# The salt bridge - systematic QM and database search study

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## Introduction

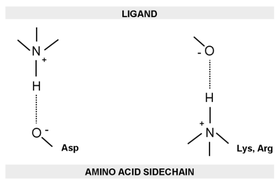
A salt bridge is a non-covalent interaction between two ionized molecules. It has two components: a hydrogen bond and an electrostatic interaction. In the case of a salt bridge formed in protein-ligand complexes, proton migrates from a side chain carboxylic acid group to an amine function of a ligand or from a side chain amine to a carboxylic ligand moiety. Typical salt bridges involve Lys/Arg as the bases and Asp/Glu as the acids. Of all the non-covalent interactions, salt bridges are the strongest one [1].

Based on the hydrogen-bond classification proposed by Gilli et al., salt bridge corresponds to the double charge-assisted hydrogen bonds ((+/-) CAHB) [2]. Over the years, these highly energetic H-bonds have been extensively studied by both experimental (thermodynamics in solution and in the gas phase, dipole moments, and IR or NQR spectroscopy) [3] and theoretical methods [4]. However, mainly low-molecular compounds or (as in the case of computational studies) very small models of interacting compounds ($NH_3$, $PH_3$, HCl) were used. Therefore, we run a systematic study on the nature of salt bridges in more biologically relevant model systems. To our knowledge, there is no data about the energy and directionality for this specific interaction.

## Methodology

### Searching of salt bridges in PDB database

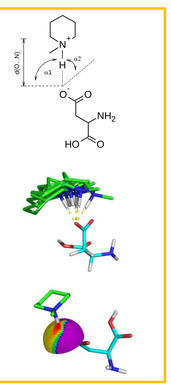
- an in-house python script was used to search the PDB database,
- pdb files were reduced to only those complexes where ligand contained one of the following functional groups: primary, secondary or tertiary amine or carboxyl,
- complexes with a distance between Asp/Glu and amine group or Lys/Arg and carboxyl group, longer than 4Å were rejected,
- the distance and angle between donor and acceptor were calculated.




**Query definition for searching of salt bridges.**

### Quantum chemistry calculations – spherical scan of interaction energy

- geometry optimization was carried out at MP2/6-31G* level using Gaussian 09,
- an in-hous script for generating spherical scan,
- single point energy calculations at MP2/6-311++G** level and with PCM model (solvent=water),
- an in-house script for visualization of interaction energy distribution.



## Results and Conclusions

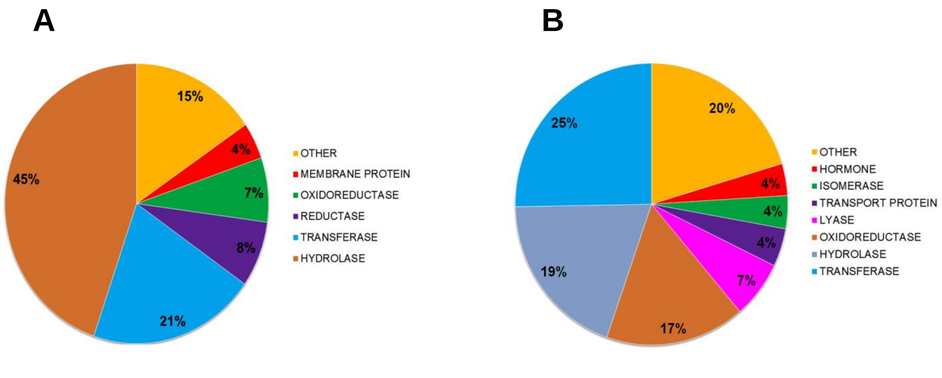



**Fig. 1. Distribution of salt bridges by protein family (based on the title information abstracted in PDB files). Chart A shows results for L-R complexes where Asp/Glu was an acceptor and protonated amine group was a donor, whereas chart B presents results for L-R complexes where Lys/Arg was a donor and carboxyl group of a ligand was an acceptor.**

### The PDB survey

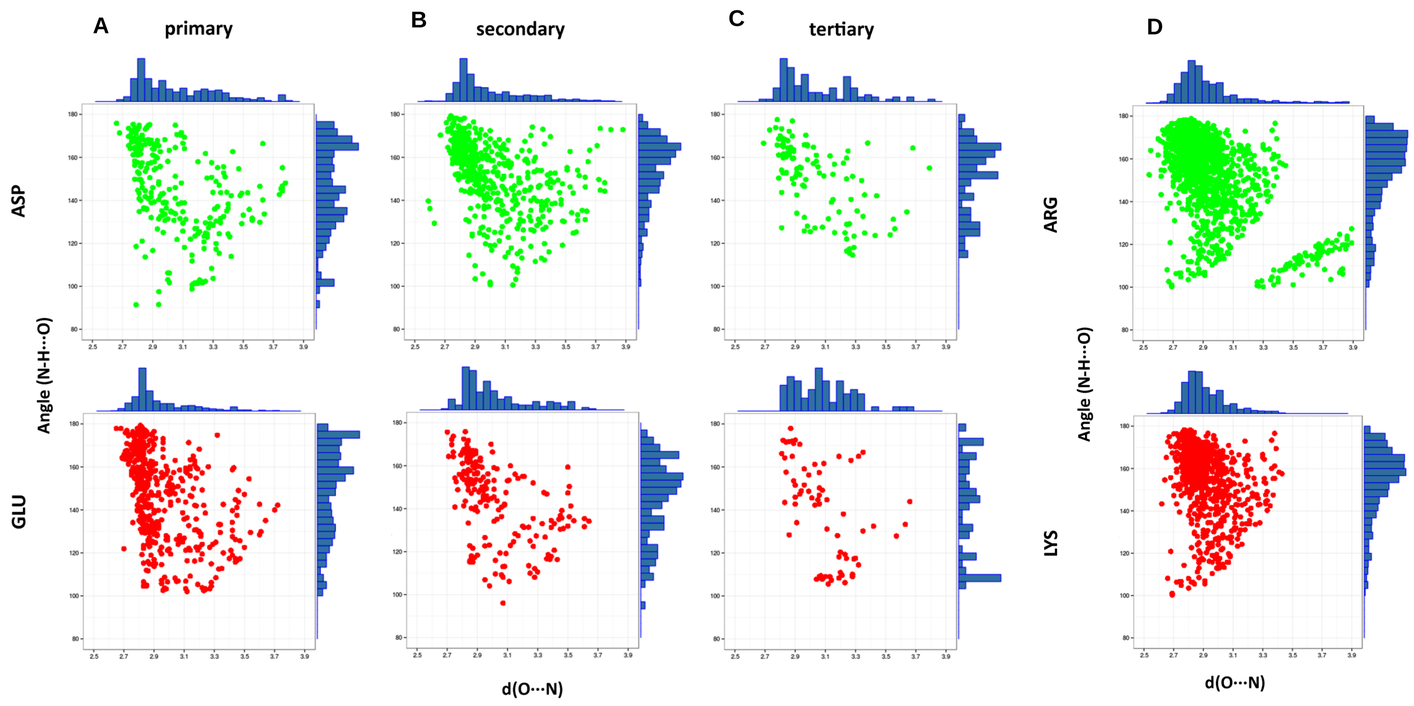
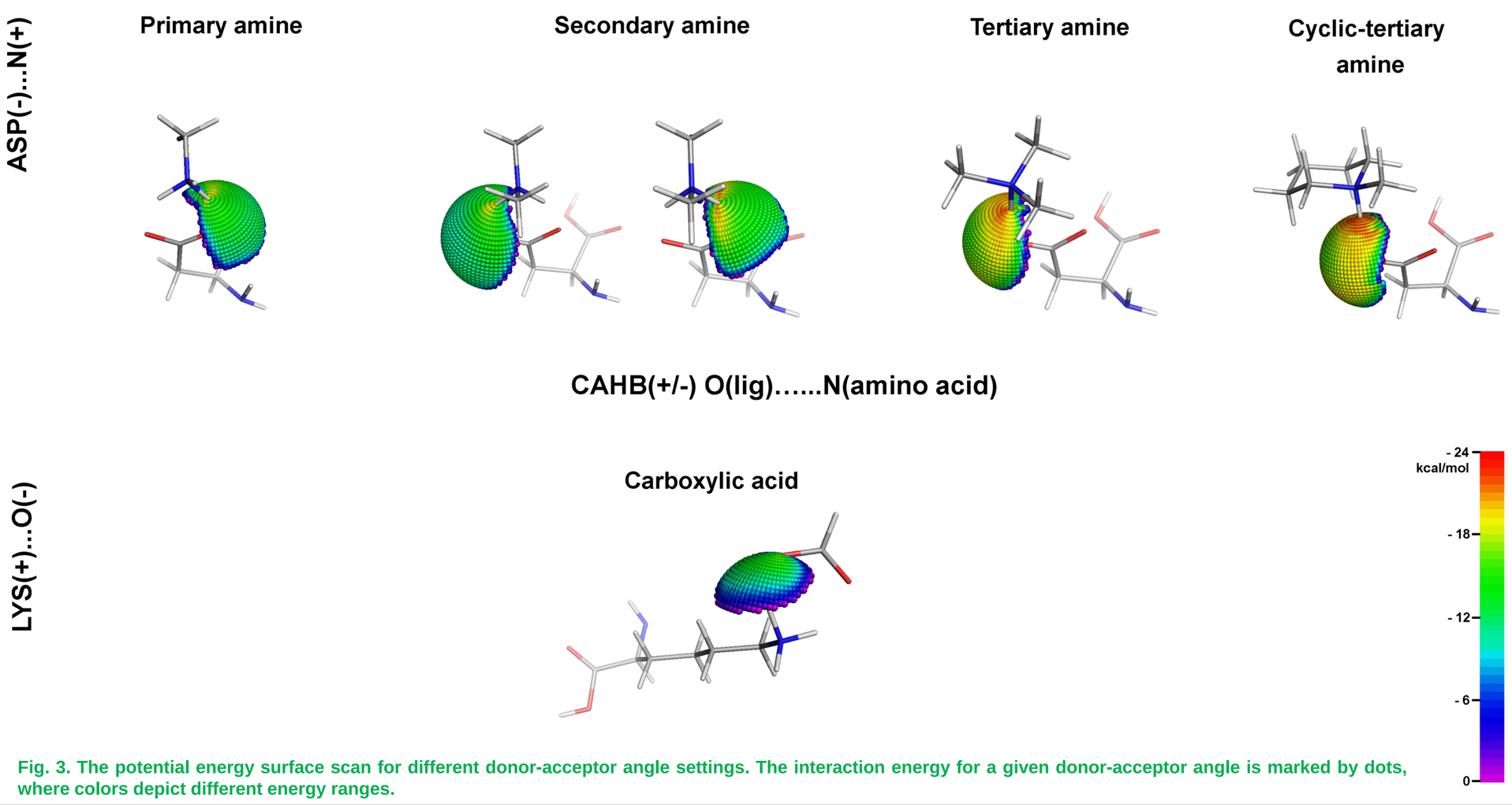



**Fig. 2. The distribution plots of hydrogen bond distance and angle between different donors and acceptors. Panels A-C present distribution plots for primary, secondary and tertiary amines as donors, panel D shows distrubutions for carboxyl group as an acceptor and Lys/Arg as donors.**

### Spherical scan of interaction energy for different model systems




- Overall, the energy of (+/-)CAHB depends on the donor-acceptor angle,
- for simple primary and secondary amines the bifurcated (+/-)CAHB can be formed,
- (+/-)CAHB is a key interaction occured in transferase and hydrolase target families,
- the most spread out interaction occured for O(lig)…N(amino acid) category,
- the mean (+/-)CAHB distance are around 2.8-2.9 Å,
- the mean (+/-)CAHB angles are more dificult to define and may vary from around 175-155 deg., hovewer for some cases (Asp+primary/tertiary and Glu+tertiary amines) second maximum is observed for angles lower than 140 deg.,
- interaction energy increases with the order primary<secondary<tertiary<cyclic-tertiary amines,

**Fig. 3. The potential energy surface scan for different donor-acceptor angle settings. The interaction energy for a given donor-acceptor angle is marked by dots, where colors depict different energy ranges.**

## References

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