Predicting Carbocation Migration in S_N1 Reactions

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01 July 2016

ABSTRACT

Charge rearrangement is fundamental to successful organic synthesis. Understanding charge stability of the carbons in intermediates allows more accurate predictions of the major final product will be. We accurately predicted the product of S_N1 substitution reaction of 2,4-dimethyl-3-pentanol and Lucas's reagent ($HCl/ZnCl_2$) to be 2-chloro-2,4-dimethylpentane (3) as a result of a 1,2-hydride shift during intermediate stages. Results of ^{13}C NMR as well as H NMR analysis supported this conclusion.

Introduction Organic molecules are ubiquitous in the world around us. These molecules give us the scents and flavors we enjoy in the products we consume. [1, 2] Organic molecules make up the biological molecules that sustain life as well constitute the main component of life-saving drug treatments for people with various kinds of illness. [3] These carbon-based molecules are frequently more easily and economically synthesized in labs than harvested from natural systems. [4, 5] The drug Taxol was first isolated from the *Taxus brevifolia* tree as an anti-tumor treatment for breast and cervical cancers. [6] This complex molecule was only available through natural production, making isolating the compound costly, time-consuming, and damaging to the population of *T. brevifolia* trees. In 1993, a new way to synthesize a more soluble version of this molecule allowed mass production and affordable distribution of this valuable cancer treatment. [3, 7] Synthesis of Taxol is a multistep process, which requires mechanistic understanding of synthesis to arrive at the final product. One such mechanism is that of rearrangement, by which charges on carbon atoms move to more stable positions in the molecule. [8] Carbanion rearrangement allowed for the invention of the Holton-method of Taxol synthesis, which counts on the movement of a negative charge form one carbon to the more stable carbon. [9] Without the understanding the how carbon stability impacts rearrangement, this method of synthesis would not be possible.

Exploration and analysis of carbocation rearrangement serves to build the foundation of knowledge that will support the future of organic synthesis and all that it serves.

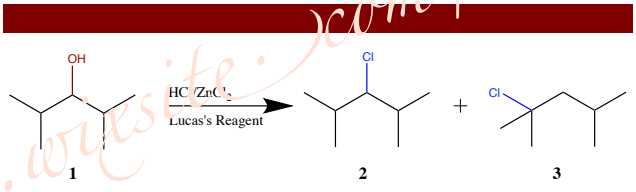

Figure 1. Reaction of 2,4-dimethyl-3-pentanol (1) with Lucas's reagent ($HCl/ZNCl_2$) to form two possible substitution products: 3-chloro-2,4-dimethylpentane (2) via S_N2 or 2-chloro-2,4-dimethylpentane (3) via S_N1.

Results and Discussion Though the reaction of a secondary alcohol might undergo substitution via either S_N1 or S_N2, multiple factors prevent the reaction from occurring using the S_N2 pathway

(Figure 1). In addition, 2,4-dimethyl-3-pentanol has multiple methyl groups that both encourage electron donation and employ steric hindrance that prevents backside attacks leading to an S_N1 reaction. We expected to see a product that confirmed this hypothesis. If the product undergoes S_N2 reaction, the chloride ion will attack the carbon as shown in Figure 2, creating Compound **2** as the major product. However, if S_N1 is employed, the leaving group will leave first, creating a carbocation that migrates to the tertiary position via a 1,2-hydride shift as seen in Figure 2. This method of substitution will yield Compound **3** as the major product.

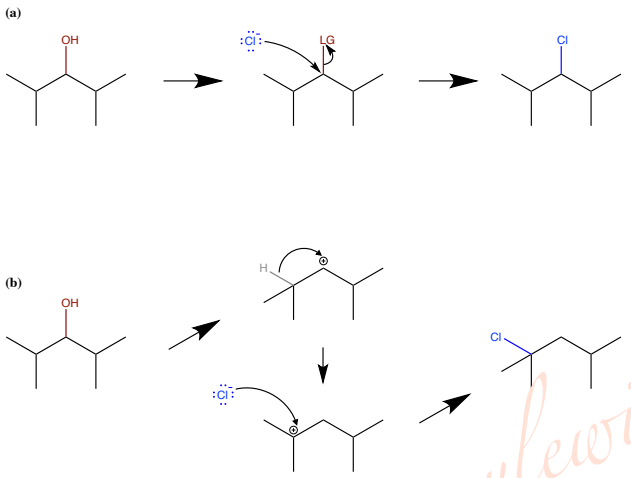

Figure 2. Mechanistic representation of substitution pathway for S_N2 (a) and S_N1 (b). (a) Chloride anion (in blue) backside-attacks the alpha carbon, causing the leaving group (LG) (in red) to leave, forming product 2. (b) The LG leaves first, forming a carbocation that migrates to the tiriary position via 1,2-hydride shift and then bonds the chloride anion.

Based on the ^{13}C and H NMR results we expect to see different unique carbon and hydrogen groups represented for these two possible products. The major S_N2 product, Compound **2**, resulting in 3 unique carbons and 3 unique hydrogens compared with the 5 unique carbons and 4 unique hydrogens of the major S_N1 product, Compound **3**.

The ^{13}C NMR (Figure S1) has 5 distinct peaks, suggesting the major product of the reaction is compound **3**. Product **2** has symmetry leading to fewer distinct carbon atoms on the molecule and fewer individual peaks on the ^{13}C NMR.

The H NMR (Figure S2) is also suggestive of Compound **3** as the major product of the reaction as predicted in Figure 3 and Table 1. The most distinguishing character being a singlet, as shown by H_A in the figure, that denotes a level of hydrogen splitting that would not be present on Product **2** as there are no unique hydrogen groups without vicinal protons. There are four distinguished groups of peaks, which also help to rule out Product **2**, as it would only have 3 unique peaks present. The proton NMR does include an apparent doublet that is unaccounted for in compound **3**. This may be a result of a mixture of both S_N1 and S_N2 products or of residual hydrogen from unreacted Lucas's reagent. There are 2 doublets present that should be there that have integral values of 2 and 6 and indicative of H_B and H_D respectively, which are representative of the predicted splits at those hyrogens. The nonet representing H_C is the least significant to differentiate between product 2 and 3 because of its similarity to the potential octet we might see in Product **2**, which would have the same integral value.

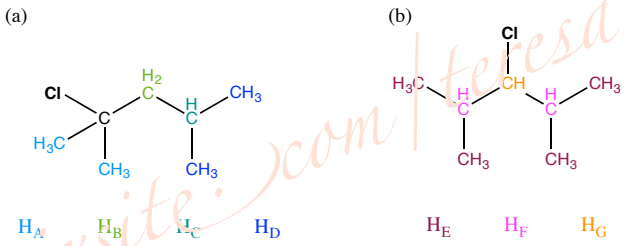

Figure 3. Distinct hydrogen groups of compound **3** (a) and of compound **2** (b) as predicted for proton NMR results (Table 1, Figure S2).

Table 1. Predicted H NMR for Product **2** versus Product **3**

Product 3		
H(n)	**Split**	**Integral**
A	Singlet	6
B	Doublet	2
C	Nonet	1
D	Doublet	6

Product 2		
H(n)	**Split**	**Integral**
E	Doublet	12
F	Octet	2
G	Doublet	1

This table referrances unique hydrogen groups in Figure 3.

Both the ^{13}C NMR and the H NMR support the hypothesis that the major product is Product **3**. Small procedural errors were made that would affect overall percent yield of the product, but for the purposes of determining which of the 2 compounds is the major product, these errors did not have an impact on the results. Future experiments of a similar nature may add to the understanding of this reaction and what factors impact the method of substitution. For example, this experiment aimed to keep the temperature between 60 and 75 °C for the duration of the reaction. This was to speed up the reaction process, but further experimentation with

increased temperature or temperatures significantly colder than room temperature may show different results. This procedure may also be useful when applied to benzylic groups with high resonance and therefore, highly stabilized carbocations.

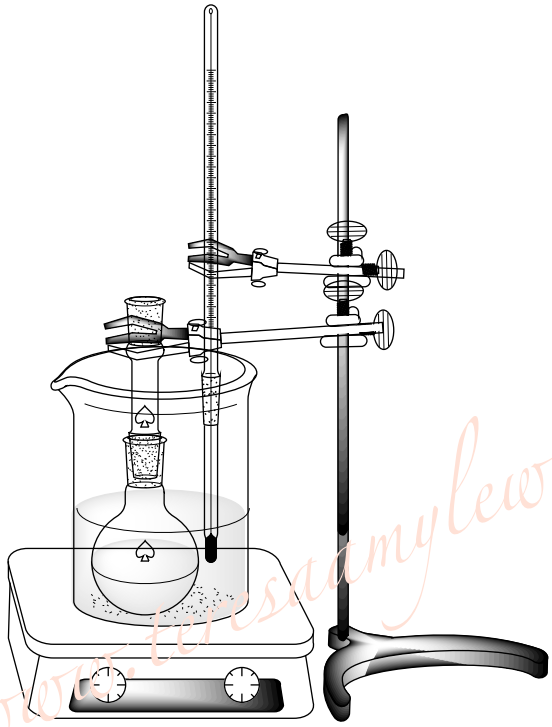

Figure 4. Experimental set-up for double-boiler method.

Experimental A double-boiler was set up using a hot plate, a thermometer, and a beaker filled approximately half way with water as shown in Figure 4. While the water heated to the temperature of 65 °C, 6.5 mL of Lucas's reagent ($HCl/ZnCl_2$) was combined with 1.50 mL of 2,4-dimethyl-3-pentol in a 25 mL ground-glass, round-bottomed flask. A stir bar was added to the mixture and an air-cooled condenser attached to the flask. The flask and condenser were secured in the double-boiler using clamps so that the mixture was below the water level in the beaker, but not so low as to submerge the cap on the round-bottomed flask. The stir bar was turned on the reaction allowed to proceed for 10 minutes. Temperature during this time was monitored and heat adjusted to remain between 65 and 74 °C. After the 10-minute process-time the mixture was removed from heat to cool to room temperature. Once cooled, approximately 5 mL of saturated sodium chloride brine was added to the flask and mixture was then transferred into a centrifuge tube for isolation. The bottom, aqueous layer was removed using a pasture pipette and discarded. The organic layer was washed with the brine and the aqueous layer was discarded twice more before being dried. Anhydrous magnesium chloride was used to dry the organic layer. The product was then transferred to a tared sample vial and massed at 1.756 g. A small portion was place in an NMR vial for processing.

References

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Supplemental

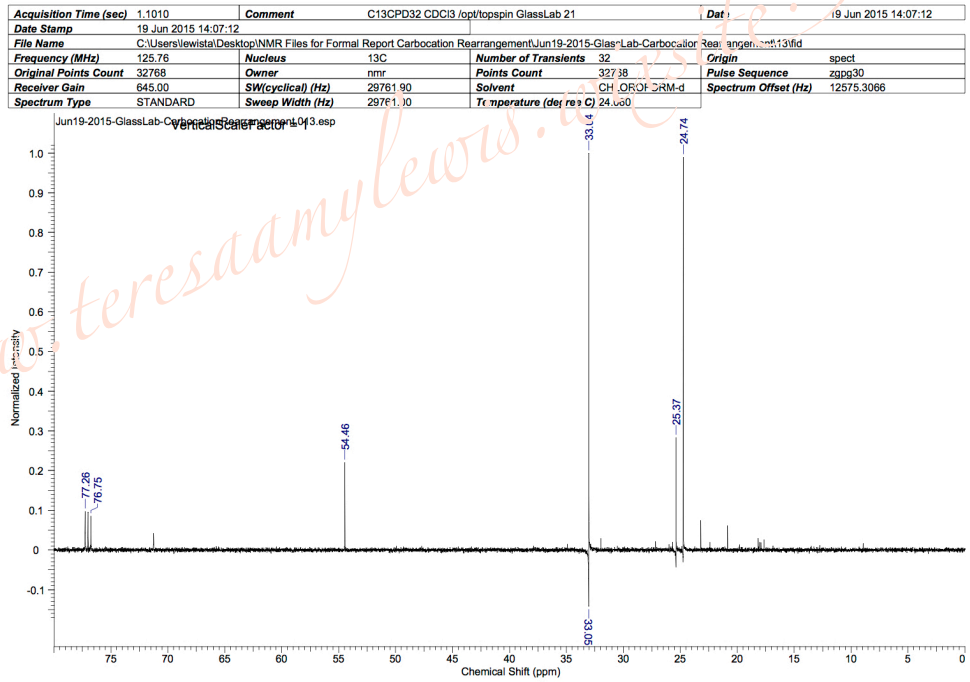

Figure S1. ^{13}C NMR of the final product. Multiple peaks are consistent with Product **3** as a lane of syemetry in Product **2** would create only 3 unique carbon groups, leading to only 3 peaks on the NMR.

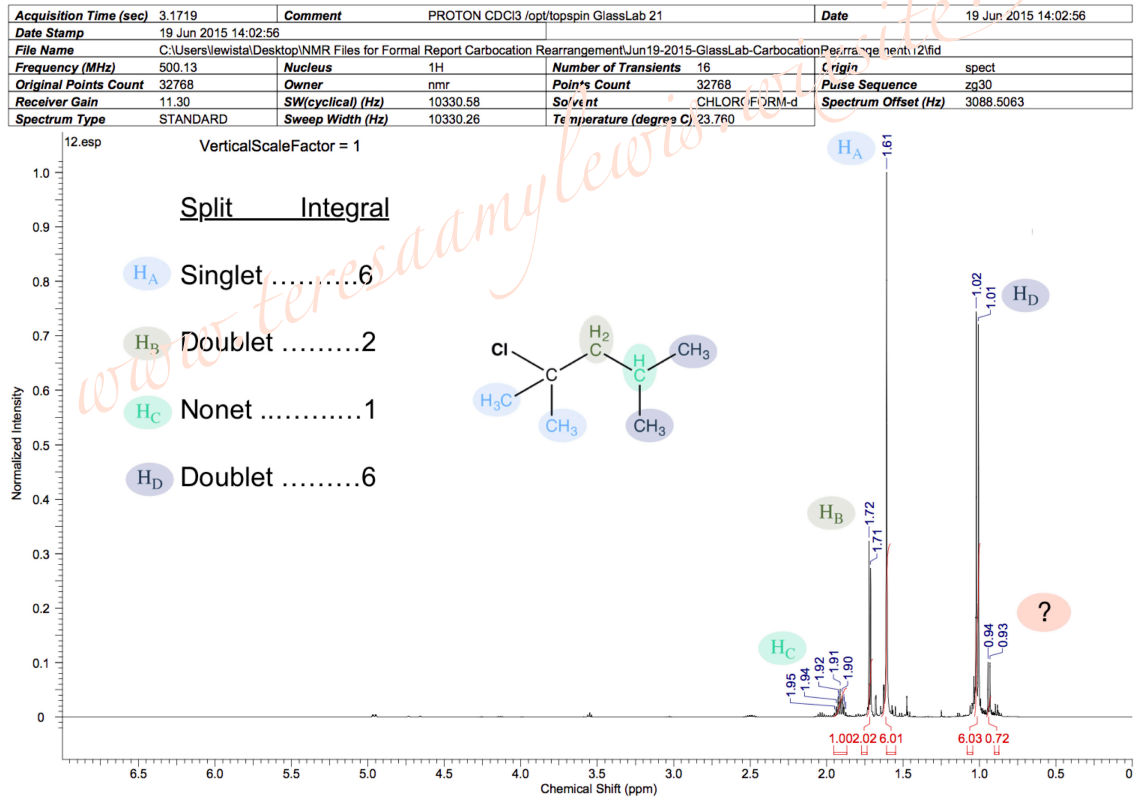

Figure S2. H NMR of the final product. A singlet, as shown by H_A denotes hydrogen splitting that would not be present on Product **2** as there are no unique hydrogen groups without vicinal protons, supporting the presence of Product **3**.