INTRODUCTION

Chemo- and regioselective reactions are crucial for efficient, high-yielding, and atom economic multistep syntheses. Basic concepts for selectivity, like Markovnikov's Rule for hydrohalogenation of carbon double bonds, are part of introductory lectures in organic chemistry.[1] Herein we emphasize the importance of ^{13}C NMR spectroscopy, in combination with the DEPT experiment, for resolving the identity of the product of addition reactions by means of a simple and rapid experimental procedure[2] adapted from a J. Chem. Educ. article published by M. W. Pelter and N. W. Walker.[3] This experiment is highly suitable for undergraduate students within the organic chemistry practical course and will increase of the familiarity of the students with analyzing and interpreting ^{13}C NMR spectra.

BACKGROUND

To properly assign a ^{13}C NMR spectrum, particularly when identifying an unknown species, it is beneficial to gain definitive information of the CH_3, CH_2, CH or quaternary (Cq) carbon atoms present. For extracting this information, the Distortionless Enhancement by Polarization Transfer (DEPT) is a particularly well-suited NMR spectroscopic method. Its pulse sequence is depicted in figure 1.
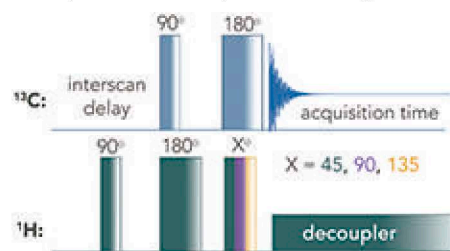

Figure 1. Pulse sequence of the different DEPT experiments (DEPT-45, -90, -135).[4]

In the proton channel a spin echo sequence ($90°x'$-τ-$180°x'$-τ) is followed by a θ = 45°, 90° or 135° pulse in the y' direction, respectively. Depending on which angle θ is chosen different signal intensities for the different carbon atoms

(CH_3/CH_2/CH/Cq) are observed in the resulting spectrum (figure 2). It is to be noted that in all the DEPT experiments quaternary carbons are not observed (herein DEPTq is not discussed), but these can be revealed by comparing with the $^{13}C\{^1H\}$ NMR spectrum. While in the DEPT-45 experiment all carbon atoms have positive intensities, DEPT-135 gives a negative peak for the CH_2 signals, and positive for the CH and CH_3 resonances. In DEPT-90 spectra all carbon signals are absent with the exception of positive CH signals.

As an interim conclusion one should note, is that by comparing the $^{13}C\{^1H\}$, DEPT-135 and DEPT-90 NMR spectra, all the different carbon atoms can be distinguished.
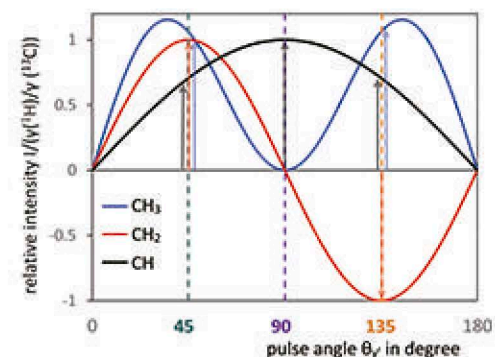

Figure 2. Signal intensities of CH_3 (**blue**), CH_2 (**red**) and CH (**black**) groups as a function of the pulse angle in the DEPT experiment.[5]

The DEPT experiment has similarities with the J modulated spin echo (Attached Proton Test, APT). The advantage of DEPT over APT is the sensitivity enhancement afforded by the polarization transfer from ^1H to ^{13}C.[5]

SYNTHETIC ROUTE

The hydrochlorination of carvone **1** can be accomplished via in situ generation of HCl employing oxalyl chloride and alumina or TMS-Cl in water.[6, 7] M. W. Pelter and N. W. Walker reported that treatment with inexpensive acetyl chloride in ethanol improves the regio- and chemoselectivity with high yields (scheme 1).
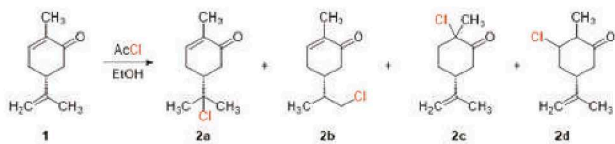
Scheme 1. Possible products of the hydrochlorination of (R)-(−)-Carvone (**1**).[3]

PROCEDURE

According to a literature procedure[1,3], monoterpene **1** was dissolved in absolute EtOH and stirred in a round-bottom flask with an attached air condenser. The flask was heated to 45 °C in a fume hood. Acetyl chloride was added dropwise to the reaction mixture, resulting in an increasingly darkened mixture. The progress of the reaction was monitored via TLC until the carvone was fully consumed (less than 90 min). Once the reaction was completed, the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. Compound **2a** was obtained as a colorless oil in 75% yield.

The $^{13}C\{^1H\}$ (5 min), DEPT-135 and DEPT-90 (2.5 min each) NMR spectra were recorded on an NMReady-60PRO.

RESULTS & DISCUSSION
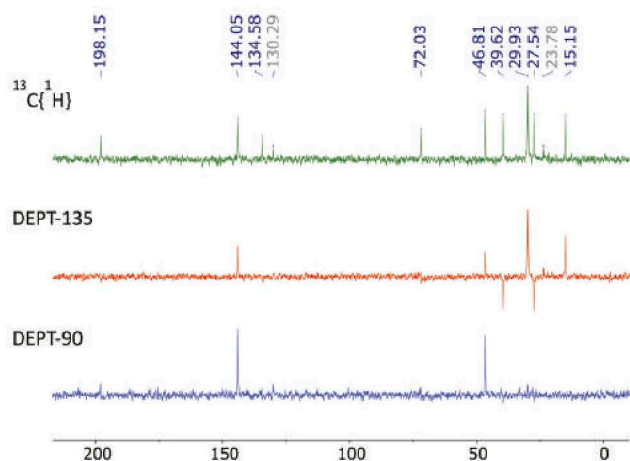
$^{13}C\{^1H\}$, DEPT-135 and DEPT-90 NMR (15 MHz, CDCl$_3$):

Figure 3. Stacked $^{13}C\{^1H\}$, DEPT-135 and DEPT-90 NMR spectra of compound **2a** in CDCl$_3$.

The signals with low intensities at 130.29 and 23.78 ppm (greyed out) refer to impurities, which were not further characterized. By comparing the stacked spectra and following the above-mentioned rules, all other observed ^{13}C NMR signals can be assigned to the different types of chemically distinct carbons:

Cq (not seen in DEPT):
  δ [ppm] = 198.15, 134.58, 72.03
CH$_3$ (positive in DEPT-135, not seen in DEPT-90):
  δ [ppm] = 29.93 (2x), 15.15
CH$_2$ (negative in DEPT-135):
  δ [ppm] = 39.62, 27.54
CH (positive in DEPT-90):
  δ [ppm] = 144.05, 46.81

Paring the intensities with the expected chemical shifts of components, all ^{13}C NMR signals can be assigned to the molecular structure of the Markovnikov product **2a** (figure 4).
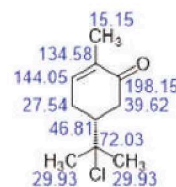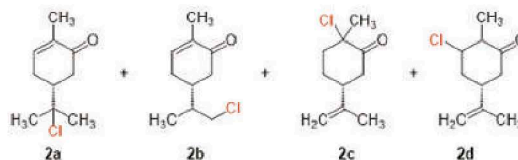

Figure 4. ^{13}C NMR signal assignment for carvone*HCl (**2a**).

It must be noted that the number of the different carbon types extracted from the NMR spectra alone, leads solely to the Markovnikov product **2a** (see table 1).

Table 1. Number of chemically distinct carbons in possible hydrochlorination products **2a-d**.

Carbon type	2a	2b	2c	2d
Cq	3	2	3	2
CH$_3$	3	2	2	2
CH$_2$	2	3	4	3
CH	2	3	1	3

CONCLUSIONS

In this experiment it was demonstrated how to utilize ^{13}C and DEPT NMR spectroscopy for determining which of the regioisomer products **2a-d** was obtained from the hydrochlorination of (R)-(−)-Carvone (**1**) with acetyl chloride in ethanol. By logical conclusion, the correct isomer **2a** was unambiguously characterized and all observed carbon resonances were assigned to its molecular structure.

REFERENCES

[1]J. Clayden, N. Greeves, S. Warren and P. Wothers, Organic Chemisry, 2nd edition, Oxford University Press Inc., New York, **2012**, p. 434.
[2]V. K. Yadav, K. G. Babu, *Eur. J. Org. Chem.* **2005**, 425−456.
[3]M. W. Pelter, N. W. Walker, *J. Chem. Educ.* **2012**, *89*, 1183−1185.
[4]Riegel, S. D.; Leskowitz, G. L. *TrAC*, **2016**, *83A*, 27-38; http://www.nanalysis.com/nmready-blog/2015/11/19/dept-a-tool-for-13c-peak-assignments (accessed December 2018).
[5]H. Friebolin, Ein- Und zweidimensionale NMR-Spektroskopie, 5th edition, Wiley-VCH Verlag GmbH, Weinheim, **2013**, p. 233.

DATA ACCESSIBILITY

The data can be processed directly on the NMReady-60 and printed and/or exported directly to a USB or networked file where it can be worked up using third party NMR processing software.

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