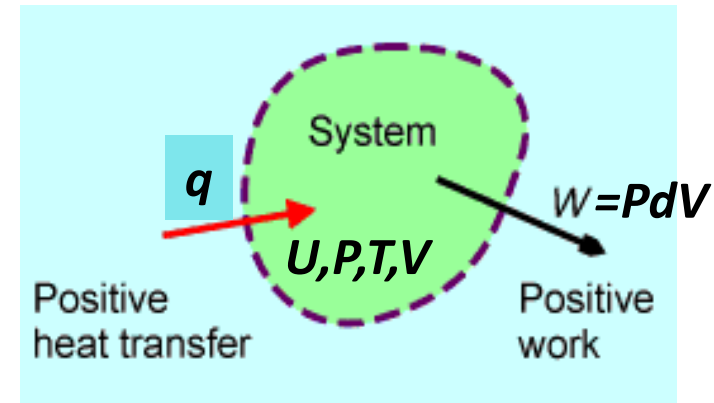
Enthalpy Definition

$$H = U + PV \qquad q = \Delta U + W \text{ (1}^{st}\text{ law)}$$

where **U** is the total internal energy of the system (potential and kinetic);

P is pressure

V is the volume of the system

$$\Delta H = \Delta U + \Delta(PV)$$

Thermodynamic Processes

- Greek roots of the thermodynamic terms:
  $$\Delta U = q - w$$
  - *isos*   equal
  - *baros*   weight
  - *adiabatos* not passable
- Isothermal T = const
- Isobaric P = const $w = P\Delta V$ *(calorimetry)*

  $\Delta U + w = q;\ \Delta U + P\Delta V = q\ ;\ \Delta(U+PV) = \mathbf{q}$

- Isochoric V = const $w = 0$ *(bomb calorimetry)*, $\Delta U = q$
- Adiabatic q = 0 $\Delta U = -w$

- Enthalpy (or heat content) **H** is defined as **U + PV**, where **P** is pressure and **V** is volume.
- Heat content (*H*) of a drug specimen measured by a **calorimeter** helps to find states, transitions and temperature ranges of stability
- It also characterizes critical events like drug binding, amorphous drug compounds

Calorimetry and Heat Capacity

$$\Delta U = q - w$$

- We can measure heat (energy) $q = \Delta U + w$

  – *transferred* to the system, or

  – *produced* by the system

  and associate it with temperature change of the system ΔT in a **calorimeter**

  Heat capacity, $C \equiv q / \Delta T$

reactions

physical changes

- Thus, the *heat capacity* of an object is defined as *the amount of heat energy required to raise its temperature by 1 K (or 1°C)*

  • The heat capacity of *1 mol* of a substance is called its ***molar heat capacity***   Per mole: "molar"

  • The heat capacity of *1 gram* of a substance is called its ***specific heat .***   Per gram: "specific"

Caution about the sign of heat *q*: exothermic reaction implies NEGATIVE heat value (the system produced heat).

Heat Capacity at constant volume, C_V
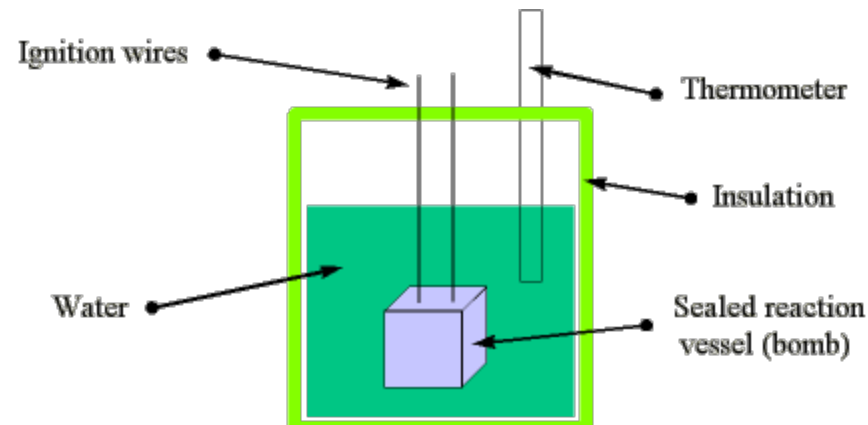
$$\Delta U = q - w$$

- At V = const, 1$^{\text{st}}$ law: $q = \Delta U$

- Bomb Calorimetry (constant-volume calorimetry)

- **Heat capacity** at constant volume

$$C_V \equiv \left(\frac{\partial U}{\partial T} \right)_V \cong \frac{q_V}{\Delta T}$$

- C_V values are tabulated.

- A practical relationship:

$$\Delta U \approx C_V \Delta T$$

Ignition wires

Thermometer

Insulation
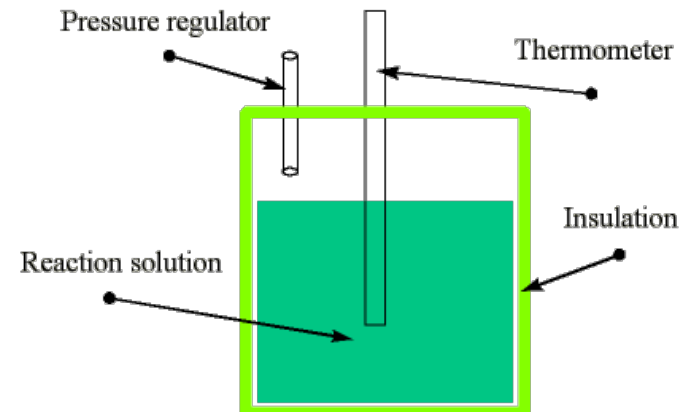
Water

Sealed reaction vessel (bomb)

Heat Capacity at constant pressure, C_P

- Most processes in chemistry and biology occur at constant pressure

- Let us design a new function of state that is directly related to heat at constant pressure.

- Notice that at P=const

$$C_P \equiv \left(\frac{\partial(U+PV)}{\partial T} \right)_P \cong \frac{q_P}{\Delta T}$$

$$w = \int_a^b P dV = PV \Big|_a^b = PV_b - PV_a$$

$$q_p = \Delta U + P\Delta V \qquad C_P = \frac{\Delta U + P\Delta V}{\Delta T}$$

Understanding Heat Capacity from Atomic Structure Degrees of Freedom of a Molecule in Gas

- Degrees of freedom (DF) are store energy
- Number of DF increases with T (bonds get excited)
- Theory: $C_v = \frac{1}{2}R \times number\_of\_DF;$ $\quad C_p = C_v + R$
- In a drug molecule C_v is $R \times$ n_vibrational_DF
- Monoatomic gas: 3 DF (translational), $C_v = 1.5R$
- Diatomic gas below vib. temp.: 5 DF (3 trans + 2 rot)
- Real values (25°C, 1 atm):

Translational Motion — 3

Rotational Motion — 2

Vibrational Motion — 2
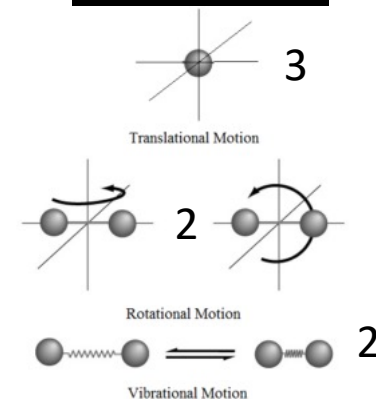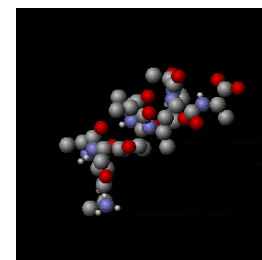
Monatomic gas	$C_{V,\,m}$ J/(mol·K)	$C_{V,\,m}/R$
He	12.5	1.5
Ne	12.5	1.5
Ar	12.5	1.5
Kr	12.5	1.5
Xe	12.5	1.5

Diatomic gas	$C_{V,\,m}$ J/(mol·K)	$C_{V,\,m}/R$
H_2	20.18	2.427
CO	20.2	2.43
N_2	19.9	2.39
Cl_2	24.1	3.06
Br_2 (vapor)	28.2	3.39

Enthalpy or Heat Content

- At P=const

- Calorimetry at constant pressure directly measures enthalpy increments, ΔH and C_P is ΔH_{1deg}

- to obtain $H(T_2)$, C_P can be integrated over T (Kirchhoff)

- H is a state function since U, P, and V are state functions

$$H = U + PV$$

$$q = \Delta U + P\Delta V$$

$$= \Delta(U + PV) \equiv \Delta H$$

$$C_p \equiv \left(\frac{\partial H}{\partial T}\right)_P \cong \frac{q}{\Delta T}$$

$$\Delta H \approx C_P \Delta T$$

(Kirchhoff)

Heats of Formation of a Molecule

- **Standard enthalpy of formation** of a compound is the change of enthalpy during the formation of 1 mole of the substance from its constituent elements (P=1bar, T usually 25 °C r 298.15 K)

- The $\Delta_f H^0$ values for most compounds are known. For example: NIST Chemistry WebBook

- Examples:

			$\Delta_f H^\ominus$ /(kJ/mol)
Ethanol	Liquid	C_2H_5OH	−277.0
Ethanol	Gas	C_2H_5OH	−235.3
Glucose	Solid	$C_6H_{12}O_6$	−1271
Isopropanol	Gas	C_3H_7OH	−318.1

Enthalpy *vs* T: Kirchhoff's Law

Can we start from ΔH at T_1 and calculate ΔH at another temperature T_2?

By definition :

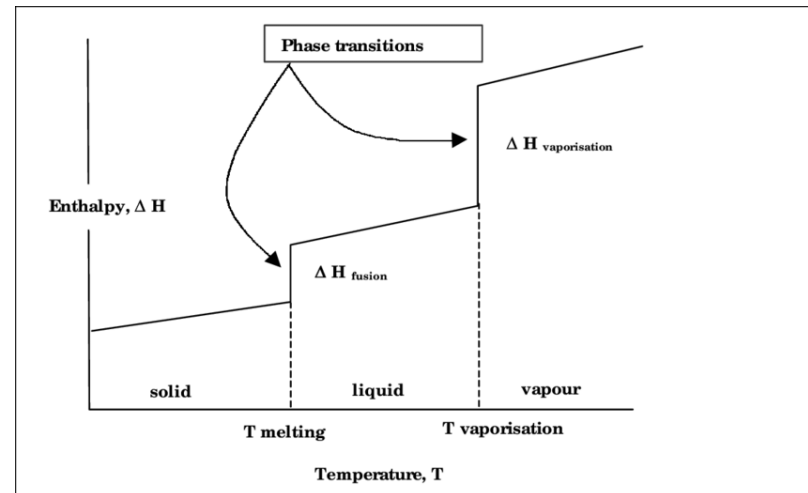$$C_P \equiv \left(\frac{\partial H}{\partial T} \right)_P$$

$$H(T_2) = H(T_1) + \int_{T_1}^{T_2} C_P dT$$

$$H(T_2) \approx H(T_1) + C_P \Delta T$$

The heat capacity itself depends on temperature, but near 270-370K in most biological reaction or transition cases we can assume C_p=const

Gustav Robert Kirchhoff, 1824-1887, a German physicist

Phase transitions

ΔH vaporisation

Enthalpy, ΔH

ΔH fusion

solid   liquid   vapour

T melting   T vaporisation

Temperature, T

Kirschhoff's Law: Example

- Enthalpy of formation of aspirin molecule is 736 kJ/mol at 298K and its heat capacity is 225 J/(mol K). Find ΔH and H at 36.6 C

- Solution:

$$H(T_2) \approx H(T_1) + C_P \Delta T$$

736+0.225 (36.6-25.0)~739 kJ/mol

Enthalpy and Internal Energy

$$\Delta H \approx \Delta U$$

- For *liquids and solids*

because the thermal expansion (volume change) is small.

- Even *if gas is produced* in a reaction, the extra 'work' is only:

   *H – U = PV = **RT** = 2.5 kJ/mol = 0.6 kcal/mol*

that is much smaller than a typical process or transition in liquids or solids (e.g. burning or dissolution, or partition)

- **Enthalpy** characterizes the internal energy changes (corrected by the pressure times volume change) in any of the *drug-related* **transitions**

Drug-Target Enthalpy of Binding

- An enthalpy difference between drug bound to the pocket and drug and pocket in solution (ΔH shown in green)

- Negative ΔH

is better (specificity)
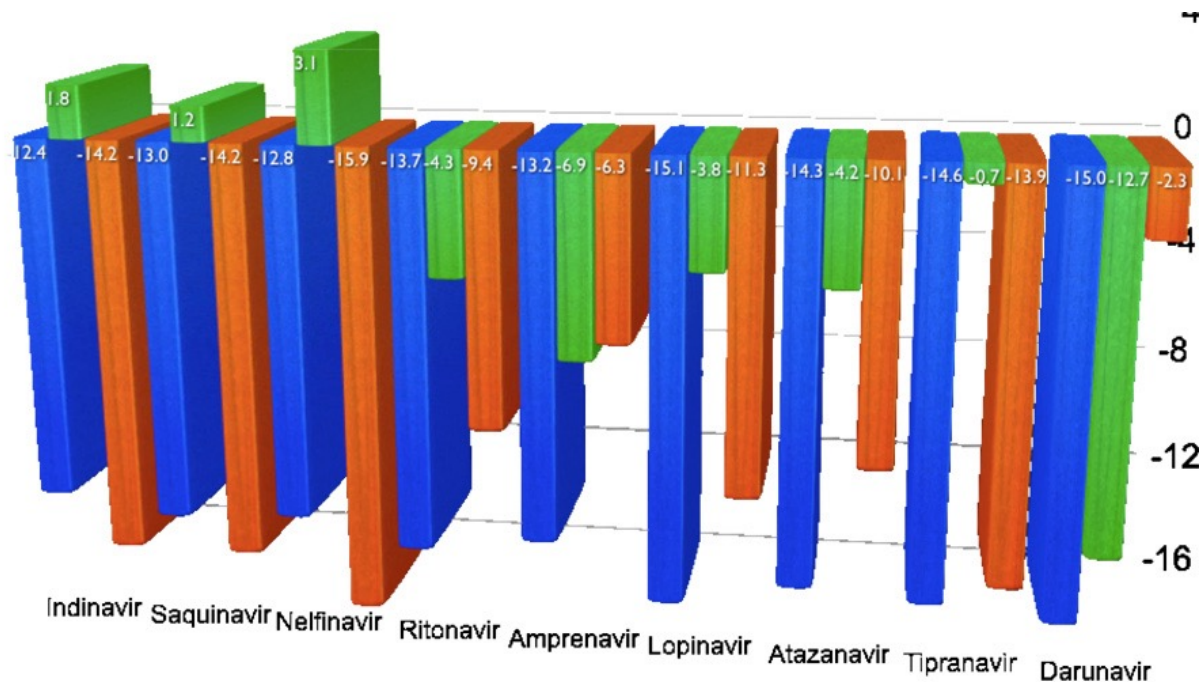
Summary

	Constant Volume	Constant Pressure
Defines	Heat at constant volume	Heat at constant pressure
Energy	Internal Energy, **U**	Enthalpy, **H=U+PV**
Contributions	*Total potential and kinetic energy*	*Total energy shifted by PV*
Heat Capacity (slope of H vs T)	$$C_v = \frac{\partial U}{\partial T}$$	$$C_p = C_v + P\frac{\partial V}{\partial T}$$
Ideal Gas	$C_v = 6_{or3or5}R/2 + Rn_{vibr}$	$$C_p = C_v + R$$
Energy Increments	$$\Delta U \approx C_V \Delta T$$	$$\Delta H \approx C_P \Delta T$$
Ground State	Only ΔU with respect to a described *ground state* (U_0) makes sense. C_V does not depend on U_0	Same for ΔH and C_P