Self-Sorting of Dynamic Imine Libraries during Distillation**

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Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 65th birthday

Nature and chemists approach organic synthesis in very different ways. Living systems are grand masters of parallel synthesis: starting with incredibly complex precursor mixtures, highly specialized enzymes operate selectively, simultaneously, and orthogonally to create many different products at once. In contrast, laboratory synthesis typically relies on reagents and catalysts with broad scope and wide functional-group tolerance; in this case, high-purity starting materials are required for the sequential preparation of individual products. Furthermore, undesirable reactivity often has to be blocked by protecting groups. In recent years, self-sorting has emerged as a promising preparative method that can enable the simultaneous synthesis of high-purity products from complex mixtures of starting materials. Self-sorting can be defined as the spontaneous reorganization of a disordered multicomponent system into a set of subsystems with fewer components and greater order. In the absence of specific enzyme catalysis, high fidelity of synthetic self-sorting is ensured by efficient error-correction mechanisms, which use the reversible formation of noncovalent and dynamic covalent bonds to continuously recycle side products as the system heads towards equilibrium. Self-sorting processes can proceed under thermodynamic or kinetic control. The former processes are characterized by a self-sorted equilibrium state; the latter are less common and are typically observed when a system is trapped in a self-sorted local energetic minimum. We recently reported a hybrid self-sorting protocol in which components of a dynamic imine mixture freely equilibrate (thermodynamic control), and sort on the basis of the rates of their removal from equilibrium through an irreversible reaction (kinetic control).

The synthetic applicability of self-sorting is frequently limited by the fact that all self-sorted species remain in the same solution. The isolation of individual components requires separation, which can be problematic in the case of fragile supramolecular complexes. Herein, we demonstrate that the self-sorting of dynamic mixtures can occur concurrently with separation to produce multiple products that are not only of high purity, but also mechanically separated. Specifically, we show that vacuum distillation can be used to sort complex libraries of \( \{\pi \times n\} \) equilibrating imines (\( n \leq 5 \)) into \( n \) pure compounds simply on the basis of the volatility of individual imines.

Imines are formed in a reversible reaction of an aldehyde with an amine. When multiple imines are present in a solution, they readily exchange their aldehyde and amine constituents. In any such equilibrating mixture, one imine has the lowest boiling point. If that compound can be distilled away selectively, its removal disturbs the equilibrium of the system and thus forces other imines to reequilibrate and produce more of the compound just removed—as dictated by the Le Châtelier principle. Provided that distillation is sufficiently selective and slower than the imine exchange, the low-boiling imine will extract its constituent aldehyde and amine from all other imines that contained them. In the process, the low-boiling imine is produced in superior yield, and the remaining equilibrating mixture is reduced in complexity through the removal of both the low-boiling imine and all its precursors. If such a sequence is repeated, multiple species can be produced with a single distillation setup.

We assessed the synthetic viability of this proposition in an experiment which examined the behavior of a mixture prepared from two aromatic aldehydes \( 1 \) and \( 2 \) and two anilines \( A \) and \( B \) (Scheme 1). To ensure that the resulting imines had significantly different boiling points, we chose aldehydes and anilines of different molecular masses and assumed that a higher mass would lead to a higher boiling point. The heating of these four reactants under dehydrative conditions produced a mixture of all possible imines: \( 1A, 1B, 2A, \) and \( 2B \). The most volatile of the four was \( 1A \)—the product of the reaction of the lighter aldehyde with the lighter amine; conversely, the least volatile imine was the product \( 2B \) of the heavy–heavy combination. Vacuum distillation (90–115°C, 0.10 mmHg) of this mixture began with the selective removal of low-boiling \( 1A \). With the depletion of \( 1A \) and \( 2A \) and \( 2B \) started decomposing to produce more of \( 1A \); eventually, these two compounds were completely consumed in the process, and the only imine remaining in the distillation flask was \( 2B \). Compounds \( 1A \) (most volatile, light distillation fraction) and \( 2B \) (least volatile, heavy distillation fraction) were isolated in virtually quantitative yield (96 and 98%, respectively) and in very high purities, as evidenced by \(^1H\) NMR spectroscopy (98 and 99%, respectively; see the Supporting Information for details). Three additional higher-boiling \( [2 \times 2] \) combinations (see the Supporting Infor-
Information) were subjected to similar distillation conditions with analogous results: the high-yielding production of the most volatile and least volatile fractions, with virtually no evidence of “crossed” products.

These encouraging results suggested to us that a more complex mixture could be sorted in an analogous manner during a distillation. A [3 × 3] imine mixture (Scheme 2) was created from aldehydes 1–3 and anilines A–C. The most volatile of the nine imines formed was 1A—the combination of the lightest aldehyde and the lightest aniline. Its preferential removal from the mixture by distillation (110–120°C, 0.10 mmHg) caused the decomposition of its precursors 2A, 3A, 1B, and 1C. Once all of 1A had been distilled off (90% yield, 98% purity), five imines—1A, 2A, 3A, 1B, and 1C—had been removed from the mixture. In essence, the selective distillation of 1A extracted the most volatile aldehyde 1 and the most volatile aniline A out of all other imines that contained them. Of the four imines that remained (2B, 3B, 2C, and 3C), compound 2B was the next most volatile. An increased distillation temperature (150°C, 0.10 mmHg) enabled its isolation in very high yield (94%, 100% purity) with the concurrent elimination of 3B and 2C from the equilibrium mixture. Ultimately, the only compound remaining in the distillation flask was the least volatile imine 3C, which was isolated in 99% yield (89% purity). Two additional [3 × 3] experiments were performed (see the Supporting Information).

Next, we examined a [4 × 4] mixture (Scheme 3) produced from aldehydes 2–5 and anilines B–E. 1H NMR spectroscopy revealed the presence of at least 12 imines; overlapping peaks probably obscured the presence of an even larger number of species. According to the logic of the [2 × 2] and [3 × 3] experiments, the distillation of this mixture produced, in this order, 2B (88%), 3C (91%), 4D (77%), and 5E (85%). A
second [4 × 4] experiment is described in the Supporting Information.

In our most complex experiment, we constructed a [5 × 5] library of presumably 25 imines (Scheme 4; the exact number of imines could not be confirmed by 1H NMR spectroscopy because of overlapping peaks) from aldehydes 1–5 and anilines A–E. Again, imine 1A was distilled first (77% yield, 96% purity as determined by NMR spectroscopy); in the process, imines 2A, 3A, 4A, 5A, and 1B–E were all eliminated from the equilibrium mixture. The second step of the distillation saw the isolation of 2B (80% yield, 96% purity) at the expense of 3B, 4B, 5B, and 2C–E. Imine 3C was isolated third (80% yield, 99% purity), with the removal of 4C, 5C, 3D, and 3E. In the final step of the distillation, imine 4D (73% yield, 99% purity) was formed and distilled at the expense of 5D and 4E. The residue in the distillation flask was identified as 5E (80% yield, 83% purity). Effectively, one reaction enabled us to access five compounds simultaneously, all in yields greater than 70%.!

Figure 1 illustrates the typical purities of products obtained from the distillative self-sorting of an exemplary [4 × 4] mixture (discussed in Scheme 3): four isolated fractions are essentially pure compounds, as evidenced by the segments of their 1H NMR spectra in the bottom panel of Figure 1. As could be expected, the final distillation residue (lowest spectrum, compound 5E) is the least pure fraction.

In this hybrid self-sorting protocol, both kinetic and thermodynamic factors play a role in the outcome of self-sorting. Although evaporation rates determine which imines will be isolated as the exclusive products, the underlying thermodynamic equilibrium is required to maximize the yields of these products. In that respect, this distillative self-sorting is conceptually similar to our recently reported self-sorting of an imine mixture through an irreversible oxidation.[7] The chief difference is that the method used to irreversibly disturb the equilibrium and initiate a self-sorting sequence: in the current study, a physical transformation (evaporation) is used, whereas we used a chemical stimulus (oxidation) in our previous study. Taken together, these results suggest that hybrid self-sorting should be very broadly applicable.

The success of this self-sorting method sounds a cautionary note about the use of separation techniques in the analysis of dynamic combinatorial libraries (DCLs). Distillation is clearly able to profoundly affect the composition of a
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[10] Imine mixtures were preformed in toluene at reflux. Water removal (with a Dean–Stark trap) is critical, because it prevents the hydrolysis of imines into an aniline and an aldehyde—both of which would be more volatile than the corresponding imine. After dehydration, the only dynamic reaction is imine exchange.
Imine distillation should be understood conditionally. Virtually all imines investigated in this study are solids. Upon heating, they melt and then evaporate, and solidify at various points along the distillation apparatus, from where they can be extracted by careful scratching and washing. See the Supporting Information for details.

In all distillation experiments, the major impurities were other imines—typically the “crossed” light–heavy combinations; no NMR spectroscopic evidence of other side products was found. Purity was thus estimated by comparing the integral of the \( \text{N} = \text{C} - \text{H} \) peak of the desired imine to the sum of the integrals of the corresponding peak for all other imines.

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