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Laboratory Experiment

Conversion of Adipic Acid to Bis-2-ethylhexyl Adipate Overcoming Equilibrium Constraints: A Laboratory Experiment

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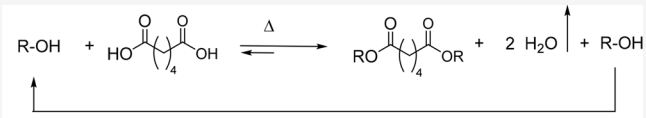
ABSTRACT: An adipic acid esterification experiment suitable for graduate students has been developed to describe the industrial manufacture of plasticizers. Students first follow the progress of the reaction with simple acid/base titration enabling measurement of the acid number. During the workup of the reaction mixture, they learn how to manage the filtration of a viscous mixture over an inert support such as Celite and practice on atmospheric and vacuum distillations. They finally learn to set a mass balance on 2-ethylhexanol using fully experimental data from their own reactions. To this end, they also learn how to retrieve from a ^{1}H NMR spectrum the required data to evaluate the purity and the yield of bis-2-ethylhexyl adipate. These tasks corroborate basic concepts related to the tools available to shift the equilibrium in reversible reactions, at the same time providing new knowledge on mass balance calculations and ^{1}H NMR.



KEYWORDS: *Graduate Education/Research, Laboratory Instruction, Hands-On Learning/Manipulatives, Industrial Chemistry, Plasticizers, Esterification*

■ INTRODUCTION

Recently, new alternative plasticizers have been launched on the market to overcome restrictions imposed on bis-2-ethylhexyl phthalate (DEHP), one of the major phthalates used worldwide. Indeed, DEHP has been listed as a substance of very high concern in the REACH legislation[1] as a consequence of demonstrated reproductive toxicity and endocrine disrupting effects on humans. Moreover, some voluntary deselection by brands has followed regulations issued by government agencies.

Therefore, various alternative non-phthalate plasticizers are increasingly used as replacements.[2] Adipic acid esters exhibit lower viscosities than phthalates and other plasticizers and are also used as plasticizers, mainly in food contact applications.[3] This behavior has been ascribed to their linear structure favoring an increased flexibility of the material at low temperature.[4] They are usually prepared by a standard esterification protocol employing a huge excess of alcohol or removing water in order to shift the equilibrium toward the desired ester. Bis-2-ethylhexyl adipate (**3**), one of the most commonly used adipates, has also been recently prepared with a biocatalytic route[5] under vacuum in order to remove water produced by the esterification or with acidic ionic liquid catalysis.[6]

The master's degree program in industrial chemistry at Università degli Studi di Milano includes a practical session to carry out the synthesis of industrially relevant compounds. Under this program, the industrial synthesis of adipate **3** (Scheme 1) was chosen to be adapted to facilities commonly available in an academic laboratory.

The program of the same practical session encompasses also the synthesis of adipic acid (**1**) through the green hydrogen peroxide oxidation of cyclohexene[7] and 2-ethylhexanol (**2**) through sodium borohydride reduction of 2-ethylhexanal under phase transfer catalysis conditions.[8] Therefore, careful planning allows students to use both reagents prepared in previous experiments for the adipate **3** synthesis in a circular economy perspective. In addition, the costs of the whole program and wastes produced could also be reduced.

The laboratory activity was anticipated by a 1 h class covering the description of all details of the experiment as well as the fundamentals of the industrial synthesis and increasing concerns due to the release of plasticizers in the environment. During the last two decades, the experiment has been conducted each academic year individually by 40−55 students in two 4 h consecutive laboratory sessions.

The experiment might also be useful as an advanced undergraduate level lab since the esterification reaction is a subject of basic organic chemistry courses.

■ OVERCOMING THE EQUILIBRIUM: THE EXPERIMENT

The carboxylic acid esterification is an equilibrium reaction typically performed by heating under acidic conditions and using a large excess of alcohol. This general procedure requires a

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Scheme 1. Adipic Acid (1) Esterification with 2-Ethylhexanol (2)

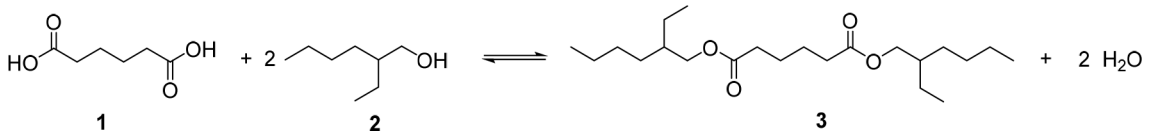

Figure 1. (left) Multiple reaction setup. (right) Alcohol/aqueous interface.

final basic workup, producing aqueous wastes, to remove the acid before separating the excess alcohol from the product. Following an alternative approach, the azeotropic removal of water can be performed through the addition of an inert solvent.[9] This method brings the drawback of requiring the additional solvent distillation step.

In order to shorten the procedure and to foster the knowledge of the principles of green chemistry,[10] a solventless route (principle 5, benign solvent and auxiliaries) was chosen. A trap to remove water generated during the reaction, at the same time recycling the coevaporated, water immiscible, 2-ethylhexanol, was used to shift the reaction equilibrium toward the desired adipate product, providing the highest conversion of both reagents. Indeed, following Le Chatelier's principle, under such conditions the equilibrium will continuously be shifted, thus producing more adipate until consumption of the reagents.

Experiment Overview

Briefly, the reaction flask was charged with adipic acid (**1**) and 2-ethylhexanol (**2**) (1.5 equiv) and heated at reflux with an infrared hot plate. A single stirring hot plate could be used to heat at reflux three different reaction mixtures, thus enabling the reduction of costs for the laboratory equipment (Figure 1, left).

However, similar results, although at slightly longer reaction times, related to the longer time needed to take the reaction mixture to reflux, have been obtained by using standard heating mantles instead of the infrared hot plate.

From an atom economy (principle 2, atom economy) and industrial standpoint, it is crucial to reduce the amount of excess alcohol. Therefore, only a slight excess of 2-ethylhexanol (**2**) was employed in this experiment. Students were required to set a mass balance calculation in order to determine the amount of alcohol **2** losses during the entire procedure. This additional point to address reinforces the theoretical basis about the mass balance in industrial processes with a practical live example built with personal data gathered during the experiment.

The initially heterogeneous mixture became homogeneous and started to boil in less than 10 min, and vapors were condensed with a reflux condenser. The condensate was collected into a receiving capillary tube where water and 2-ethylhexanol formed two different layers. The upper alcohol layer could thus be continuously recycled to the reaction flask, whereas the water generated from the esterification accumulated in the lower layer and could thus be removed from the reaction environment (Figure 1, right). In order to reduce reaction times, a known amount of water was added in the capillary tube before the start of the experiment. Therefore, the alcohol started to be recycled just after a few minutes following the beginning of condensation of vapors in the reflux condenser and liquid dripping in the capillary tube. Thus, students could visualize *in vivo* the progress of the equilibrium reaction. During the experiment they were asked to calculate the expected amount of water to be generated at complete conversion. The multiple reaction setup was shown to be helpful in stimulating the students' discussion and collaboration. Moreover, they remained actively involved in accurate checking of the level of the aqueous/alcohol interface in the capillary tube to avoid water recycling in case the water level reached the returning point of the tube (Figure 1, right). In such a case they opened the stopcock to drain some water.

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The formation of the adipic acid monoester is known to occur quickly due to the inherent acidity of adipic acid, with adipic acid itself acting as a Brønsted acid catalyst. The mixture was stirred at reflux for 90 min before the progress of the reaction was checked by taking a sample to follow the adipic acid consumption and measuring the first acid number (AN_1).[11] Although potentiometric (ASTM D664-95, reapproved 2001) and thermometric acid number (ASTM D8045) methods are known, students measured the residual acidity by simply adding with a buret a 0.1 M NaOH solution to a sample dissolved in aqueous/ethanolic solvent in the presence of phenolphthalein as an indicator.[12] At this stage AN_1 mean values of around 15−20 were usually obtained, corresponding to adipic acid conversion in the range of 90%.

Then, a catalytic amount of titanium tetrabutoxide (**5**) (2 drops, ≈0.02 g) was added to promote the highest conversion to the desired adipate **3**.[13] The Lewis acid **5** counteracts the decreasing reaction rate by activating the carboxylic acid reaction with 2-ethylhexanol (**2**), thus enabling equilibrium to be reached faster.

The catalyst **5** is derived from titanium, one of the most abundant and safe transition metals on Earth.[14] The heating of the reaction mixture was continued for another 60−90 min depending on how much time students had left before the end of the day 1 session. The reaction mixture was left at room temperature overnight, and the second session started the next day with a second AN measurement (AN_2, mean values 2−8) which usually confirmed an almost complete (99−95%) conversion.[15] It is worth noting that, when the same reaction was carried out with a standard reflux condenser instead of the previously described trap, the AN_2 value was found to be 55 with a conversion of 63% only.[16] The reaction mixture was then filtered over Celite to remove any titanium byproducts,[17] and the filter cake was washed with dichloromethane (DCM) to recover any adsorbed product. The resulting mixture was then subjected to atmospheric distillation to recover DCM, followed by vacuum distillation to recover the excess 2-ethylhexanol (**2**).

The laboratory is equipped with a vacuum network providing 2−3 mmHg at each bench site; therefore, it was considered unpractical and time-consuming to distill the adipate **3** due to its high boiling point.[18] However, ^{1}H NMR recorded on the distillation residue usually exhibits clean signals of the adipate **3** only. A third AN (AN_3) of the final product was recorded on the distillation residue. Although AN_3 might in principle be higher than AN_2 (the concentration of unreacted adipic acid is expected to be higher after excess **2** is distilled off), the same was found to be lower in 80% of cases. This result can be clearly ascribed to conditions during Celite filtration of the crude reaction mixture (quality of the filter cake prepared, temperature, yield of adipate **3** formed affecting residual adipic acid solubility, duration of filtration) favoring the removal of some unreacted adipic acid. On the other hand, an increased AN_3 was observed in the other 20% of cases.

DCM was chosen in order to save time in the evaporation step, taking advantage of its low boiling point. Although it might be replaced by greener solvents such as higher boiling ethyl acetate or 2-methyltetrahydrofuran, no hazard was caused by the use of DCM since the distillation was carried out at atmospheric pressure under the fume hood and no DCM vapors might be lost in the environment. On the other hand, the recovered DCM was pure and might be recycled for other uses.

2-Ethylhexanol Mass Balance

The mass balance equation (eq 1) enables determination of the amount of 2-ethylhexanol (**2**) losses (A_{losses}) during the entire experimental procedure.

$$A_{losses} = A_{in} - A_{reacted} - A_{dist} - A_{NMR} \quad (1)$$

On one hand, the initial amount of **2** (A_{in}) and the excess **2** recovered by vacuum distillation (A_{dist}) are both readily available as experimental data. On the other hand, the exact amount of **2** reacted ($A_{reacted}$) to form the desired adipate **3** can only be determined by carefully inspecting the ^{1}H NMR spectrum of the distillation residue. Indeed, the ^{1}H NMR spectrum can show if any alcohol **2**, derived by a imperfect distillation, was still present (A_{NMR}) together with the adipate **3**. If this is the case, it is also possible to determine the amount of alcohol **2** present (A_{NMR}) along with the adipate **3** and correct the yield of the latter in order to determine the reacted alcohol ($A_{reacted}$).[19] Common A_{losses} values resulted in the range of 10−60% in weight of the amount of excess alcohol used.

■ HAZARDS

All experiments were carried out under a well-ventilated hood. Safety measures for students included wearing lab coats, goggles, and gloves. Adipic acid cause serious eye damage, and 2-ethylhexanol may cause skin or respiratory irritation and serious eye irritation and be harmful if inhaled.

Deuterochloroform is harmful if swallowed; the vapor might cause serious eye, respiratory, and skin irritation, and it is a possible carcinogen. Dichloromethane causes skin irritation and serious eye irritation, may cause drowsiness or dizziness, and is suspected of causing cancer.

NaOH is corrosive to metals and causes severe skin burns, eye damage, and respiratory irritation. Detailed information regarding the safety hazards of all chemicals used in this experiment should be obtained from safety data sheets (SDS).

■ LEARNING OBJECTIVES

The experiment can be used as a tool to enhance students' understanding of reversible reactions and to improve their laboratory skills through an unusual method to follow the progress of the reaction in organic chemistry experiments, product isolation, and characterization.

Students learned how to personally convert the raw data (free induction decay, FID) recorded on the NMR instrument by others into the final spectrum. They also learned how to use ^{1}H NMR to ascertain the structure of the desired product, look for impurities, and determine the molar ratio of different compounds in a mixture.[20]

Students learned how to use the acid number method to evaluate the acidity of various mixtures as usually occurs in many industrial fields such as petroleum or vegetable oil analysis. Examples of alternative uses of the acid number were given in the introductory class.

The AN_2−AN_3 comparison could raise in students the awareness of the need to critically evaluate all experimental results to deeply understand the course of the reactions.

The mass balance model of the breakdown of 2-ethylhexanol during the experiment provided the occasion to become familiar with important calculations in the industrial field.

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■ ASSESSMENT

The students wrote and submitted the laboratory report within 2 weeks after the end of the entire practical session including this experiment. The report was required to include the description of the detailed experimental procedure along with all experimental data and reagent hazards as taken from their SDS. Students were also asked to give possible explanations about the amount of alcohol losses as resulted by their own mass balance.

Nearly all students (80%) could include in their report a correct mass balance and gave reasonable explanations about 2-ethylhexanol losses. These are mainly due to some **2** left in the trap and adherent to internal walls of the reflux condenser. Many students (70%) could drive the distillation procedure to completion and had no sign of 2-ethylhexanol (**2**) in their ^{1}H NMR spectra. Most of the others (95%) could determine correctly the residual amount of 2-ethylhexanol impurity in adipate **3** using ^{1}H NMR data.[21] All students could get a nice ^{1}H NMR spectrum from the received raw data.

Students rarely wrote comments about an AN_2-AN_3 comparison. They usually simply considered it reasonable to find $AN_3 < AN_2$ as a result of the purification procedure without mentioning that it is the result of partial adipic acid retention over Celite. They showed good skills in the titration procedure enabling them to get accurate results even using a low titrant volume.

The assessment was carried out using the submitted report during an oral interview. The average score was approximately 86%. In particular, the following issues were considered:

- use of the double arrow in the reaction scheme to describe the reversible reaction
- adipate purity
- quality of the ^{1}H NMR spectra and correct determination of 2-ethylhexanol residue in the final adipate
- inclusion of a correct 2-ethylhexanol mass balance
- presence or not of comments about acid number results

■ CONCLUSION

In summary, during this experiment students can generate and isolate in reasonably good yields (64% mean yield) bis-2-ethylhexyl adipate (**3**) by using a scalable procedure.

The adipic acid esterification is a good reaction to outline the principle of equilibrium reactions that is often underestimated by students who tend to write the esterification as an irreversible reaction (single arrow).

Different skills are developed to provide a deep understanding of the chemical reaction and the purification procedure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00951.

Notes for instructors (PDF, DOCX)
Students' handout (PDF, DOC)
^{1}H NMR spectra of pure adipate **3** and adipate **3** with trace amounts of 2-ethylhexanol (PDF, DOC)

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Notes

The author declares no competing financial interest.

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(16) The AN_1 was found to be 70 (conversion 52%).
(17) Titanium alkoxides hydrolysis leads to complex titanium compounds mixtures (see ref 13).
(18) The boiling point of 2-ethylhexyl adipate (**3**) is 190−200 °C at 1 Torr. Murai, K.; Akazome, G.; Tsujisaki, N.; Sakurai, M. Plasticizers

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(19) See the Supporting Information for details.
(20) See the Supporting Information for details.
(21) In most cases the amount of residual adipic acid does not affect the calculation and can be neglected.

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