# Isomer Selectivity in the Cyclization of Pseudoionone

nanalysis

INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy helps to answer a magnitude of analytical queries. As an inherently quantitative method, qNMR is becoming an increasingly accepted alternative to other quantitative methods like liquid chromatography (HPLC). It is renowned for its structural elucidation capabilities, being sensitive to the electronic surroundings of each active nucleus in the analyte mixture, giving rise to much more connectivity information than any other method. Also, the data acquisition is fast and does not require calibration. Because of this, NMR spectroscopy has emerged as one of the most important analytical methods in organic chemistry. Benchtop NMR instruments help to address the accessibility to this powerful technique, making it the ideal tool for industrial applications and academic teaching.

BACKGROUND

Ionone (**2**) can be generated by cyclization of pseudoionone (**1**), which is commercially available but can also be synthesized via aldol condensation in one step from acetone and citral.[1,2] The cyclization reaction converts **1** into a mixture of α- (**2a**) and β-ionone (**2b**, **Scheme 1**). The different number of conjugated double bonds and the carbonyl function in α- and β-ionone make them distinguishable and detectable via UV–Vis and IR spectroscopy, which were primarily employed for investigating these isomer mixtures in some literature reports, as well as with isomer ratio determination via refractive index.[2-5] In contrast, NMR spectroscopy provides a lot of structural information making it a very powerful analytical technique for distinguishing isomers with similar physical properties.
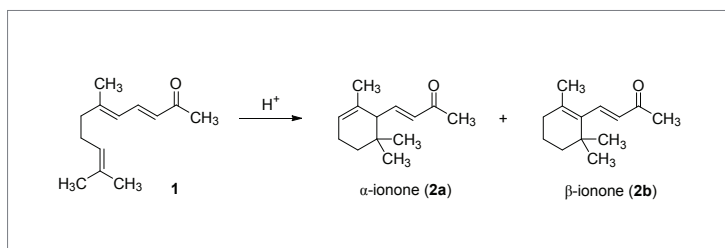
Scheme 1. Cyclization of pseudoionone (1) to α- and β-ionone (2a and 2b).[2]

While both isomers find application in the perfume industry for their odors,[6] β-ionone is an important precursor in the pharmaceutical, cosmetics, and personal care industry, such as for the synthesis of vitamin A (retinol, **Scheme 2**).[7,8] An isomer selective synthesis is, hence, highly desirable.
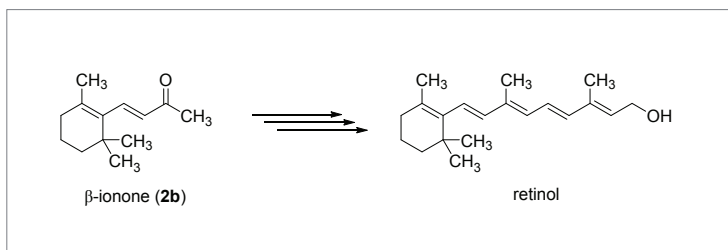
Scheme 2. β-Ionone (2b) is an important precursor in the retinol synthesis.

Generally, it is known that weak acids like phosphoric acid give product mixtures with a higher α-ionone ratio, whereas strong acids like sulfuric acid lead to higher β-ionone ratios.[5,9] A more systematic approach investigating the influence of the acidic reagent was published by Royals *et al.*,[4] who investigated the yield and selectivity of the cyclization reaction by optimizing the acid reagent system (**Table 1**).

Table 1. Impact of the acidic reagent on the ionone isomer ratio in the cyclization reaction.[4]

#	Acidic Reagent	Time[a] [min.]	Temperature[a] [°C]	Overall Yield	α/β-Ionone Ratio[b]
1	100 g 100% H_3PO_4	10	20	41%	39/61
2	100 g 94% H_3PO_4	25	25	71%	74/26
3	150 g 85% H_3PO_4	25	30	60%	77/23
4	60 g H_2SO_4 (conc.)	5	25	34%	13/87
5	100 g 75% H_2SO_4	25	25	67%	21/79
6	100 g 60% H_2SO_4	60	20	29%	95/5
7	70 g H_2SO_4 (conc.), 30 g glacial acetic acid	20	25	72%	10/90
8	50 g H_2SO_4 (conc.), 50 g glacial acetic acid	30	25	69%	38/62

[a] 20 g pseudoionone was added dropwise to the vigorously stirred reagent at 5-15° C over 15-30 minutes. The mixture was then stirred for the time and at the temperature indicated. [b]Calculated from refractive index.

The ratio of the isomeric mixture can be adjusted by the choice of the employed acid. Phosphoric acid (85%) leads to the highest ratio of isomer **2a** (α/β 77/23, **Table 1** entry 3), whereas the employment of concentrated sulfuric acid mixed with glacial acetic acid (70/30 % w/w) favors the generation of isomer **2b** (α/β 10/90 entry 7).

Interestingly, while dilution of the reagents with water for both phosphoric and sulfuric acid results in a decrease of the β-ionone formation (**Table 1** entry 1-6), small additions of glacial acetic acid to concentrated sulfuric acid can optimize the β-ionone ratio (**Table 1** entry 7) but for stronger dilution it decreases again (**Table 1** entry 8).

Despite the fact that cyclization of pseudoionone has been investigated for more than a century,[10] the kinetics and detailed reaction mechanism providing an explanation for why stronger acids (*i.e.*, sulfuric acid) favor the generation of β-ionone and weak acids (*i.e.*, phosphoric acid) lead to product mixtures with a higher α-ionone ratio are still not fully resolved.[7]
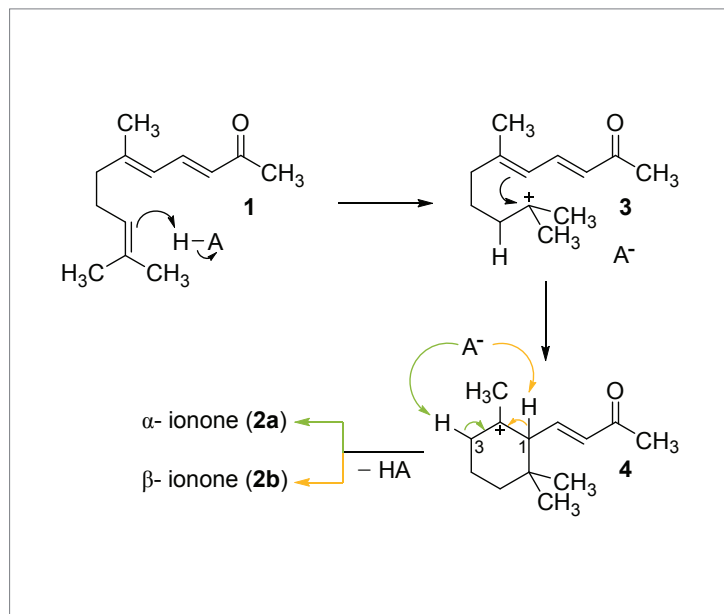
Scheme 3. Simplified reaction mechanism of the cyclization.[2,7]

In general, as depicted in **Scheme 3**,[2,7] pseudoionone (**1**) is protonated by the acid HA generating the stabilized tertiary carbocation **3**. Subsequent 6-*endo*-trig cyclization forms the six-membered ring species **4**. Finally, deprotonation at the 3- or 1- position generates α- (**2a**) and β-ionone (**2b**), respectively. Again, empirical investigations show that the latter is facilitated by employing undiluted (strong) acids.

EXPERIMENTAL PROCEDURE

Pseudoionone, phosphoric acid (85%), sulfuric acid (95-98%), and glacial acetic acid were used as received from Sigma Aldrich.

a) α-Ionone (**2a**)

Based on a literature method,[3] pseudoionone (**1**, 2.0 g, 10 mmol, 13 wt% resp. acid) was added dropwise to a stirring solution of phosphoric acid (85%, 15 g) at room temperature. After stirring for 1 h, the reaction mixture was slowly poured into cold water (20 mL). The resulting solution was extracted with diethyl ether (3x10 mL) and the combined organic layers were washed with water until neutral pH and dried over $MgSO_4$. The solvent was reduced under vacuum to yield the crude product mixture of α- (**2a**) and β-ionone (**2b**) in an isomer ratio of α/β = 79/21. Please note that in the original literature a steam distillation of the crude product was mentioned, which was herein not performed.

b) β-Ionone (2b)

Based on a different literature method,[2] a 70/30 (% w/w) sulfuric acid/glacial acetic acid solution was prepared by slowly adding concentrated H_2SO_4 (2.55 mL, 4.67 g) to glacial acetic acid (1.95 mL, 2.05 g) at 0° C. Pseudoionone (1, 1.4 g, 7.3 mmol, 20 wt% resp. acid) was added dropwise to this solution while stirring at the same temperature. After the addition of the substrate, the mixture was stirred at room temperature for 20 minutes. Cold water (30 mL) and diethyl ether (10 mL) were carefully added to the product mixture, the organic layer was separated, and the aqueous layer was extracted with additional diethyl ether (10 mL). The combined organic layers were washed with an aqueous solution (2x15 mL) of $NaHCO_3$ (5% w/v) and NaCl (10% w/v). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield β-ionone (2b) without a detectable impurity of 2a.
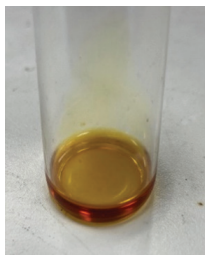
RESULTS AND DISCUSSION

The cyclization reaction of pseudoionone (1) was performed with two different acidic reagents and the obtained products were analyzed via benchtop NMR.

In the 60 MHz ^{1}H NMR spectrum of the product mixture from the reaction with phosphoric acid (85%) the signals of the two isomers can unambiguously be differentiated by the signals in the olefinic region (**Figure 1**).
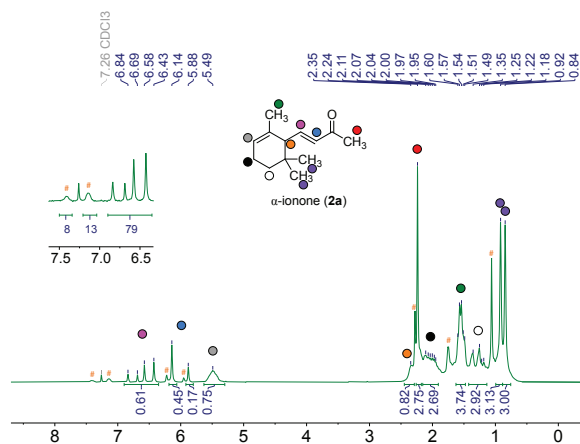

Figure 1. ^{1}H NMR (60 MHz) spectrum of the product mixture from the reaction with H_3PO_4 (85%) primarily leading to α-ionone. The signals of β-ionone (2b) are indicated with #.

In contrast to the β-isomer counting two, α-ionone (2a) counts three olefinic hydrogen atoms. Interestingly, the α/β ratio of 79/21 as calculated by the respective integration areas is in good agreement with the literature[4] (compare **Table 1** entry 3).

The signals of the α,β-unsaturated ketone fraction including the vicinal alkene hydrogen atoms (pink and blue circles) appear as a doublet of doublets and a doublet at 6.63 and 6.01 ppm, respectively, and sharing a large coupling constant of $^3J_{HH}$ = 15.8 Hz. The signal of the olefinic CH of the cyclohexene fraction (grey circle) appears as a broad resonance centered at 5.49 ppm.

By consulting the ^{1}H NMR spectrum of β-ionone (2b, **Figure 2**), the corresponding signals in the mixture can be assigned to the respective

isomer despite the convolution of the signals. It is noteworthy that the geminal methyl groups (purple circles) do not appear as a doublet but as two singlets at 0.92 and 0.84 ppm, respectively. The difference in the chemical shift can be attributed to the different through-space interaction between the CH group (orange circle) and the C_4-fragment.

Royals *et al.*[4] reported an α/β isomer ratio of 90/10 for the 70/30 (% w/w) sulfuric acid/acetic acid reagent system as determined via refraction index measurements (compare **Table 1**, entry 7). Interestingly, in the 60 MHz ^{1}H NMR spectrum (**Figure 2**) of the product mixture from the same reaction prepared herein, the signals corresponding to ionone 2a are not observed, which suggests a selective formation of β-ionone (2b). In the olefinic region, the two alkene hydrogen atoms share a large coupling constant of $^3J_{HH}$ = 16.4 Hz similar to the one observed for isomer 2a. For the hydrogen atom in β-position to the ketone (pink circle), only one ^3J-coupling is present due to the absence of a neighbouring CH group. However, a $^5J_{HH}$ = 0.9 Hz coupling, despite not being fully resolved at 60 MHz, can be observed and assigned to the coupling along the conjugated double bonds with the CH_3 group (green circle). Furthermore, the absence of this CH group results in the sp^3 hybridization of this carbon atom. Because of this, the geminal methyl groups (purple circle) now collapse to one singlet at 1.06 ppm as their spatial surrounding and electronic environment are nearly identical.
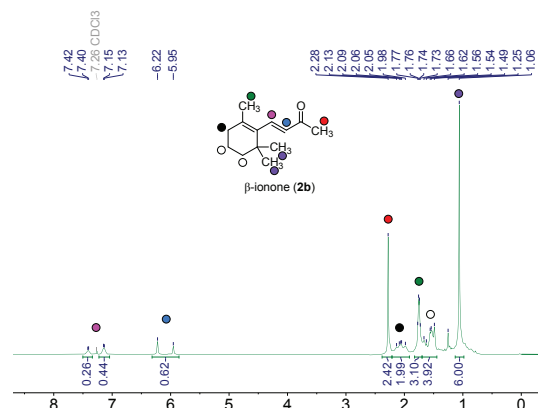

Figure 2. ^{1}H NMR (60 MHz) spectrum of the product mixture from the reaction with H_2SO_4/glacial acetic acid (70/30 % w/w) leading to β-ionone (2b).

CONCLUSION

In summary, two cyclization reactions starting from pseudoionone were performed. Dependent on the acidic reagent used, different selectivity for the generation of α- and β-ionone were obtained. The product mixtures were analyzed using benchtop NMR. The isomer ratio of both reaction products was obtained, and the spectra were fully assigned to the molecular structures. By employing benchtop NMR, the information about the qualitative and quantitative presence of the isomers is directly available from the 1D ^{1}H NMR spectra as α- and β-ionone can be distinguished via 60 MHz benchtop NMR.

References

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