Interactions of water with protein aromatic residues – *ab initio* study on model compounds

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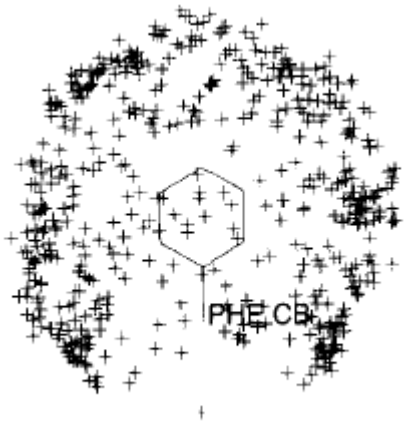
Interactions of aromatic residues in proteins with water

- Important for structure and activity of proteins
- Participation in protein folding
- Assistance in protein-ligand interactions
- Stabilization of local protein structure
- Contribution to hydration energy
- **Hydrophobic pockets with limited number of water molecules**

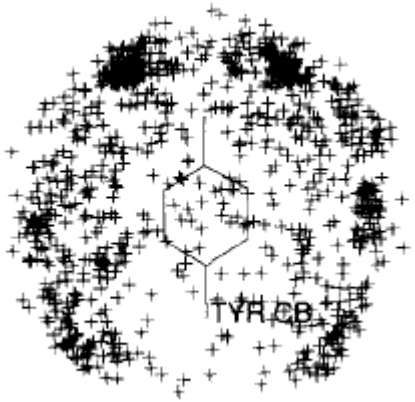
J. L. Atwood, F. Hamada, K. D. Robinson, G. W. Orr, R. L. Vincent, *Nature* 349, 683 (1991).
T. Steiner, A. M. M. Schreurs, J. A. Kanters, J. Kroon, *Acta Crystallogr. Sect. D* 54, 25 (1998).

WATER AND AROMATIC RESIDUES IN PROTEIN CRYSTAL STRUCTURES

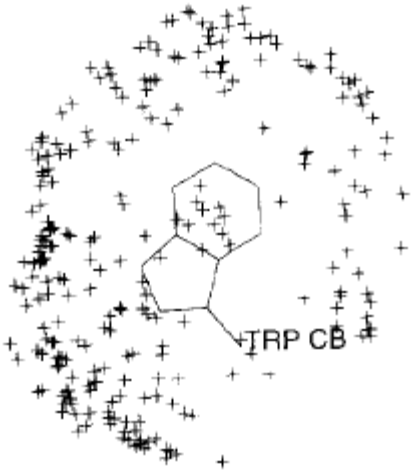
Resolution ≤ 1.5 Å
Water within 4.5 Å of any ring atom



64% of **Phe** residues
2 water molecules per residue on average



85% of **Tyr** residues
3 water molecules per residue on average

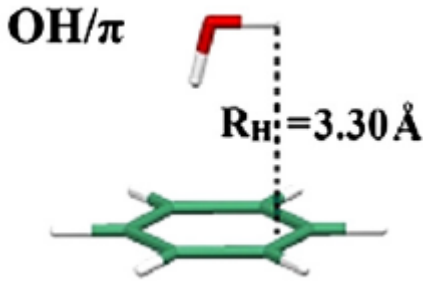


80% of **Trp** residues
2.5 water molecules per residue on average

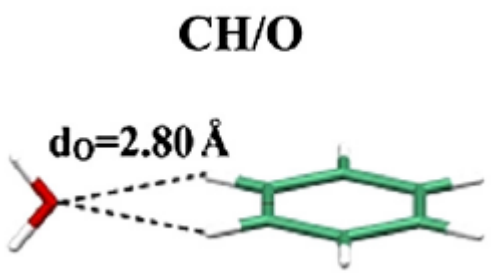
K. Håkansson, *Int. J. Biol. Macromol*. 18, 189 (1996).

WATER/BENZENE DIMERS

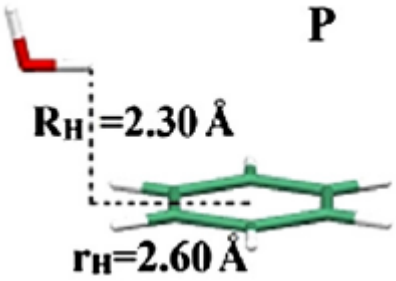
BENZENE = model compound for PHENYLALANINE residue



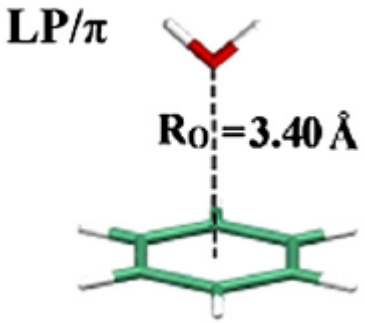
ΔE = -3.22 kcal/mol



ΔE = -1.51 kcal/mol



ΔE = -2.32 kcal/mol



ΔE = +0.55 kcal/mol

D. Ž. Veljković, G. V. Janjić, S. D. Zarić, *CrystEngComm* 13, 5005 (2011).

G. V. Janjić, D. Ž. Veljković, S. D. Zarić, *Cryst. Growth Des*. 11, 2680 (2011).

M. Egli, S. Sarkhel, *Acc. Chem. Res*. 40, 197 (2007).

WATER/BENZENE/WATER TRIMERS

- Gaussian 03
- Møller–Plesset perturbation theory of the second order (MP2)
- *cc-pVTZ* and *cc-pVQZ* basis sets
- *BSSE* corrected energies
- *NPA* at MP2/cc-pVQZ level

dimer binding energy

$$\Delta E(W1/B) = E_{W1B}^{W1B} - E_{W1}^{W1B*} - E_{B}^{W1*B}$$

trimer binding energy

$$\Delta E(W1/B/W2) = E_{W1BW2}^{W1BW2} - E_{W1}^{W1B*W2*} - E_{B}^{W1*BW2*} - E_{W2}^{W1*B*W2}$$

SYNERGETIC EFFECTS

cooperativity energy

$$\Delta E_{COOP} = \Delta E(W1/B/W2) - \Delta E(W1/B) - \Delta E(W2/B) - \Delta E(W1/W2)$$

synergetic energy

$$\Delta E_{SYNERG} = \Delta E(W1/B/W2) - \Delta E(W1/B) - \Delta E(W2/B)$$

dimer + monomer approach

$$\Delta E(W1/BW2) = E_{W1BW2}^{W1BW2} - E_{W1}^{W1B^*W2^*} - E_{BW2}^{W1^*BW2}$$

$$\Delta E(W1/B) = E_{W1B}^{W1B} - E_{W1}^{W1B^*} - E_{B}^{W1^*B}$$

$$\Delta\Delta E = \Delta E(W1/BW2) - \Delta E(W1/B)$$

SYNERGETIC EFFECTS

cooperativity energy

$$\Delta E_{COOP} = \Delta E(W1/B/W2) - \Delta E(W1/B) - \Delta E(W2/B) - \Delta E(W1/W2)$$

synergetic energy

$$\Delta E_{SYNERG} = \Delta E(W1/B/W2) - \Delta E(W1/B) - \Delta E(W2/B)$$

dimer + monomer approach

$$\Delta E(W1/BW2) = E_{W1BW2}^{W1BW2} - E_{W1}^{W1B^*W2^*} - E_{BW2}^{W1^*BW2}$$

$$\Delta E(W1/B) = E_{W1B}^{W1B} - E_{W1}^{W1B^*} - E_{B}^{W1^*B}$$

$$\Delta\Delta E = \Delta E(W1/BW2) - \Delta E(W1/B)$$

SYNERGETIC EFFECTS

cooperativity energy

$$\Delta E_{COOP} = \Delta E(W1/B/W2) - \Delta E(W1/B) - \Delta E(W2/B) - \Delta E(W1/W2)$$

synergetic energy

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dimer + monomer approach

$$\Delta E(W1/BW2) = E_{W1BW2}^{W1BW2} - E_{W1}^{W1B^*W2^*} - E_{BW2}^{W1^*BW2}$$

$$\Delta E(W1/B) = E_{W1B}^{W1B} - E_{W1}^{W1B^*} - E_{B}^{W1^*B}$$

$$\Delta\Delta E = \Delta E(W1/BW2) - \Delta E(W1/B)$$

WATER/BENZENE/WATER TRIMERS

rigid contact

varying contact

ΔE(W1/B/W2)*	OH/π	CH/O	P	LP/π
OH/π	-6.04	-5.16	-5.50	-3.12
CH/O	-5.17	-2.71	-3.89	-0.54
P	-5.52	-3.91	-4.67	-1.94
LP/π	-3.13	-0.54	-1.92	+1.49

*** in kcal/mol**

rigid contact

varying contact

ΔΔE*	OH/π	CH/O	P	LP/π
OH/π	+0.40	-0.42	+0.04	-0.42
CH/O	-0.44	+0.31	-0.06	+0.43
P	+0.04	-0.07	-0.03	-0.15
LP/π	-0.46	+0.43	-0.16	+0.40

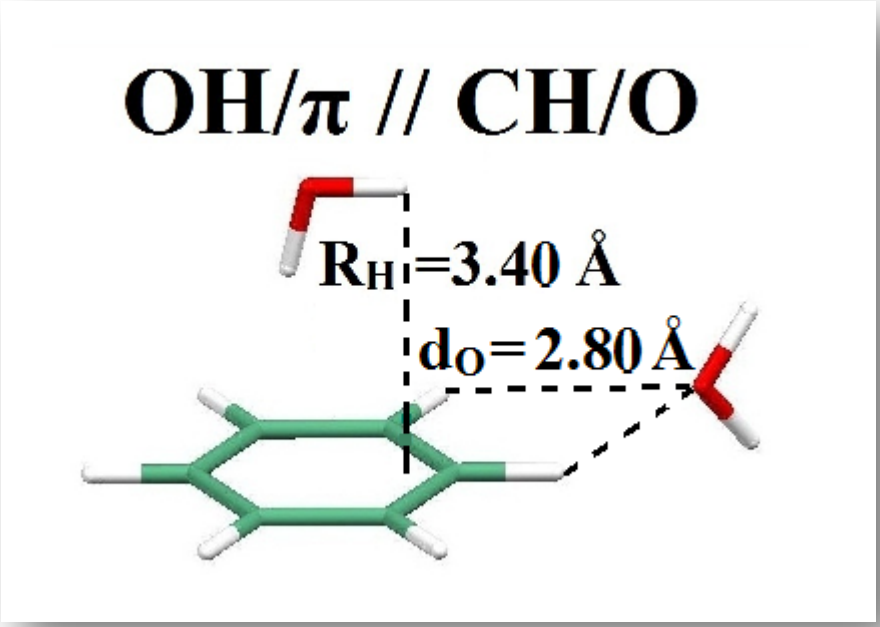
*** in kcal/mol**

POSITIVE SYNERGY

✓**OH/π // CH/O**
✓**CH/O // OH/π**

✓**OH/π // LP/π**
✓**LP/π // OH/π**

Δq (OH/π, benzene→water) = 2.1 me
Δq (CH/O, water→benzene) = 1.1 me



ΔE(W1/BW2) = -3.64 kcal/mol
ΔE(W1/B) = -3.22 kcal/mol

ΔΔE = -0.42 kcal/mol

stronger OH/π interaction!

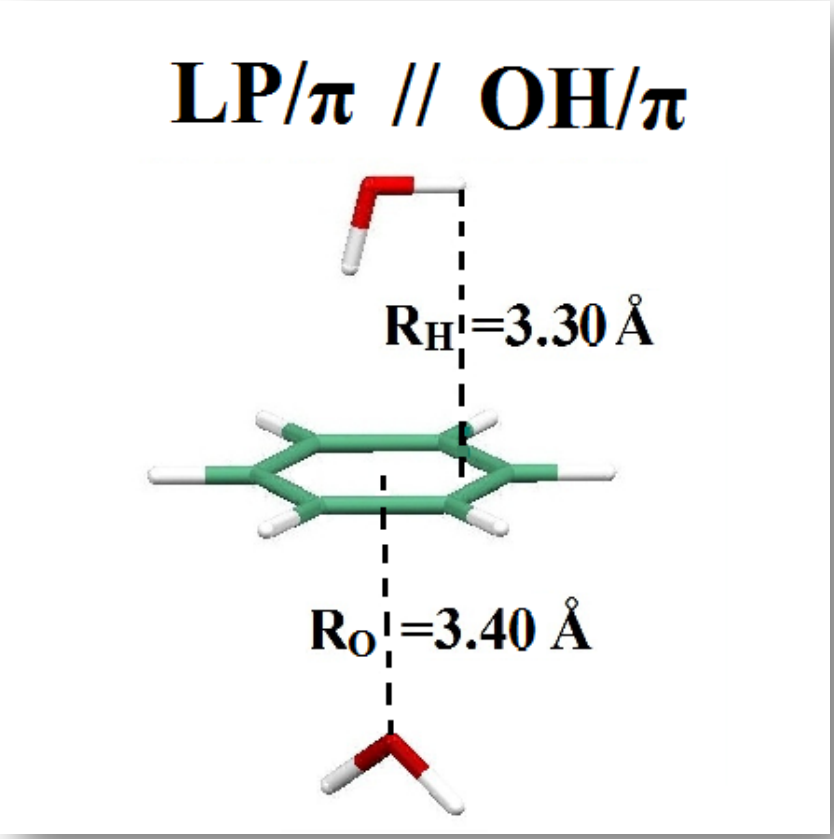
POSITIVE SYNERGY

✓OH/π // CH/O
✓CH/O // OH/π

✓OH/π // LP/π
✓LP/π // OH/π

ΔE(W1/BW2) = +0.09 kcal/mol
ΔE(W1/B) = +0.55 kcal/mol
_____
ΔΔE = -0.46 kcal/mol

less repulsive LP/π interaction!!!



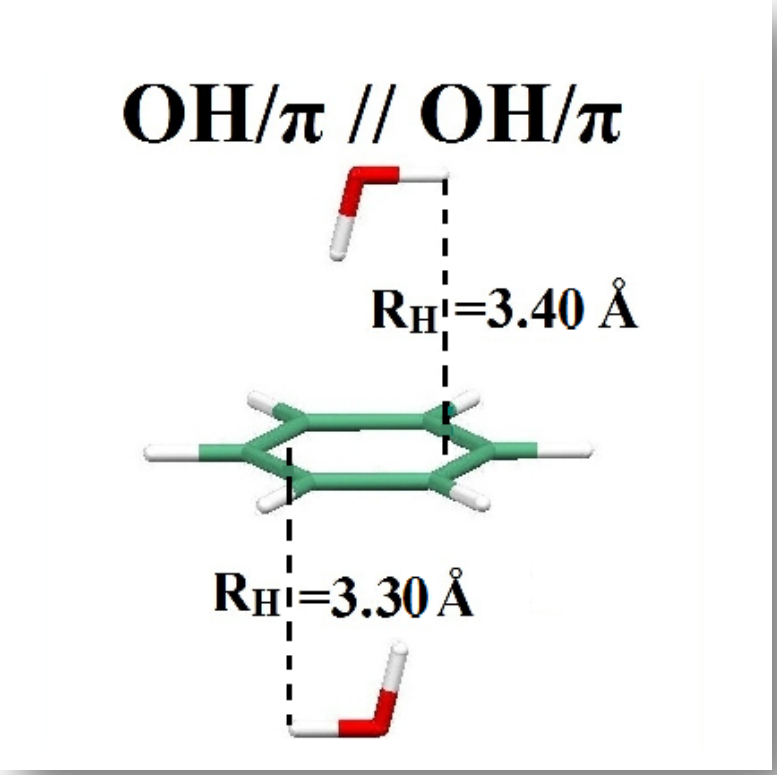
D. P. Malenov, G. V. Janjić, D. Ž. Veljković, S. D. Zarić, *Comp. Theor. Chem.* 1018, 59 (2013).

NEGATIVE SYNERGY

- ✓**OH/π // OH/π**
- ✓**CH/O // CH/O**

- ✓**LP/π // LP/π**
- ✓**CH/O // LP/π**
- ✓**LP/π // CH/O**

Δq (OH/π, benzene→water) = 2.1 me
Δq (CH/O, water→benzene) = 1.1 me



ΔE(W1/BW2) = -2.82 kcal/mol
ΔE(W1/B) = -3.22 kcal/mol

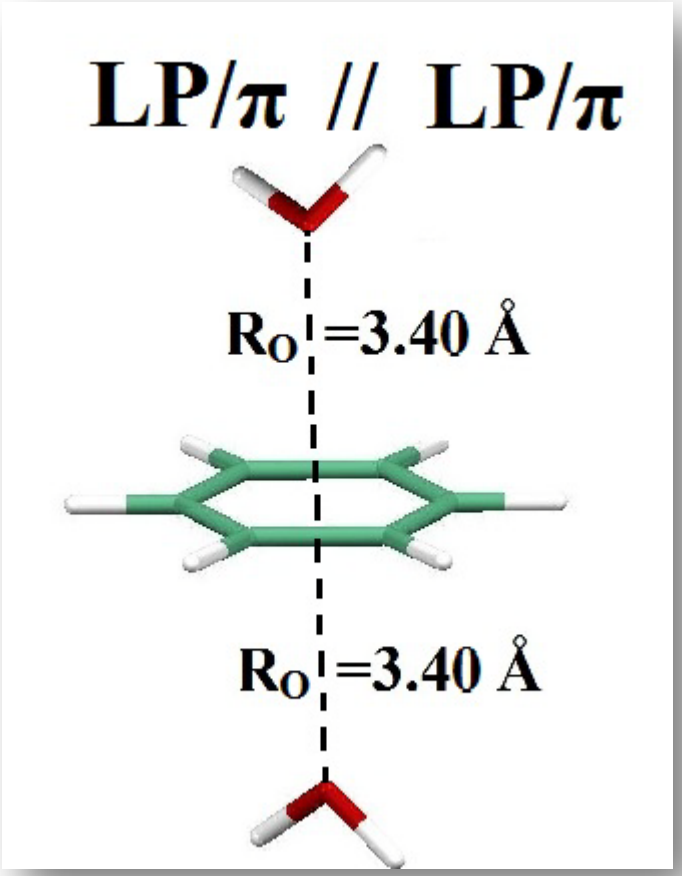
ΔΔE = +0.40 kcal/mol

weaker OH/π interaction

NEGATIVE SYNERGY

- ✓OH/π // OH/π
- ✓CH/O // CH/O

- ✓LP/π // LP/π
- ✓CH/O // LP/π
- ✓LP/π // CH/O



ΔE(W1/BW2) = +0.98 kcal/mol
ΔE(W1/B) = +0.55 kcal/mol
_____
ΔΔE = +0.43 kcal/mol

more repulsive LP/π interaction!!!

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NO SYNERGY

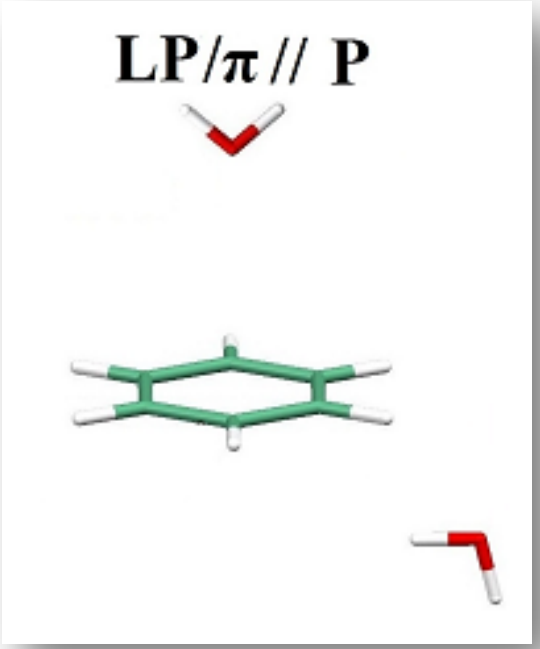
- ✓**P// OH/π**
- ✓**OH/π // P**
- ✓**P // CH/O**
- ✓**CH/O // P**
- ✓**P // P**

abs(ΔΔE) = 0.03 – 0.07 kcal/mol

Δq (P, benzene→water) = 0.6 me

Borderline cases?

- ✓**P// LP/π**
- ✓**LP/π // P**



Positive synergy, but still substantially lower than within other systems

CONCLUSIONS

- The energy of the Phe$(H_2O)_2$ trimer increases in comparison to energy of Phe(H_2O) dimer, except when at least one repulsive interaction is present.
- Synergy of two phenylalanine residue/water interactions can be both positive and negative, depending on the types of interactions involved.
- Two interactions of the same type weaken each other, as well as CH/O and LP/π interactions.
- OH/π interactions strengthen CH/O and LP/π interactions and vice versa.
- Parallel alignment interactions do not influence other interactions significantly.
- The calculated mutual influences of interactions are related to charge transfer.

ACKNOWLEDGEMENTS

Prof. Snežana Zarić
Dušan Veljković
Dr Miloš Milčić
Jelena Andrić
Dubravka Vojislavljević-Vasilev
Suzana Đurđević
Dr Goran Janjić
Dr Vesna Medaković
Dr Dušan Sredojević
Dragan Ninković
Predrag Petrović
Jovan Dragelj

Dr Horst Borrmann from MPI CPfS at Dresden, Germany

DAAD foundation, Germany (fellowships + grants)

Humboldt foundation, Germany (fellowships + grants)

Swiss National Science Foundation - SCOPES Program

SupraChem@Balkans.eu

Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 172065)