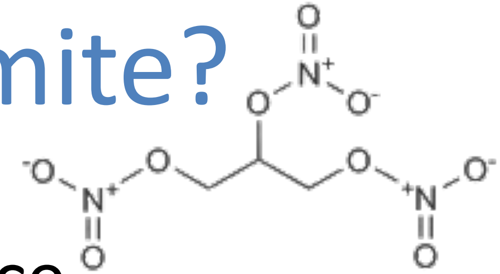
# Heat, Enthalpy of drug Formation, Enthalpy of Reaction, Binding, Cycles, Drug Dissolution

Objectives:

- Learn to look up Enthalpy of Formation
- Learn to evaluate Enthalpy of Reaction, Dissolution
- Understand the pharmacological implications of exothermic or endothermic drug transitions

$$H = U + PV$$

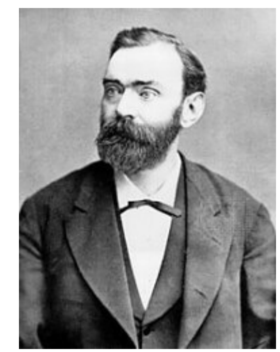
# **Nitroglycerin**: drug or dynamite?



- used to treat angina and heart failure since 1879 (glycerin + nitric acid + sulfuric acid)
- Mechanism: converts into Nitric Oxide (•NO), a potent vasodilator, wound healing
- NO-synthase activated by garlic, morphine, L-arginine increases NO
- $4\ C_3H_5(ONO_2)_3\mathit{(liq)} \rightarrow 12\ CO_2 + 10\ H_2O + 6N_2 + O_2 + 4 \bullet 1415$ kJ of heat
- Density = 1.6 g/mL (MM 227.09) , 4 moles -> 570 mL; Products: 710 L

Warning: Nitroglycerin patch **explosions** during defibrillation may be due to voltage breakdown involving the metal mesh in some patches.

Ascanio Sobrero
First synthesized NG



Alfred Nobel
Fellow student of Sobrero

# Specific Heat (per mass)

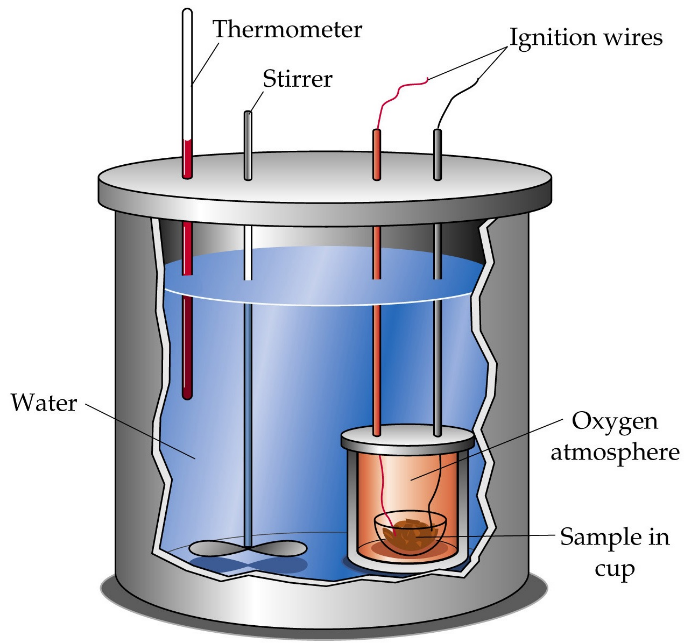
- Enthalpy: $H = U+PV$
- $P=const$:   $\Delta H=q$
- Calorimetry: $\Delta H= s m \Delta T$

  s : specific heat,

  $s_{water} = 4.186$ J/(g °C)

  Or 1 cal/(g °C)  in calories

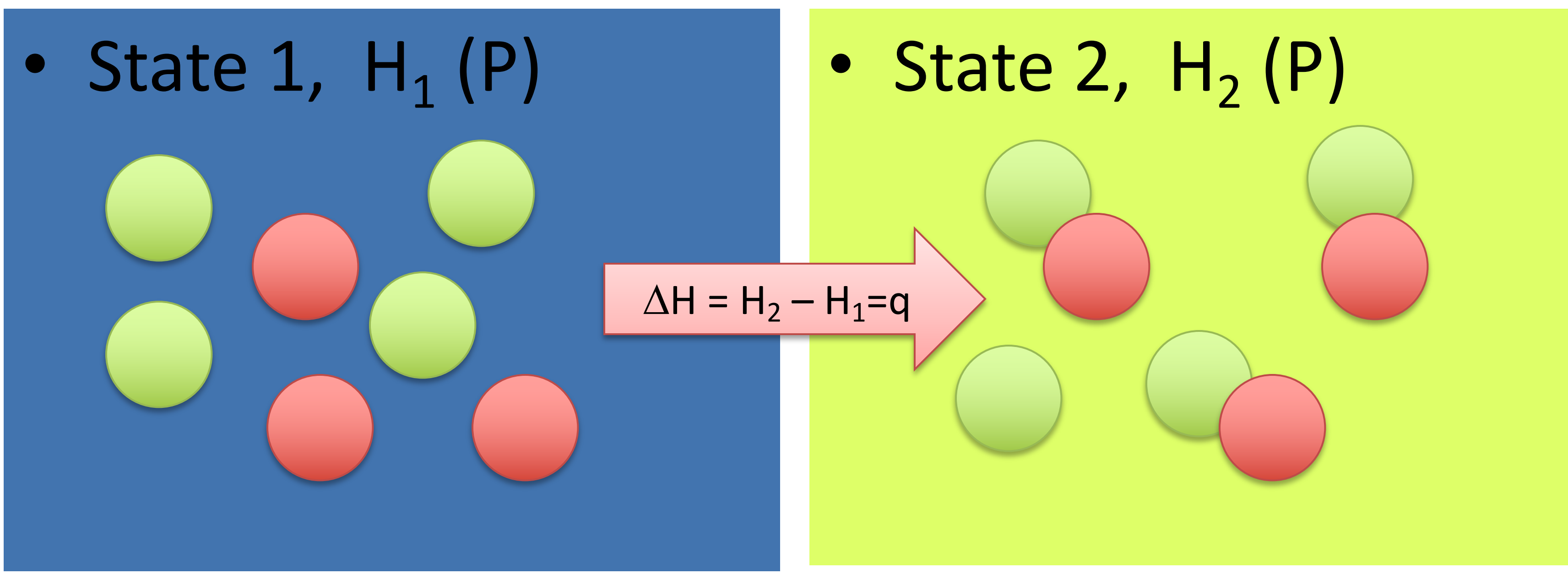
  $m$ : mass of in grams




**Caution about the sign of heat *q*:  exothermic reaction means NEGATIVE heat.**

# ΔH between two states with the same element composition at constant pressure

ΔH shows which state has lower internal energy (corrected by PΔV)
ΔH defines if the heat is produced or absorbed during the transition



# Chemical energy of formation of a drug from elements in their simplest stable state, $\Delta_f H$

- *Enthalpy* of formation: **H** gets *lower* as covalent *bonds* are formed
- *Burning* (reaction with $O_2$) is an overall *increase* of the number of bonds and/or the 'strengths' of bonds. Some bonds are formed, some broken but to total balance is forming *more* bonds or *stronger* bonds.

- The reference states for the $\Delta_f H$ values are single elements in solid, liquid or gas forms:
  - **Liquid**: Hg and $Br_2$
  - **Gas**: He, Ne, Ar, Kr, Xe, Rn (inert gases) an $H_2$, $O_2$, $N_2$, $F_2$, $Cl_2$

# Enthalpies of formation

- Imaginary reaction: formation of a substance, in a given state (s/l/g/aq), from its elemental components, in their *standard states*. ( '*aq*' means *aqueous solution* )
- The reaction can occur at different T and P conditions
- $\Delta H_f°$ is the *molar enthalpy of formation*
- The *standard state* of a substance, mixture, or solution is an arbitrarily chosen reference point; often its state at STP: P = 1 bar, T = 273 K or ~300K).

- The **standard states of elements** are:
  - **Liquid**: Hg and $Br_2$
  - **Gas**: He, Ne, Ar, Kr, Xe, Rn (inert gases) an $H_2$, $O_2$, $N_2$, $F_2$, $Cl_2$
  - **Most stable solid allotrope**: other elements (e.g. graphite for C)
- $\Delta H_f°$ for an element in its standard state is 0.
- $\Delta H_f°$ values for many substances are tabulated.
- E.g. http://webbook.nist.gov/chemistry/
- https://en.wikipedia.org/wiki/Standard_enthalpy_of_formation
- Solid allotrope (*allo*- other, *trope* – form): eg graphite & diamond

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# Some $\Delta H_f°$ values at $25^0C$ [kJ/mol]

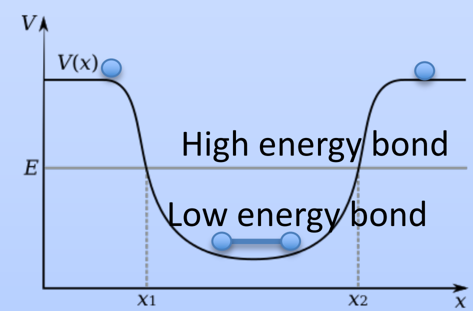
Water

| | | | |
|---|---|---|---|
| Mercury, bromine | liquid | Hg, $Br_2$ | 0 |
| Inert gases | gas | He, Ne, Ar, Kr, Xe, Rn | 0 |
| Hydrogen, oxygen, nitrogen, fluorine, chlorine | gas | $H_2$, $O_2$, $N_2$, $F_2$, $Cl_2$ | 0 |
| Carbon | Solid (graphite) | C | 0 |
| Carbon | Solid (diamond) | C | 1.8 |
| Ammonia | aqueous | $NH_3$ | -80.8 |
| Ammonia | gaseous | $NH_3$ | -46.1 |
| Sodium carbonate | solid | $Na_2CO_3$ | -1131 |
| Sodium chloride (table salt) | aqueous | NaCl | -407 |
| Sodium chloride (table salt) | solid | NaCl | -411.12 |
| Sodium chloride (table salt) | liquid | NaCl | -385.92 |
| Sodium chloride (table salt) | gaseous | NaCl | -181.42 |
| Sodium hydroxide | aqueous | NaOH | -469.6 |
| Sodium hydroxide | solid | NaOH | -426.7 |
| Sodium nitrate | aqueous | $NaNO_3$ | -446.2 |
| Sodium nitrate | solid | $NaNO_3$ | -424.8 |
| Sulphur dioxide | gaseous | $SO_2$ | -297 |
| Sulphuric acid | liquid | $H_2SO_4$ | -814 |
| Silica | solid | $SiO_2$ | -911 |
| Nitrogen dioxide | gaseous | $NO_2$ | +33 |
| Nitrogen monoxide | gaseous | NO | +90 |
| Water | liquid | $H_2O$ | -286 |
| Water | gaseous | $H_2O$ | -241.8 |
| Carbon Dioxide | gaseous | $CO_2$ | -393.5 |

# Forming a Chemical Bond Reduces **H**

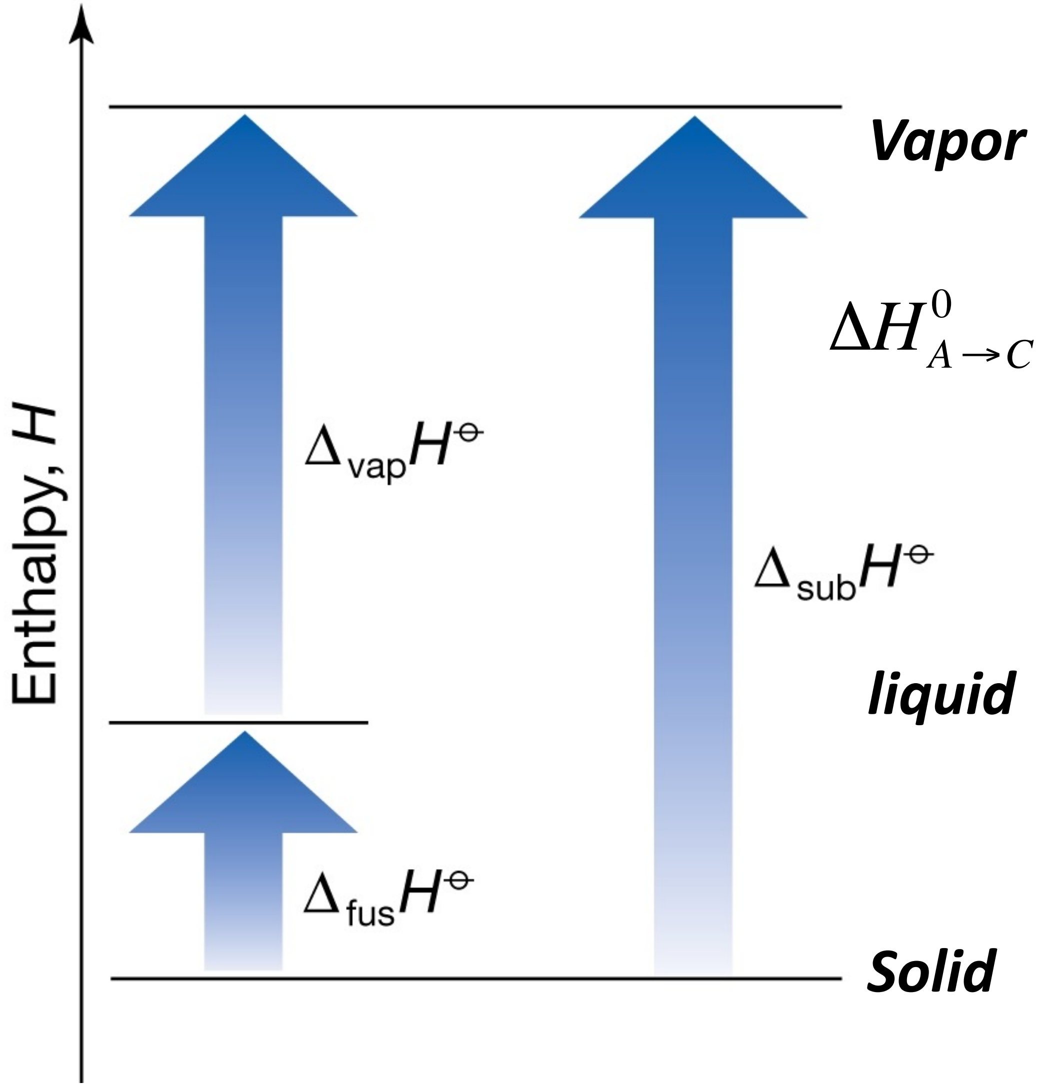
*Bond breaking* Energy (kJ/mol). The bond *formation* energy is *negative* (reaction is exothermic), opposite sign of the bond-breaking E

| | | | | | |
|---|---|---|---|---|---|
| 297 | H-I | 347 | C-C | 163 | N-N |
| 364 | H-Br | 611 | C=C | 418 | N=N |
| 368 | H-S | 837 | C:::C | 946(315) | N:::N |
| 389 | H-N | 305 | C-N | 222 | N-O |
| 414 | H-C | 615 | C=N | 590 | N=O |
| 431 | H-Cl | 891 | C:::N | | |
| 436 | H-H | 360 | C-O | | |
| 464 | H-O | 736 | C=O | | |
| 565 | H-F | 339 | C-Cl | | |
| 151 | I-I | 142 | O-O | | |
| 159 | F-F | 498(249) | O=O | | |
| 193 | Br-Br | | | | |
| 243 | Cl-Cl | | | | |




Need positive energy (e.g. a photon) to break a bond

# Additivity, path independence




$$\Delta H^0_{A \to C} = \Delta H^0_{A \to B} + \Delta H^0_{B \to C}$$

Abbreviations:

**vap** : vaporization (liquid to gas)

**sub**: sublimation (solid to gas, eg CO2)

**fus:** fusion or melting (solid to liquid)

# Forward and Reverse Processes

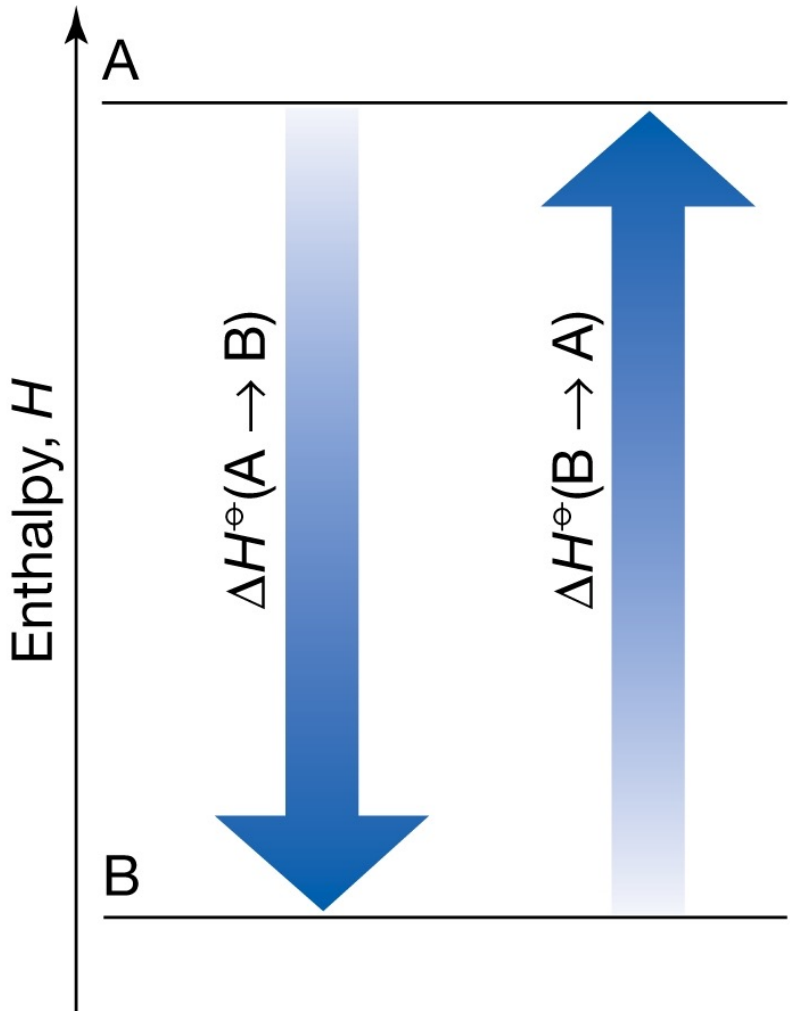
- Standard enthalpy changes of forward and reverse processes must differ only in sign

$$\Delta H^0_{A \to B} = -\Delta H^0_{B \to A}$$

- Example: vaporization and condensation (T=373K):

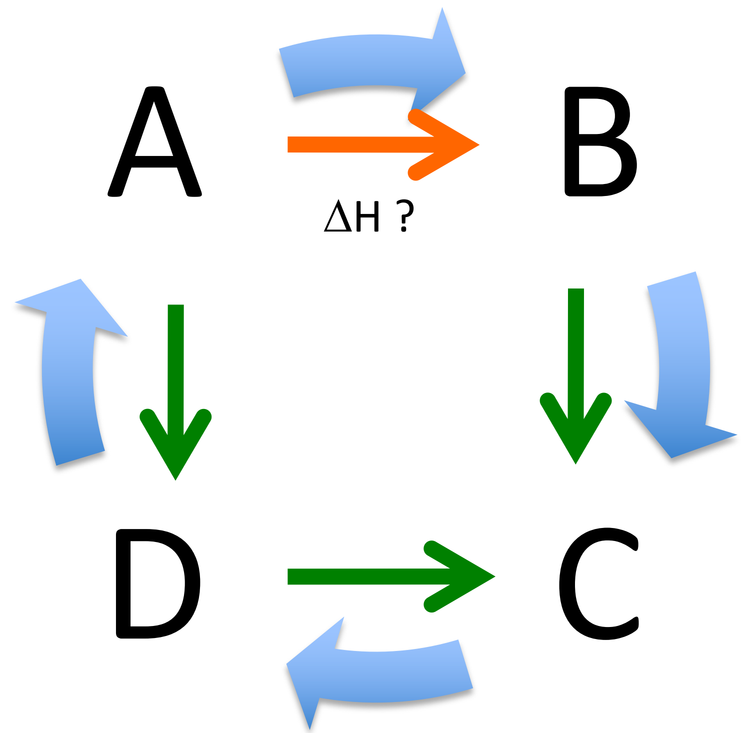
$$\Delta H^0_{water \to vapor} = 40.68 kJ / mol$$

$$\Delta H^0_{vapor \to water} = -40.68 kJ / mol$$



# Thermodynamic Cycle

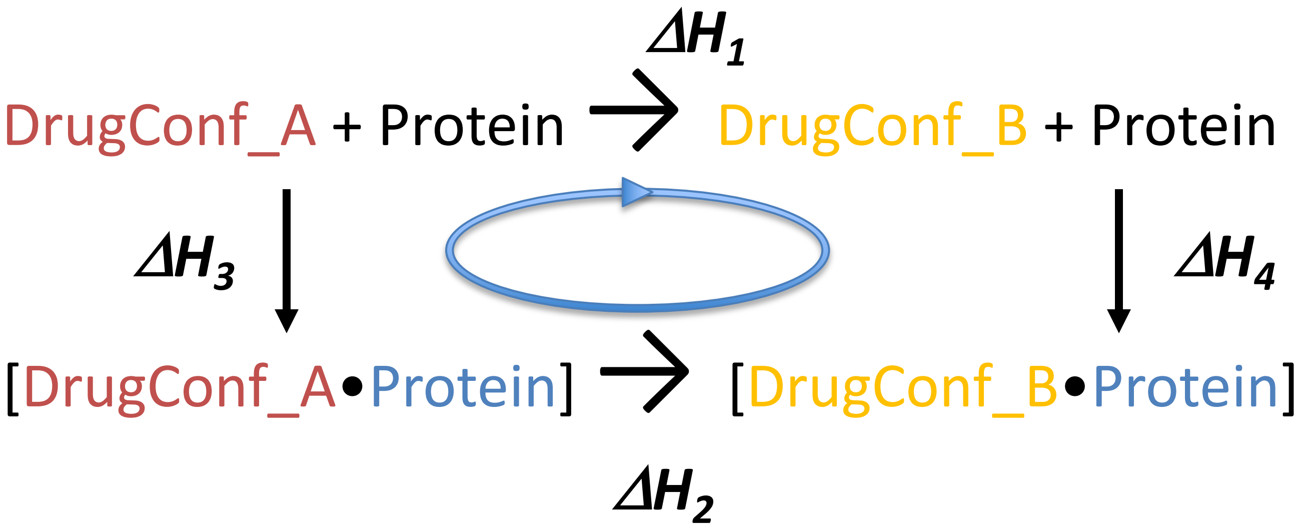
- Choose multipliers by *stoichiometry* and *orient transitions*
- Go clockwise and $\Sigma \Delta H_{XY}=0$
- Flip a sign of $\Delta H$ if arrow is in the opposite direction.




Example: 4 states and 3 **known** transitions, and one **unknown** transition

$$\Delta H^0_{A\to B} + \Delta H^0_{B\to C} - \Delta H^0_{D\to C} - \Delta H^0_{A\to D} = 0$$

# Example: drug-binding



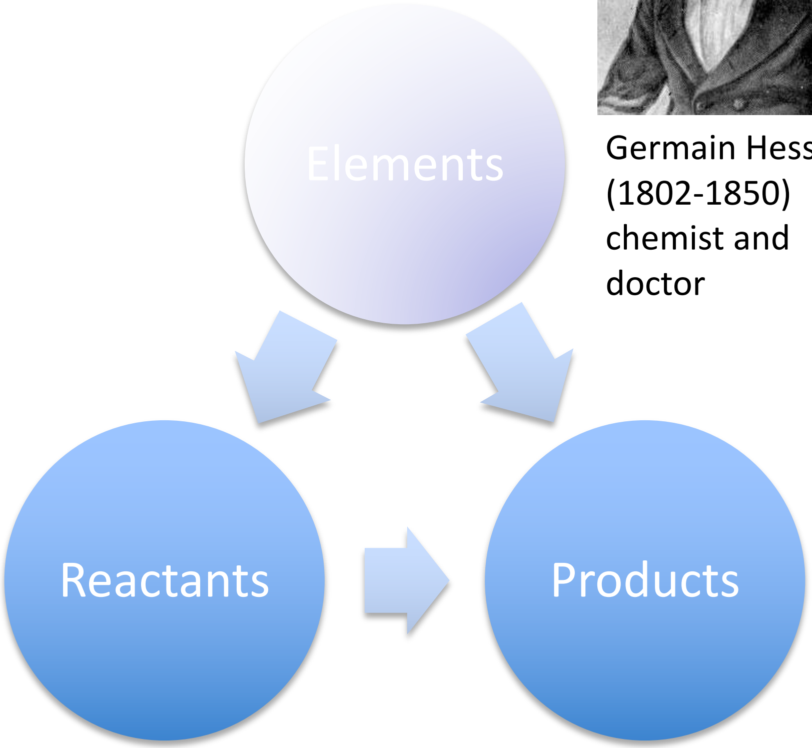

$$\Delta H_1 - \Delta H_2 - \Delta H_3 + \Delta H_4 = 0$$

*If one of the terms is unknown, it can be found from the other three*

# Hess' Law for a reaction

- From *heats of formation to the heat of reaction*
- Direct consequence of the fact that **H** is a state function
- Watch stoichiometry coefficients ( $\nu_i$). Example:

Germain Hess (1802-1850) chemist and doctor




$2H_2 + O_2 \Rightarrow 2H_2O$

$\nu_{H2} = 2 \quad \nu_{O2} = 1 \quad \nu_{H2O} = 2$

$$\Delta H^0_{reaction} = \sum \nu_p \Delta H^0_{f(products)} - \sum \nu_r \Delta H^0_{f(react)}$$

Use: $H(T) = C_p \Delta T$ to calculate $\Delta H$ at higher temperature, if the reaction is done at higher T

# Thermochemical Characterization of Reactions and Transitions

## Initial State $\Rightarrow$ Final State

- $\Delta H = H(\text{final state}) - H(\text{initial state})$
- $\Delta H \equiv$ heat of reaction or transition
  - $\Delta H < 0$ means "$\Rightarrow$" is *exothermic* (produces heat)
  - $\Delta H > 0$ means "$\Rightarrow$" is *endothermic* (absorbs heat)

## Covalent Bond formation is exothermic

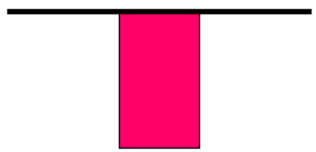
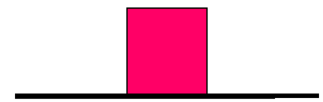
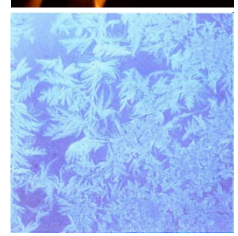
- **Counting bonds: Example: burning**

  **2 $H_2$ (2 bonds) + $O_2$ (1 bond) => 2$H_2O$ (4 bonds)**

  **Balance: + 1 bond** $\Delta H$ is negative

  Number of covalent bonds **increases** : exothermic

# Reaction examples: enthalpy

| $\Delta H$ | – | + |
|---|---|---|
| |  |  |
| | • **Burning** (covalent bonds formed)<br>• Freezing (non covalent)<br>• Condensation<br>• Acid-base neutralization   | <br>• Melting<br>• Evaporation (always) |
| | Bonds form or get stronger, heat is produced | Bonds break, or get weaker, substance gets colder |

# Example: drug dissolution (exo- or endo-?)

- Drug(*solid*) + $H_2O$ ⇔ Drug(*aq*)
- Molar heat of reaction at infinite dilution: 1 mole of drug dissolved at infinite amount of H2O (drug already present in solution may affect dissolution enthalpy)
- No covalent bonds change during dissolution (except pH-dependent protonation/deprotonation)
- The interaction balance is delicate, includes drug-drug water-water and drug-water bond strengths.
- If the reaction involves strong non-covalent bond breakage, it may be endothermic
- If crystal interactions are weak but drug-water interactions are strong – dissolution is exothermic

**Drug Dissolution:**
Micro-crystal size affects kinetics/rates but not equilibrium (ie whether dissolves)

| Enthalpy change of solution for some selected compounds | | |
|---|---|---|
| hydrochloric acid | $HCl$ | -74.84 |
| ammonium nitrate | $NO_{2-}NH_{4-}$ | +25.69 |
| ammonia | $NH_3$ | -30.50 |
| potassium hydroxide | $KOH$ | -57.61 |
| caesium hydroxide | $CsOH$ | -71.55 |
| sodium chloride | $NaCl$ | +3.87 |
| potassium chlorate | $KClO_3$ | +41.38 |
| acetic acid | $CH_3COOH$ | -1.51 |
| sodium hydroxide | $NaOH$ | -44.51 |
| Change in enthalpy $\Delta H^o$ in kJ/mol in water at 25°C[1] | | |

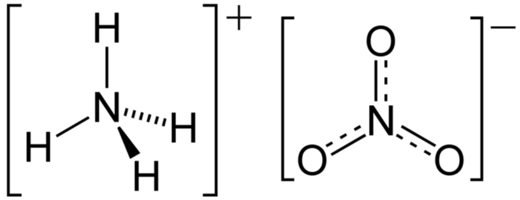
- Q: does negative value mean dissolution?

# Molar heat of dissolution at 298 K

| Substance | ΔH dissolution (kJ/mol) | |
|---|---|---|
| HCl (gas) | -74.84 | no gas interactions, strong water int |
| Ammonia (gas) | -30.50 | |
| Acetic Acid (liquid) | -1.51 | |
| NaCl | 3.88 | |
| Ammonium Nitrate | 25.69 | |
| Potassium Chlorate | 41.38 | |
| Lidocaine HCl | 43.5 | strong crystal int, weaker water int |
| Procaine HCl | 30.5 | |

**Balance of ΔH contributions in dissolution**

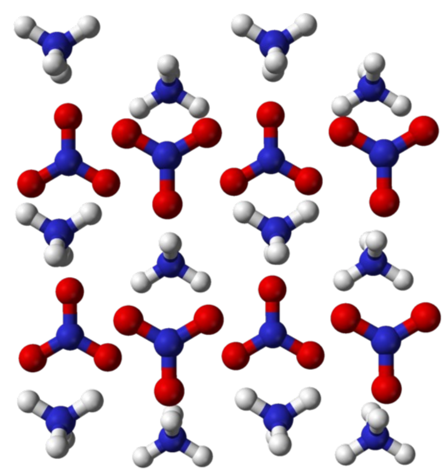
1. Breaking solute attractions for liq or solids (endothermic)
2. Breaking water-water attractions (endothermic)
3. Forming water-solute interactions (exothermic)

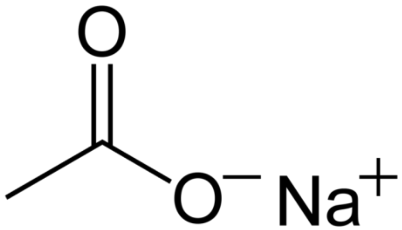


# Ice Packs

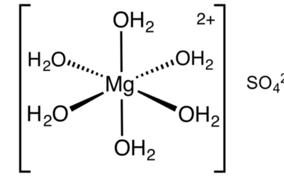
- Ammonium nitrate and ammonium chloride dissolve in water *endothermically* *(strong interaction)*
- Mixing (+$NH_4$ )(-$NO_3$) with water separates the ions
- Exchanging strong ionic bonds for weaker polar bonds (less bonds -> positive ΔH -> cold)
- For ammonium nitrate

$$\Delta H \text{ dissolution} = +25.69 \text{ kJ/mol}$$




# Heat Pads

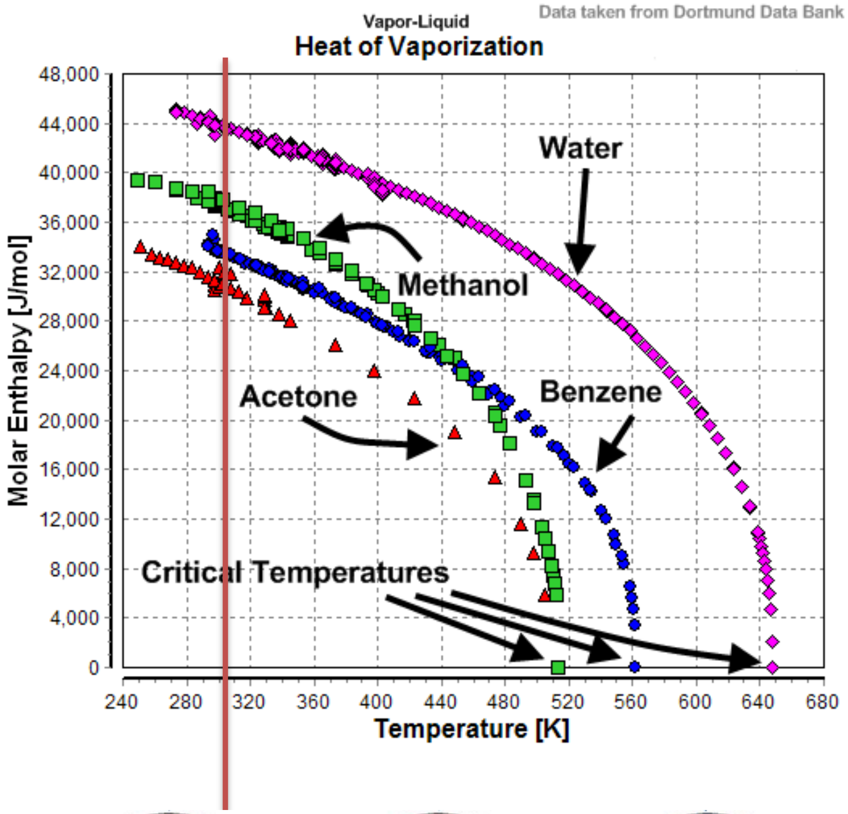


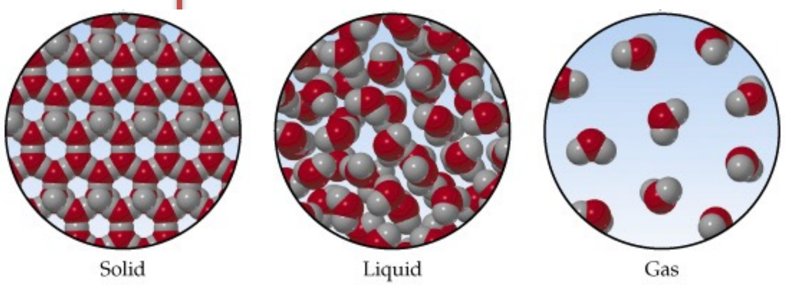

- Crystallization: Sodium-acetate : weaker bonds in water to stronger ionic bonds
- heat of crystallization of sodium acetate tri-hydrate is -35.9 to -39.3 kJ/mol


- Dissolution: magnesium sulfate : weaker bonds to stronger bonds
- anhydrous $MgSO_4$ is about -54.37 kJ/mol
- includes formation of a hydrate Epsomite (very *exothermic*) + its dissolution in water (slightly endothermic)

# ΔH : *evaporation* is endothermic

- Evaporation: liq→gas
- ΔH = 44kJ/mol @ 300K
- ΔU = 44-RT = 41.5kJ/mol
- 3.7 non-covalent bonds (hydrogen bonds) per molecule in water, zero in gas
- Number of bonds decreases: system gets colder: evaporation is **endothermic**.

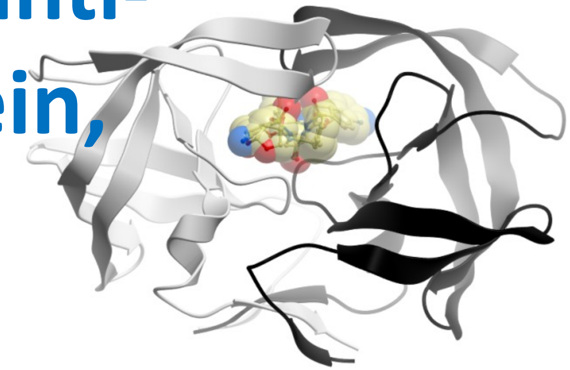


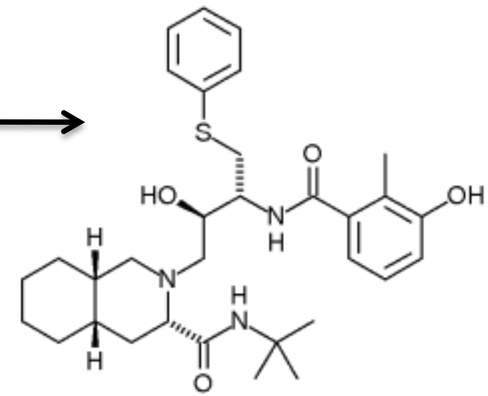
# Example: protein/ligand binding

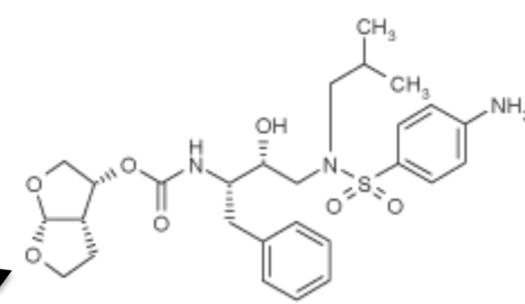
- P for *protein* (target), L for *ligand* (or drug D)
- Assume simple 1:1 stoichiometry: **P + L ⇔ PL**
- Molar heat of reaction: 1 mole of **P** + 1 mole of **L** form 1 mole of **PL**
- The reaction is often *(but not always!)* exothermic
- Attn: The reaction is (typically) reversible:
  - not all reactants (P & L) are converted to products (PL)
  - heat is proportional to the amount of product that is formed
  - used in determination of binding affinities by ITC

# Enthalpy of binding of several anti-HIV drugs to their target protein, HIV protease



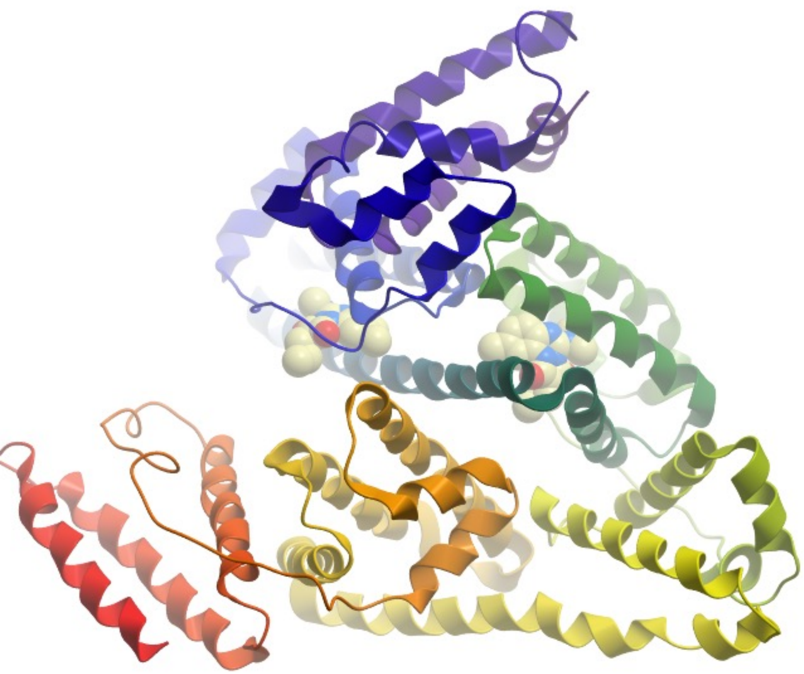
| Generic Name | MW | ΔH (kcal/mol) |
|---|---|---|
| Nelfinavir | 567.8 | 3.1 |
| Indinavir | 613.8 | 1.8 |
| Saquinavir | 670.8 | 1.2 |
| Tipranavir | 602.7 | -0.7 |
| Lopinavir | 628.8 | -3.8 |
| Atazanavir | 704.9 | -4.2 |
| Ritonavir | 720.9 | -4.3 |
| Amprenavir | 505.6 | -6.9 |
| Darunavir | 547.7 | -12.7 |

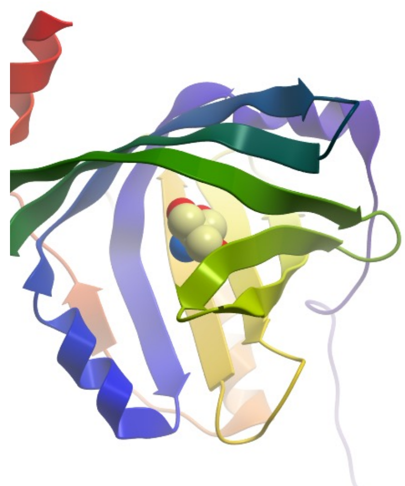


# Molar heat of drug binding to blood plasma proteins

| Drug | Protein | ΔH binding (kcal/mol) |
|---|---|---|
| Propranolol | α1-acid glycoprotein | -11.1 |
| Warfarin | human serum albumin | -2.44 |





| Normal Plasma Range | (mg/dL) |
|---|---|
| **Albumin** | **3,500 - 4,500** |
| **Pre**albumin (**Transthyretin**) | 10 - 40 |
| **α1-Globulins** | 300 - 600 |
| α1 Acid Glycoprotein (orosomucoid) | 55 - 140 |
| α-Fetoprotein approx. | 0.001 |
| Retinol Binding Protein | 3 - 6 |
| Thyroxine Binding Globulin | 1 - 2 |
| Transcortin | 3 - 3.5 |
| **α2 Globulins (excl.lipoproteins)** | **400 - 900** |
| Ceruloplasmin | 15 - 60 |
| Haptoglobin Type 1-1 | 100 - 220 |
| Haptoglobin Type 2-1 | 160 - 300 |
| Haptoglobin Type 2-2 | 120 - 260 |
| α2 Macroglobulin | 100 - 280 |
| **β-Globulins (excluding lipoproteins)** | **600 - 1,100** |
| C-Reactive Protein | < 1 |
| Hemopexin | 50 - 100 |
| β2 Microglobulin approx. | 0.2 |
| Transferrin | 200 - 320 |
| **γ-Globulins** | **700 - 1,500** |

# Enthalpy change is sometimes positive
# Why does water evaporate?

A standard enthalpy of vaporization (or "heat of vaporization"):

$$H_2O(l) \rightarrow H_2O(g)$$

$\Delta_{vap}H° = +40.66$ kJ/mol at 373 K

- Coming next: Entropy and Gibbs Free Energy