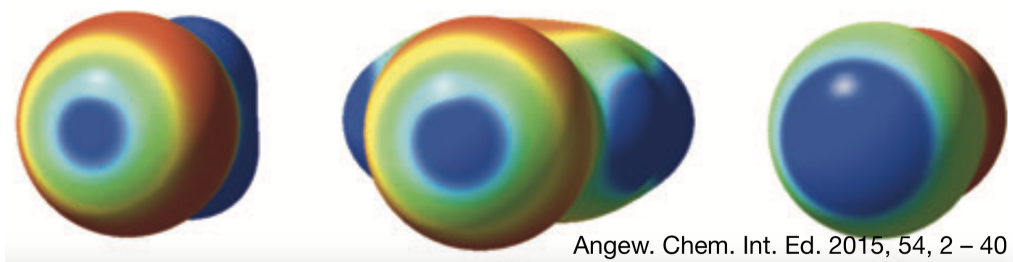
Computational chemistry methods in drug design: Quantum chemical approaches



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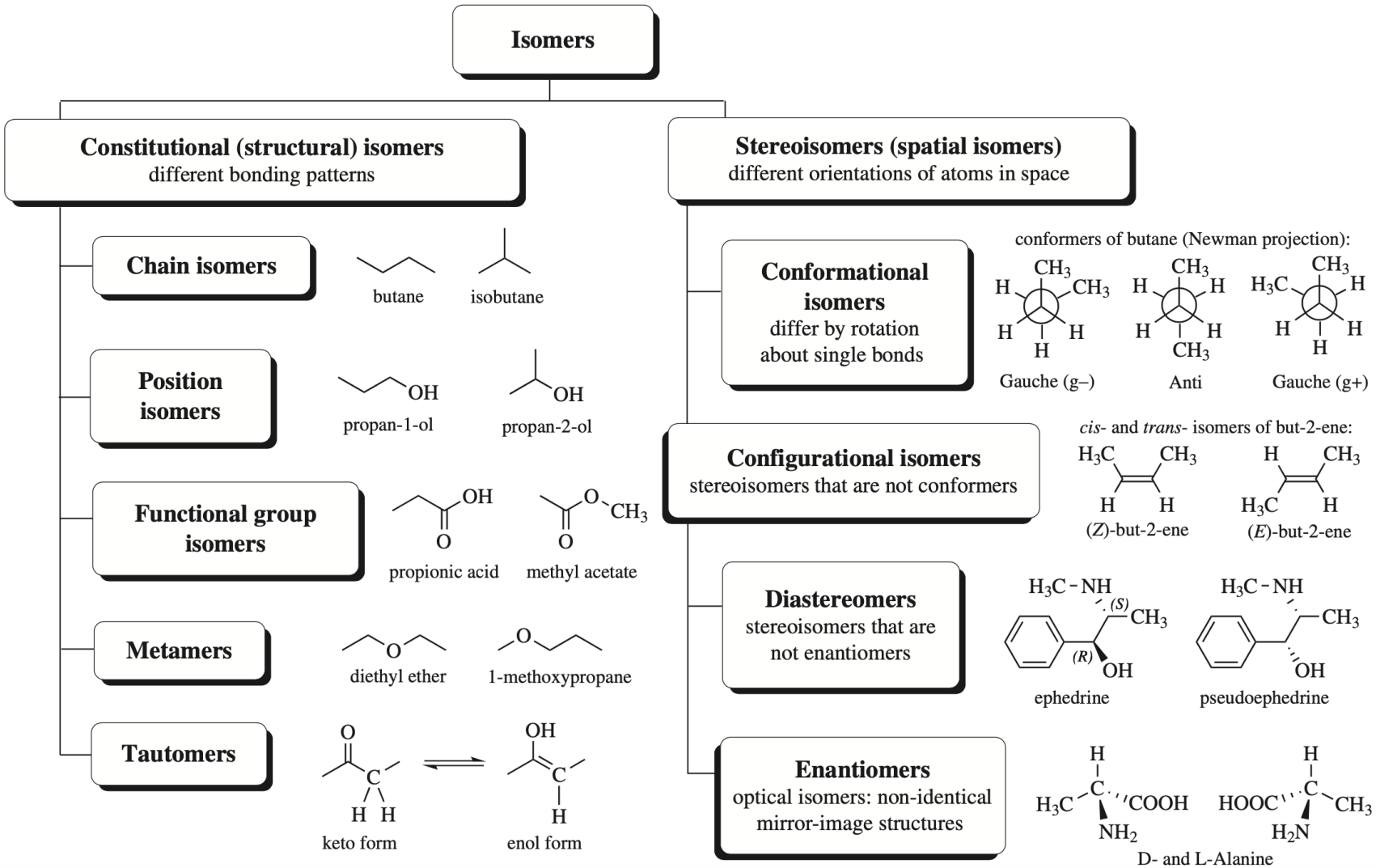
MC-610, NIPER Hyderabad: Lecture 5 (May 29, 2021)

Applications

Isomers



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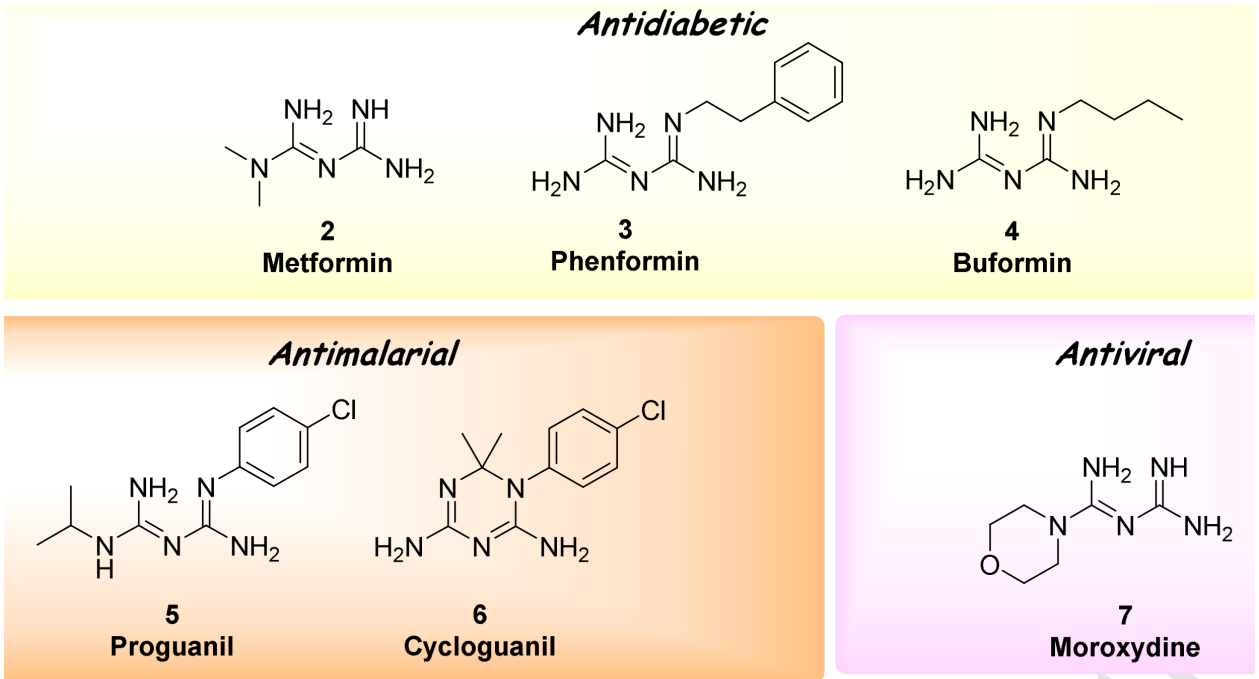
Biguanides

- A class of molecules–studied extensively in medicinal applications
- Drugs having biguanide as pharmacophore:



– by Bharatam P.V. et al. J. Mol. Struc. **1152**, 61 (2018).

Structures and energetics of Biguanides

- Tautomeric forms are:

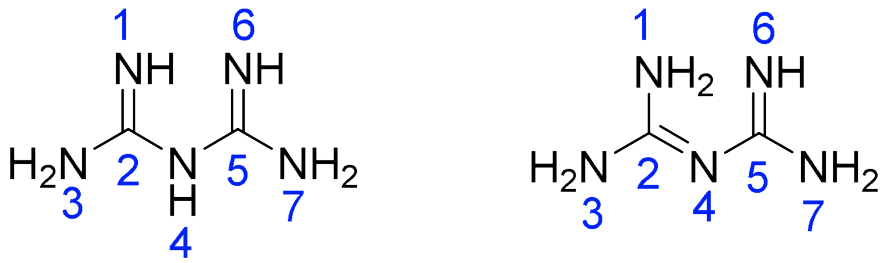


Fig. 3 The minor (**1a**), major (**1b**) tautomeric forms of biguanide

Calculated at level of theory 6-31+G* basis	Relative energy of structure **1a** w.r.t. **1b** (kcal/mol)
HF	11.26
MP2	11.76
B3LYP	9.67

– by Bharatam P.V. et al. J. Mol. Struc. **1152**, 61 (2018).

Structures and energetics of Biguanides

- Why structure **1b** is more stable than **1a**?
- Stabilization may be arising from the resonance

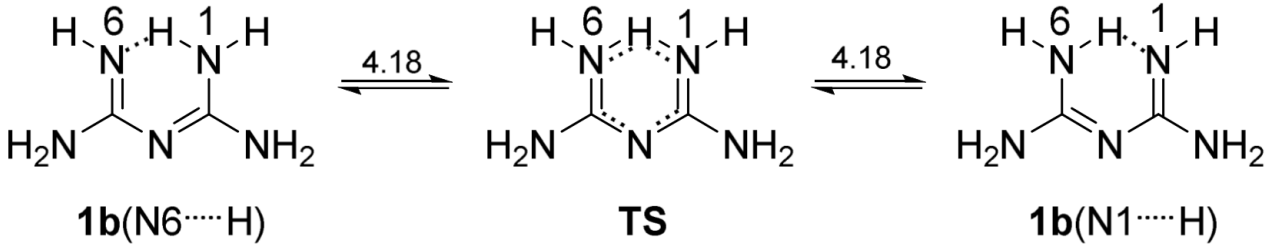
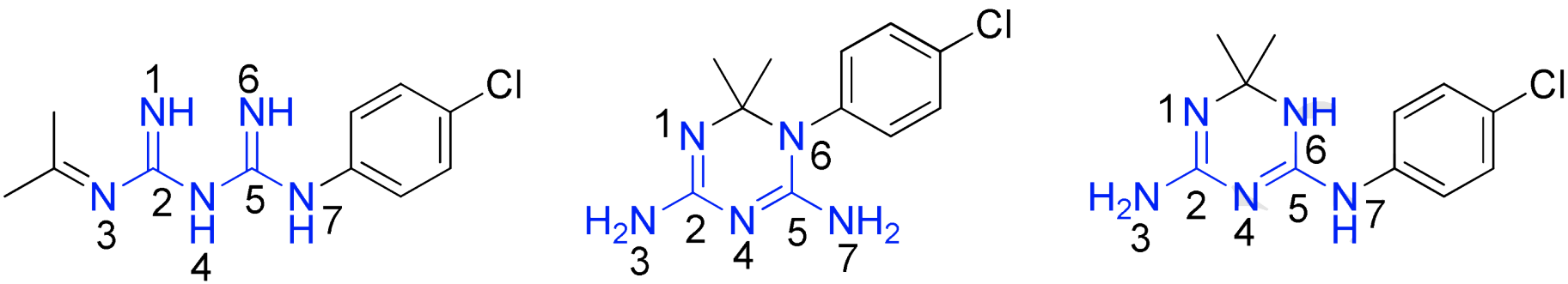


Fig. 19 1,5-H shift between N1 and N6 leading to dynamic equilibrium between two resonating structures. Energy values are in kcal/mol calculated at G2MP2/6-31+G*.[242]

– by Bharatam P.V. et al. J. Mol. Struc. **1152**, 61 (2018).

Biguanide derivative: Proguanil

- Proguanil, an antimalarial drug is inactive itself, however its active cyclic form is cycloguanil
- Similarly, cycloguanil exists in many forms



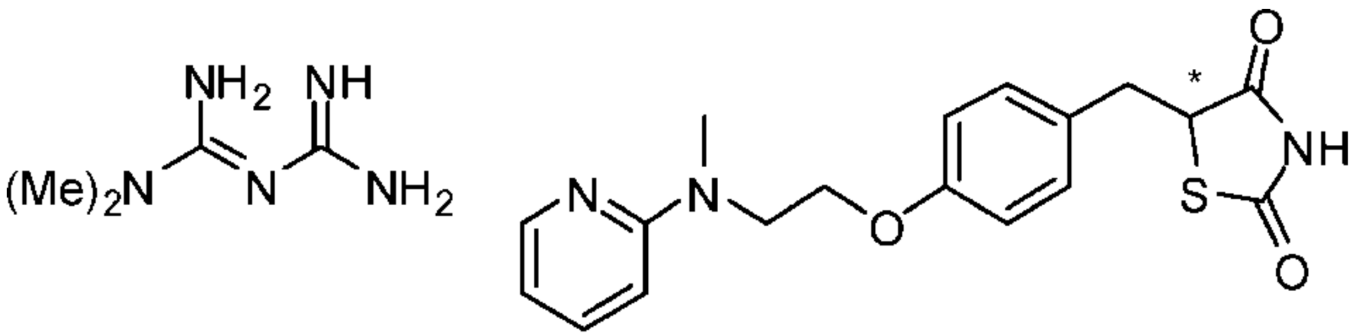
6a **6b** **6c**

Fig. 13 Linear (**6a**) and cyclic (**6b** and **6c**) isomers of cycloguanil.[211]

– by Bharatam P.V. et al. J. Mol. Struc. **1152**, 61 (2018).

Metformin and glitazones: does similarity in biomolecular mechanism originate from tautomerism in these drugs?

METFORMIN AND GLITAZONES

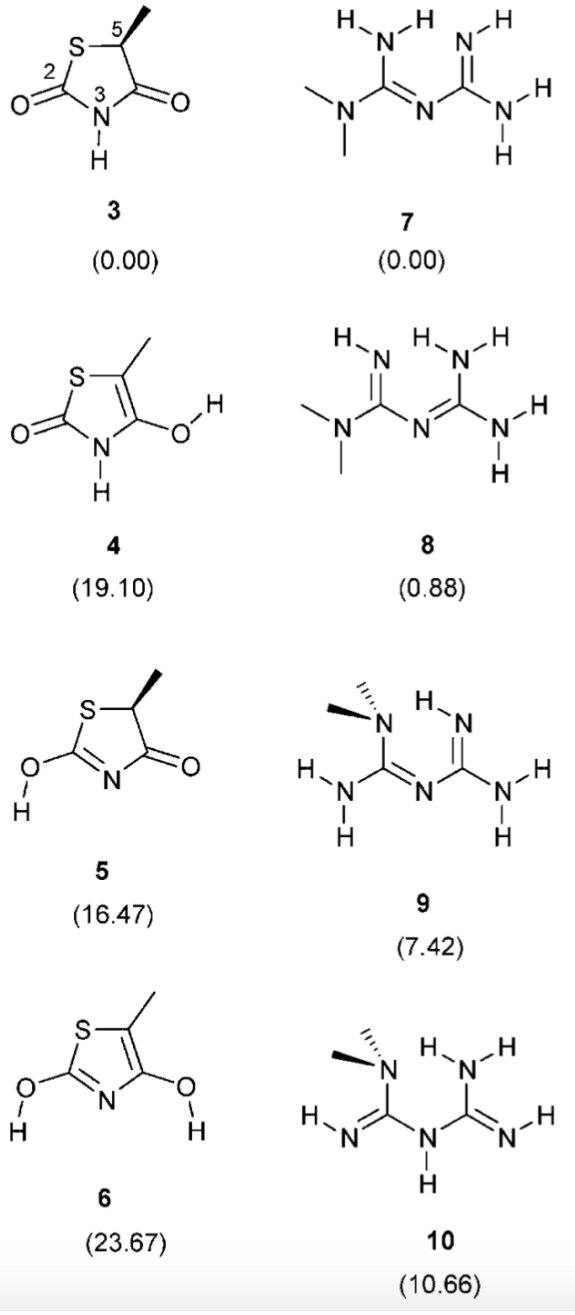


- Both belong to a class of antidiabetic drugs

– by Bharatam P.V. et al. J. Phys. Org. Chem. **21**, 20 (2008).

Metformin & glitazones: Structures and energetics

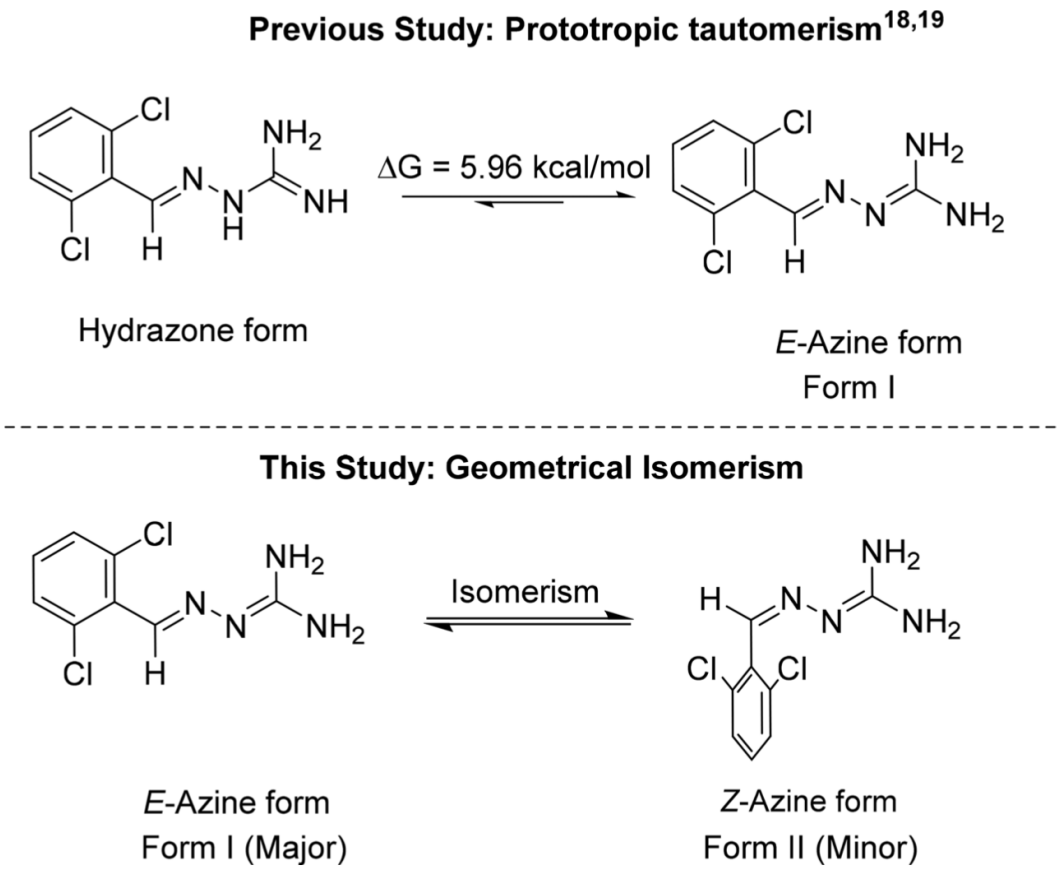
- Methylthiazolidinedione (**3**) is taken as a representative geometry for the glitazones
- Both exist in many tautomeric forms obtained using G2-MP2/6-31+G* theoretical calculations
- Out of many tautomeric forms, structures **3** and **7** were found to be the most favorable tautomeric forms of glitazones and metformin, respectively. Energies (kcal/mol) of tautomers are given in parentheses.



– by Bharatam P.V. et al. J. Phys. Org. Chem. **21**, 20 (2008).

Guanabenz: Structures and energetics

- Guanabenz is a drug used for the treatment of hypertension
- Exists in two forms, **I** and **II** by X-ray diffraction studies; Complemented by theoretical studies (B3LYP/6-311++G (d,p) and wB97X-D/6-311++G (d,p)): form **II** is 2.13 kcal/mol higher in energy than form **I**

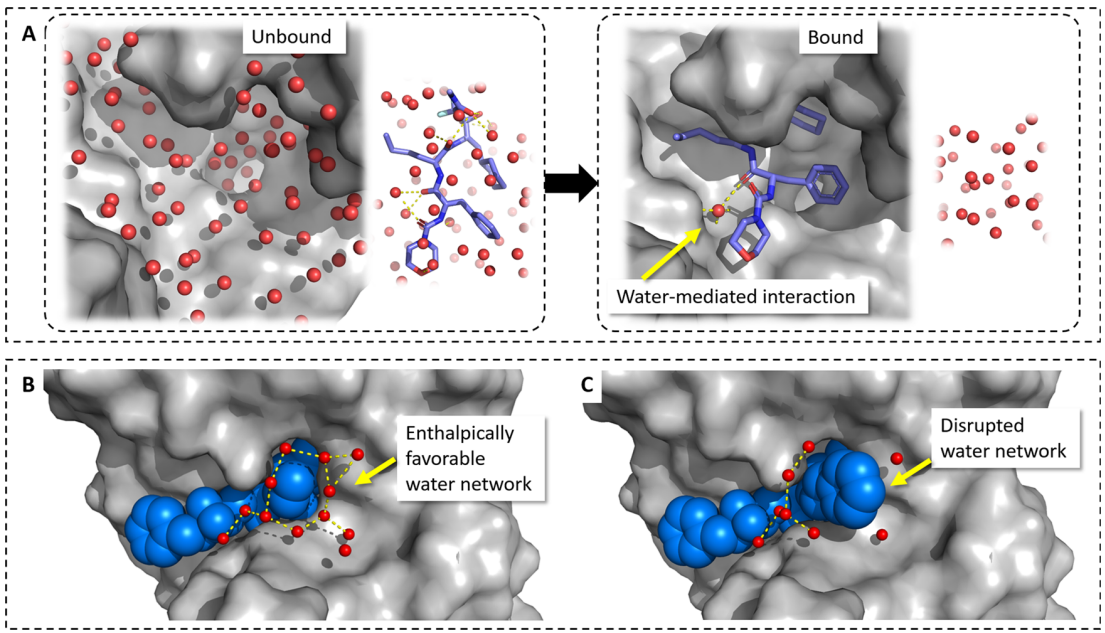


– by Bharatam P.V. et al. Cryst. Growth Des. **19**, 3183 (2019).

Theoretical aqueous solvation calculations for design of ligands

- Water is a crucial player in protein-ligand binding processes.
- Ligands are optimized to replace energetically unfavorable water molecules
- Enthalpically favorable water molecules are often utilized
- How about entropically favorable protein-ligand binding processes?

$$\Delta G = \Delta H - T\Delta S$$



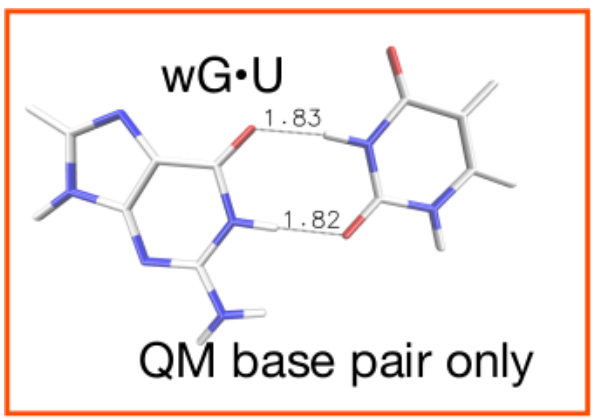
Lill M.A. et al. Commun. Chem. **3**, 19 (2020).

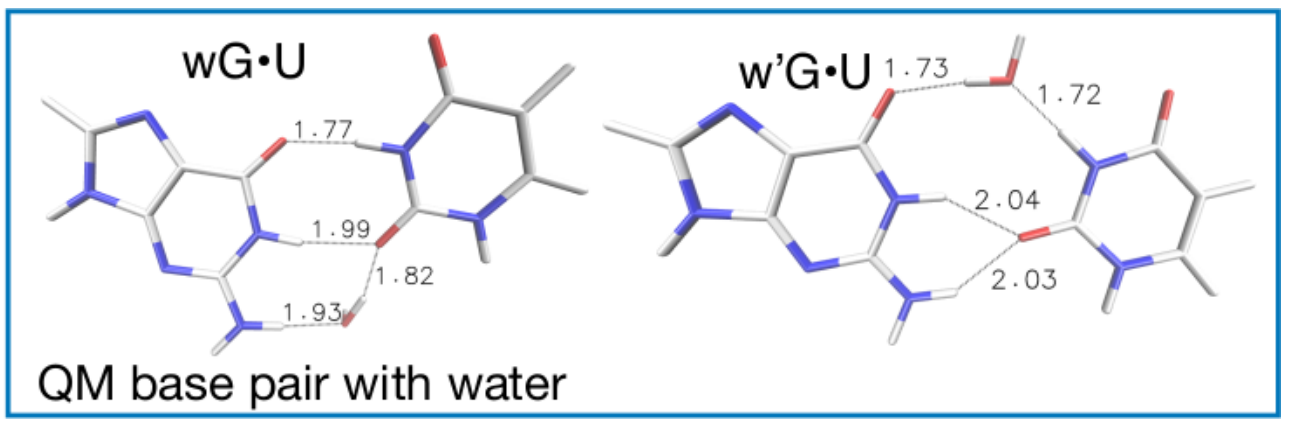
Methods for calculating solvation free energies

- Up to this point, the molecules and atoms were isolated (e.g., in a vacuum). – termed as gas-phase calculations
- Now, how do we include water in our calculation set-up?
- Solvation in molecular calculations usually fall into two main classes: explicit solvent molecules inclusions and continuum models.

Solvation with explicit solvent molecules

- Include explicit water molecules, maybe first add one or two directly in your QM calculations
- An example: RNA G∘U base pair model calculated at B3LYP/6-311++G (d,p). Here, water addition to the model, make favorable interaction by about 2 kcal/mol

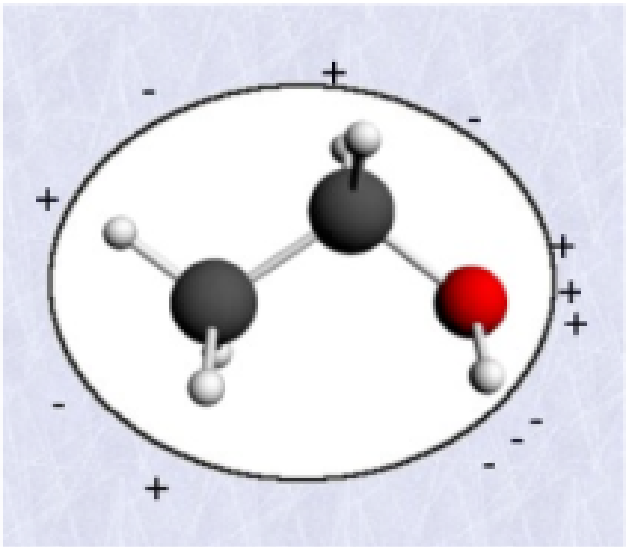




– by Chandorkar S. et al. Int. J. Mol. Sci. **22**, 5411 (2021).

Solvation continuum model

- Often a solvent molecule may not bond directly to the molecule of interest, or participate directly in a reaction that is under investigation
- Solvents of different dielectric interact differently also, may interact differently as well with various species involved in a reaction, e.g., reactant, intermediate, product, transition state.
- Solvent medium as represented by a single dielectric. Each continuum model contains some parameters, for example the dielectric of the solvent (Ex. dielectric constant: vacuum 1, protein core 4–20, water 80)



What do you need to specify to run a QM calculation?

- Molecule
- Molecular charge
- Spin multiplicity
- Basis sets
- Methods
  – in case of DFT: combination of exchange functional (S, B, B3 etc.) & correlation functional (VWN, LYP, P86 etc.)
  – in case of wavefunction based methods: HF, CISD, MP2, CCSD(T) etc.
- Finally, SOFTWARES: GAUSSIAN, MOLPRO, TURBOMOL, PSI3, GAMESS etc.

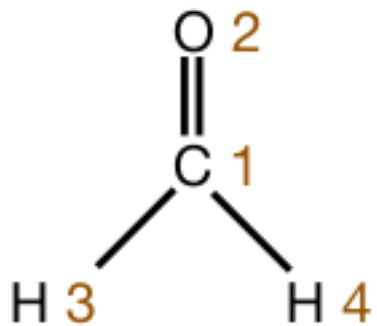
Example of a GAUSSIAN input file: internal coordinate

```
%mem=60MB
%chk=/scratch/test1.chk
#P HF/6-31G(d)

Title: Single point energy calculation of formaldehyde

0 1
C1
O2   1   r2
H3   1   r3   2   a3
H4   1   r4   2   a4   3   d4

r2=1.20
r3=1.0
r4=1.0
a3=120.
a4=120.
d4=180.
```

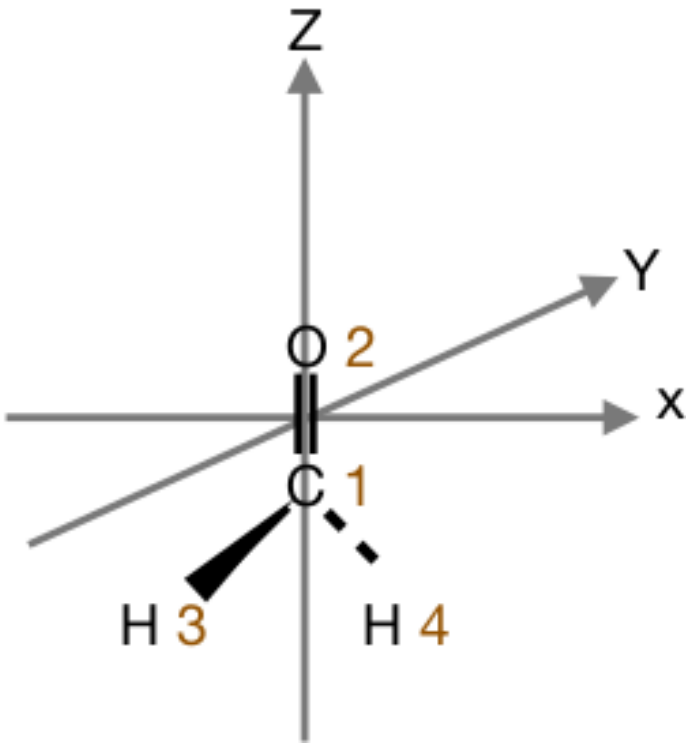


Example of a GAUSSIAN input file: Cartesian coordinate

```
%mem=60MB
%chk=/scratch/test1.chk
#P HF/6-31G(d)

Title: Single point energy calculation of formaldehyde

0 1
C   0.000000   0.000000  -0.537500
O   0.000000   0.000000   0.662500
H   0.000000   0.866025  -1.037500
H   0.000000  -0.866025  -1.037500
```



Assignment

- Significance of the study
- Results
- Conclusion

Article: Bharatam P.V. et al. J. Phys. Org. Chem. **21**, 20 (2008).