A computational study of the mode of action of the DAD photoswitch in the $Na_V1.5$ channel

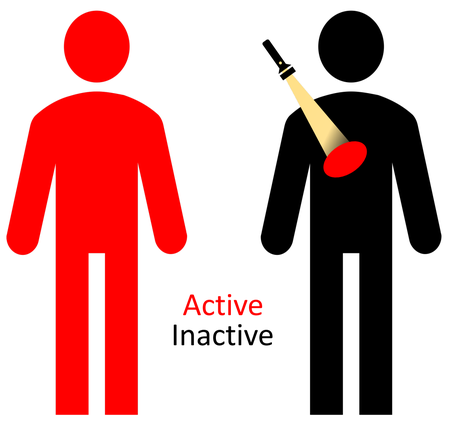
IBER 2023

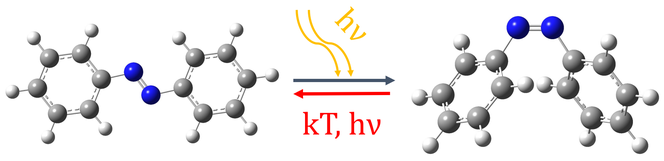
Lucía López-Pacios[1], Vito F. Palmisano[1,2], Juan J. Nogueira[1,3] and Lara Martínez-Fernández[1,3]

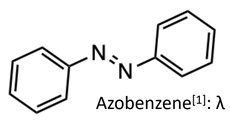
[1]Department of Chemistry, Universidad Autónoma de Madrid, 28049, Madrid, Spain
[2]Theoretical Chemistry Group, Zernike Institute for Advanced Materials, University of Groningen, 9747 AG, Groningen, The Netherlands
[3]Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049, Madrid, Spain

Motivation

Photopharmacology



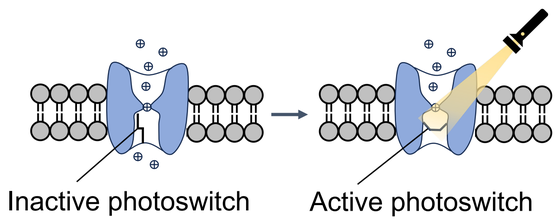


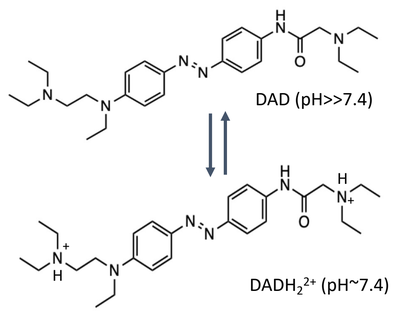


Conformation in the dark
- Biologically inactive
- Non-toxic everywhere

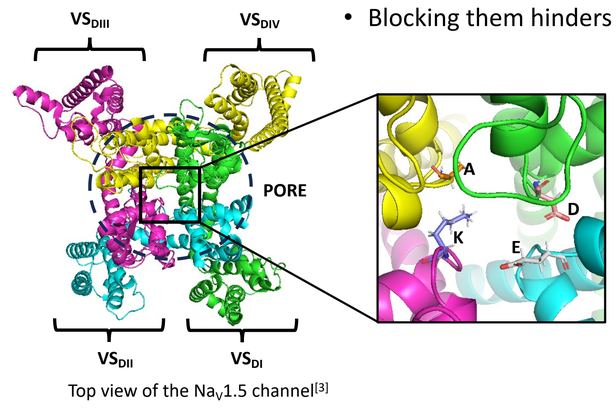
Conformation upon irradiation
- Biologically active only in the desired target

Derivation of azobenzene ↑ λ
DAD[2]: λ = 454 nm





Ion channels



Top view of the $Na_V1.5$ channel[3]

- Transmembrane proteins that control ion transport.
- Key in neuronal transmission and muscle contraction.
- Blocking them hinders signal propagation.

Computational details

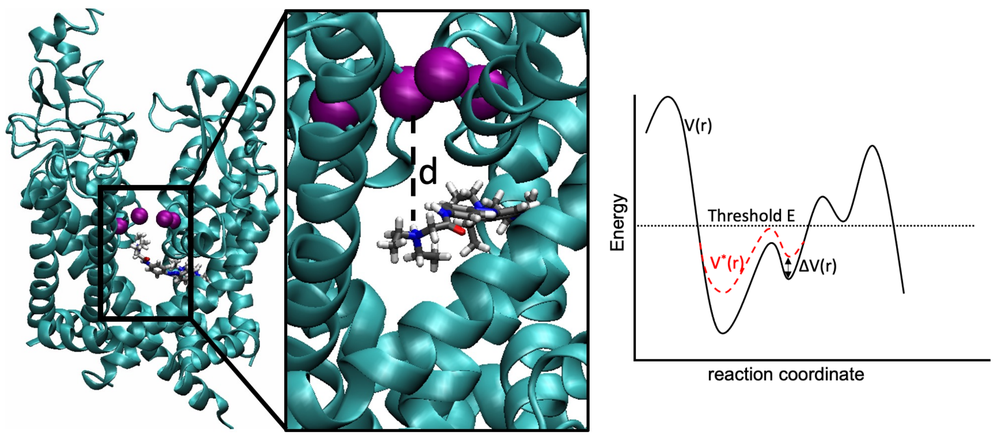
- Binding Pocket search ($DADH_2^{2+}$)

Docking → (Preliminar pockets) → GaMD (More accurate pockets) → cMD (Stabilization of pockets) → MMGBSA (ΔG of pockets)

- Absorption spectra
  - Static: vacuum (TDDFT, CASSCF, CASPT2) and solvent (LR-PCM-TDDFT) → DAD, $DADH_2^{2+}$, azobenzene
  - Dynamic: solvent (LR-PCM-TDDFT, QM/MM) and pockets (QM/MM) → QM región = $DADH_2^{2+}$

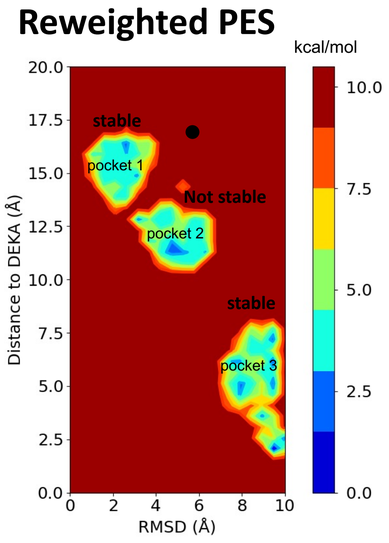
- Photoisomerization (DAD, $DADH_2^{2+}$, azobenzene): vacuum (TD-DFT) and solvent (LR-PCM-TDDFT)

GaMD reaction coordinate

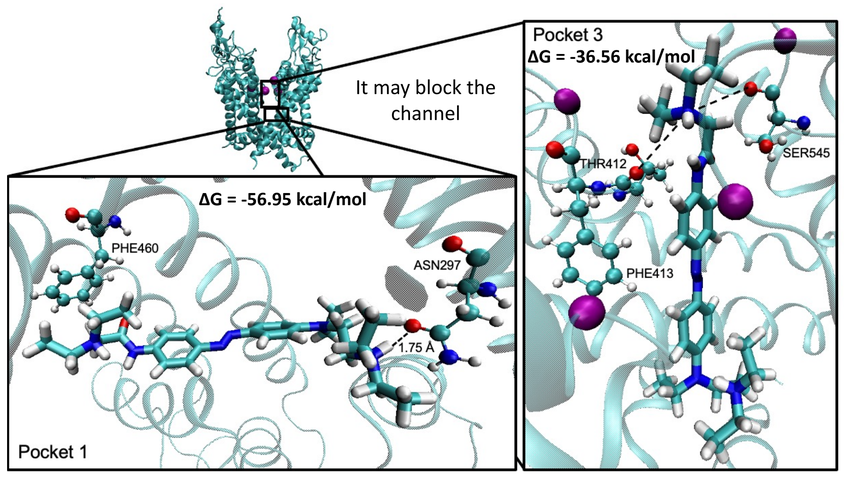


Binding pocket search

Reweighted PES



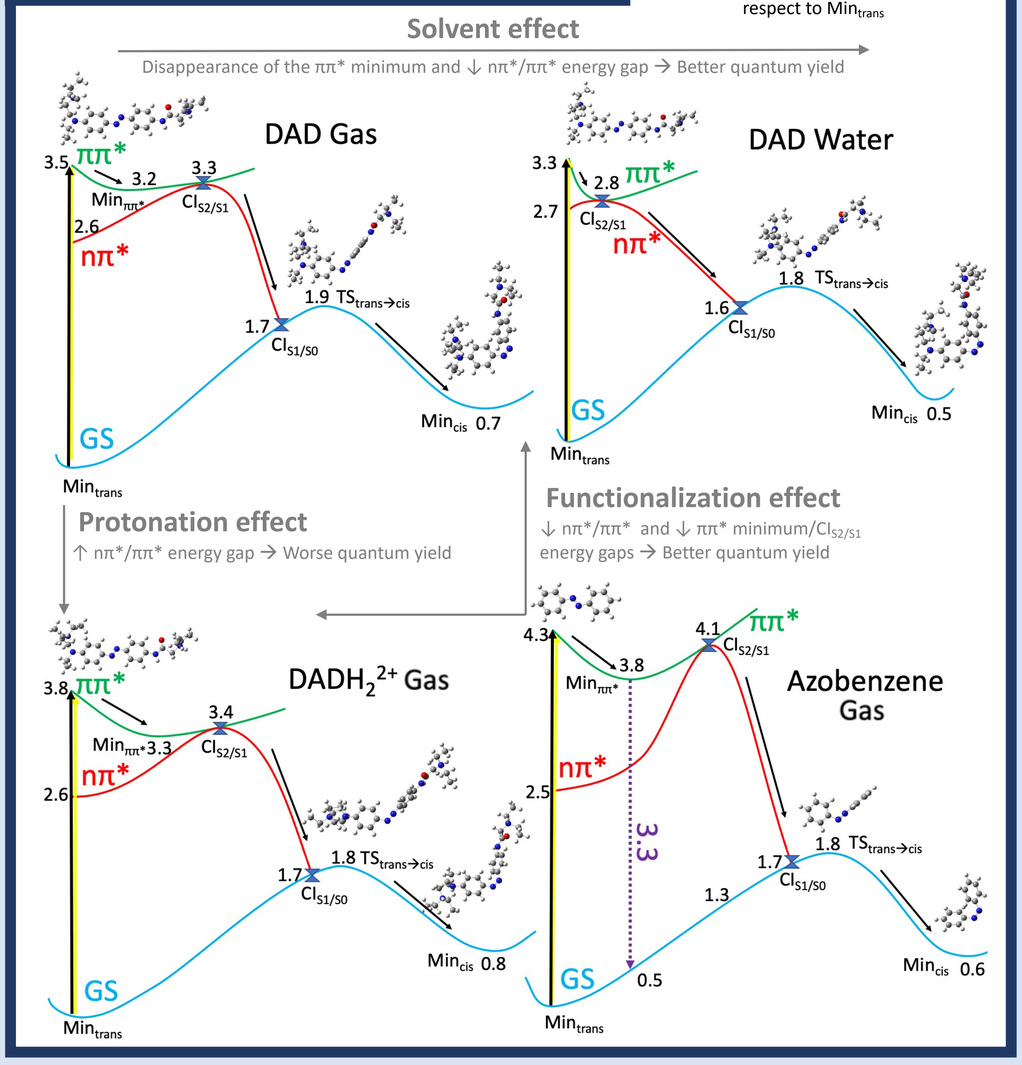
MMGBSA Analysis



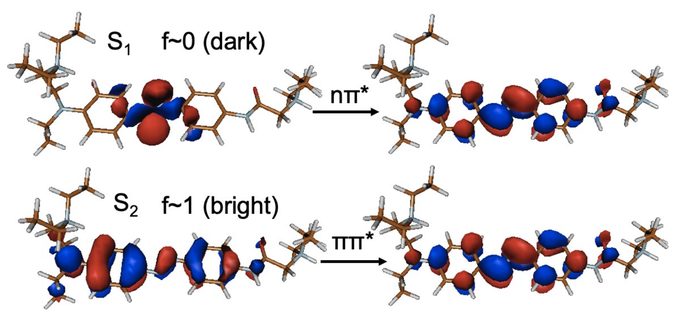
Most important contribution to stabilisation: electrostatic

Photoisomerisation

Energies in eV at M06-2X/cc-pVDZ with respect to Min_{trans}



Absorption spectra

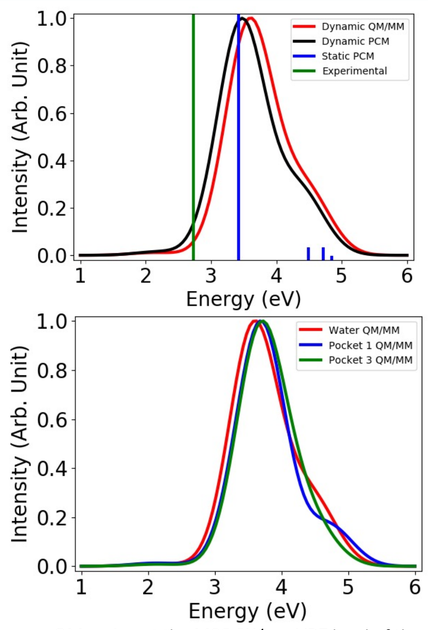


Solvent effect and functionalization
- ππ* (S_2)↓
- nπ* (S_1) ↑

} S_2-S_1 gap ↓

Protonation effect
- ππ* (S_2) ↑
- nπ* (S_1) ↓

} S_2-S_1 gap ↑



QM region at the M06-2X/cc-pVDZ level of theory

Conclusions

- Pocket 1 is the most favourable pocket for $DADH_2^{2+}$.
- The nπ*/ππ* gap
  - ↓ Polar solvents, Derivation of azobenzene
  - ↑ DAD protonation
- Among the considered systems, the most favourable photoisomerization occurs for DAD in water.
- The QM region will be increased to take into account the protein environment more accurately.

References

1. Jianqiang Zhao *et. al*., *J. Theor. Comput. Chem.*, **2021**, 1200, 113244.
2. Laura Laprell *et. al*., *J. Clin. Investig.*, **2017**, 127(7), 2598-2611.
3. Daohua Jiang *et. al*., *Cell*, **2021**, 184(20), 5151-5162.e11.
4. Juan J. Nogueira *et. al*. *The Oxford Handbook of Neuronal Ion Channels*, **2019**.

Universidad Autónoma de Madrid

MoBioChem
Modeling Biology and Chemistry