CORRELATIONS AMONG SOLUBILITY AND CRYSTAL STRUCTURE:
A CRYSTALLOGRAPHIC AND SPECTROSCOPIC STUDY OF THE ANTIMALARIAL DRUG PIPERAQUINE

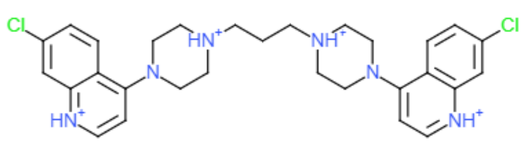
UNIVERSITÀ DEGLI STUDI DI MILANO

Pietro Sacchi[1], Giovanni Macetti[1], Silvia Rizzato[1], Laura Loconte[1], Fabio Beghi[1], Leonardo Lo Presti[1,2,3]

1. Department of Chemistry, Università degli Studi di Milano, via Golgi 19, I-20133, Milano, Italy
2. CNR-ISTM, Istituto di Scienze e Tecnologie Molecolari, via Golgi 19, I-20133, Milano, Italy
3. Center for Materials Crystallography, Aarhus University, Langelandsgade 140, 8000

Motivation

Piperaquine (PQ) is a potent antimalarial drug used worldwide.[1] The understanding of its properties and their relation with molecular recognition can help to (i) gain insights on its mode of action and (ii) develop new drugs, able to counteract the increasing adaptability of the malaria parasite.



Crystal Growth

Crystals of PQ salts were grown by slow evaporation of solvent from concentrated aqueous solutions of inorganic acids, in which neutral PQ was dissolved.

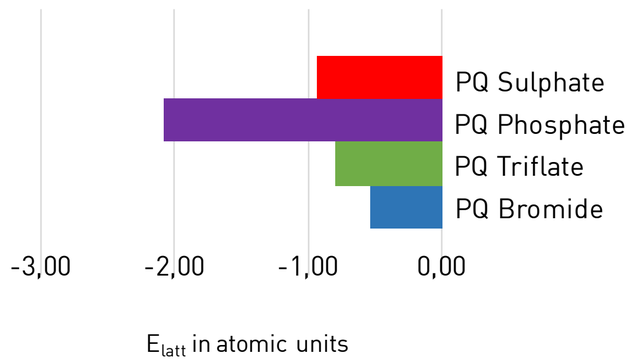
The crystals were then grinded and the identity of the powders was confirmed by comparison of experimental XRPD diffractograms with simulated patterns from the corresponding crystal structures.

Single-crystal X-ray diffraction data were collected with monochromatic Mo Kα radiation.

Conclusions

- The crystal structure of four different Piperaquine^{4+} salts have been determined
- The dependence of the solubility on temperature was measured in the range 20 °C - 50 °C for all PQ salts
- Preliminary solid state DFT studies show partial correlation between measured solubility and lattice enthalpies

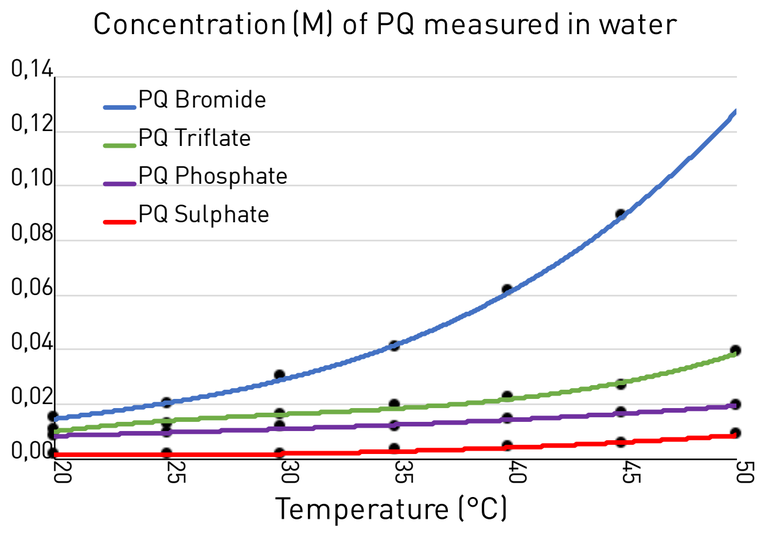
Energy Estimates

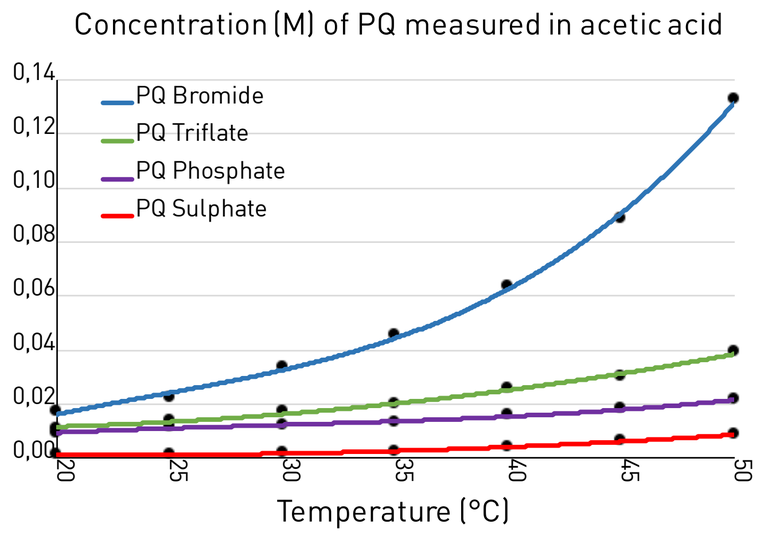


Lattice energies have been estimated at the B3LYP/6-311-G** theory level using a simple Born-Haber cycle.[2]

The anomalous value of PQ Phosphate is to be ascribed to the use of an incomplete model.

Solubility





Samples of PQ salts suspensions in water were collected at different temperatures and the absorbance was measured in water and in 1N acetic acid at 349 and 344 nm, respectively.[3]

Calibration curves were built using commercially available PQ phosphate.

Crystal Structures

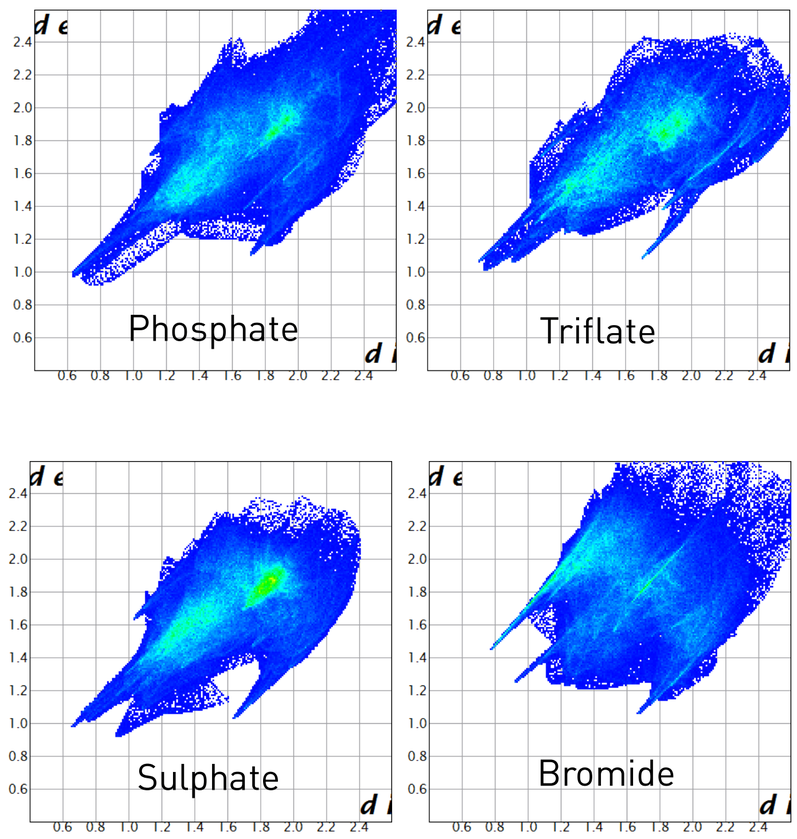
Table1 - Crystallographyc data for PQ salts

Compound	PQ phosphate*	PQ sulphate	PQ triflate	PQ bromide
Formula	$H_4PQ^{4+},(H_2PO_4^-)_4,4(H_2O)$	$H_4PQ^{4+},(HSO_4^-)_5,6.5(H_2O),H_3O^+$	H_4PQ^{4+}, $4(OTf^-)$, $3(H_2O)$	$H_4PQ^{4+},Br^-_5,3(H_2O),H_3O^+$
Space Group	P21/n	Cc	C2/c	P-1
a	22.2666(10)	21.4922(7)	19.031(4)	7.4298(2)
b	7.4487(3)	7.3576(2)	18.208(4)	14.3820(4)
c	27.8893(12)	29.6485(10)	16.149(3)	17.6634(4)
α	90.000	90.000	90.000	88.9355(9)
β	107.384(1)	101.6530(10)	118.92(3)	80.4143(9)
γ	90.000	90.000	90.000	84.7012(9)
T	150 K	120 K	298 K	120 K
Max. resolution	0.714	0.736	0.714	0.716
Abs. coefficient	0.373	0.469	0.417	5.608
R_{int}	0.033	0.015	0.026	0.020
data/paramenter	14.94	18.92	18.81	20.29
R1	0.058	0.046	0.063	0.024
wR2	0.178	0.132	0.187	0.057
GooF	1.044	1.045	1.064	1.025

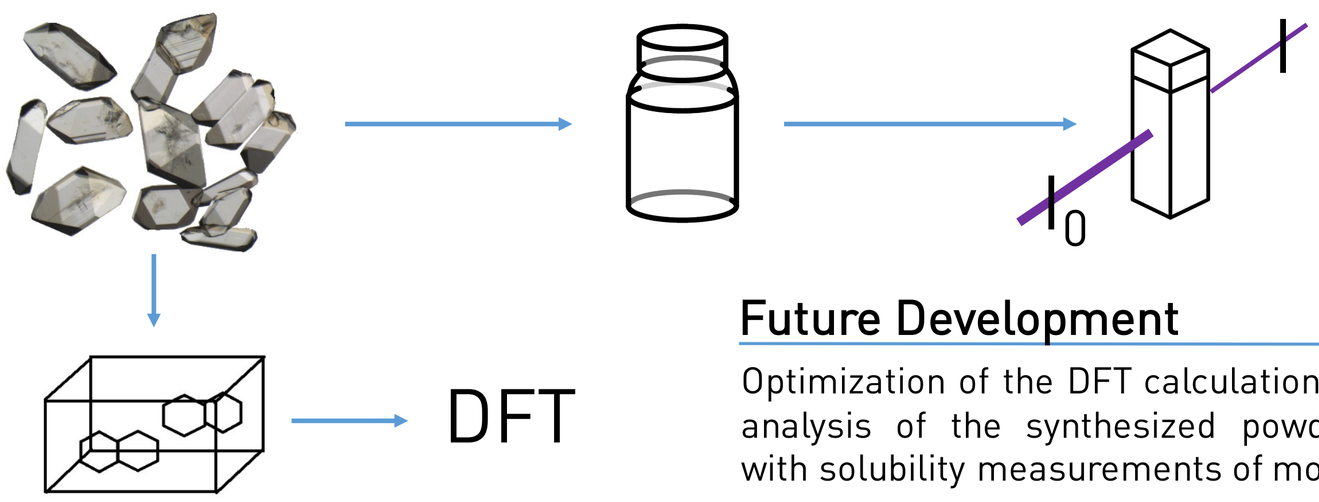
*PQ Phospate was refined using SQUEEZE due to solvent disorder

2D Fingerprint Plots

The main intermolecular contacts can be identified with 2D fingerprint plots and are Charge Assisted Hydrogen Bonds (spikes) and π-stacking interactions (bright green diffuse areas).[4]



Method



Future Development

Optimization of the DFT calculations and thermal analysis of the synthesized powders, together with solubility measurements of more PQ salts.

A paper reporting these findings is in preparation.

References

[1]Davis *et al.*, *Drugs* 2005, 65(1), 75
[2]Dovesi *et al.*, *Int. J. Quantum Chem.* 2014, 114, 1287
[3]Ali Daneshfar *et al. J. Chem. Eng. Data* 2009, 54, 2170
[4]McKinnon *et al.*, *Acta Crystallographica Section B: Structural Science*. 2004, 60, 627

Acknowledgments

This research was funded by the Unimi Development Plan–Line 2, Action B, project NOVAQ (Understanding structure-function relationships in 4-aminoquinoline drugs: an experimental and theoretical route toward novel antimalarials), nº PSR2015-1716FDEMA_08