Structural Model Complexes for 2-Oxoglutarate Dependent Iron Enzymes

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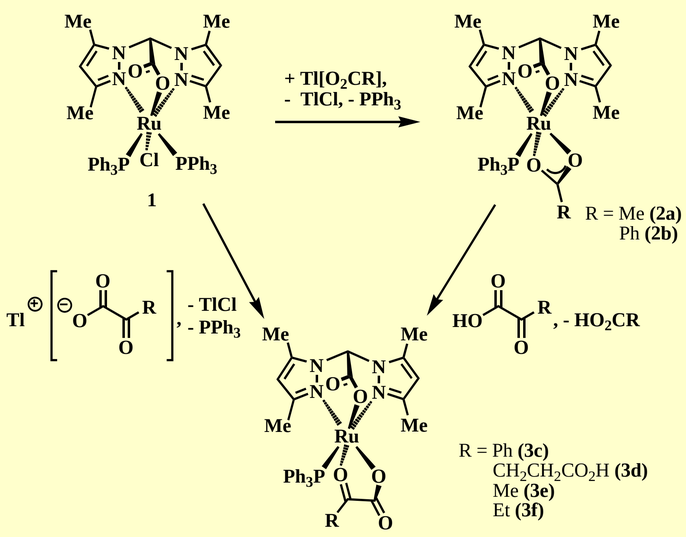
2-Oxoglutarate Dependent Iron Enzymes

In recent years protein structures of several 2-oxoglutarate dependent mononuclear non heme iron(II) oxygenases were resolved, such as deacetoxy-cephalosporin C synthase (DAOCS) [1] and taurine dioxygenase (TauD) [2].
In the active site of these enzymes the iron(II) centre is coordinated by two histidines and one aspartate or glutamate, the so-called 2-His-1-carboxylate facial triad [3]. The 2-oxo-glutarate co-substrate is bound via one carboxylate and the 2-oxo group to the iron center (Fig.1).



Scheme 1: Synthesis of carboxylato complexes

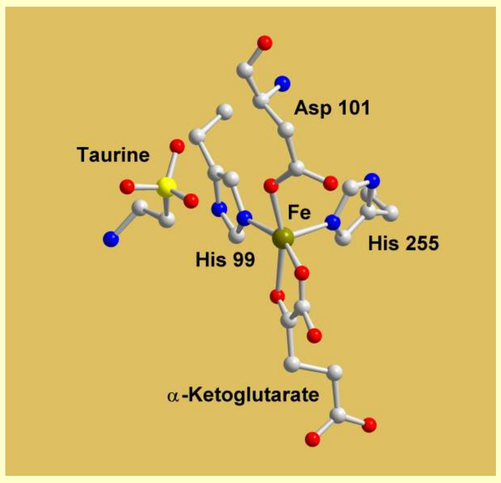


Fig.1: Active site of TauD with 2-oxoglutarate and taurine substrate (PDB-Code: 1GY9) [2]

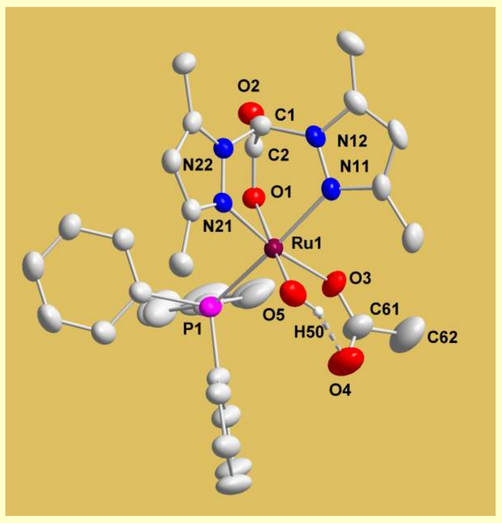


Fig.2: X-ray structure of [(bdmpza)Ru(H_2O)(OAc)(PPh_3)]

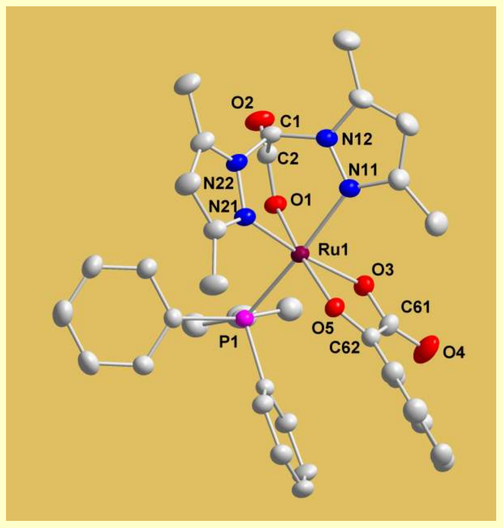
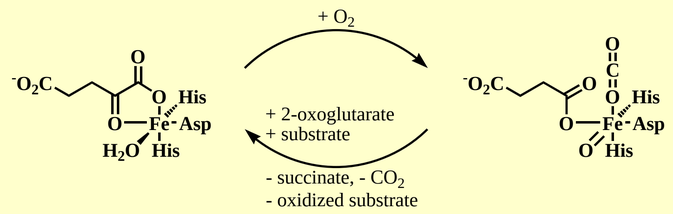


Fig.3: Molecular structure of [(bdmpza)Ru($O_2CC(O)Ph$)(PPh_3)]

Carboxylato and 2-oxo carboxylato complexes are obtained by reaction of the ruthenium(II) complex [(bdmpza)RuCl(PPh_3)$_2$] [4] (bdmpza = bis(3,5-dimethylpyrazol-1-yl)acetate) with the corresponding thallium carboxy-lates (Scheme 1) [5].
Reaction of the carboxylato complexes with 2-oxo acids also yields the 2-oxo carboxylato complexes. This reaction can be compared with the regeneration step of 2-oxoglutarate dependent enzymes (Scheme 2).
The coordination of the 2-oxo acid in the model complex is the same as in the enzyme (Fig. 1 & 3). The keto function binds *trans* to the carboxylate group of the aspartate or glutamate in the enzyme and *trans* to the carboxylate group of the bdmpza ligand in the model.



Scheme 2: Reaction cycle in 2-oxoglutarate dependent emzymes

Iron Enzyme Inhibitors

The 2-oxoglutarate analogue *N*-oxalylglycine is a lead structure for inhibitors of enzymes such as prolyl 4-hydroxylase [6] and factor inhibiting HIF (FIH) (Fig.4) [7]. These inhibitors might be used in the therapy of rheumatoid arthritis and other fibrotic diseases [6].
The 2-benzoyl-cyclohexane-1,3-diones type herbicides are potent inhibitors for the 4-hydroxyphenylpyruvate dioxygenase (HPPD). These triketons are also of pharma-ceutical use for treatment of tyrosinaemia [8].

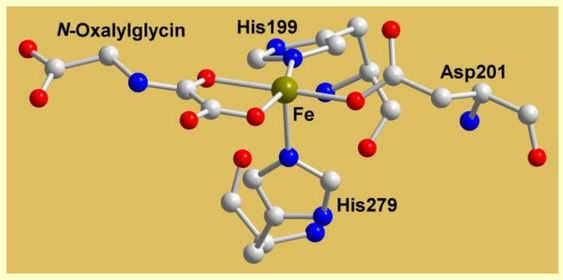
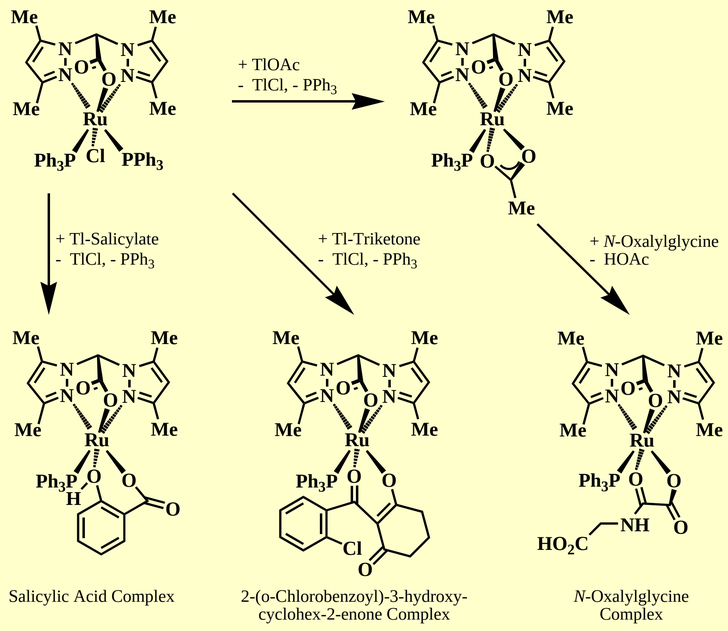


Fig.4: X-ray structure of the active site of FIH with *N*-oxalylglycine inhibitor (PDB-Code: 1H2K) [7]

We were able to obtain ruthenium model complexes with *N*-oxalylglycine, a triketone type inhibitor and salicylic acid (Scheme 3).



Scheme 3: Synthesis of inhibitor complexes

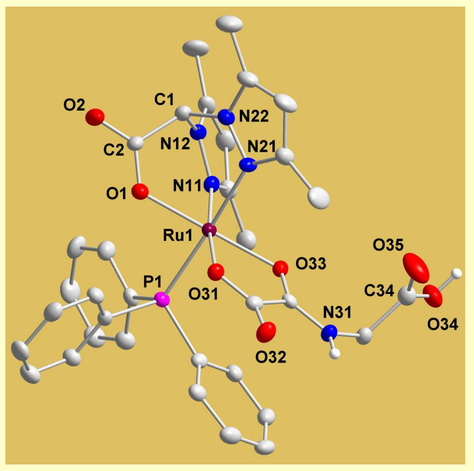
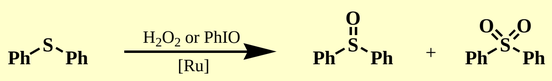


Fig.5: Molecular structure of a ruthenium model complex bearing *N*-oxalylglycin

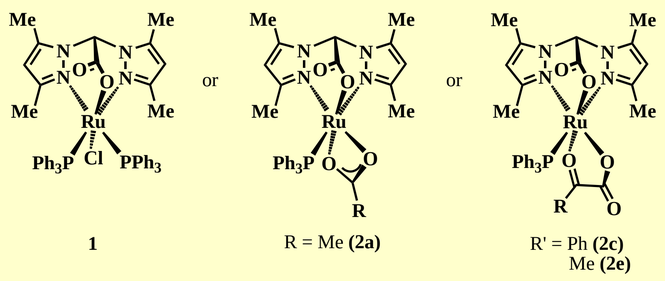
Oxidation Catalysis

The ruthenium complexes 2**a - 2f** are good structural models for 2-oxo-glutarate dependent enzymes. So far we observed no activation of molecular oxygen by these complexes (Scheme 6). Nevertheless, using oxidizing agents like H_2O_2 or iodosobenzene they oxidize diphenylsulfide (Scheme 4) and cyclohexene (Scheme 5) in a bio-inspired "peroxide shunt" type reaction.

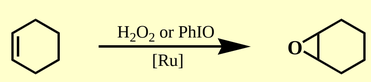


Scheme 4: Oxidation of diphenylsulfide

catalyst (10 mol%)	oxidizing agent	turnover	turnover number
(bdmpza)Ru(PPh_3)(O_2CCH_3) **3a**	H_2O_2	37.8	3.78
(bdmpza)Ru(PPh_3)(O_2CCH_3) **3a**	PhIO	75.3	7.53
(bdmpza)Ru(PPh_3)($O_2CC(O)Ph$) **3c**	H_2O_2	97.2	9.72
(bdmpza)Ru(PPh_3)($O_2CC(O)Ph$) **3c**	PhIO	69.8	6.98
(bdmpza)Ru(PPh_3)($O_2CC(O)Me$) **3e**	H_2O_2	21.7	2.17
(bdmpza)Ru(PPh_3)($O_2CC(O)Me$) **3e**	PhIO	51.7	5.17



Scheme 6: Catalytic active model complexes



Scheme 5: Oxidation of cyclohexene

catalyst (10 mol%)	oxidizing agent	turnover	turnover number
(bdmpza)Ru(PPh_3)$_2$Cl **1**	H_2O_2	-	-
(bdmpza)Ru(PPh_3)$_2$Cl **1**	PhIO	42.1	4.21
(bdmpza)Ru(PPh_3)(O_2CCH_3) **3a**	H_2O_2	37.8	3.78
(bdmpza)Ru(PPh_3)(O_2CCH_3) **3a**	PhIO	75.3	7.53
(bdmpza)Ru(PPh_3)($O_2CC(O)Ph$) **3c**	H_2O_2	97.2	9.72
(bdmpza)Ru(PPh_3)($O_2CC(O)Ph$) **3c**	PhIO	69.8	6.98
(bdmpza)Ru(PPh_3)($O_2CC(O)Me$) **3e**	H_2O_2	-	-
(bdmpza)Ru(PPh_3)($O_2CC(O)Me$) **3e**	PhIO	51.7	5.17

Literature:

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