Modification of Hydroxamic Acid Containing Compounds for Improved Metal Chelation

By

Karan Arora,[1] Lamarque Coke,[1] Earl Benjamin III, Ellis Benjamin[1]

[1]Chemistry Program, NAMS, Stockton University, 101 Vera King Farris Drive, Galloway, NJ 08205-9441

Introduction

- This research is to investigate the interaction of modified hydroxamic acids to determine specific metal chelation interactions. Hydroxamic acids are important moieties in the binding of Zinc metal in the active site of proteins necessary for cell proliferation including that of the TNFa Converting Enzyme (TACE) or ADAM17. TACE is a protein that cleaves membrane bound TNFa into the soluble form allowing for increased inflammation response in the region of cellular damage. The removal of the Zinc metal blocks the inflammatory response thereby slowing many disease progression. Many diseases including Alzheimer's disease and cancer progression increases in the presence of an inflammatory response.   Through the use of modified hydroxamic acid we sought to understanding the metal chelation.
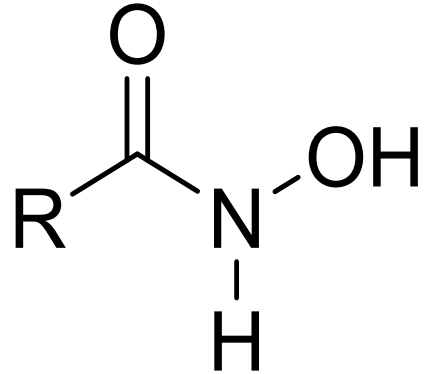
Hydroxamic Acid

Figure 1. Hydroxamic Acid (HXA)

- Hydroxamic acid is an N-hydroxyl amide moiety.
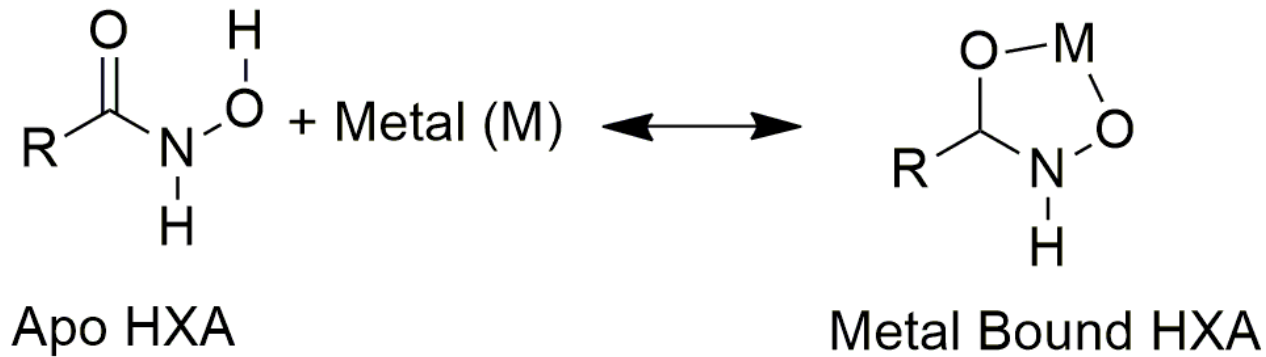
Metal Binding of Hydroxamic Acid

Figure 2. Metal Binding of Hydroxamic Acid (HXA)

- Hydroxamic acid chelation normally binds in a bidentate configuration between the carbonyl and the hydroxyl group of the hydroxamic acid (Figure 2). Difference between the binding energies of the hydroxamic acids can determine the overall stability of the metal chelation. This can be calculated by using the DG with the products being the Zinc bound HXA and the reactant being the apo HXA and the Zinc metal.

Specific Aims

- This research sought to use hydroxamic acid as a model to understanding Zinc chelation:
  - The interaction of electron withdrawing group length on the interaction of the HXA
  - The interaction of electron donating group length on the interaction of the HXA.
  - The energy effects of electron withdrawing groups (EWG) on hydroxamic acids.
  - The energy effects of electron donating groups (EDG) on hydroxamic acids.
  - The trends found with the inclusion of halogens.

Experimental Design

- Molecules were designed in Cambridgesoft ChemDraw and minimized using MM2 in Chem3D. Ab initio calculation were done using Gaussian. The method used a Ground State DFT B3LYP with the base set 631++G. With the exception Iodo derivative being DFT B3LYP with the base set 321G. (Data was recorded in au units and then converted to Kcal/mol (multiplied by 627.52))

Calculations

The Bonding of Apo Hydroxamic acid vs Zinc Bound Hydroxamic Acid.

1) This experimental data determines the energy for the binding of the metal to the hydroxamic acid.

$$\Delta G = ((\text{Metal Bound HXA}) - (\text{Apo HXA} + \text{Metal}))$$

2) The average energy interactions based on EDG length, EWG length, and Halogens.

$$\text{Average Energy} = ((\text{Apo HXA}) + (\text{Metal Bound HXA})) / 2$$

3) The trends of EWG length, EDG length, and Halogen were calculated using MS Excel.

4) The overall stabilization energy was calculated by the average energy of the molecule vs the standard hydroxamic acid.

Results - EWG Length
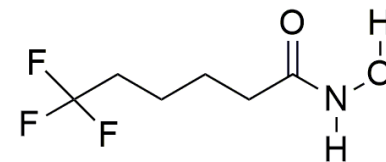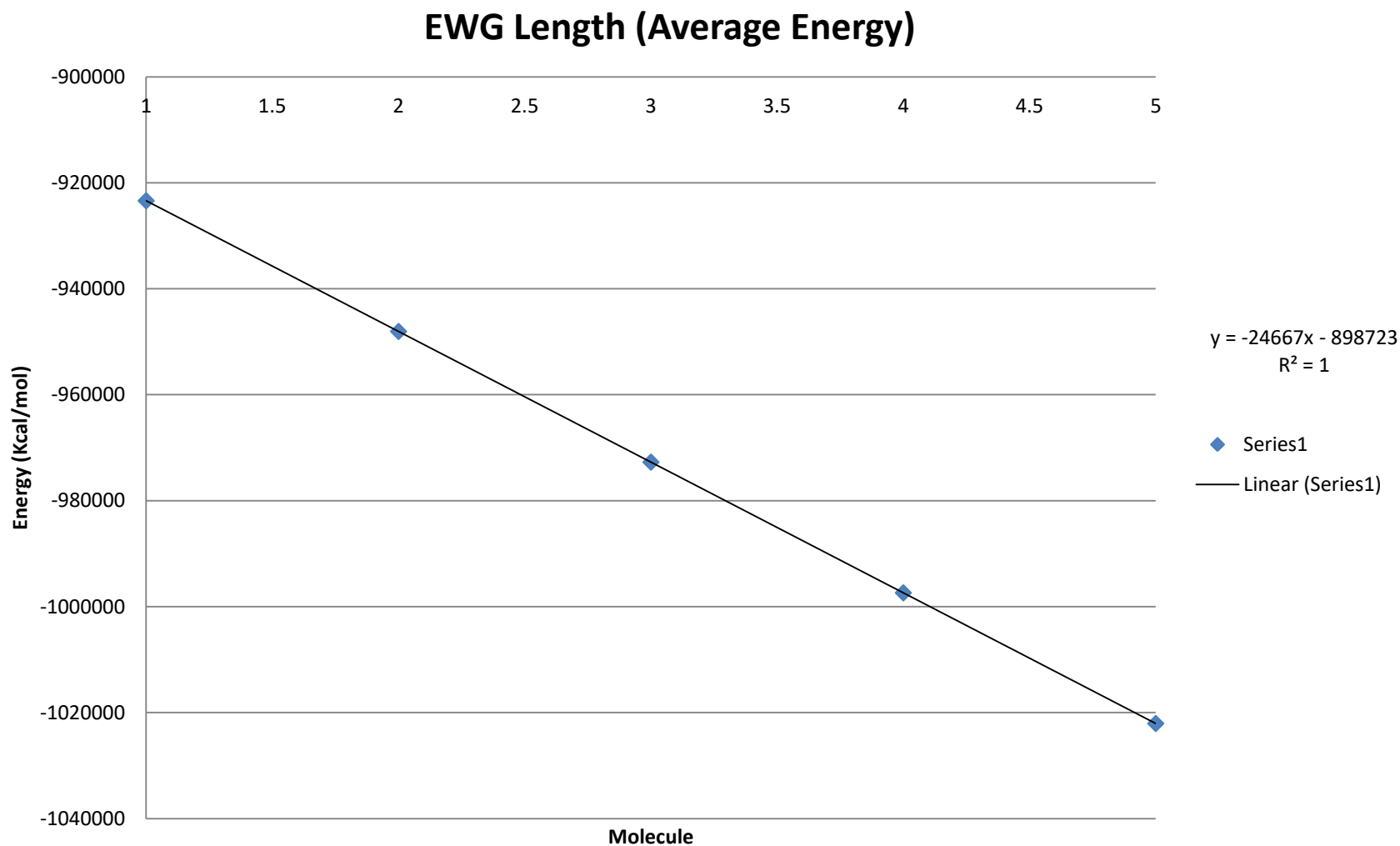
Electron Withdrawing Group (Length)
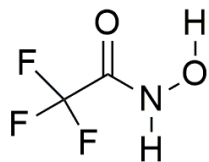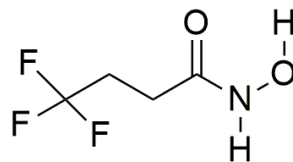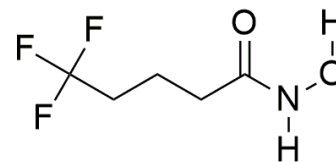
Molecule	ΔG (EWG length)
1	10.7268
2	11.7611
3	11.3544
4	11.1716
5	11.4825

Average 11.299 (0.385)

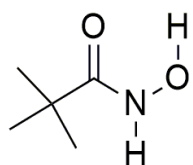- These are the EWG Length experimental tri-fluoromethane molecules.
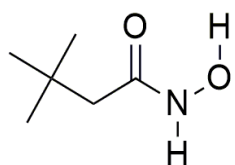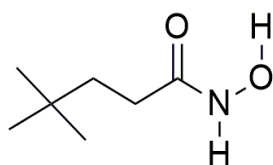
Result - EWG Length (Average)

EWG Length (Average Energy)

y = -24667x - 898723
R² = 1

◆ Series1

— Linear (Series1)

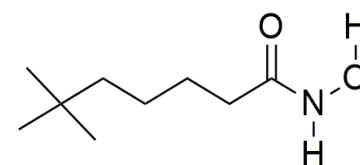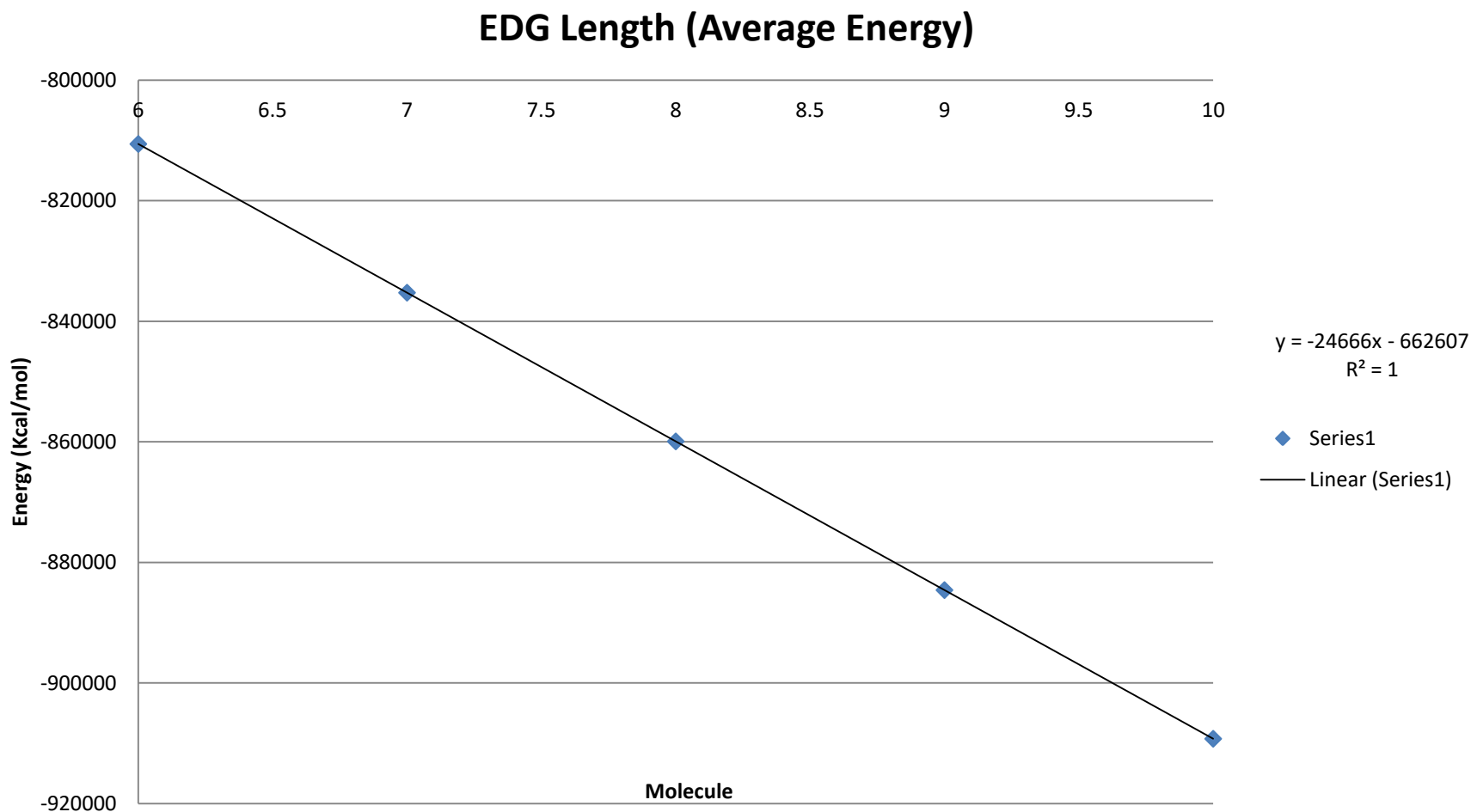# Results - EDG Length

Electron Donor Group (Length)
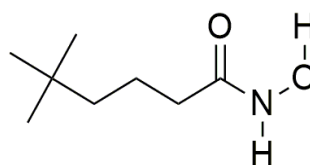
Molecule	ΔG (EDG length)
6	19.6297
7	11.8935
8	11.4005
9	11.4146
10	11.4298

Average 13.154 (3.626)

Result - EDG Length (Average)

EDG Length (Average Energy)
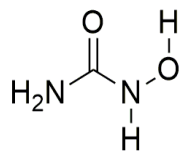

$y = -24666x - 662607$
$R^2 = 1$

◆ Series1
── Linear (Series1)

Results - ΔG EDG Length

Base Molecule
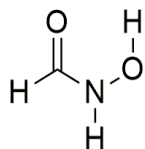
11

Donors
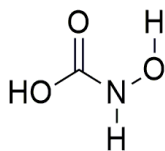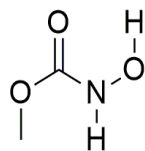
12   13   14   15

16   17   18   19

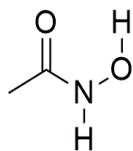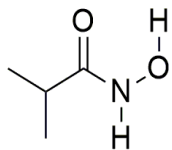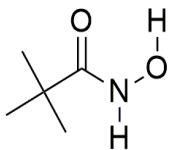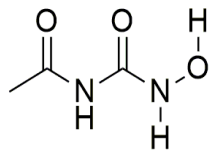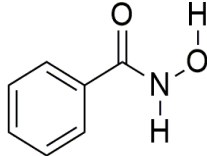| Molecule	ΔG (Donors)
11	*10.5930*
12	26.3558
13	17.8952
14	6.3369
15	12.0109
16	11.0510
17	19.6825
18	4402.2620
19	2.5601

Results - EDG (Average)

EDG (Average Energy)
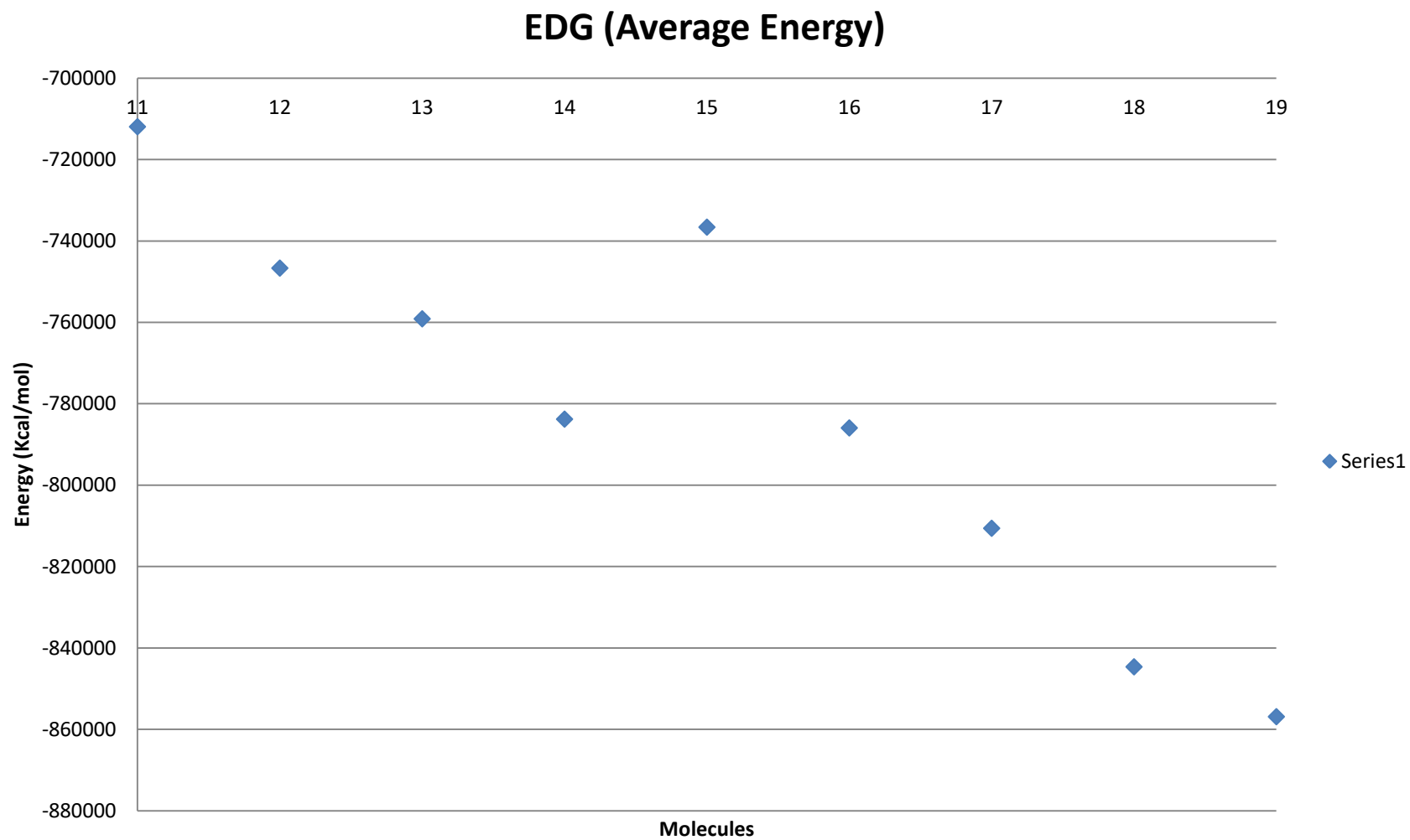
Results – ΔG EWG

Base Molecule

20

Withdrawers
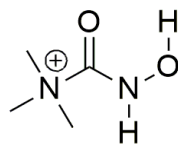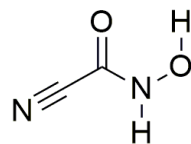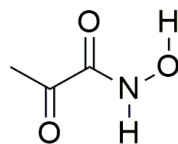
21   22   23   24   25   26   27
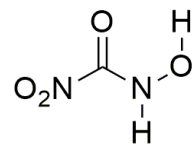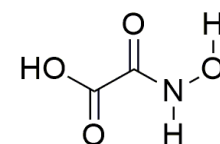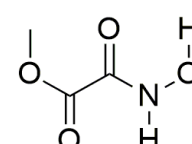
Molecule	ΔG (Withdrawers)
20	**10.5930**
21	-8.9164
22	-50.8228
23	5.7112

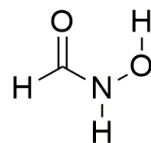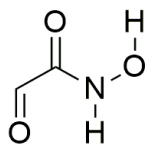| Molecule	ΔG (Withdrawers)
24	-9.9438
25	-48.0526
26	-11.9731
27	0.1564

Results - EWG (Average)
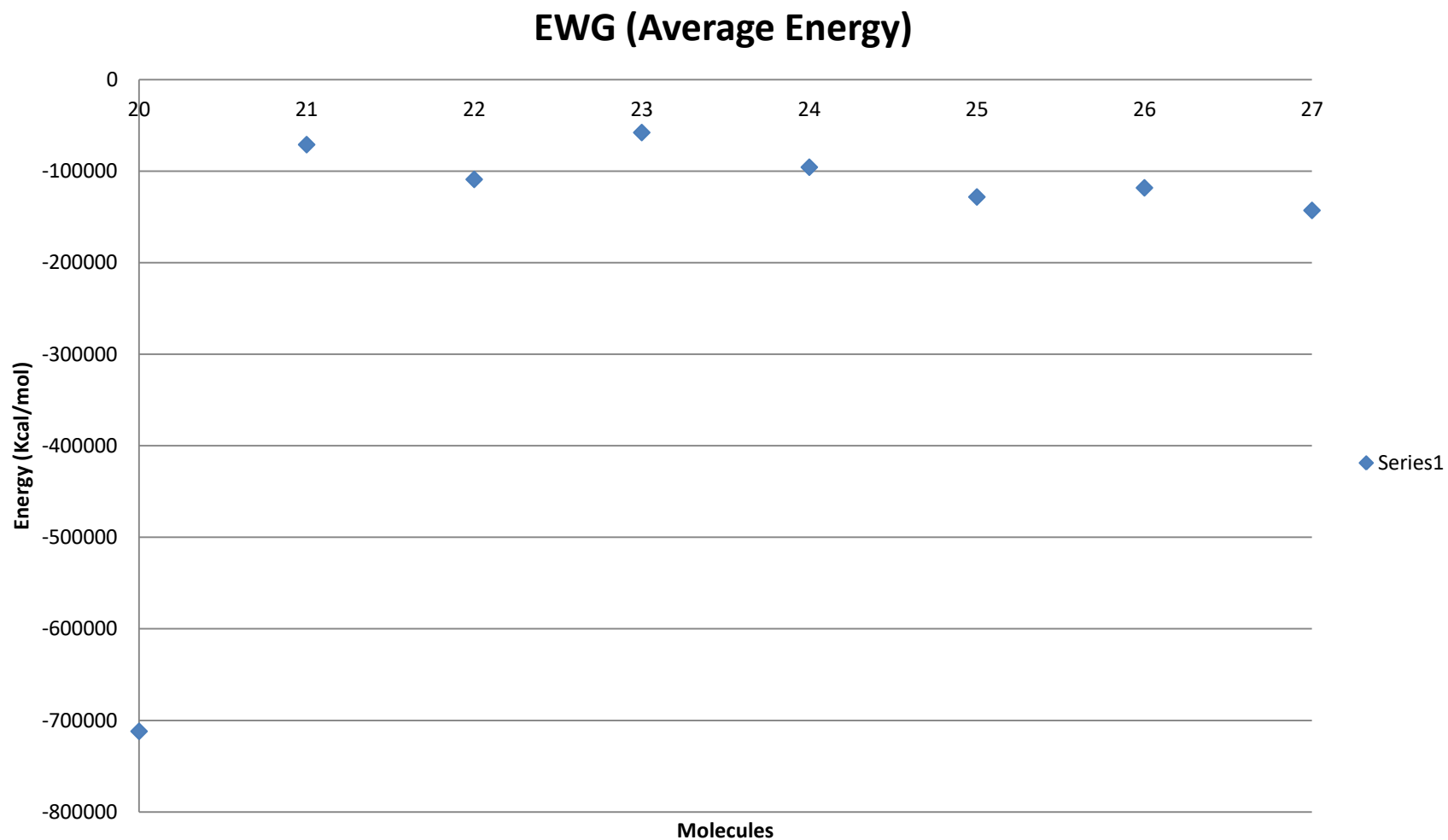
Results – ΔG Halogen

Base Molecule
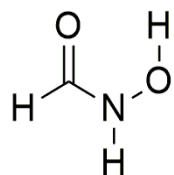
28

Halogens
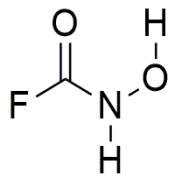
29   30   31   32
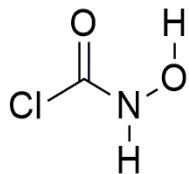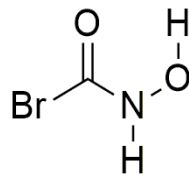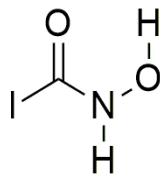
Molecule	ΔG (Halogens)
28	*10.5930*
29	8.0303
30	10.7065
31	9.3601
32	5274.5222

Results - Halogen (Average)

Halogen (Average Energy)

$y = -456277x^2 + 3E{+}07x - 4E{+}08$
$R^2 = 0.9885$

♦ Series1

—— Poly. (Series1)
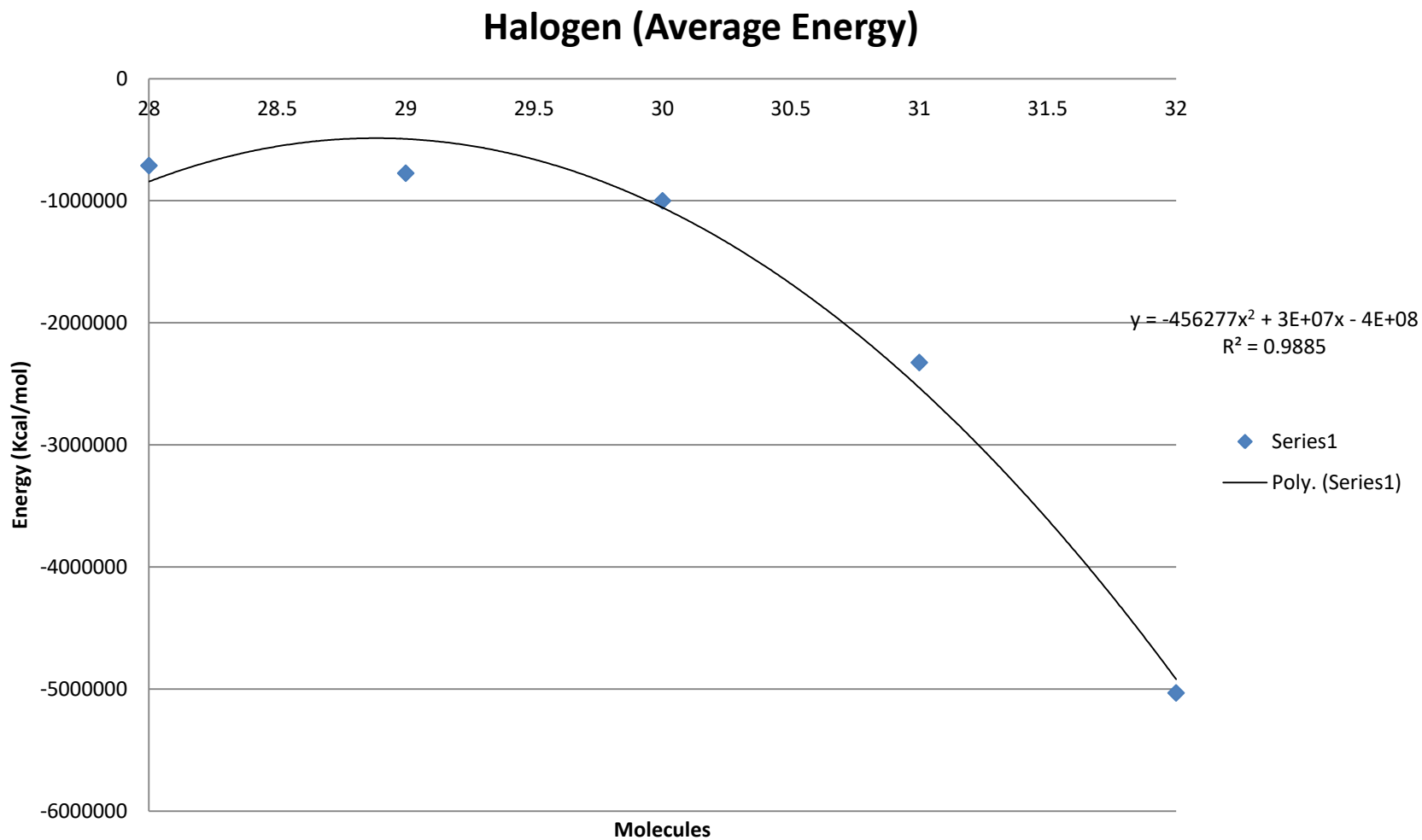
Discussion - ΔG EWG Length

- The results indicates that there is a DG difference between the direct binding of an tri-fluoromethane EWG attached to the HXA and a at least one carbon linker of 1 Kcal/mol with no littler difference thereafter. This indicates that direct binding of the EWG to the HXA has the greatest effect with little linker effect thereafter.

Discussion - EWG Length (Average)

- The graph of this data shows a linear line with an R^2 value of 1. The slope of the line is -24667 with an intercept of -898723. By using the intercept we are able to calculate the energy of the tri-fluoromethane of -898723 Kcal/mol.

Discussion - ΔG EDG Length

- The results indicates that there is a DG difference between the direct binding of an tri-methylmethane EDG attached to the HXA and a at least one carbon linker of 8 Kcal/mol with no littler difference thereafter. This indicates that direct binding of the EDG to the HXA has the greatest effect with little linker effect thereafter. When compared to the EWG difference there seems to be a greater effect when directly attached.

Discussion - EDG Length (Average)

- The graph of this data shows a linear line with an R^2 value of 1. The slope of the line is -24666 with an intercept of -662607. By using the intercept we are able to calculate the energy of the tri-methylmethane of -662607 Kcal/mol. Using a direct biosteric comparison with the tri-fluoromethane EWG we can see that in this case the EWG was favorable with an insignificant difference in slopes.

Discussion - ΔG EDG (Average)

- This data shows a series of electron donating groups directly attached to the HXA to determine the overall DG of the binding of a Zinc (II) ion compared to the standard HXA. The results find a most of the results comparable to the standards energy of 10.5930. The overall DG energy is not favorable however many are smaller than the standard HXA. Only molecule 18 showed a large difference in the energy of the bound vs unbound states. No rational reason was found and this molecule will be studies further.

Discussion - EDG (Average)

- The graph of this data shows a series of 8 molecules which maintains electron donating groups directly attached to the HXA when compared to the standard HXA. The data finds the average energy of EDG slightly lower than the control indicating more stable molecules when compared to the standard. All of the 8 molecules are lower energy than the standard molecule indicating increased stability. The most stable EDF group is the addition of a phenyl group to the HXA moiety. Future research will look at molecule 19.

Discussion - ΔG EWG (Average)

- This data shows a series of electron withdrawing groups directly attached to the HXA to determine the overall DG of the binding of a Zinc (II) ion compared to the standard HXA. The results find a most of the results comparable to the standards energy of 10.5930. Molecules 21, 22, 24, 25, and 26 were found to be favorable when compared to the standard.

Discussion - EWG (Average)

- The graph of this data shows a series of 7 molecules which maintains electron withdrawing groups directly attached to the HXA when compared to the standard HXA. The data finds the average energy of EWG significantly higher than the control indicating less stable molecules when compared to the standard.

Discussion - ΔG Halogens

- This data shows a series of halogens directly attached to the HXA to determine the overall DG of the binding of a Zinc (II) ion compared to the standard HXA. The results find a large difference between molecules 28 - 31 and 32 the iodo attached molecules. The difference between the iodo-bound and iodo-apo molecules is highly unfavorable.

Discussion - Halogens (Average)

- The graph of this data shows a series of 4 halogen attached molecules when compared to the standard HXA. The data finds the average energy of halogen significantly lower with a second order polynomial line fit with an R^2 value of 0.9885. This indicates that as the size of the halogen attachment increases the energy becomes significantly smaller.

Conclusion

- This study indicates a trend that EDG are the best molecules to use to increase the stability of the HXA. These EDG have to be bound directly to the HXA with linkers showing little to no difference in binding energy. The best binding molecule was a phenyl attached HXA. The halogen student found the larger the size the more stable the molecule with the iodo being the most stable.