SARS-COV-2 MAIN PROTEASE INHIBITION WITH CARMOFUR: A COMPUTATIONAL STUDY

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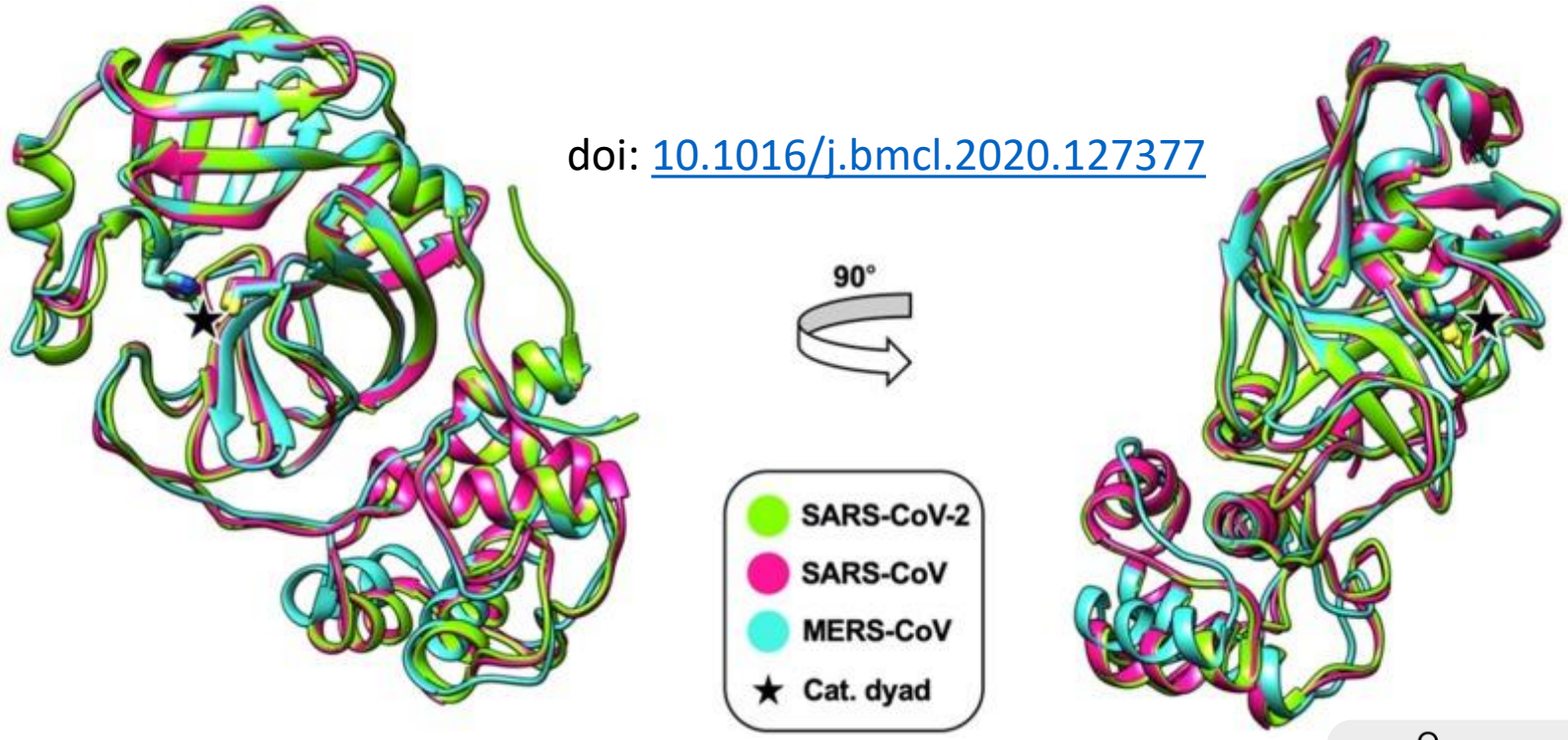
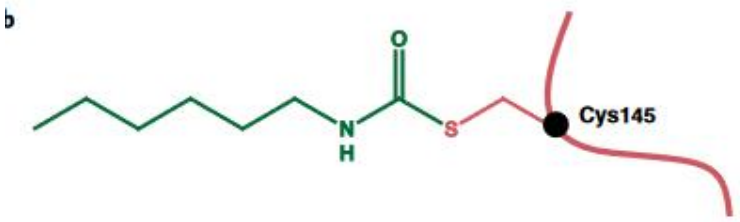
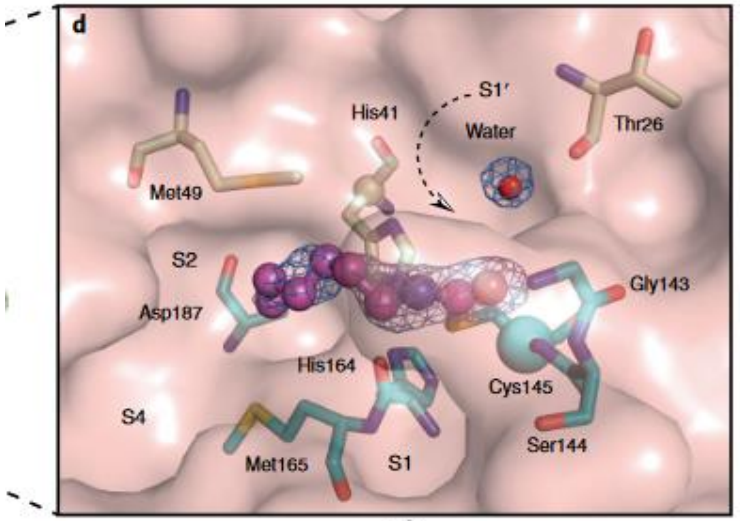
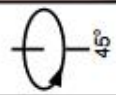
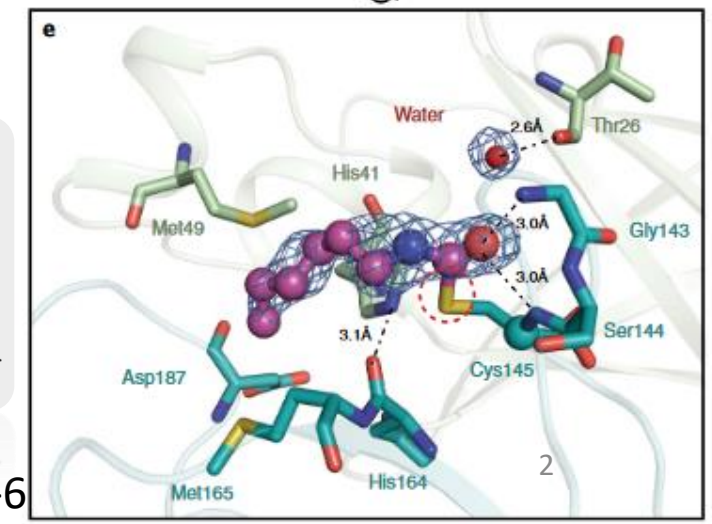
SARS-CoV-2 main protease











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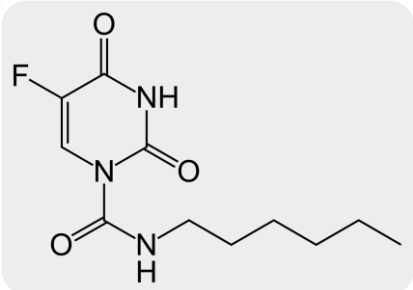
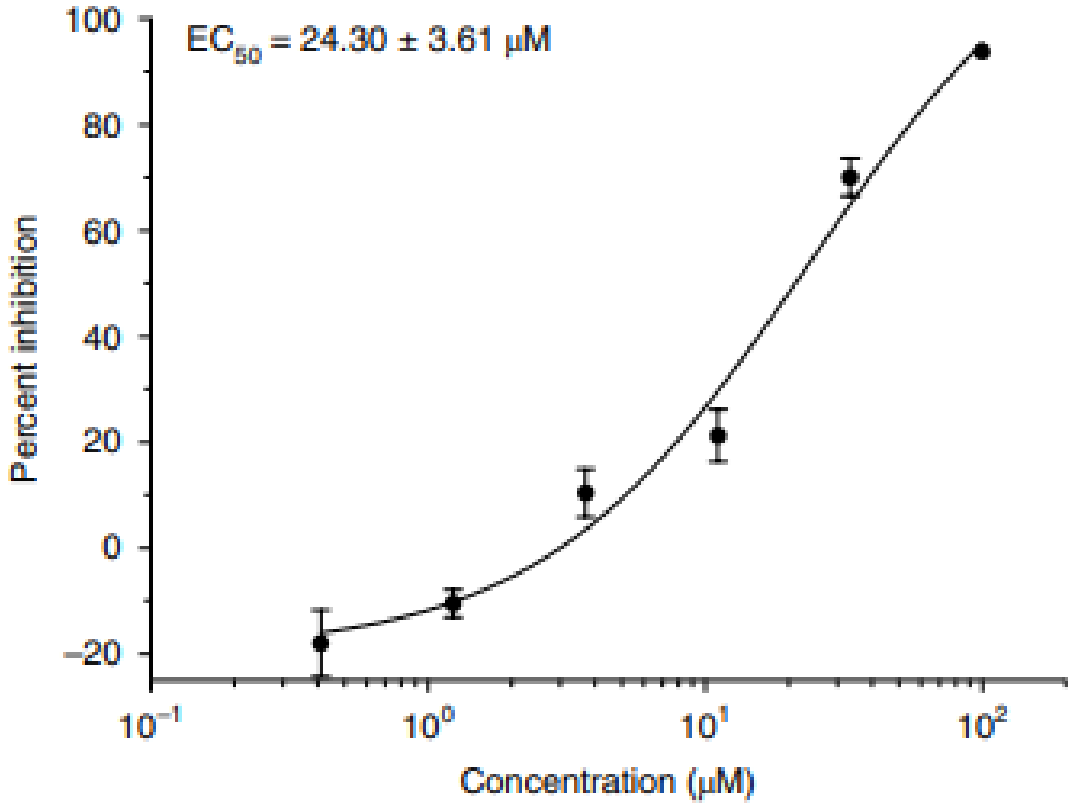
M^{pro} is an important enzyme in the viral replication cycle

Carmofur – a pyrimidine analogue used as an antineoplastic agent



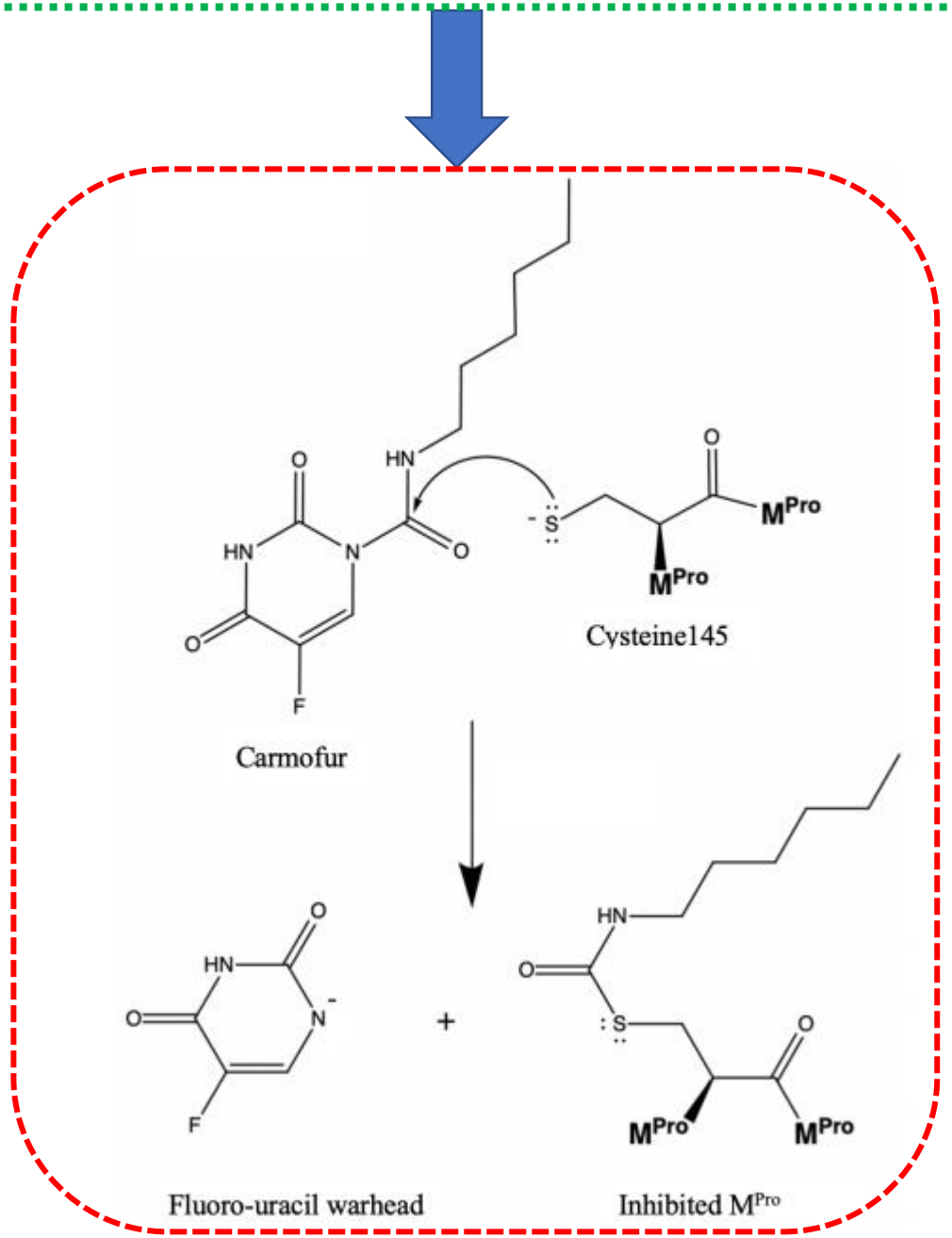
Crystal structure 7BUY (resolution: 1.60 Å)
https://doi.org/10.1038/s41594-020-0440-6

How does carmofur work?

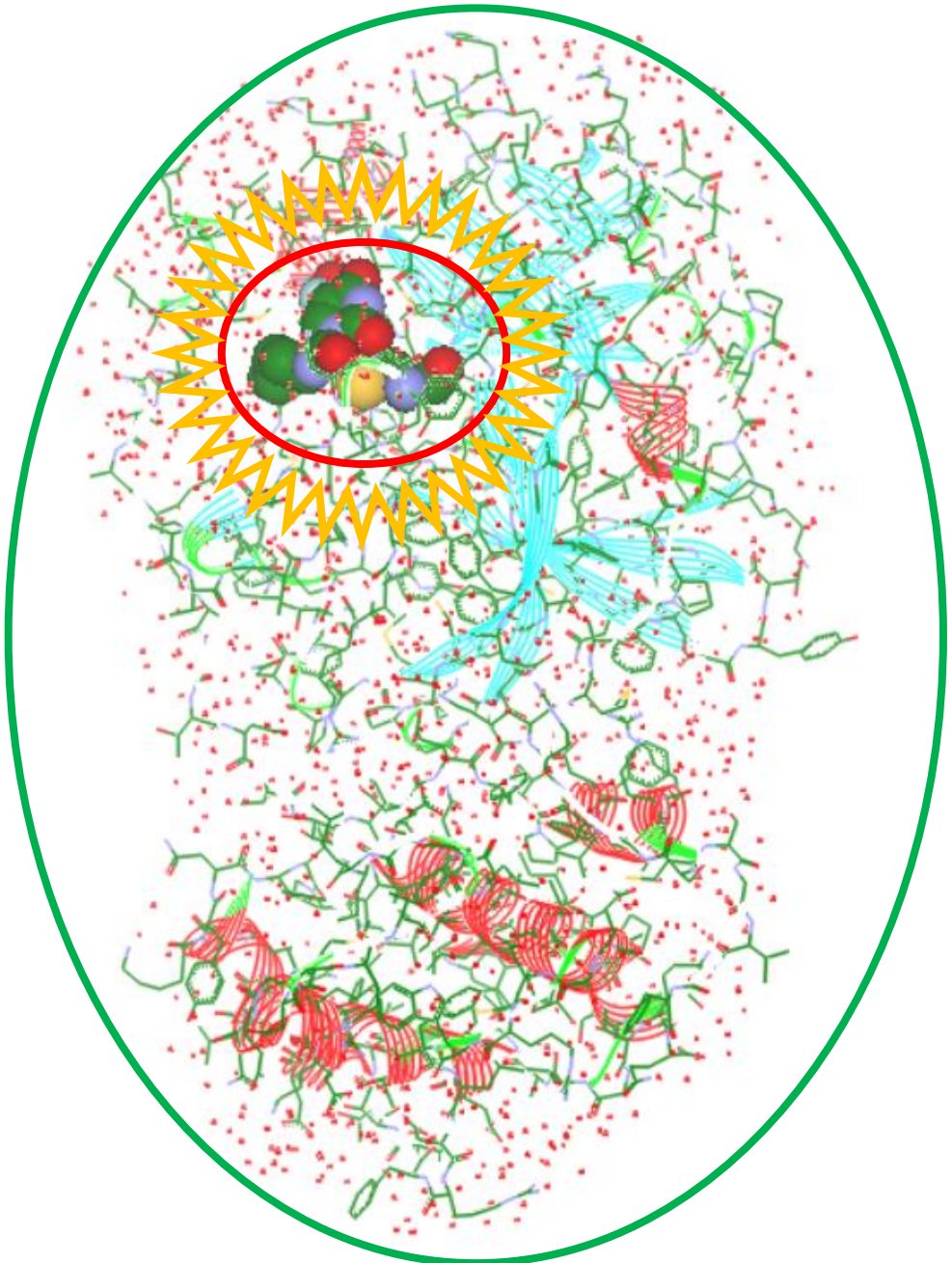


Experiment: covalent product, known catalytic diad.
https://doi.org/10.1038/s41594-020-0440-6

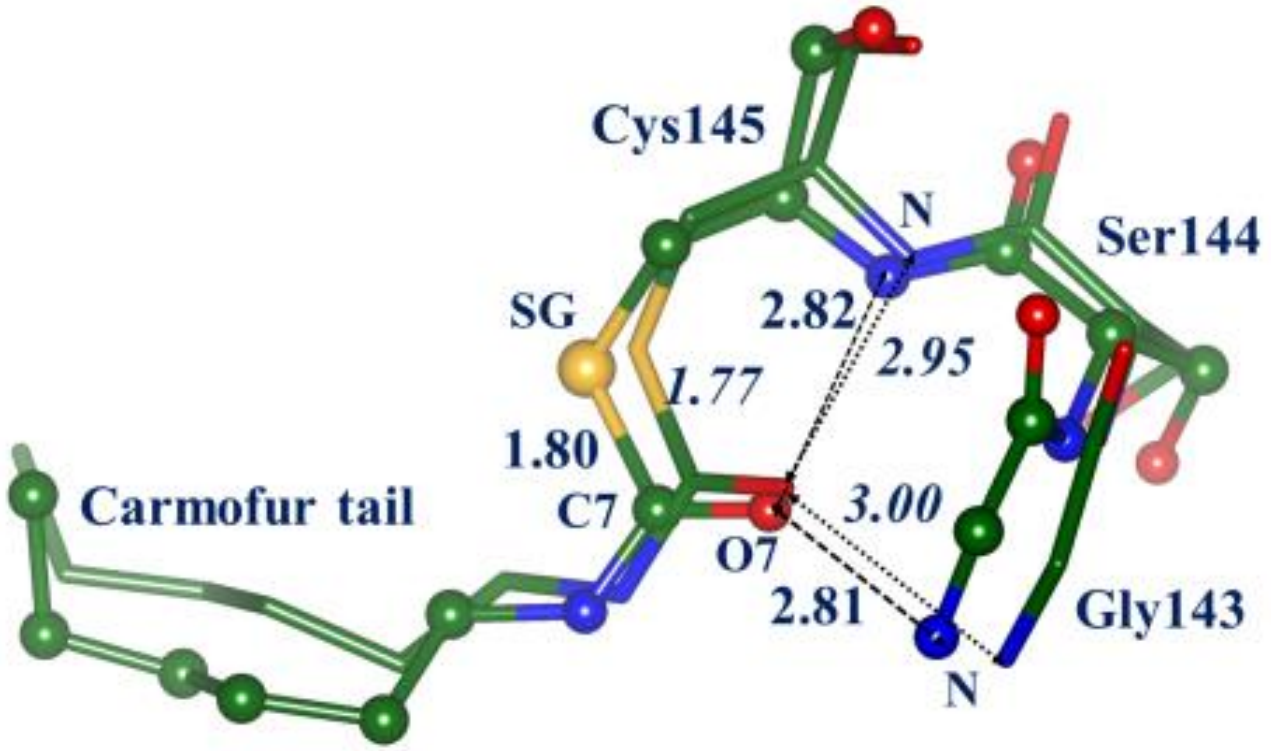
For a substrate: His 41 accepts the proton from Cys145



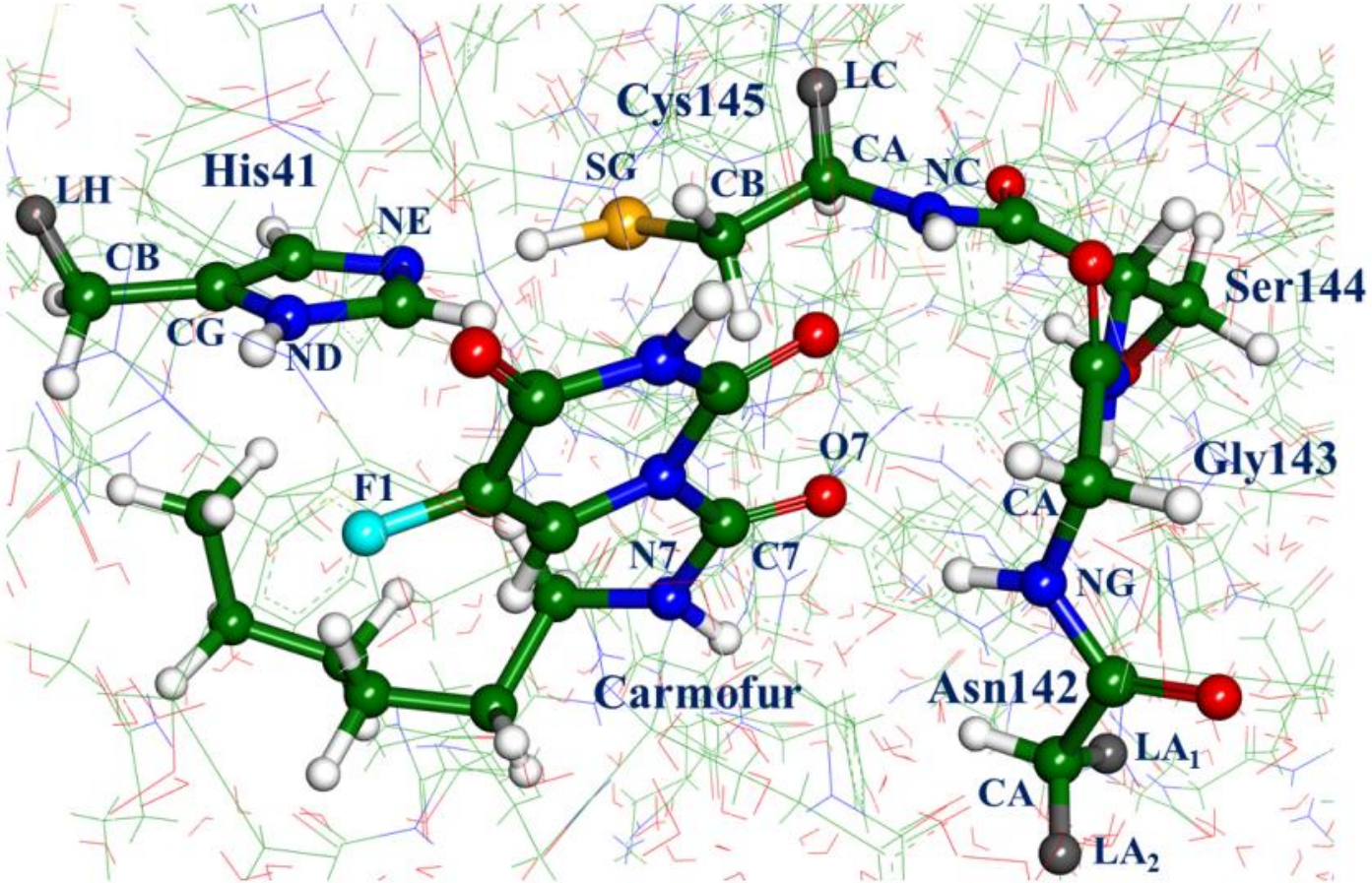
E(tot)=E(QM)+*E(QM/MM)*+E(MM)



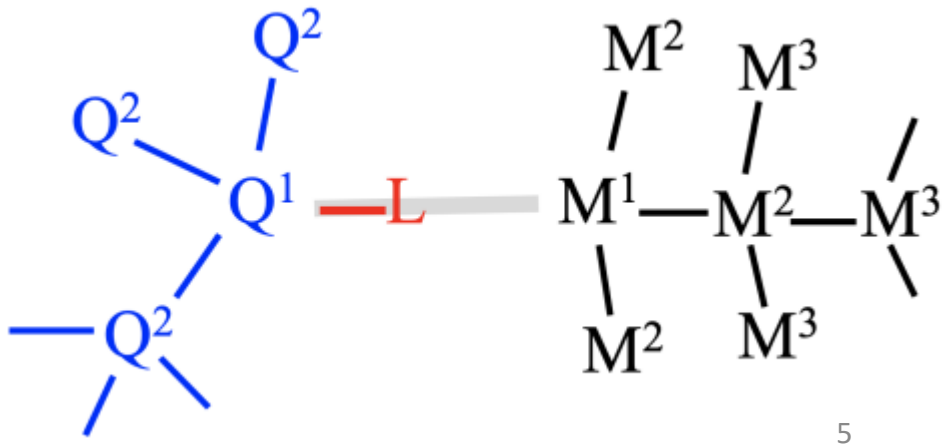
Direct comparison of QM/MM results to the experiment

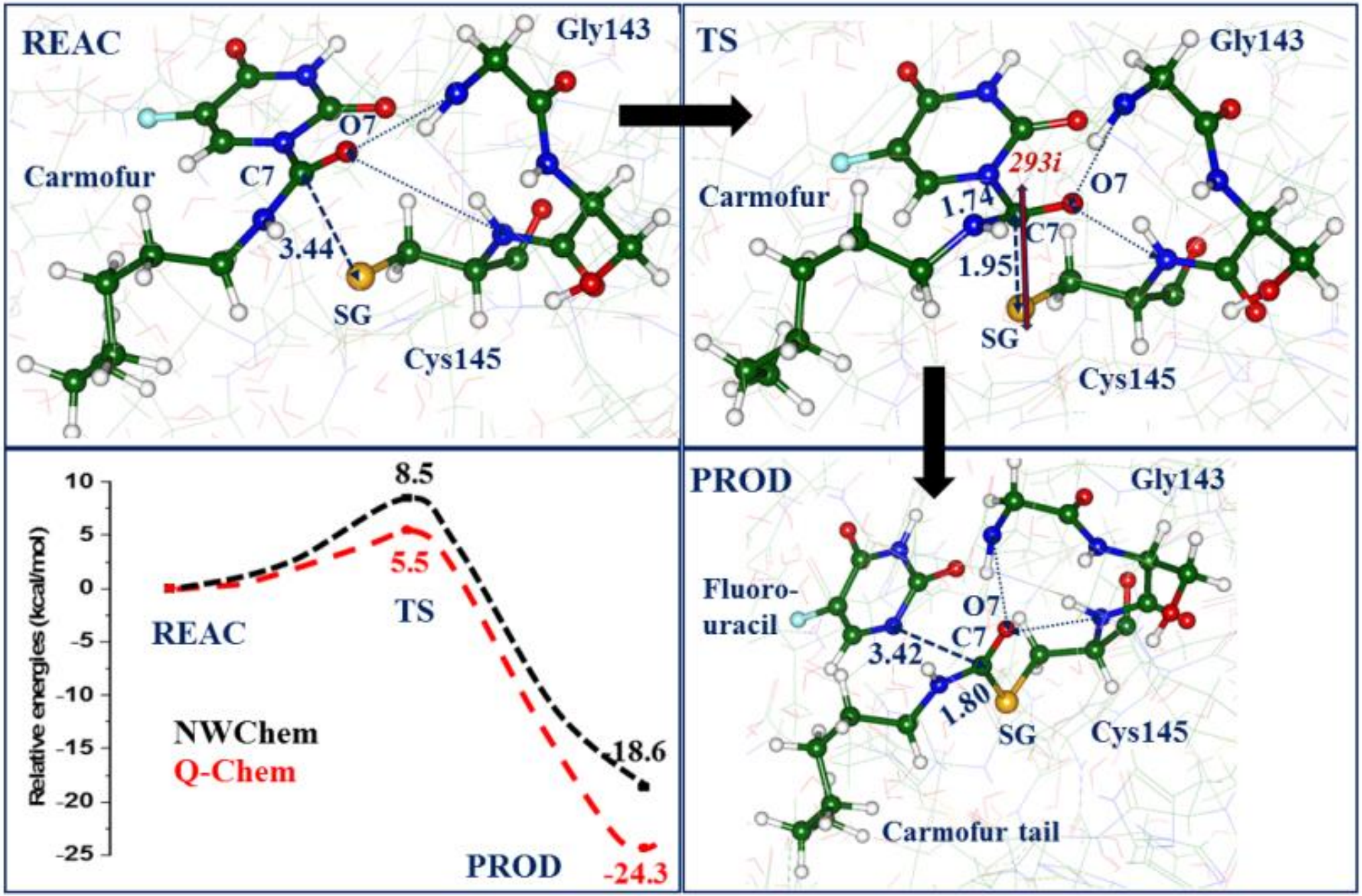


Model system description



- "Electrostatic embedding"
- NWChem, QChem
- 83 atoms: carmofur, side chain/backbone atoms from His41, Asn142,Gly143, Cys145, one water molecule, and 4 hlink atoms
- PBE0-D3/6-31G**//AMBER
- No electrostatic cutoff

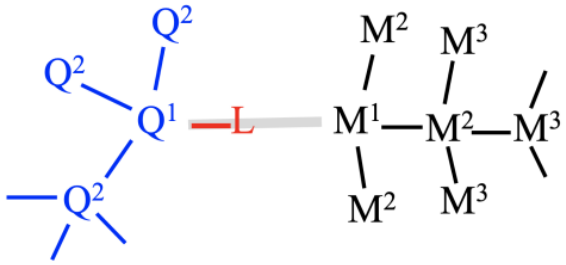



REAC
Gly143
O7
Carmofur
C7
3.44
SG
Cys145
TS
Gly143
293i
Carmofur
1.74
O7
C7
1.95
SG
Cys145
Relative energies (kcal/mol)
10
5
0
-5
-10
-15
-20
-25
8.5
5.5
REAC
TS
NWChem
Q-Chem
18.6
PROD
-24.3
PROD
Gly143
Fluoro-
uracil
O7
C7
3.42
1.80
SG
Cys145
Carmofur tail

Energy contribution	Software	Energy (a.u.) REAC	Energy relative to REAC (kcal/mol)	
			TS	PROD
QM in gas phase	NWChem	-2474.6967	13.9	-5.4
	Q-Chem	-2474.6983	14.1	-5.2
QM in MM charges	NWChem	-2474.5907	12.2	-5.7
	Q-Chem	-2474.6637	12.9	-5.1
QM + QM/MM	NWChem	-2475.1349	14.9	-9.7
	Q-Chem	-2474.9139	11.5	-17.0
MM	NWChem	-39.1656	-6.3	-8.9
	Q-Chem	-39.2451	-5.9	-8.8
Total energy QM + QM/MM + MM	NWChem	-2514.3005	8.5	-18.6
	Q-Chem	-2514.1591	5.5	-25.8

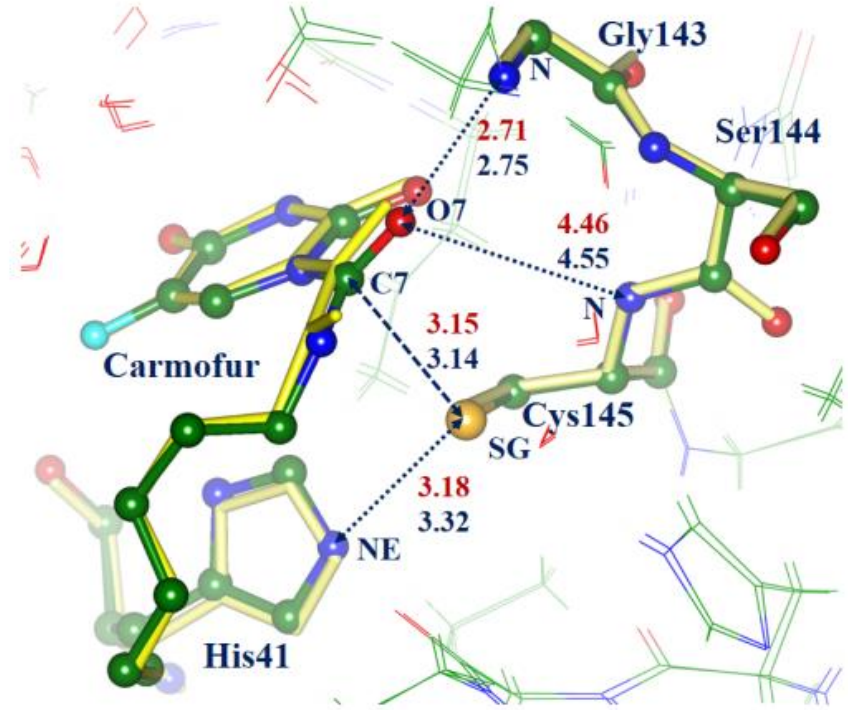
Single point energy with the NWChem located structures!

Explicit contributions from charges:
charge-nuclei
charge-density



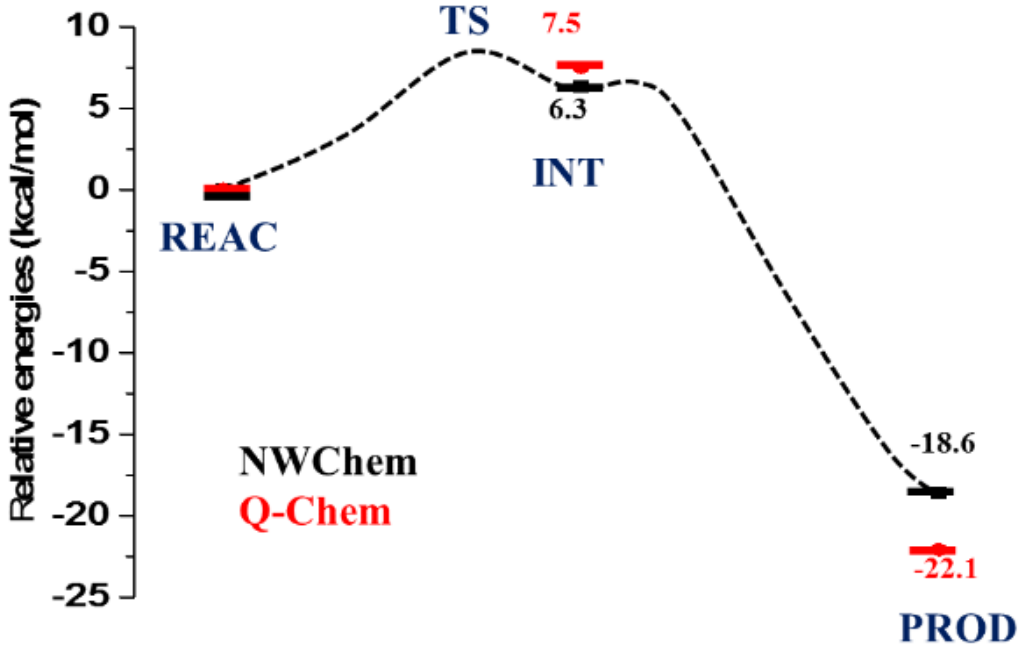
What, another profile!?

density static vs density espfit



Structures optimized by NWChem

by QChem



Not a huge difference for REAC, but able to locate an intermediate!

Energy contribution	Software	Energy (a.u.) REAC	Energy relative to REAC (kcal/mol)	
			INT	PROD
QM in MM charges	NWChem	-2474.5961	13.5	-3.5
	Q-Chem	-2474.6833	10.9	-5.6
QM + QM/MM	NWChem	-2475.1218	7.1	-16.8
	Q-Chem	-2474.9402	11.2	-16.6
MM	NWChem	-39.1798	-0.8	-1.8
	Q-Chem	-39.2606	-5.8	-5.3
Total energy QM + QM/MM + MM	NWChem	-2514.3017	6.3	-18.6
	Q-Chem	-2514.2008	5.5	-21.9

UGLY

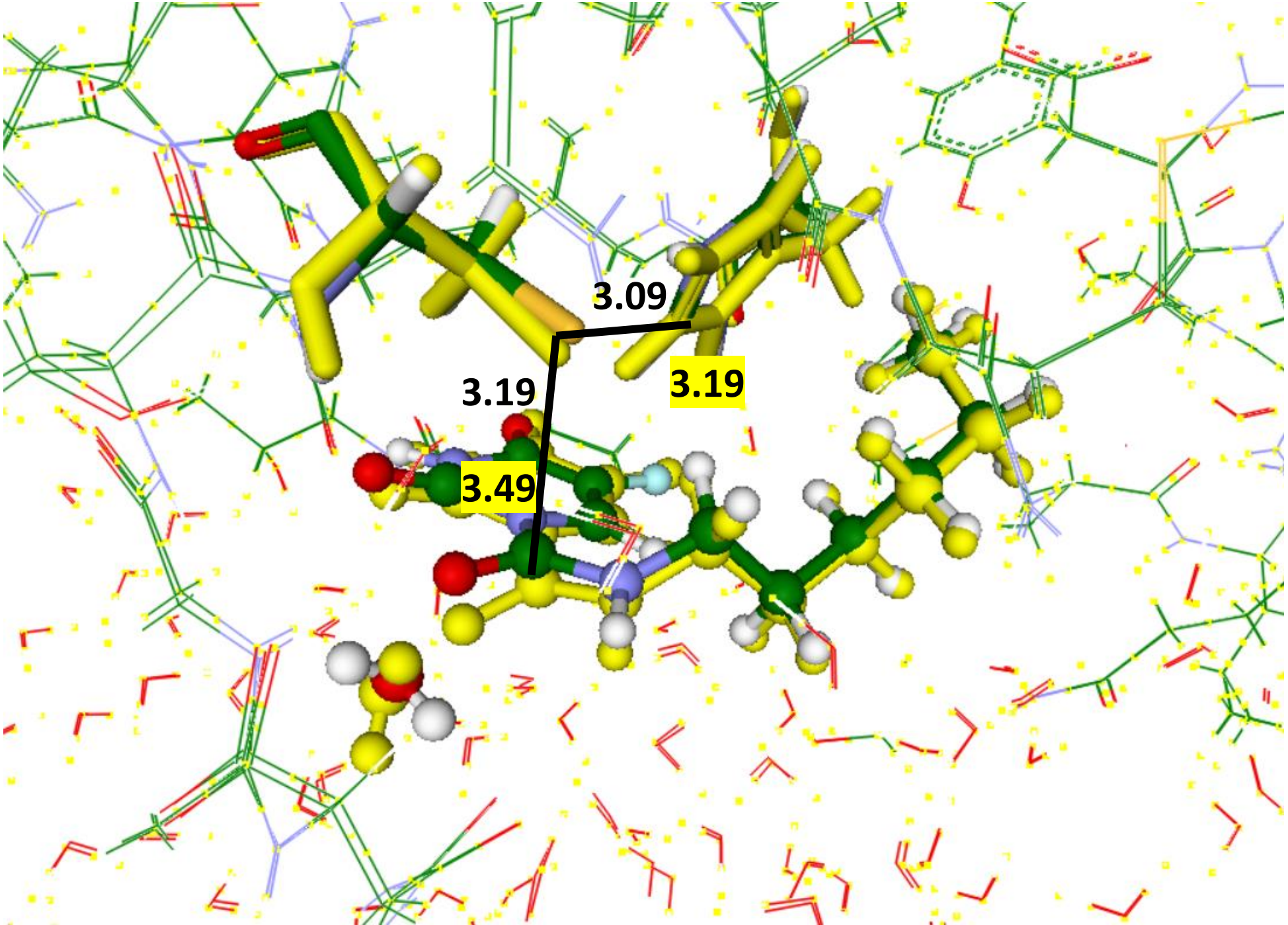
WTF?

OK

WTF?

NWChem

QChem



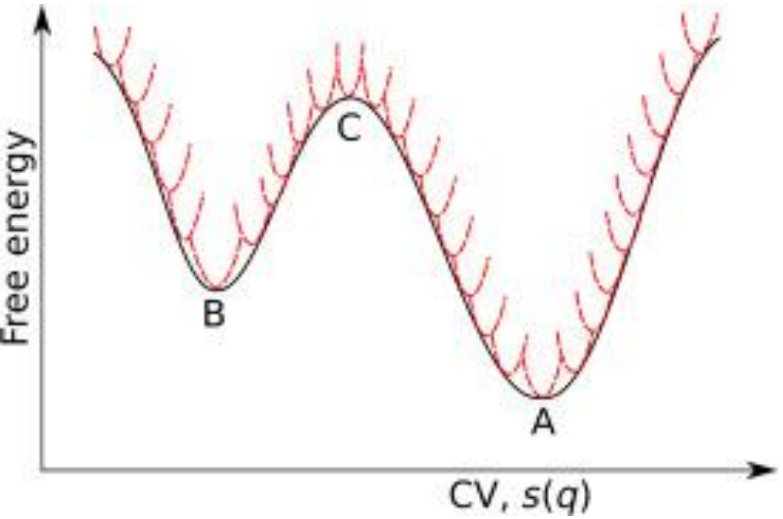
Takeaways:

- Difference in QM/MM boundary charge treatment leads to significant discrepancies in the total and relative energies
- A number of close-lying minima on the PES of an enzyme => change some options or software = end up in different minima for the same kind structure

- *Qualitatively QM software "agrees" that carmofur is a potent covalent inhibitor*

…but what about the first stage?...and free energy calculation?

Umbrella integration/WHAM



$$E_{bias} = E_{unbias} + \omega_i(\xi)$$

$$\omega_i(\xi) = \frac{1}{2}K(\xi - \xi_i)^2$$

$$P_i^u(\xi) = \frac{\int \exp[-\beta E(r)]\delta[\xi^r(r) - \xi]d^{Nr}}{\int exp[-\beta E(r)]d^{Nr}}$$

$$P_i^u(\xi) = P_i^b(\xi)exp[\beta\omega_i(\xi)]exp[-\beta\omega_i(\xi)]$$

$$E_{unbias} = -\left(\frac{1}{\beta}\right)\ln P_i^b(\xi) - \omega_i(\xi) + F_i$$

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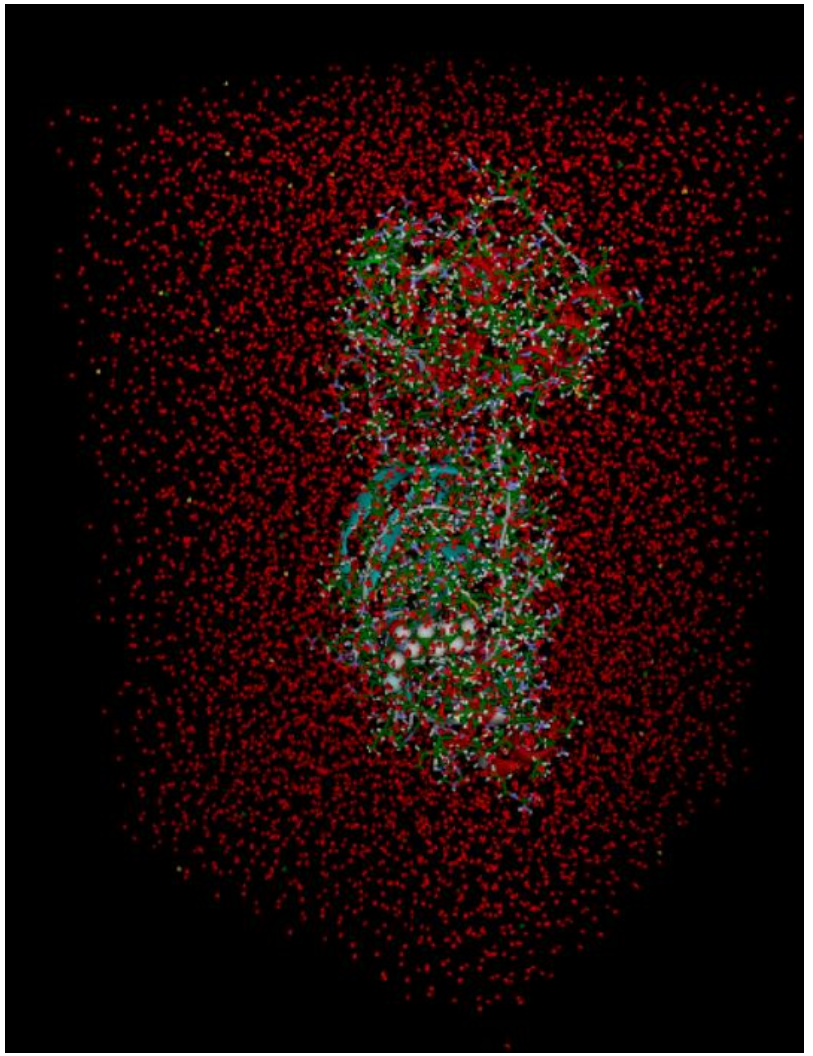
doi:**10.1063/1.2052648**

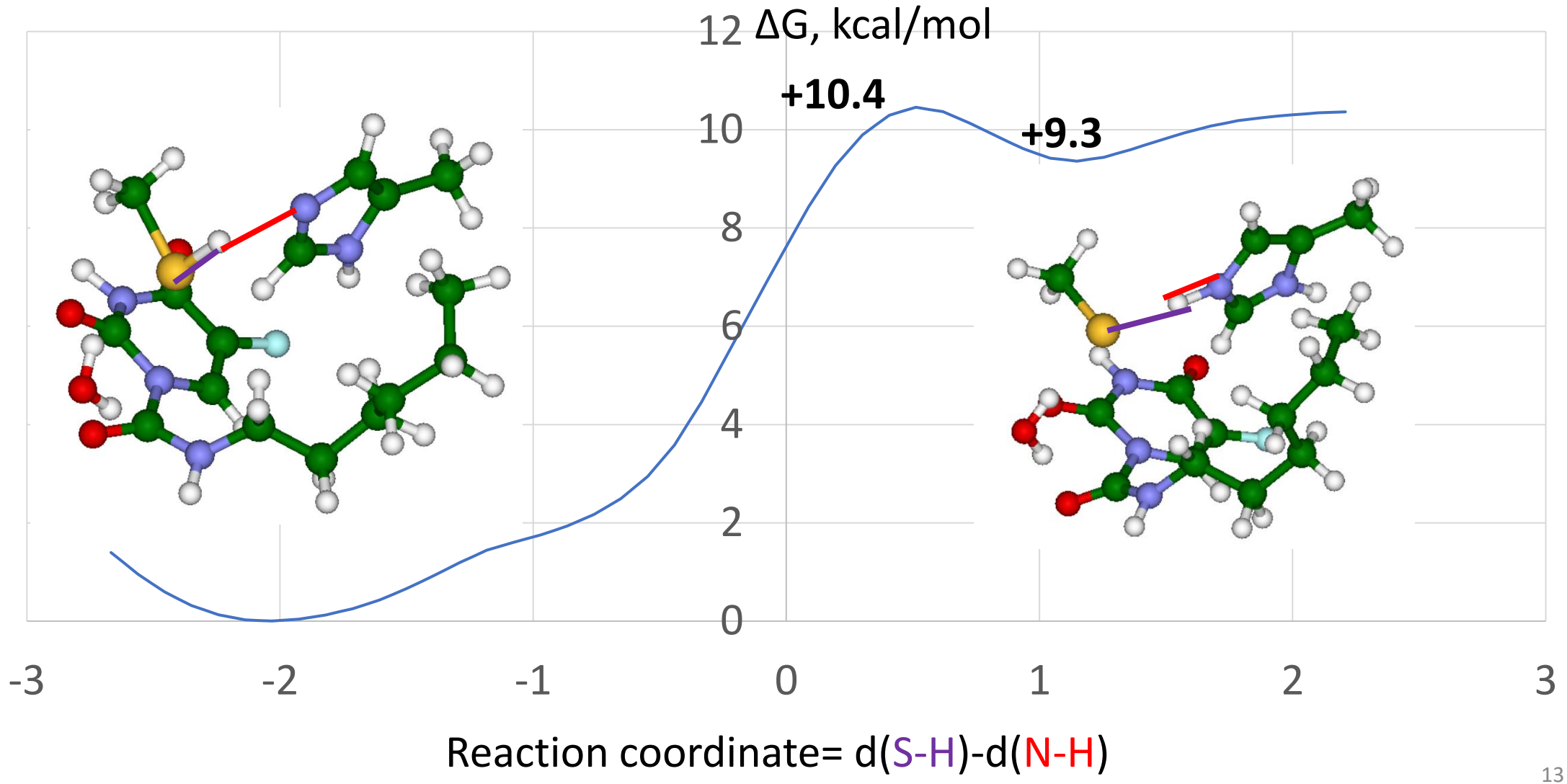


33157 atoms, NPT, PME/PBC

Terachem/NAMD

PBE0/6-31G** /CHARMM36

For a substrate: His41 accepts the proton from Cys145



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