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Studies on the mechanism of quaternization of the catharanthine part of vinblastine and vincristine

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ABSTRACT

A quaternization reaction was observed at the tertiary nitrogen atom of the catharanthine part of vinblastine instead of the expected cyclopropanation in the Simmons–Smith reaction utilizing diiodomethane and diethylzinc. Investigating the energetic relations, thermodynamic stabilities and the interactions between the molecular orbitals by quantum chemical calculations elucidated the unexpected methylation and confirmed the reaction mechanism. Although the history of the Simmons–Smith reaction goes back more than half a century this represents the first time that the reaction and its possible side-reaction has been studied by DFT level calculations in a complex system.

Introduction

Vindoline (**1**) and catharanthine (**2**) containing the indole skeleton are components of the dimer alkaloids vinblastine (**3**) and vincristine (**4**) which have outstanding cytotoxic activities and are used in anticancer therapy (Fig. 1). These *Vinca* alkaloids were discovered in the 1950s and were first isolated from a Madagascar periwinkle.[1] Vinblastine (**3**) and vincristine (**4**) show an inhibitory effect on the metaphase of the cell-cycle during the course of cell proliferation inhibiting the formation of the mitotic spindle which is necessary for the separation of chromosomes. Moreover, they have influence on the DNA and RNA synthesizing ability of the cell. The chemical and biological characteristics of these dimeric alkaloids are presented in several reviews.[1–3]

Recently a number of new vinblastine derivatives containing a cyclopropane ring condensed to the 14,15 positions were synthesized in our research group, namely 14,15-cyclopropano-vinblastine, -vincristine, -vinorelbine, -1-*N*-formyl-vinorelbine and -nor-5′-vinblastine. The synthesized compounds were investigated by NIH laboratories in the USA and were shown to possess significant anticancer activities on different cell lines.[4,5] The key step of the synthesis of these compounds was the coupling of catharanthine (**2**) with 14,15-cyclopropano-vindoline, since the dimer alkaloids failed to undergo direct cyclopropanation by the Simmons–Smith reaction, and only the reaction of the monomer vindoline (**1**) resulted in the expected cyclopropano derivative.

In the case of the reaction of vinblastine (**3**) with diethylzinc and diiodomethane, a quaternary salt (**5**) was obtained as the main product in 18% yield.[4] In addition a 2:1 mixture of vinamidine (**7**)[6–9] and cyclovinblastine (**9**)[10] were isolated as rearrangement products (Scheme 1). It was found that the NMR spectra of quaternary salt **5** was known in the literature[11] but without any further data. Similarly, when treating vincristine (**4**) under such reaction conditions the corresponding quaternary salt **6** was isolated in 9% yield,[4] and *N*-formylcatharinine[12] (**8**) and cyclovincristine[10] (**10**) were identified by NMR spectroscopy in a 1:1 mixture.

In the last decades a few studies have been reported regarding DFT calculations on the Simmons–Smith reaction, mostly applying ethylene as a model compound.[13] It is known that Simmons–Smith type reagents react with basic amino groups to give ammonium ylides.[14] Nevertheless, we intend to show the first computed detailed mechanism of a Simmons–Smith reaction with a complex substrate and an observed nitrogen quaternization as a competitive side-reaction. In this work we present an explanation of the reaction mechanism and the unexpected chemoselectivity.

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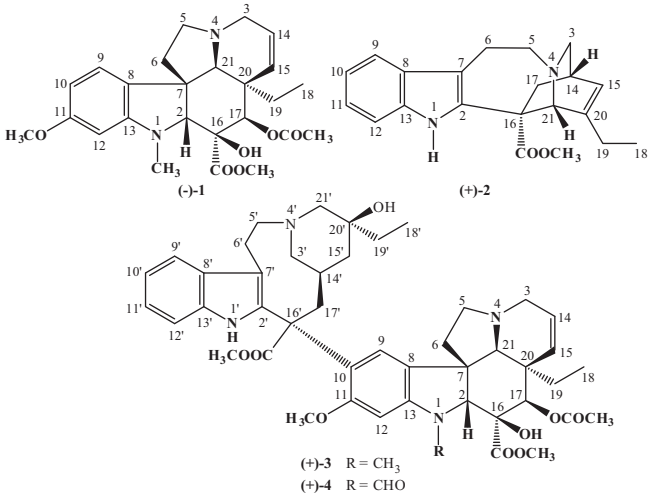
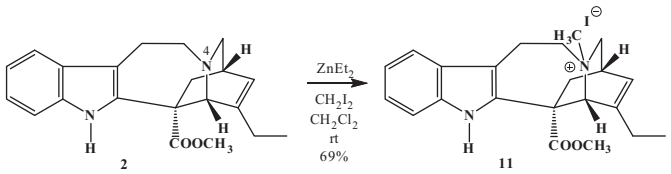


Figure 1. Alkaloids vindoline (**1**), catharanthine (**2**), vinblastine (**3**) and vincristine (**4**).

Results and discussions

In order to understand the mechanism and selectivity of the reaction, especially the quaternization of the 4′ nitrogen atom instead of cyclopropanation or quaternization at the 4 nitrogen, various reactions had to be carried out. It was established that the Simmons–Smith reaction of vinblastine (**3**) to give 14,15-cyclopropano-vinblastine in dichloromethane at reflux was unsuccessful with most of the starting material decomposing. This was followed by the reaction of catharanthine (**2**) with diiodomethane in the presence of diethylzinc in dichloromethane under Simmons–Smith reaction conditions. In this case, the *N*-methyl-catharanthine quaternary salt (**11**) was obtained in 69% yield (Scheme 2).

The direct quaternization of vindoline (**1**) and vinblastine (**3**) with methyl iodide in dichloromethane was also investigated. In



Scheme 2. Reaction of catharanthine (**2**) with diiodomethane in the presence of diethylzinc.

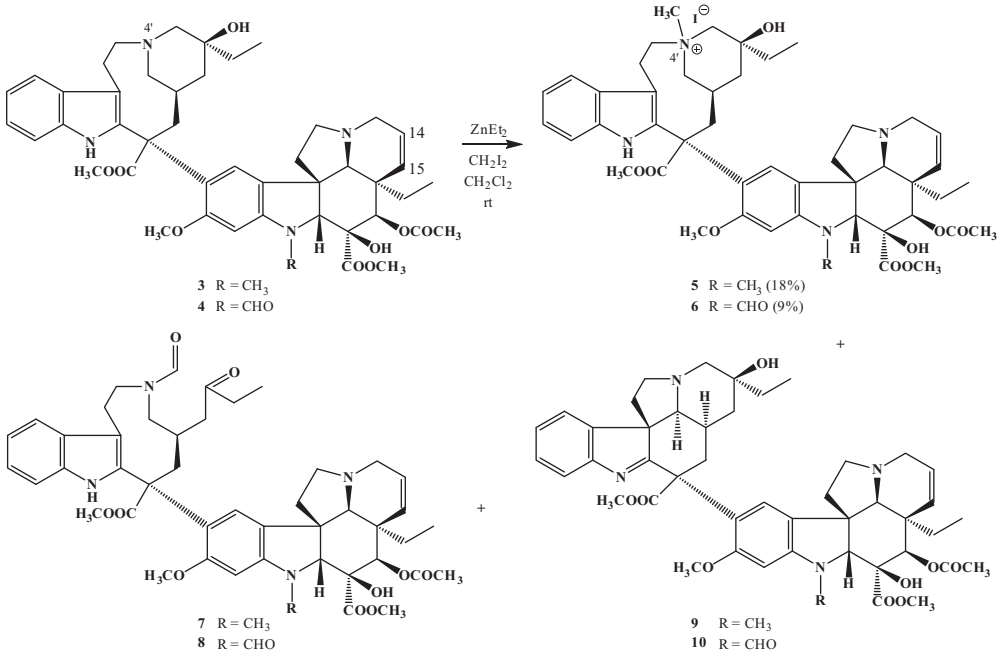
the case of **1** no reaction was observed, however, **3** could be quaternized at the 4′ nitrogen atom and the corresponding quaternary salt (**5**) was isolated in 85% yield (Scheme 3).

It could be concluded from the above experiments, that the Simmons–Smith reaction and direct methylation favoured the tertiary nitrogen atom in position 4′ of the catharanthine ring system, the tertiary nitrogen in position 4 or the 14–15 olefinic double bond in the vindoline skeleton is disfavoured.

The aim of quantum chemical computations[15–19] was to understand the reason for the quaternization of vinblastine (**3**) at the 4′ nitrogen instead of the expected 14–15 cyclopropanation under Simmons–Smith conditions. Furthermore we wished to investigate the difference between the two tertiary nitrogen atoms (4 and 4′) of the vindoline and catharanthine skeletons. As the size and number of atoms of the whole structure of vinblastine is large, for the sake of acceptable computation time, simplified structures were used for computations, based on vindoline and catharanthine.

Firstly, as two model reactions, the quaternization of trimethylamine and the cyclopropanation of ethylene with $EtZnCH_2I$, formed from diethylzinc and diiodomethane, was investigated. It was found, that the quaternization had a lower transition state (51.7 kJ mol^{-1}), than the cyclopropanation (64.4 kJ mol^{-1}). Therefore it may be stated generally, that under Simmons–Smith reaction conditions a trimethylamine-type nitrogen atom would react faster with $EtZnCH_2I$, than it would cyclopropanate the olefinic double bond.

According to our hypothesis, in the case of **3** a steric and/or energetic difference should have been found between the



Scheme 1. Reactions of vinblastine (**3**) with diethylzinc and diiodomethane.