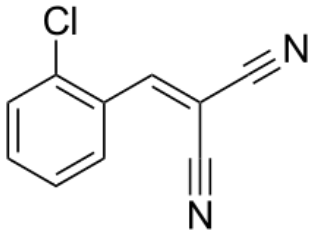
Graduate Research Plan Statement Coby Yeung

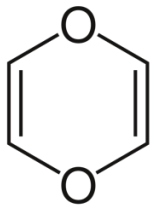
Intellectual Merit

This research plan is aiming to advance the knowledge of the reaction of CS gas to dioxin in different aspects. Proposing the reaction mechanism(s) is the first step. Quantum calculation will come after that as verification in the thermal energy aspect.

CS gas:



Dioxin:



Broader Impacts

CS gas is a commonly used "riot-control" tear gas. The heat of the bullets after firing might provoke the formation of dioxin. This research plan is for designing research that hopes to identify the reaction of dioxin formation and to show that the Hong Kong government is abusing a weapon that is going to bring a terrible man-made disaster by using non-standard tear gas bullets, which has a higher burning temperature. This research can also be a framework for studies in different aspects, for example, how the dioxin from CS gas binds to the hormone in the human body and the degradation of dioxin, formed by firing tear gas bullets, in the air.

Details (Research idea, proposed approach, and resources needed, etc)

Recently in Hong Kong, hundreds of thousands of civilians took to the street and protested against the government. The first protest was triggered by the extradition bill the government was trying to pass back in June. The bill would allow for criminal suspects to be extradited to mainland China under circumstances, which the opponents thought would risk exposing Hong Kongers to unfair trials and could be used to target activists and journalists.

Demonstrations started calling for the bill to be withdrawn completely in the beginning and it was peaceful. Polices started to use unnecessary violent toward protesters as the days go by and one of the current major demands from the protesters is an independent inquiry into alleged police brutality. The abuse of tear gases (TG), >10,000 shots, in Hong Kong by the police is one of the biggest concerns at this point since many Hong Kongers are experiencing irritation in their respiratory systems. The government stops providing the toxin level to the public, but it was available and updated frequently on an official website before all the TG shots.

2-chlorobenzylidene malononitrile (CS gas) is one of the most commonly used tear gases (TG) in the world. Previous researches have shown data to support that CS gas does affect humans in both the short and long term but mainly in the respiratory system level. Hong Kongers are facing a more crucial problem as the police were using TG bullets made in China, which have a higher

temperature while using. The high temperature excited the CS gas to react and produced dioxin. Dioxin is a toxin that causes adverse health effects. Exposure to dioxins may cause hormonal problems, infertility cancer, and damage the immune system, etc.

To perform research on the reaction from CS gas to dioxin, many factors need to be covered to approach the goal:

1. The characteristic of the TG bullets that Hong Kong police have been using – What temperature the bullets would get to after firing? What is the difference between the bullets made in China vs. other countries?
2. From Organic Chemistry aspects, what is the possible mechanism of the reaction? What molecules are involved?
3. Simulate the reaction using Computational Chemistry technology. Perform calculation on the reactant molecules with the specific parameter, temperature. What product(s) and mechanism(s) is/are the most thematically favored?

Previous researches related to the formation of dioxin would be some great resources to start with, including reactions occurred in solvents. Mechanism wise, the Organic Chemistry textbook provides some basic rules on proposing one several possible ones. During my undergraduate years, I did some chlorination researches in the Organic Physical Chemistry aspect, which can be applied to this topic.

For example, the attached poster shows my research group's work on the chlorination of cortisone and prednisone. All calculations were performed using Gaussian 16. The reactant and product complexes were optimized M11 density functional and the def2-SVP basis set. All energies were corrected to Gibbs free energies at 298 K. Transition states were confirmed to connect to the expected minima via IRC calculations. This kind of calculation can be done on the CS gas to dioxin reaction with defined specific parameters with enough information on the TG bullets and reasonable proposed reaction mechanism. More complicated calculations with similar concepts can come after this framework and focus more on the degradation of dioxin, as well as how the dioxin molecules bind to a hormone within the human body.

References

1. Dioxins and their effects on human health. World Health Organization. World Health Organization.
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Density Functional Studies on the Chlorination of Cortisone and Prednisone

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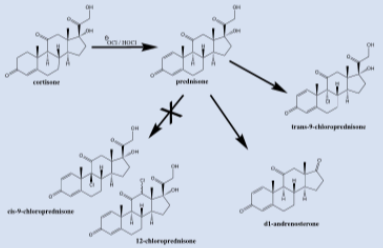
Introduction

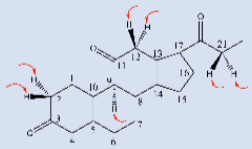
Cortisone and prednisone are two common glucocorticoids (GCs), a subclass of steroid hormones that are involved in glucose metabolic regulation and adrenal cortex synthesis in most vertebrates. GCs are an essential part of immune system feedback, especially as they relate to inflammation reduction. Between 2000 and 2009, prednisone alone was prescribed more than 170 million times in the US alone. Due to this heavy use, GCs have become easily detectible in wastewater streams.

Wastewater is typically treated via chlorination prior to release. Hypochlorous acid (HOCl) is widely used for this purpose. Previous experimental studies[1] reveal that chlorination of water samples containing cortisone and prednisone yield primarily *trans*-9-chloroprednisone and d1-andrenosterone. Interestingly, no other chlorinated cortisones or prednisones are detected.

The toxicity of chlorinated GCs is unknown, but chlorinated organics are generally more toxic than their parent compounds. Therefore, it is imperative to understand the mechanism of GC chlorination.



Under the experimental condition of pH 7, hypochlorite anion ($^-$OCl) and hypochlorous acid (HOCl) are the dominant Cl-containing species.[2] Therefore, one likely mechanism is enolization promoted by hypochlorite followed by chlorination via HOCl.



Standard numbering for steroids. Enolizable protons are indicated with red arrows.

Objectives

- Model the base-promoted enolization of cortisone and prednisone using $^-$OCl as the base, at each enolizable position.
- Model the chlorination of each respective enolate using HOCl as the chlorinating agent.
- Model the transformation of cortisone to prednisone.
- Model the transformation of prednisone to d1-andrenosterone.
- Predict the most likely products with the goal of supporting observed product distribution.

Theoretical Methods

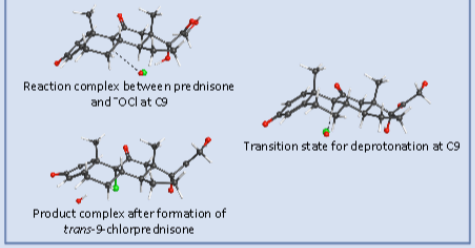
All geometries were optimized using the M11 density functional and the def2-SVP basis set. Bulk aqueous solution was modeled using the SMD continuum solvation model. All energies were corrected to Gibbs free energies at 298 K and 1 M aqueous solution.

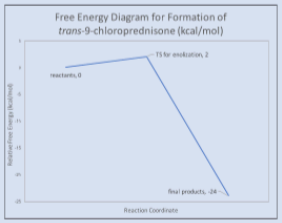
All minima are confirmed to have zero imaginary vibrational modes, while all transition states are confirmed to have one and only one imaginary vibration mode. Transition states were confirmed to connect to the expected minima via IRC calculations.

All calculations were performed using Gaussian 16.[3]

Results and Discussion

Representative chlorination reaction: Hypochlorite deprotonates GC, forming enolate which is chlorinated with no further kinetic barrier.

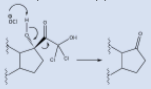




Free Energies of Activation for Enolization of Cortisone and Prednisone (kcal/mol)

Position	$\Delta G^{\ddagger}$ (cortisone)	$\Delta G^{\ddagger}$ (prednisone)
C2 (cis)	9	N/A
C2 (trans)	10	N/A
C9 (trans)	3	2
C12 (cis)	16	16
C12 (trans)	6	7
C21 (pro-S)	6	6
C21 (pro-R)	3	3

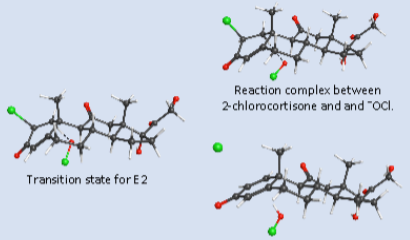
- Enolization at C9 , leading to 9-chloro products, is predicted to be kinetically favorable.
- Enolization at C21 is predicted to be kinetically favorable, potentially leading to andrenosterone products as follows.

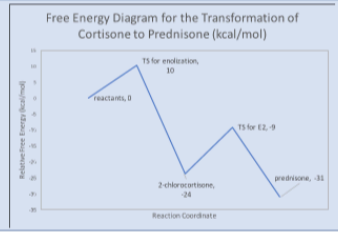


- Enolization at C12 (*trans*) is highly disfavored kinetically.
- The rate determining step is enolization. Chlorination appears to proceed with no further barrier, although steric crowding hinders *cis*-C9 and C12 products.

Results and Discussion

Transformation of cortisone to prednisone via E2, following initial chlorination at C2.





Conclusions

- Base-promoted enolization of cortisone and prednisone is predicted to occur in the presence of aqueous hypochlorous acid / hypochlorite solution at pH 7.
- C9 and C21 enolates are highly favored kinetically, supporting experimental observations.
- The rate determining step is always enolate formation, and the overall chlorination reactions are all exergonic by approximately 25 kcal/mol.
- Steric interactions with the C10 and C13 methyl groups and the C17 sidechain appear to hinder formation of *cis*-C9 and both C12 products. Further work is needed to quantify the hindrance.
- Additional studies are necessary to model the cleavage of the C17 sidechain.

References and Acknowledgements

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