

Scent Transmutation: A New Way To Teach on Chemical Equilibrium, Distillation, and Dynamic Combinatorial Chemistry

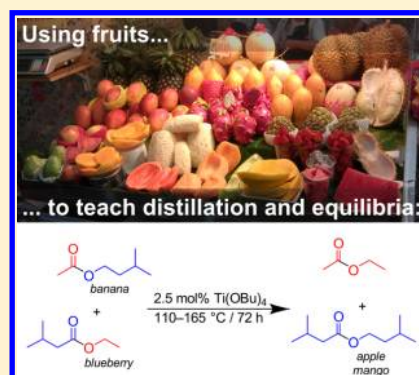
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S Supporting Information

ABSTRACT: Esters are volatile and pleasantly smelling compounds, commonly used as food additives. Using $\text{Ti}(\text{O}i\text{Bu})_4$ -catalyzed acyl exchange, we demonstrate a scent transmutation experiment, in which two fragrant esters swap their acyl and alkoxy substituents and are, during the course of a reactive distillation, quantitatively converted into two different esters with distinct fragrance properties. We view this simple and appealing experiment as highly suitable for instructional use, since it can be used to teach the concepts of chemical equilibrium, distillation, transesterification, dynamic combinatorial chemistry, and the industrially relevant process of reactive distillation.

KEYWORDS: Upper-Division Undergraduate, Chemical Engineering, Laboratory Instruction, Organic Chemistry, Physical Chemistry, Hands-On Learning/Manipulatives, Esters, Equilibrium, NMR Spectroscopy, Gas Chromatography



Chemical equilibrium is one of the key concepts in all of chemistry and is being taught in undergraduate curricula throughout the world. The behavior of equilibrated mixtures that are disturbed from equilibrium is governed by the well-known Le Châtelier's principle that "a system always kicks back",¹ that is, an equilibrium shifts to replenish the mixture components that were removed by the disturbing stimulus. Le Châtelier's principle is viewed as relatively intuitive; at the same time, its immense practical and industrial importance may not be fully appreciated by undergraduate students, as curricula spend little to no time establishing connections between basic physicochemical principles and industrial processes.

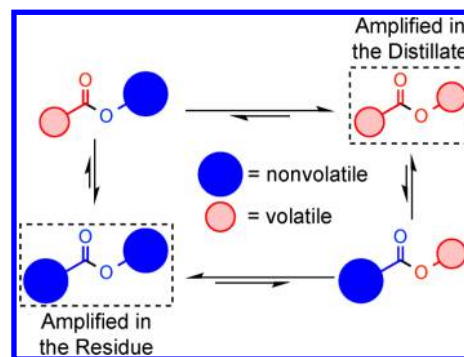
Our group has had a long-standing interest in *reactive distillation*, which is both a very direct application of the Le Châtelier's principle and a widely used process in chemical industry. In a reactive distillation, a chemical reactor doubles as a distillation setup, as the product is continuously being distilled away from the equilibrating reaction mixture. As the volatile product is being removed, the remainder of the mixture shuffles to replenish it, until the starting materials are completely exhausted and the pure product(s) are isolated in high yields. Reactive distillation yielded some of the chemical industry's biggest savings over the past three decades in terms of construction, energy, and raw material cost. Many compounds are industrially produced by reactive distillation, including esters, ethers, and some alkylated aromatic hydrocarbons.² Here, we present a series of reactive distillation experiments that illustrate this process using fragrant compounds. We view this simple and appealing set of experiments as highly instructive and think that they could easily be adapted to the undergraduate lab curriculum, where they could be utilized to

teach the concepts of chemical equilibrium, Le Châtelier's principle, and reactive distillation.

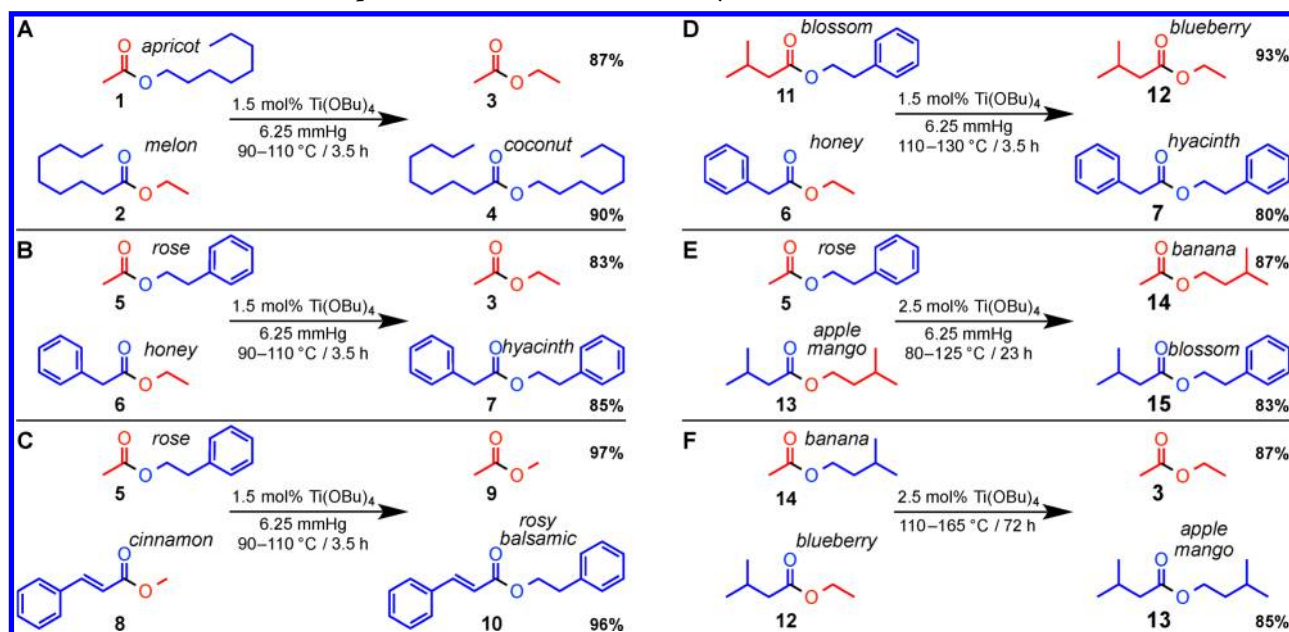
EXPERIMENTAL OVERVIEW

Consider a hypothetical library of four esters (Scheme 1), constructed by random transesterification of an equimolar mixture of two carboxylic acids and two alcohols. When this mixture is exposed to titanium(IV) butoxide catalyst, an acyl exchange,³ that is, the swapping of acyl and alkoxy substituents between the esters, will ensue. Because the acyl exchange reaction is reversible, the four esters will freely transfer material

Scheme 1. Ester Transmutation Transforms Two Moderate Volatility Esters into the Highly Volatile Ester That Is Distilled Away (Shown in Red) and the Low-Volatility Ester That Remains in the Distillation Residue (Shown in Blue)



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Scheme 2. Ester Transmutation Experiments Performed in this Study^a

^aOrganoleptic properties of selected compounds are given next to their structures.

among themselves, and a dynamic equilibrium will eventually be established. Such an equilibrating collection of esters is called a *dynamic combinatorial library* (DCL).⁴ Through the reversible acyl exchange, the DCL is capable of adapting to external stimuli by changing its composition. Subjecting a DCL to distillation, either at atmospheric or lowered pressure, removes the most volatile ester (shown in Scheme 1 as the red–red combination), typically formed from the alcohol and the carboxylic acid of lower molecular masses. As this volatile ester is removed, the remainder of the mixture reequilibrates to produce more of it, and this process continues until essentially all of the volatile alkoxy and the volatile acyl groups are removed as the distillate. At the same time, the distillation residue is vastly enriched in the least volatile compound (blue–blue combination), at the expense of the two esters of intermediate volatility. In essence, the most and the least volatile esters are amplified, while the crossover esters of moderate volatility are sacrificed. This process can be iteratively repeated in more complex libraries;^{5a} our group has shown^{5b} that ester libraries with as many as 16 members can be reduced in complexity to just four final products during the course of a reactive distillation. In related dynamic *imine* libraries, even greater simplification was possible:^{5c} a starting DCL with 25 imine constituents could be reduced to just five final products.

Perhaps an even more interesting case occurs if the distillation does not start with a four ester mixture, but instead uses the two “wrong” esters, that is, the two crossover red–blue combinations from Scheme 1, which have intermediate volatility. An outcome of a reactive distillation in this case is essentially an *ester transmutation* experiment, in which two moderate-volatility esters quantitatively give rise to two different compounds, a highly volatile and a nonvolatile ester, and the high yields of this reaction are driven by fractional vacuum distillation.

As many esters are pleasantly smelling (and essentially nontoxic) compounds⁶ and some are even approved as food additives by the US Food and Drug Administration (FDA),⁷ we envisioned that an ester transmutation experiment could also

proceed with a dramatic change in odors from the mixture of two starting esters to the two final products. Such an experiment would allow the change in the chemical composition to literally be smelled during the course of the reaction. To create such a *scent transmutation* experiment, all that was needed was a judicious choice of starting esters, so that they have easily identifiable aromas different from those of the product esters.

In this article, we describe the use of the $\text{Ti}(\text{OBu})_4$ -catalyzed transesterification in the synthesis of two ester products with different organoleptic properties from the two starting esters. We also demonstrate how the yields of the resulting products can be quantified by nuclear magnetic resonance (NMR) spectroscopy and gas chromatography (GC). This experiment illustrates several important experimental techniques and theoretical concepts: (a) fractional distillation, both at atmospheric and lowered pressure; (b) chemical equilibrium, exemplified by the $\text{Ti}(\text{OBu})_4$ -catalyzed ester exchange; (c) ester organoleptic properties; and (d) the use of internal standard methods to quantify product yields using NMR spectroscopy and GC. The experiments described here have been performed with an undergraduate researcher (N.S.E.) but have not been deployed in the regularly scheduled undergraduate laboratories. Nevertheless, we believe that they could be easily adopted for such use; in our view, this series of experiments would be particularly suitable for organic chemistry students in their third and fourth years, who have already been exposed to the theory of esterification reactions.

RESULTS

The six scent transmutation experiments shown in Scheme 2 have been standardized. All of them employ commercially available and FDA-approved ester starting materials. The first five experiments (Scheme 2A–E) were performed under a reduced pressure, which can be achieved using a small vacuum pump, such as those used for rotary evaporators. The last experiment (Scheme 2F) utilized atmospheric pressure, but this distillation took significantly longer to complete.

The very first experiment (Scheme 2A) will be used to illustrate the principles that guide all other reactive distillations presented here. The two starting esters were octyl acetate (1) and ethyl octanoate (2), with distinct aromas of apricot and melon, respectively. Equimolar amounts of these two esters were placed into a round-bottom distillation flask and exposed to 1.5 M % of $\text{Ti}(\text{OBu})_4$ as the catalyst. The mixture was placed under vacuum and heating commenced. We found that the progress of reactive distillation was better followed by monitoring the temperature of the external heating oil bath, rather than the temperature of the vapors (as would be the case in a standard distillation). If the oil bath temperature is kept between 90 and 110 °C, only ethyl acetate (3) will distill out of the reaction mixture. After the distillation of this material was complete (in approximately 3.5 h), the heating was stopped and the distillation setup was disassembled. Octyl octanoate (4) was the dominant component of the distillation residue.

The two product compounds could be qualitatively identified by their smell. Ethyl acetate has an aroma that some liken to pineapple or pears, but it is also so frequently used in everyday life that describing its aroma as “nail polish remover” is probably more accessible to the undergraduate student population. Octyl octanoate (4), in contrast, has a heavy odor of coconut and is clearly distinct from the two starting materials.⁸

Following the qualitative identification of distillation products, their yields were quantified by a combination of NMR spectroscopy and GC. NMR quantification was performed in chloroform-*d*, using 1,3,5-trimethoxybenzene as the internal standard (with two diagnostic singlets at δ 6.04 and 3.73 ppm). Known (i.e., weighed) amounts of the distillate and the distillation residue were placed into two separate NMR tubes and then known (but not necessarily identical) amounts of the internal standard were added into each NMR tube. The tubes were filled with chloroform-*d* and the corresponding spectra were taken. From the relative integrations of the peaks associated with the internal standard and those associated with each of the esters, molar amounts of each ester in the entire distillate (or distillation residue) could be readily calculated (see Supporting Information for further details). While both the distillate and the distillation residue consisted mostly of a single ester, these fractions also contained small amounts of other possible esters that could be quantified using NMR spectroscopy. If the multiple products present in the distillate or distillation residue differed in at least one peak in their NMR spectra, they could have been accurately quantified using NMR spectroscopy alone. As an example, the reaction shown in Scheme 2C resulted in a distillation residue which had diagnostic peaks at 7.67 ppm (doublet) and 3.82 ppm (singlet). While the former peak corresponded to a mixture of two possible cinnamates (8 and 10), the later was representative of only methyl cinnamate (8), and so the amount of pure 10 could have been deduced by subtracting the integral values of the two peaks. However, in cases where the overlap of the peaks was too extensive to permit full quantification, GC was used as the alternative quantification method.

Gas chromatographic quantification utilized dodecane as the internal standard. Since the relative integration in gas chromatography depends on the compound's identity, correlation factors had to be elucidated for each individual ester. Specifically, a known amount of dodecane was mixed with five different known amounts of each of the corresponding esters. These mixtures were then injected into the gas chromatograph

and the corresponding integrations of dodecane and the ester were compared to establish a correlation factor, which was averaged over five measurements at different concentrations (see Supporting Information for details). With gas chromatography, yields of esters could be determined even in cases where NMR spectroscopy proved problematic because of significant overlap among the peaks.

DISCUSSION

If this procedure were to be used as a basis of a future laboratory experiment, some common problems should be anticipated during its execution. None of them presents a safety risk or jeopardizes the learning outcomes, but we still offer here some advice on how to best handle such issues. The first common problem could be the low yield of the distillate, often coupled with a highly impure distillation residue. This issue would suggest that the reactive distillation did not proceed to completion. The remainder of the experiment can still proceed as planned: the distillate should have clear olfactory properties that should allow its identification, although the residue will present a mixture of three odors and its qualification may prove ambiguous. The quantification part of the experiment can proceed without any problems. In fact, running a shorter (and incomplete) reactive distillation may be a practical way to fit this experiment into a shorter time slots, in situations where, for example, class scheduling may present some restrictions. Another potential problem may be the occurrence of impure distillate and/or distillation residue. This would suggest that the distillation was too fast, removing not only the most volatile but also one (or both) of the “crossover” esters of intermediate volatility. The solution here is obvious: lower the temperature of the oil bath. However, while qualification of odors in this case is very likely to fail, quantification can still proceed without significant modifications to the procedure. Finally, it may be challenging for students, and even more experienced chemists, to accurately describe odors of individual esters.⁸

For the full separation during the course of reactive distillation, the experiments shown in Scheme 2A–D require 3.5 h, and those in Scheme 2E–F require more than 20 h. The last two experiments are significantly longer than the typical organic laboratory period in U.S. universities (~4 h). Thus, only the first four reactive distillations would be suitable for adaptation into hands-on experiments; the last two could be performed in the form of demonstrations, if needed.

SAFETY CONSIDERATIONS

As with all distillations, care should be exercised to avoid distilling the mixture to dryness. Vacuum distillations present an inherent risk of glassware implosion, which could cause cuts, burns, and other injuries. Appropriate vacuum-rated glassware should be used and carefully inspected for cracks before each use. All organic solvents and ester starting materials used in this work are highly flammable. Chloroform-*d* is toxic and anticipated to be a human carcinogen. Tetrahydrofuran is toxic as well. $\text{Ti}(\text{OBu})_4$ causes severe skin burns and eye damage. Dodecane is fatal if swallowed and enters airways.

The ester compounds utilized in this experiment are inhalation hazards if used in very high concentrations. However, all of the utilized esters are FDA approved⁷ as food additives, precisely on account of their pleasant aromatic properties. Therefore, inhaling small amounts of these materials should pose no health risks. The recommended way of

assessing the organoleptic properties of individual esters is to (a) put a drop of an ester sample onto a strip of filter paper, (b) shake the strip (so that most of the ester evaporates), and then (c) hold the strip briefly to one's nose, similar to the way perfumes are sampled in department stores.

Hot glassware must be handled with care. Personal protective equipment—including safety goggles, lab coats, and gloves—should be worn at all times and experiments carried out in the fume hood to avoid any exposure to hazardous compounds.

CONCLUSION

In summary, the scent transmutation protocol presented in this article constitutes a simple way to simultaneously teach students about several experimental techniques and fundamental concepts. First, it teaches how to perform vacuum distillation, a skill that many incoming graduate students in Chemistry Ph.D. programs appear to lack. Second, it demonstrates the pleasant olfactory properties of many esters and highlights the fact that these are used in the flavoring of foods. From a fundamental perspective, this procedure reinforces the concepts of equilibrium, Le Châtelier's principle, and the law of mass action. Additionally, it demonstrates how these principles can yield dynamic combinatorial libraries capable of adapting to external pressures through changes in their chemical composition. Finally, we hope that the industrially relevant process of reactive distillation will now be more familiar to undergraduate students and hopefully encourage them to look for further connections between the principles they learn in classrooms and industrial processes that yield products that surround them.

ASSOCIATED CONTENT

Supporting Information

List of reagents and equipment; instructor's notes, including pre-lab quizzes and detailed experimental data; student handout, which includes detailed procedures for reactive distillation and product quantification experiments. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(8) It may be useful to provide the reader with cursory instructions on how to use appropriate terms to describe odor. For example, “balsamic” is a term best suited for heavy and sweet odors: cocoa, vanilla, or cinnamon. “Floral” or “flowery” is the generic term for odors of various flowers; and “fruity” is the generic term for various fruits. In reactions presented in Scheme 2A and 2F, identification of scent transmutation products should not be too challenging, as all odors are associated with fruits, and each of the four components is quite distinct from the others. In reactions presented in Scheme 2B–E, the two starting materials should be easily discriminated; the distillate of each reaction is also very distinguishable from the two starting materials. For instance, the distillate of reaction shown in Scheme 2B is ethyl acetate (3), with a light fruity odor. In contrast, ethyl phenylacetate (6) brings a honey-balsamic odor that is very strong, while the odor of phenylethyl acetate (5) is reminiscent of a fine rose. The inconvenience resides in the odor difference between the product phenylethyl phenylacetate (7) and its two starting materials. This product has a very heavy sweet odor that can be described as rose or hyacinth, but also a distinctive honey note that can overlap with either 5 or 6. Although it is not insuperable to identify them, the reader should bear in mind the scent change is not only dependent on terminology of the odor but also relies on the threshold concentration of the target compound (defined as the lowest concentration at which a chemical compound can be distinguished with certainty from a blank under standard conditions). Similar ambiguity may be encountered in identifying the products of reactions shown in Scheme 2C–E.