Ligand-Protein Interactions

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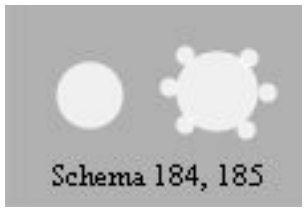
Lucretius, about 50 B.C.
***De Rerum Natura*, Book II,**
Section "*Atomic Forms and Their Combinations*"

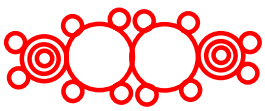
We see how quickly
through a colander
The wines will flow; how,
on the other hand,
The sluggish olive-oil
delays: no doubt,
Because 'tis wrought of
elements more large,
Or else more crook'd
and intertangled.

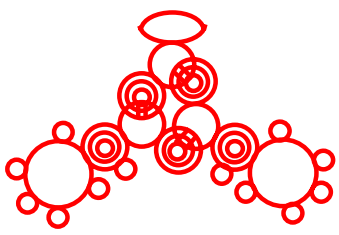
The book "Chemische Studien" (Chemical Studies), Vienna, 1861, of the Austrian school teacher Joseph Loschmidt contains aready structures that are formulated like the benzene ring (Kekulé, 1865) and like today's molecular modelling pictures. August Kekulé knew this book latest in 1862.

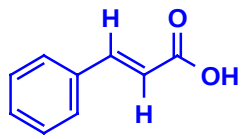


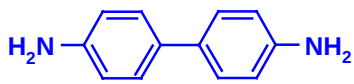
„Wir nehmen für den Kern das Symbol Sch. 184 an, und behandeln denselben ganz so, als ob er ein sechsstelliges Element wäre."
(J. Loschmidt in „Chemische Studien", 1861, p. 30)

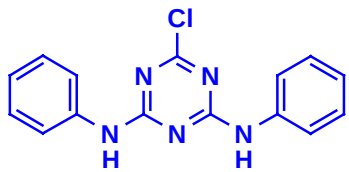
Loschmidt Constitution Formulas (1861)



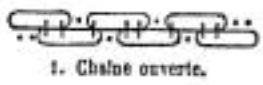








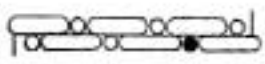
The Benzene Formula of August Kekulé (1865)



1. Chaîne ouverte.

2. Chaîne fermée.

3. Benzine.



4. Benzine chlorée.

5. Benzine bi-chlorée.

Benzene

„Reports of the Thirsty Chemical Society“ (Berichte der Durstigen Chemischen Gesellschaft), 1886

cited from

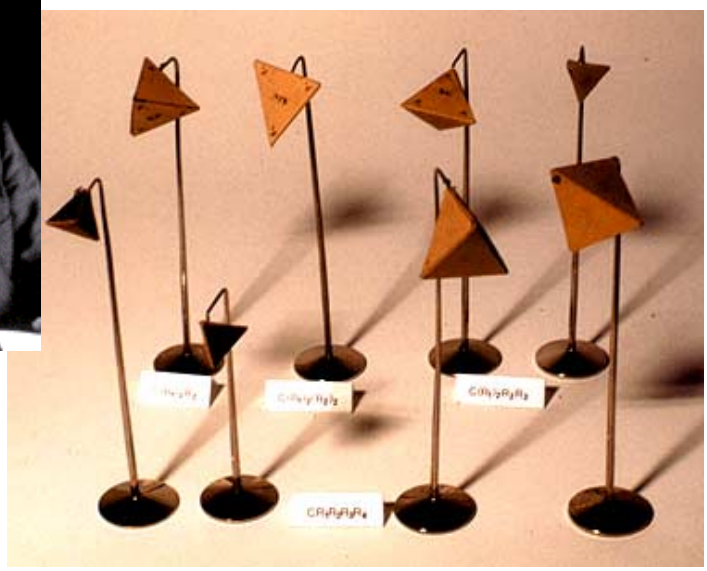
E. Bäumler, Ein Jahrhundert Chemie, Econ Verlag Düsseldorf, 1963, p. 20

The Arrangement of Atoms in Space - van't Hoff, 1874-77

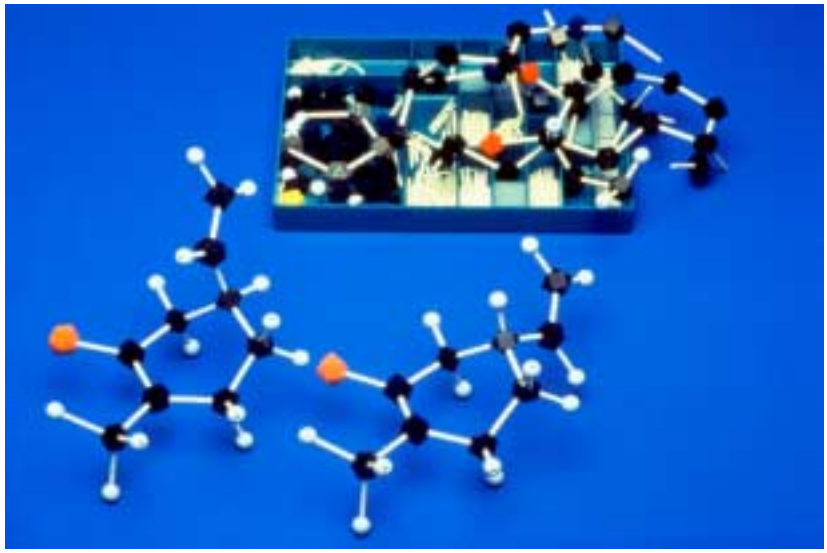
Models of Different Tetrahedric Carbons

van't Hoff

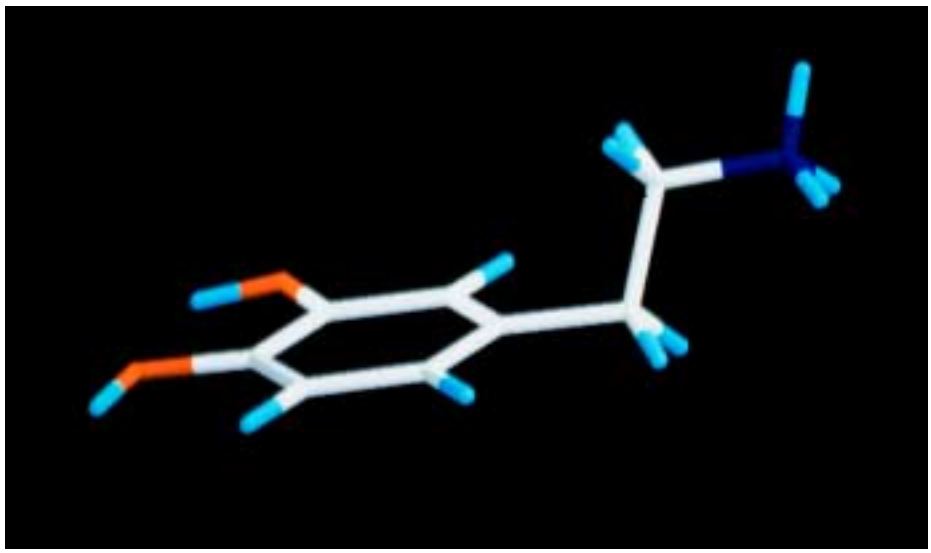
(1904)



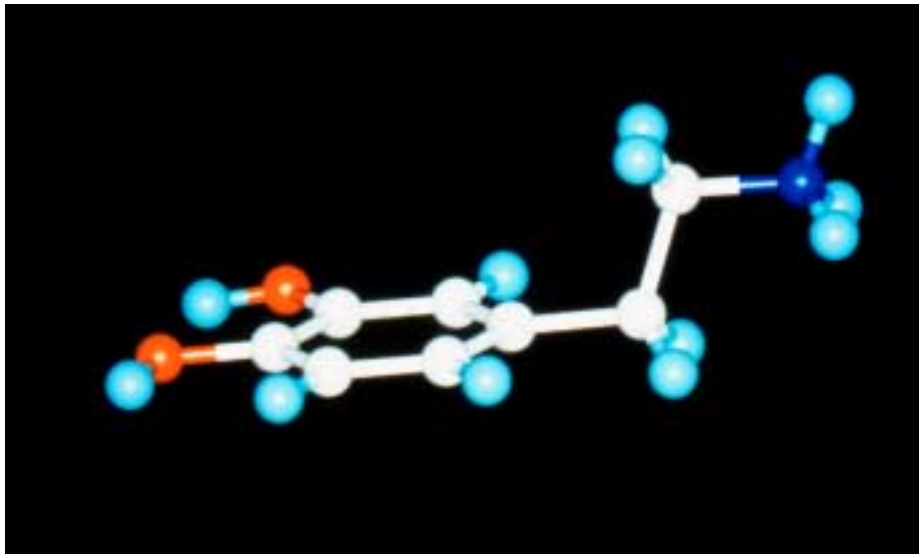
Molecular Models of d- and l-Carvone



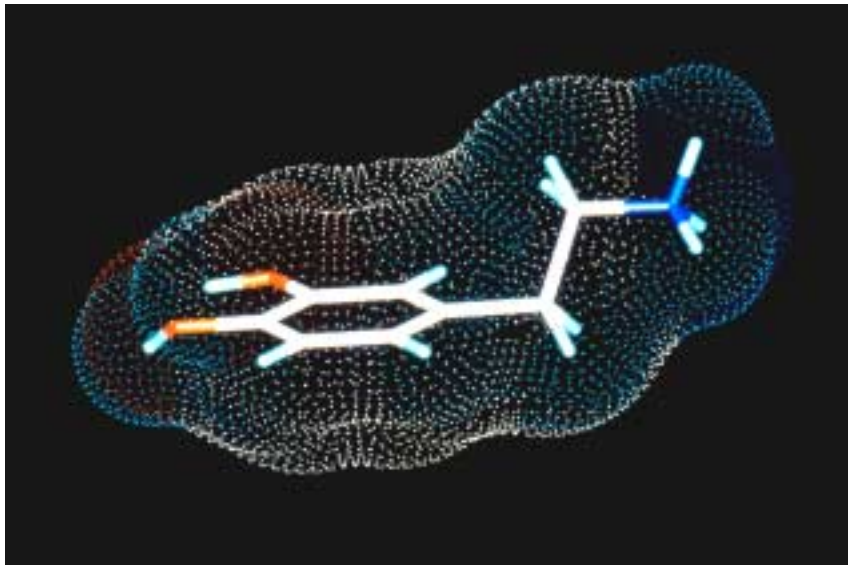
Molecular Model of Dopamine



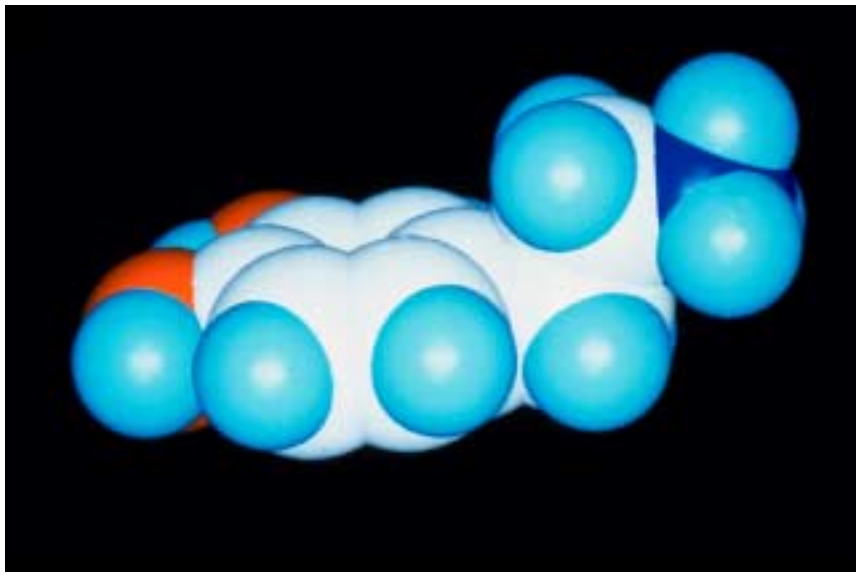
„Ball and Stick“ Model of Dopamine



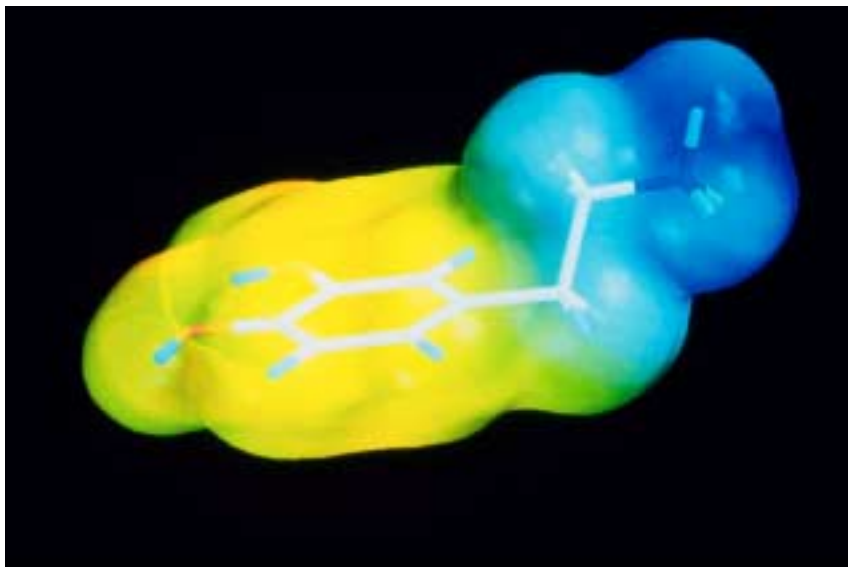
„Dotted Surface“ Model of Dopamine



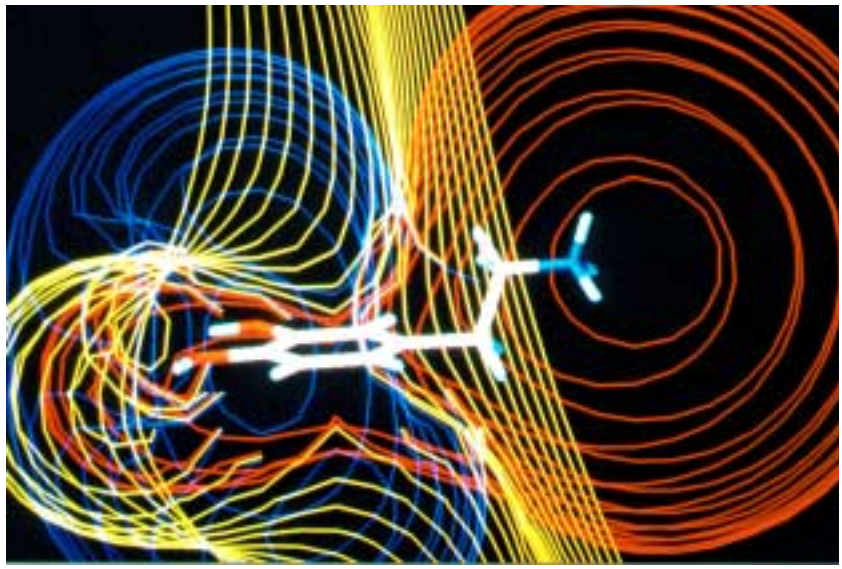
„Space-Filling“ (CPK) Model of Dopamine



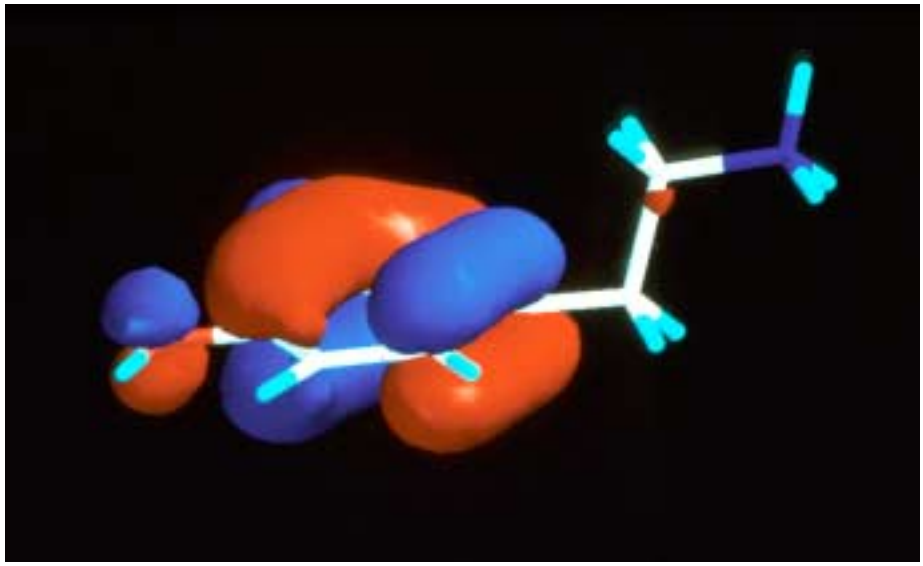
„Colour-Coded Surface“ Model of Dopamine



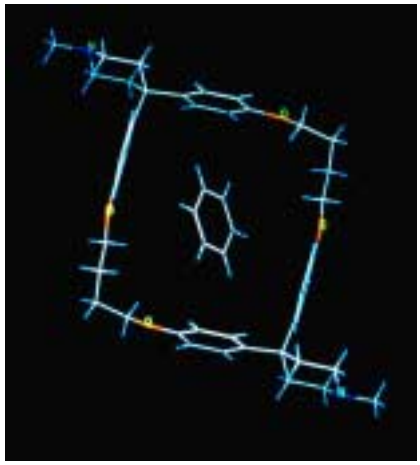
Molecular Electrostatic Potential of Dopamine

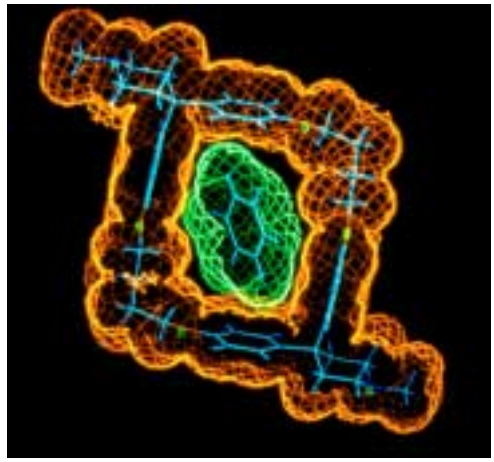


Dopamine, HOMO and LUMO Potentials

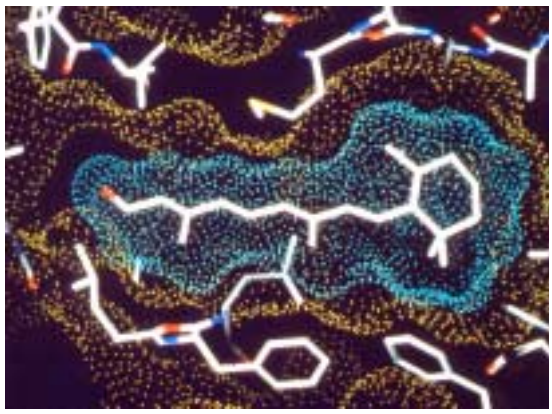


Molecular Modelling of a Host-Guest Complex Benzene in a Macrocyclic Ring System



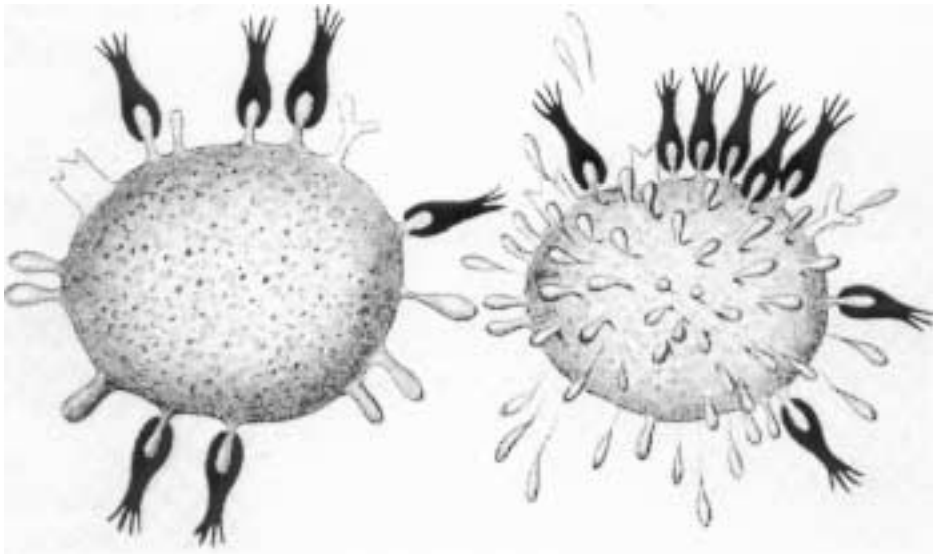


Lock and Key Concept (Emil Fischer, 1894)



"To use a picture, I would like to say that enzyme and glucoside have to fit like a lock and a key, in order to exert a chemical action on each other".

Toxins and „Receptors“ (Paul Ehrlich, around 1900)



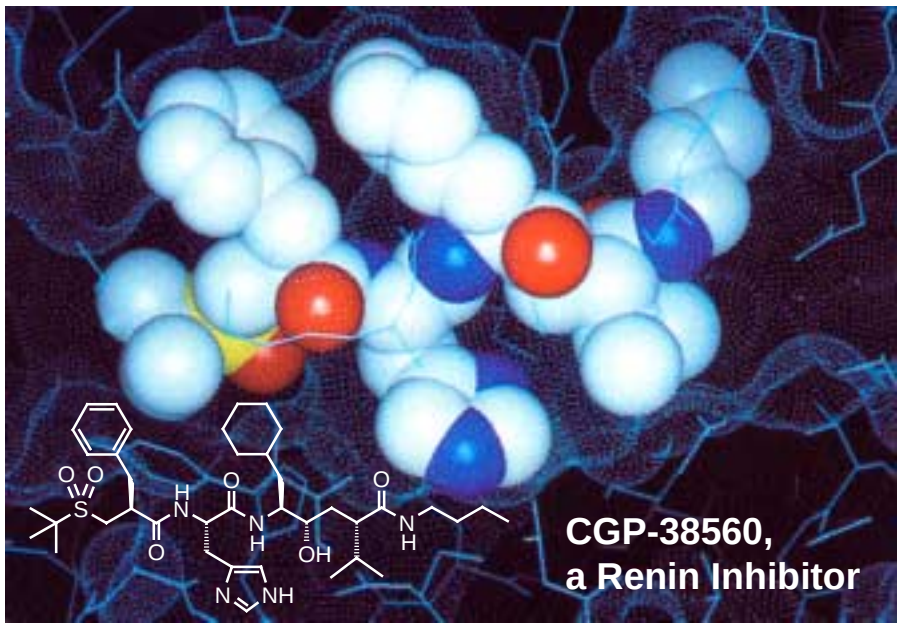
Paul Ehrlich (1854-1915)

Henry Moore

Two Forms

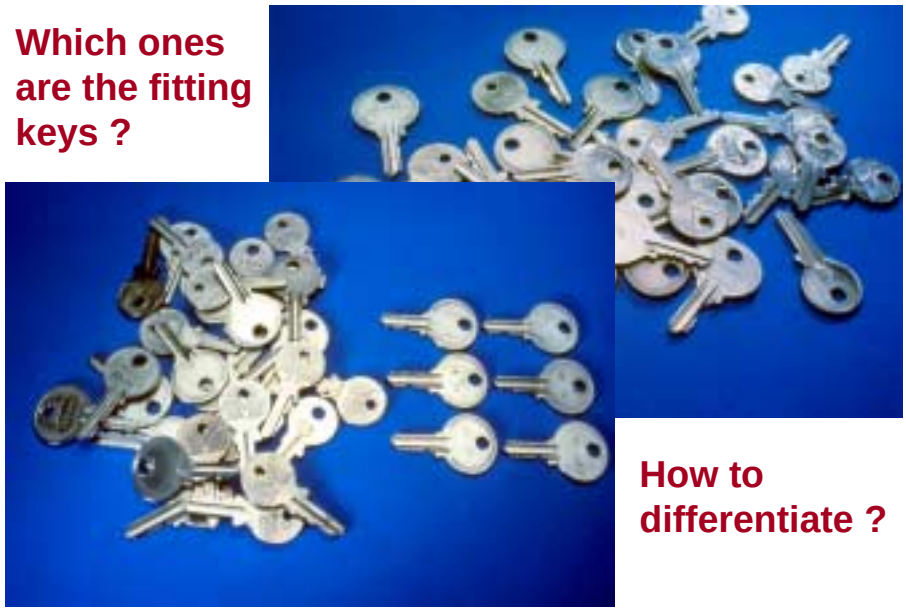
Pynkado wood, 1934

Metropolitan Museum of Art, New York



CGP-38560, a Renin Inhibitor

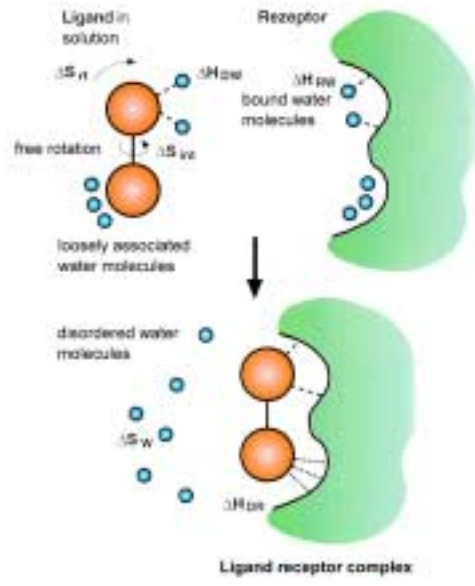
Which ones are the fitting keys ?



How to differentiate ?

Peter Andrews Diagram

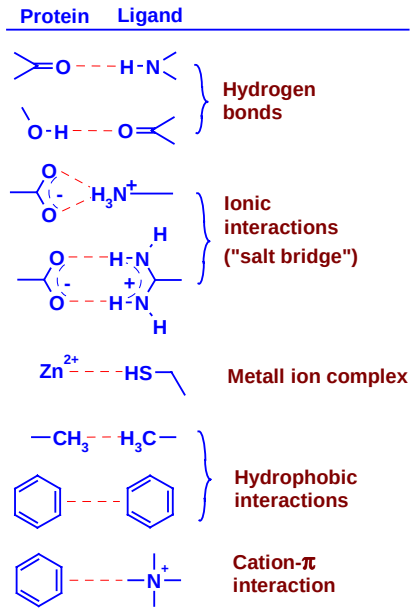
Enthalpic and Entropic Contributions to Ligand Affinity



Important Non-Covalent Ligand-Protein Interactions

The inhibition constant K_i is a measure of the strength of the ligand-protein interaction

$$\Delta G = \Delta H - T\Delta S$$
$$= RT \ln K_i$$



Hugo Kubinyi, www.kubinyi.de

3D Structures, Superposition of Molecules and Pharmacophore Hypotheses

Experimental determination of 3D structures:
- X-ray structure analysis, 2D NMR

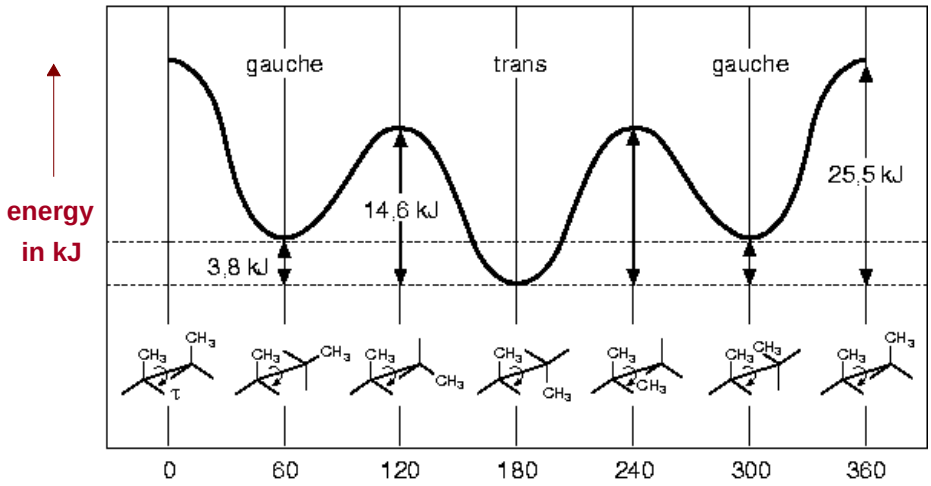
Generation of 3D Structures
- Concord, CORINA (rule-based systems)
- Force field and QC methods

Multiple 3D structures
- Systematic and Monte-Carlo search, molecular dynamics simulation, rule-based systems

Superposition of molecules
- „rigid fit“, „field fit“ (SEAL)

Pharmacophore hypotheses
- „Active analog approach“, 3- and 4-point pharmacophores, CATALYST

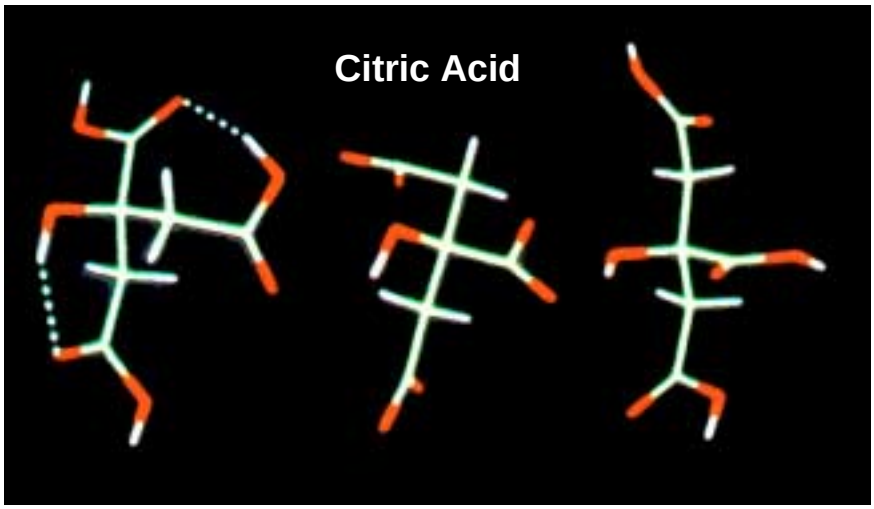
3D-Structures: Conformational Analysis



2D-3D Conversion and Conformational Analysis

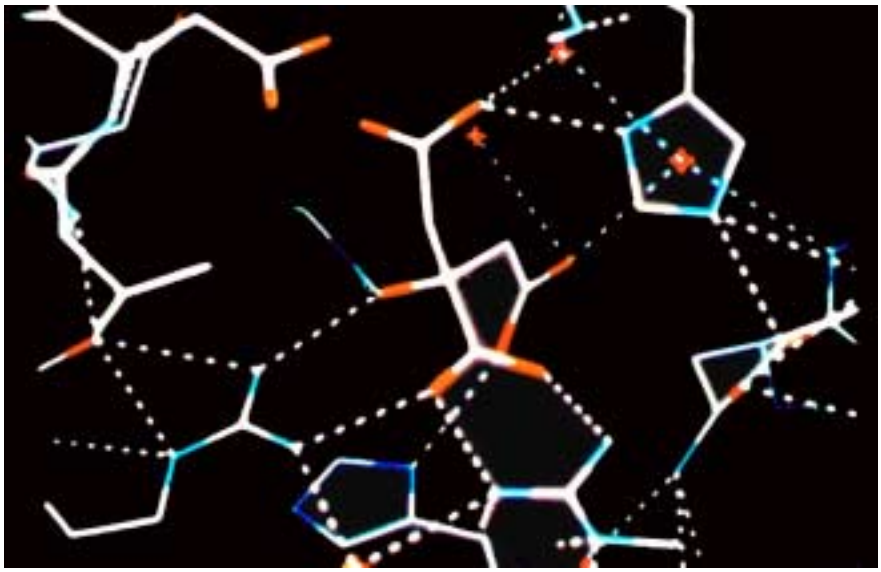
- Conformations are local energy minima of a molecule
- Generate a start structure
- Sample the conformational space
  MD, MC, GA, rule-based approaches
- Minimize structure if necessary

The Relevance of Different Conformations

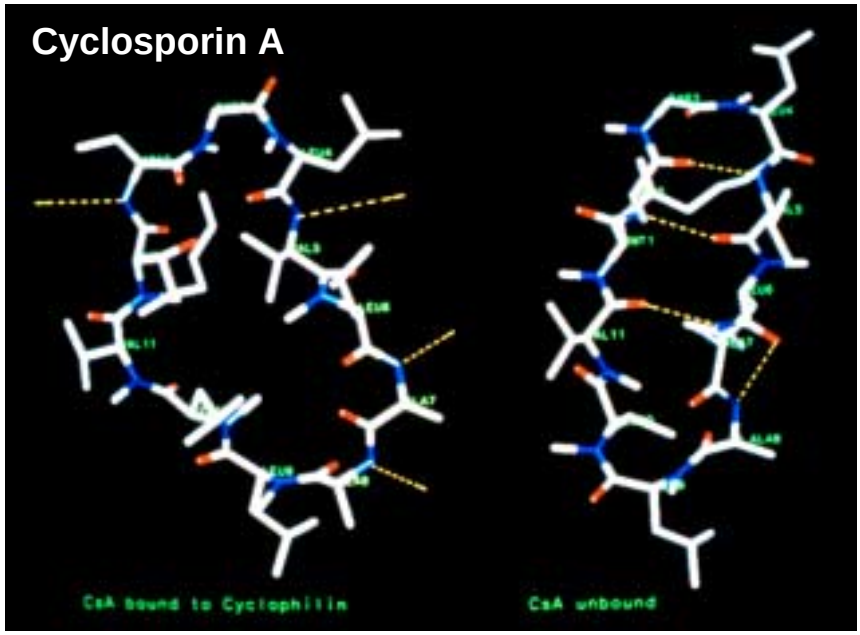


a) in vacuo b) in water c) in the crystal

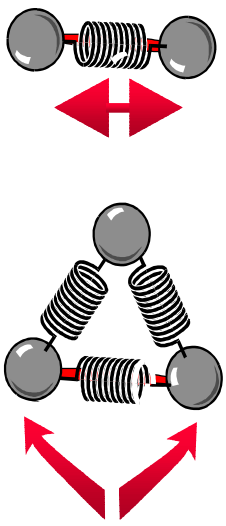
Binding Mode of Citric Acid in Citrate Synthase

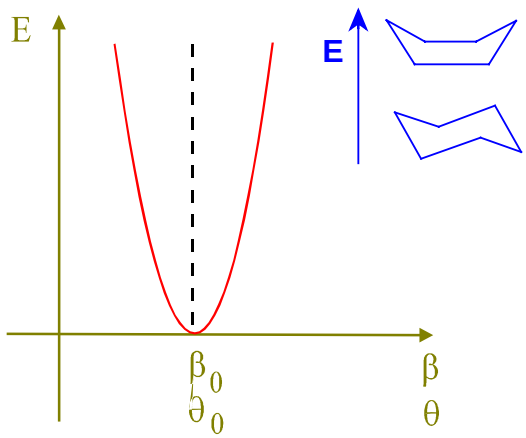


Cyclosporin A



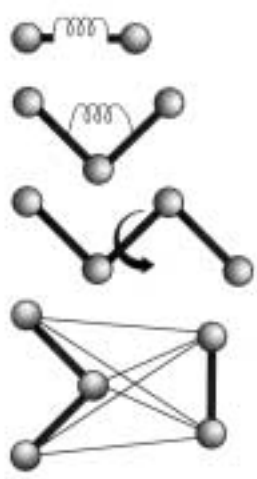
Molecular Mechanics - Force Fields



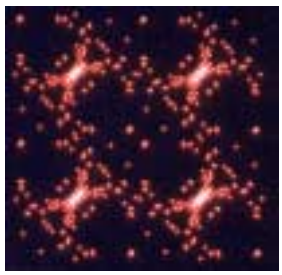


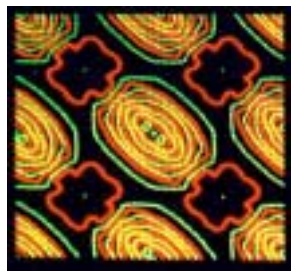
Force Field Terms

$$E = \sum_{bond} K_r \left(r - r_0\right)^2 + \sum_{angl} K_\theta \left(\theta - \theta_0\right)^2 + \sum_{dihed} K_\phi \left[1 + \cos\left(n\phi - \gamma\right)\right] + \sum_{ij} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{\varepsilon r_{ij}} \right]$$

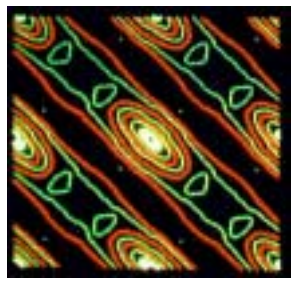


Preferred Torsion Angles in Phe-X-Phe

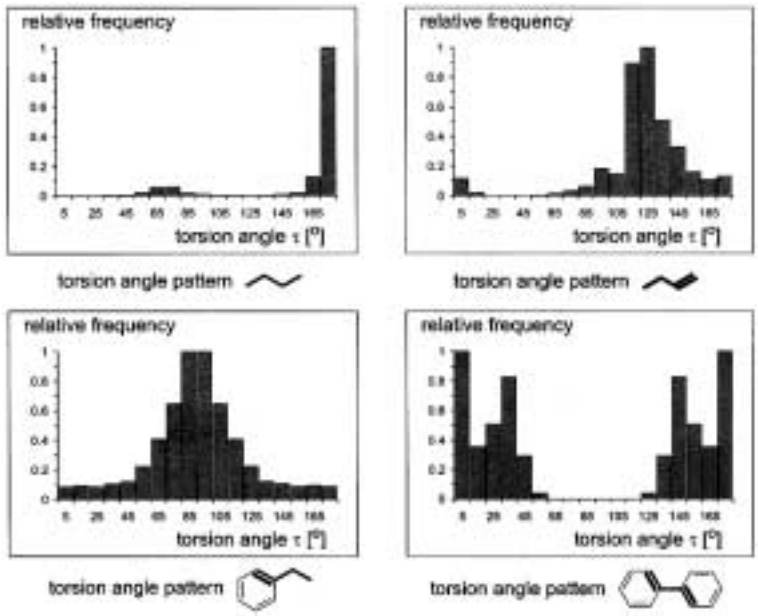




diphenyl-methane (X = CH_2)



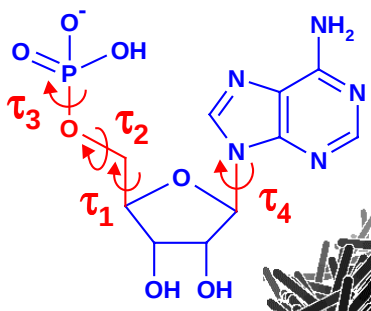
diphenyl ether (X = O)

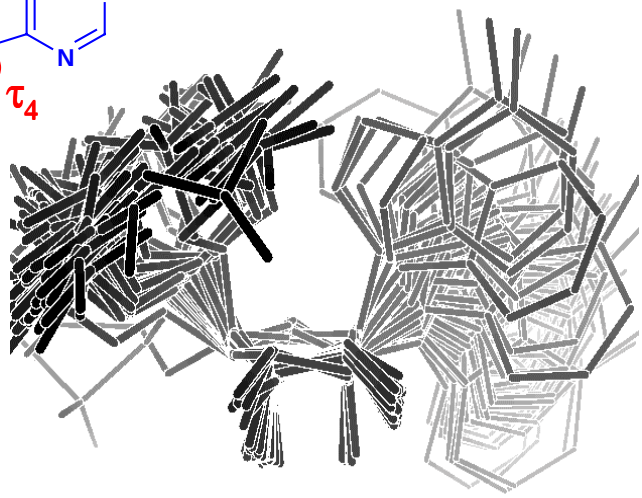


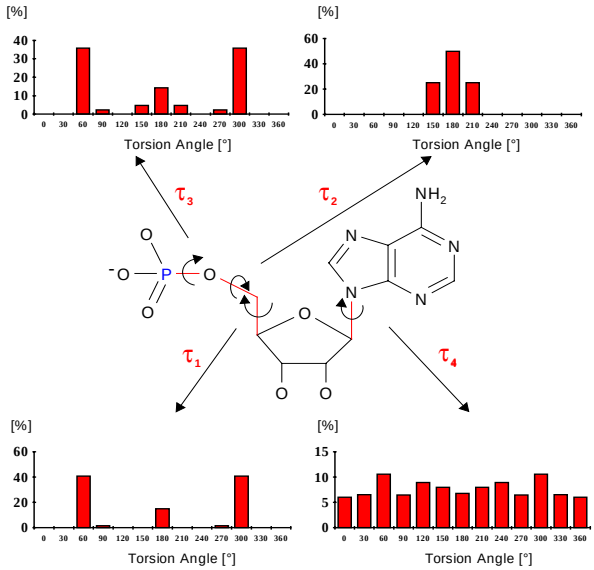
Torsion Angle Patterns

(from CCD)

Conformer Population of Nucleotides (from PDB)



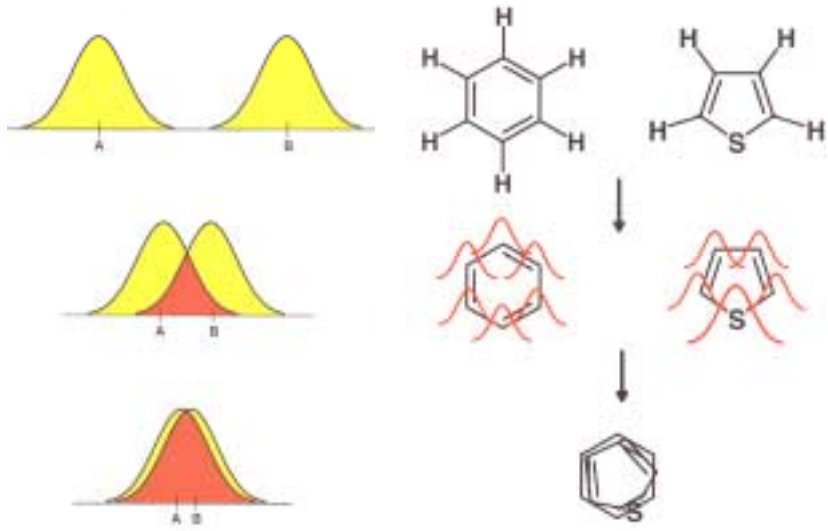




Rule-based System for the Prediction of Multiple 3D-Structures

Torsion angle statistics from the Cambridge Crystallographic Database

Superposition of Molecules: Alignment by SEAL

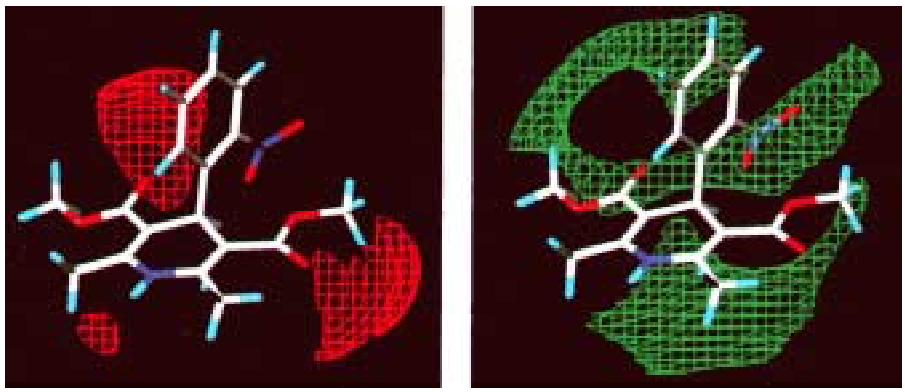


GRID Molecular Interactions Fields

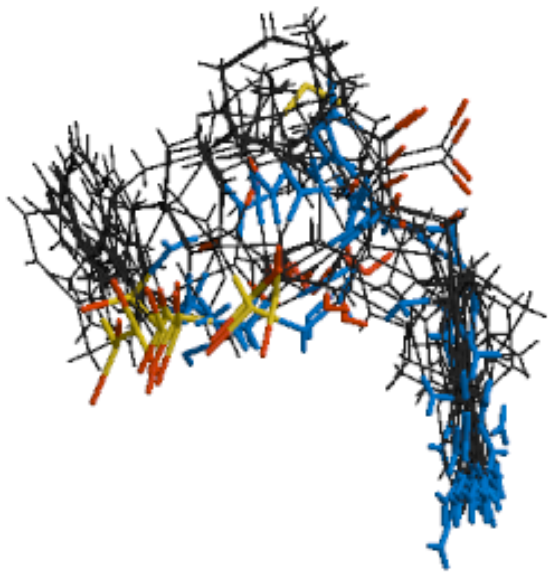
Peter Goodford, 1984; R. C. Wade, in 3D QSAR in Drug Design, H. Kubinyi, Ed., ESCOM, 1993, pp. 486-505

- **GRID calculates interaction energies between atomic probes or functional groups and a ligand or a protein at equally distributed grid points.**
- **Considers force field parameters like van-der-Waals and electrostatic interactions.**
- **Contains basic concepts to include side chain flexibility.**
- **Used for CoMFA and docking.**

GRID Molecular Interaction Fields (P. Goodford)



GRID molecular interaction fields of nifedipine
a) hydroxy probe (left; contour map at –3.5 kcal mol^{-1}) and
b) methyl probe (right; contour map at –1.4 kcal mol^{-1}).



Superposition of Thrombin Inhibitors

(coordinates from X-ray structure analyses of the inhibitor complexes)

Molecular Superposition of D Receptor Ligands