UNIVERSITI TEKNOLOGI MARA

FIRST PRINCIPLES INVESTIGATION ON THE POLYMORPHS OF SYMMETRICALLY SUBSTITUTED THIOUREA DERIVATIVES

NUR NAJWA ALYANI BINTI MOHD NABIL

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science

Faculty of Applied Sciences

March 2019

ABSTRACT

Polymorphism is a well-known phenomenon where a compound is able to form more than one crystalline form in the solid state. Compounds having this ability would display different stabilities for different forms, hence affecting its applicability. In this study, polymorphism on 26 symmetrically substituted thiourea derivatives, which possess rotational flexibility in the C–N bond, were carried out using theoretical investigations. To find the yet to be found possible stable configurations, exhaustive computations at the adequate level of theory B3LYP/def2-TZVP were performed on the monomers and dimers of the compounds. Rotating the substituents along the C–N bond, starts from the existing stable configuration shows that energetically CT and TT configurations are equally preferable. The TT configuration had relatively higher energy compared to CT configuration, with relative energy ranging from 0.0044 to 0.3093 eV. The CC configuration is not preferred with higher relative energy range from 0.0947 to 7.2727 eV. The topology analysis of non-covalent interaction, frontier molecular orbital and electrostatic potential were used to complement the energetic results, in which the interactions involved in the systems of interests are further elucidated. It was found that molecules in TT configuration are more preferable to be electron acceptor (N_T site), while those in CT configuration are preferable to be electron donor (S_T site). Furthermore, comparison between monomer and dimer systems indicates that the characteristic of the two systems is almost similar. Thus, the study provides theoretical basis to the experimental results that the SSTD are preferable to be coexisting in TT and CT configurations.

ACKNOWLEDGEMENT

First of all, thanks to ALLAH S.W.T, the Most Beneficent and the Most Merciful. Alhamdulilah, I had finished my Master's study.

It is with immense gratitude that I acknowledge the support and help of my supervisor, Dr. Ang Lee Sin, for his constant guidance, moral support, criticism and patient during my research. This research would not complete without his assistance and encouragement throughout Master's study.

Appreciation goes to Univeristi Teknologi MARA (UiTM), UiTM Institute of Graduate Studies (IPSIS), UiTM Perlis coordinator (Dr. Shukor Sanim Mohd Fauzi). I cannot find words to express my gratitude to colleague and people who willingly helped and encouraging me throughout this study. Thanks also to those directly or indirectly contributed to this research.

Finally, I must express my very profound gratitude to my parents;

and , and family for providing me with unfailing support and continuous encouragement throughout my years of study and process of researching and writing this thesis. To all my siblings, Nur Farhana Syazwani, Muhammad Naim, Muhammad Najmi and Nur Fatin Ayuni. This accomplishment would not have been possible without them. Alhamdulillah.

Thank you.

TABLE OF CONTENTS

CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Polymorphism is a phenomenon that occurs as a compound is able to exist in more than one crystal structure. It has aroused a good deal of interest as it can occur during discovery, development and manufacturing process of compounds. This phenomenon has been the focus of many industries such as pharmaceutical and chemical industries [1, 2]. As different molecular arrangements would affect a compound's chemical and physical properties, such as colour, chemical stability and solubility, the uses of a compound have to be approach with cautious [3].

The early incident that attracted particular attention to the spontaneous appearance of the stable polymorph occurred in 1996. The polymorph of anti-HIV drugs Ritonavir was found approximately two years after the drug had been launched. The appearance of the stable polymorph forced Abbott Laboratories to remove the drug from the market for reformulation to overcome the lower bioavailability of the new, more stable form. Patients were denied temporarily access to an important drug and the company lost an estimated $250 million dollars in sales [4]. Until recently, more compounds were revealed to be a polymorphic compound [1, 5, 6]

Generally, polymorphism refers to different structural forms of a chemical substance. McCrone defined polymorphism as "the existence of a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state" [7]. Several terminologies have been used to describe polymorphism. Concomitant polymorph happens as crystals are formed simultaneously from the same solvent and crystallization flask under identical crystal growth condition. When different conformers of the same molecule occur in different crystal form, it is known as conformational polymorph. Conformational isomorphism is the existence of multiple conformations in the same crystal structure and pseudopolymorphism is the occurrence of the same molecule with different type or stoichiometry of solvent in the