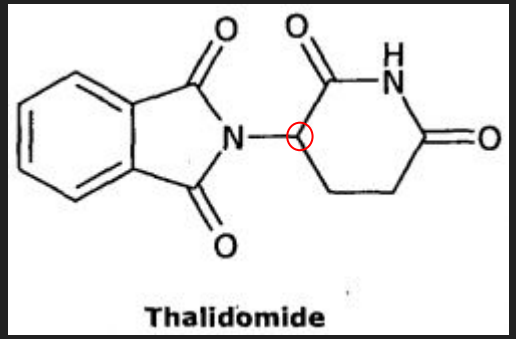
Thalidomide Racemization



Thalidomide

Alan Yu
April 29, 2021

Thalidomide's History

Marketed in West Germany in 1957 as a sedative but later used by pregnant women for morning sickness.

Shortly after, many side effects were seen in babies from the mothers that took this drug.

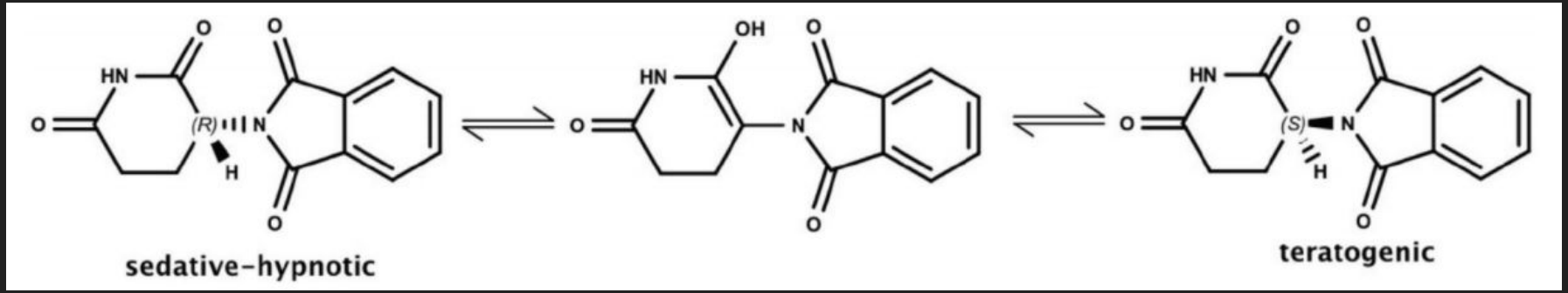
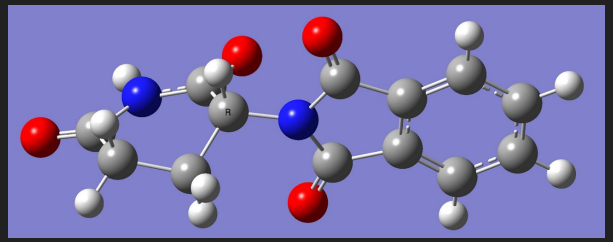


Figure from Reference 1.

Question that lies ahead: The marketed version was the R enantiomer, but how come the S enantiomer exists within the body?

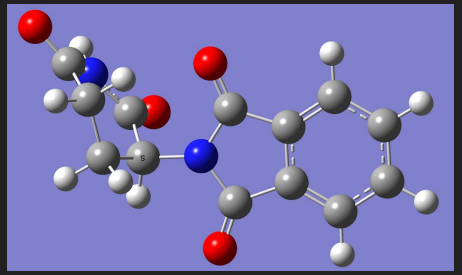
General Reaction



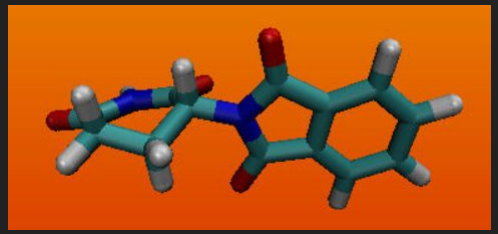
R Enantiomer

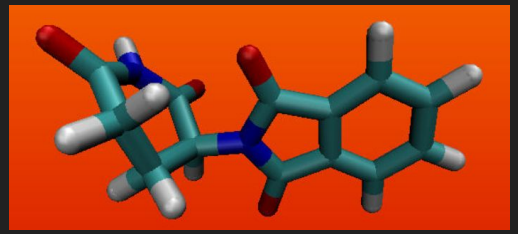
⇌

Biological System: pH ~7.4



S Enantiomer





Tautomerization Mechanism

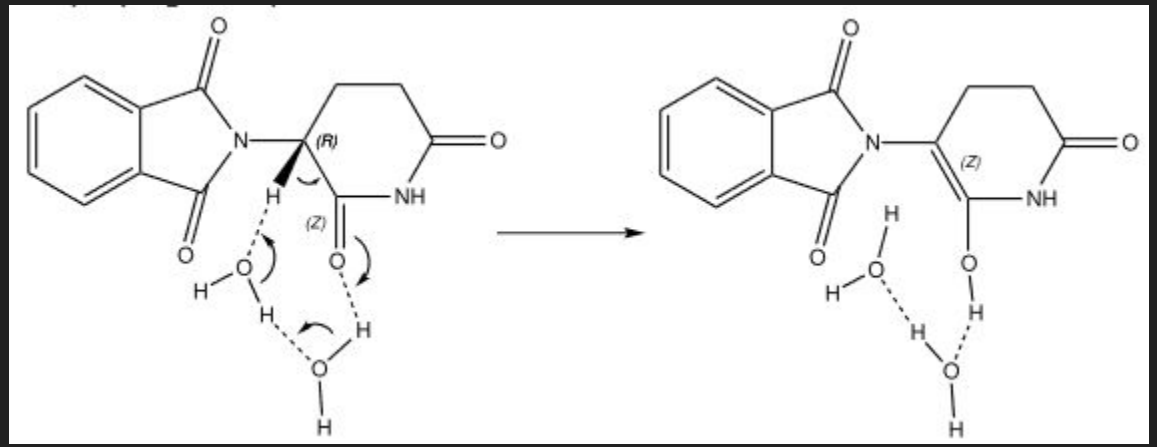


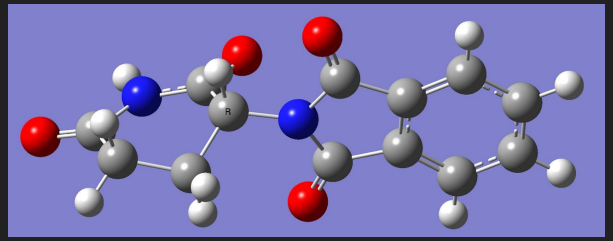
Figure from Reference 2.

Thermochemistry Calculations: R → S

1. $C_{13}H_{10}N_2O_4$ (R) + $2H_2O$ ⇌ $C_{13}H_{10}N_2O_4$ (I) + $2H_2O$

HF 6-31G:

Start:



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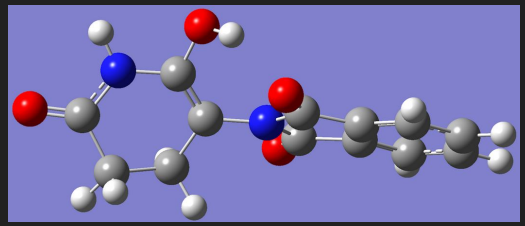


R-Thalidomide: G = -568.4859053 kcal/mol

Enol: G = -568.4673859 kcal/mol

$\Delta G_{298.15K}$= -568.4673859 kcal/mol + 568.4859053 kcal/mol

$\Delta G_{298.15K}$= 0.0185194 kcal/mol

BLYP 6-31G:

R-Thalidomide: G = -571.7674436 kcal/mol

Enol: G = -571.7503385 kcal/mol

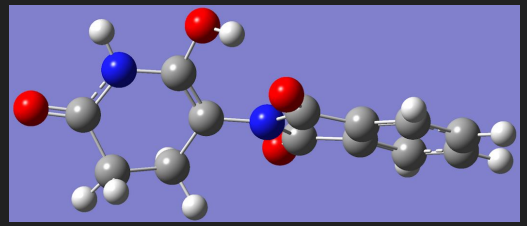
$\Delta G_{298.15K}$= 0.0171051 kcal/mol

Thermochemistry Calculations: R → S

2. $C_{13}H_{10}N_2O_4$ (I) + $2H_2O$ ⇌ $C_{13}H_{10}N_2O_4$ (S) + $2H_2O$

HF 6-31G:

Start:



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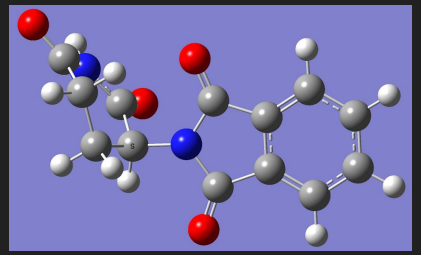


Enol: G = -568.4673859 kcal/mol

S-Thalidomide: G = -568.4830879 kcal/mol

$\Delta G_{298.15K}$ = -568.4830879 kcal/mol + 568.4673859 kcal/mol

$\Delta G_{298.15K}$ = -0.015702 kcal/mol

BLYP 6-31G:

Enol: G = -571.7503385 kcal/mol

S-Thalidomide: G = -571.7656552 kcal/mol

$\Delta G_{298.15K}$ = -0.0153167 kcal/mol

K_{eq} of the R → S conversion:

HF 6-31G:

$$\Delta G^{Total}_{298.15K} = 0.0028174 \text{ kcal/mol}$$

$$K_{eq} = e^{-\Delta G/RT} = 0.995$$

This means that this reaction has almost the same amounts of both the R and S enantiomer, but having just a little more of the R enantiomer than the S enantiomer.

BLYP 6-31G:

$$\Delta G^{Total}_{298.15K} = 0.0017884 \text{ kcal/mol}$$

$$K_{eq} = e^{-\Delta G/RT} = 0.997102$$

Again, about the same but slightly more R enantiomers than S.

Thermochemistry Calculations: R → S at Body Temp

BLYP 6-31G:

R-Thalidomide: G = -571.7689602 kcal/mol Enol: G = -571.7518245 kcal/mol

$\Delta G_{310.15K}$= 0.0171357 kcal/mol

Enol: G = -571.7518245 kcal/mol S-Thalidomide: G = -571.7671781 kcal/mol

$\Delta G_{310.15K}$= -0.0153536 kcal/mol

$\Delta G^{Total}_{310.15K}$= 0.0017821 kcal/mol

$K_{eq} = e^{-\Delta G/RT} = 0.997113$

B3LYP 6-31G:

R-Thalidomide: G = -571.9182644 kcal/mol Enol: G = -571.9011688 kcal/mol

$\Delta G_{310.15K}$ = 0.0170956 kcal/mol

Enol: G = -571.9011688 kcal/mol S-Thalidomide: G = -571.9161686 kcal/mol

$\Delta G_{310.15K}$ = -0.0149998 kcal/mol

$\Delta G^{Total}_{310.15K}$ = 0.0020958 kcal/mol

$K_{eq} = e^{-\Delta G/RT} = 0.996605$

Computation Times

Method	Basis Set	Shortest Time	Longest Time	Average Time
Hartree Fock @ 298.15K	6-31G	5 min 6 sec	5 min 18 sec	5 min 12 sec
BLYP @ 298.15K	6-31G	23 min 50 sec	25 min 59 sec	25 min 9 sec
BLYP @ 310.15K	6-31G	25 min 12 sec	28 min 10 sec	26 min 30 sec
B3LYP @ 310.15K	6-31G	26 min 28 sec	37 min 31 sec	30 min 55 sec

Wrapping Up

What I want to do next is to explore much more expensive methods to calculate the thermochemistry to see if the free energy actually reaches a value closer to 0.

I would also like to explore simulations of Thalidomide binding to Cereblon, CRBN.

After exploring the simulation of Thalidomide binding, I would also like to consider a different version of Thalidomide such as Fluorinated Thalidomide pictured below.

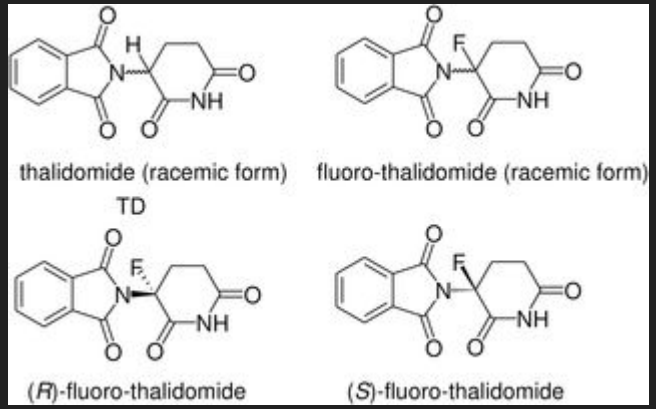
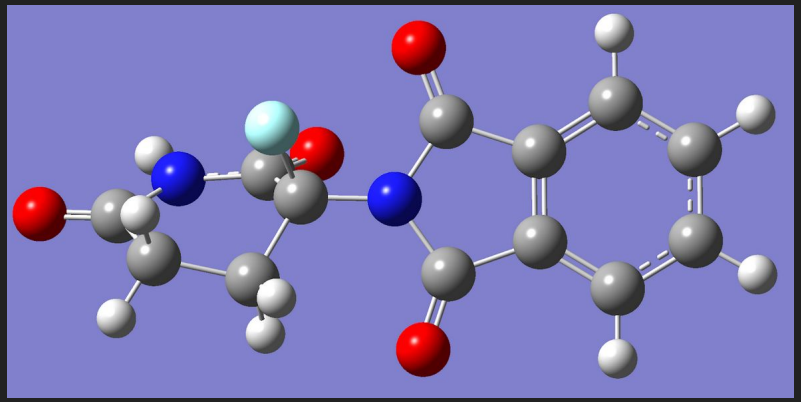


Figure from Reference 3.



References

1. Braga, Rodolpho & Alves, Vinicius & Silva, Arthur & Nascimento, Marilia & Silva, Flavia & Lião, Luciano & Andrade, Carolina. (2014). Virtual Screening Strategies in Medicinal Chemistry: The State of the Art and Current Challenges. Current Topics in Medicinal Chemistry. 14. 1899-1912. 10.2174/1568026614666140929120749.
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3. https://doi.org/10.1371/journal.pone.0182152
4. Tokunaga, E., Yamamoto, T., Ito, E. et al. Understanding the Thalidomide Chirality in Biological Processes by the Self-disproportionation of Enantiomers. Sci Rep 8, 17131 (2018). https://doi.org/10.1038/s41598-018-35457-6