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Highly Efficient and Robust Enantioselective Liquid–Liquid Extraction of 1,2-Amino Alcohols utilizing VAPOL- and VANOL-based Phosphoric Acid Hosts

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The large-scale production of enantiopure compounds in a cost-effective and environmentally friendly manner remains one of the major challenges of modern-day chemistry. The resolution of racemates through enantioselective liquid–liquid extraction was developed as a suitable solution but has remained largely underused, owing to a lack of highly efficient and robust chiral hosts to mediate the process. This paucity of hosts can in part be attributed to a poor understanding of the underlying principles behind these processes hindering the design of more efficient selectors. A previously untested class

of hosts, VAPOL and VANOL derived phosphoric acids, has been studied in depth for the efficient enantioselective liquid–liquid extraction of 1,2-amino alcohols. A systematic investigation of extraction parameters was conducted, revealing many key interactions and DFT calculations illustrate the binding modes for the 1:1 complexes that are involved in chiral recognition. The resulting, now-optimized, procedures are highly robust and easy to implement. They are also easily scalable, as demonstrated by U-tube experiments.

Introduction

One of the major challenges of modern-day chemistry is to obtain enantiopure compounds on large scale for the agrochemical, pharmaceutical, fine chemical, or fragrance and flavor industries.^[1] Whereas some chiral compounds can be obtained by agriculture or fermentation,^[2] large-scale production by synthetic or separatory routes has proven more efficient in yielding the amounts and, more importantly, the variety needed.^[3] Although the synthetic route has provided much in terms of variety, it often struggles somewhat in providing the required amounts in a cost-efficient manner.^[4] Alternatively, the separation of racemates offers far better scalability and cost efficiency but suffers from lower versatility and technical issues such as problems with solids handling in the case of resolution by crystallization.^[5] Attempts at expanding the versatility of separatory techniques have been made but have encountered similar cost-effectiveness issues.^[6] Enantioselective liquid–liquid extraction (ELLE) was investigated as an alternative method combining cost-efficiency, simplicity of handling, scalability, and versatility. Based on the early work of Cram on chiral rec-

ognition,^[7] multiple reports have demonstrated its potential in all of these categories.^[6c, 8] Relying on continuous selective transport by a host of preferentially one of the enantiomers of a racemate from one phase to another, an ELLE process can be operated by using a series of mixing separation devices working in a countercurrent flow. Since hosts and solvents can be continuously recycled, this is potentially a highly economical and environmentally friendly system. Currently, the main drawback of this method, which, to our knowledge, prevents it from being industrially applicable, is a lack of highly enantioselective and robust chiral hosts (operational selectivity $\alpha_{op} > 1.5$).^[1a, 9, 10] Known host categories,^[7, 10, 11] (crown ethers, amino acid derivatives, BINOL derivatives, Cu, Ln, Zn, Co, Ru complexes, tartrates, quinines, or guanidinium derivatives) function, with isolated exceptions, only at a proof of concept level. This can in part be attributed to a poor understanding of the underlying principles behind these processes hindering the design of more efficient selectors. The field of ELLE has therefore stagnated in recent years, with only a few new results appearing, such studies by the groups of Schuur^[12] and Tang,^[13] who have expanded upon these systems. Therefore, achieving a deeper understanding of the chemical principles and physical properties behind this technique is vital if new, more selective hosts are to be developed for the ELLE of a wider range of compounds. Our recent work on highly selective SPINOL-based phosphoric acid hosts demonstrated the efficiency of this approach.^[14] However, in view of their lengthy synthesis, these SPINOL-based hosts are not readily available. Therefore, in an attempt to further expand the scope of ELLE and deepen our understanding of the mechanism of action of chiral phosphoric acids towards this process, we turned our attention to more

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Figure 1. Phosphoric acid hosts used for enantioselective liquid–liquid extraction.

readily available backbones, such as VAPOL and VANOL (Figure 1).

Since their discovery in 1993,^[15] both VAPOL and VANOL have served as highly efficient organocatalysts, owing to their unique vaulted structure.^[16] Their synthesis on multigram scale has been well described,^[17] VAPOL and VANOL phosphoric acids (**PA1** and **PA2**) have the significant advantage of being readily available and are therefore easily applicable in ELLE on both laboratory and industrial scale.

Principles of enantioselective liquid–liquid extraction

To better understand the fundamentals of ELLE and therefore the reach of this manuscript, we will give here a short description of the methodology used and an explanation of the meaning of the units employed. ELLE employs the principles of asymmetric host–guest interaction chemistry in combination with extraction or transport over multiple phases. A typical ELLE system contains two immiscible liquid phases, where one phase is composed of a solution of a racemic guest and the other holds a solution of the chiral host. As described by the groups of Lehn^[20] and Cram,^[7] enantioselective extraction occurs through chiral recognition between the host and one enantiomer of the guest, resulting in the formation of a single diastereomeric complex that is soluble only in the host phase. This results in phase separation of the two guest enantiomers, inducing an enantiomeric excess, opposite in sign, in both phases. A subsequent back extraction in a third phase, usually employing the same solvent as for the feeding phase, allows for liberation of the bound enantiomer and regeneration of the host, allowing for the setup of a continuous flow system.

The efficiency of this process is usually described by three different parameters, the enantiomeric excess of one of the two phases (*ee*, herein the aqueous phase), the distribution (*D*), and the operational selectivity (α_{op}). The distribution *D* is the ratio between the concentration of one of the enantiomeric guests in the organic host phase and its concentration in the aqueous phase [Eq. (1)]. The operational selectivity α_{op} is defined as the ratio between the distributions of the two enantiomers [Eq. (2)] and thus gives a quantitative evaluation of the overall efficiency of the process. Although the *ee* can give a first impression of the value of a given extraction, it is α_{op} that really determines the usefulness. One of the main advantages of an ELLE is that full resolution of each enantiomer can be ob-

tained with only a relatively small α_{op} by employing a multi-stage extraction system.^[10,14] The number of sequential countercurrent extractions required to achieve full resolution determines the viability of the system. From a practical point of view, it is commonly accepted that an α_{op} of 1.5,^[10] representing 25 stages, is the minimal threshold for a system to be viable. The relationship between the operational selectivity and the minimal number of fractional stages needed to obtain a given level of resolution is described by the Fenske equation [Eq. (3)], as depicted in Figure 2 for *ee* = 99%. A decrease in

Figure 2. Relationship between number of stages and α_{op} according to Equation (3) for *ee* = 99%. Reproduced from Ref. [10] with permission from the Royal Society of Chemistry.

the number of stages with an increase of α_{op} is clearly visible, leading to an ideal, seldom reached, situation at $\alpha_{op} \geq 7$ where a further decrease in stages becomes minimal.

$$D_i = \frac{[i]_{org}}{[i]_{aq}} \quad (i = R, S) \quad (1)$$

$$\alpha_{op} = \frac{D_R}{D_S} \quad (2)$$

$$N_{min} = \frac{\ln \left(\frac{x_R/(1-x_R)}{x_S/(1-x_S)} \right)}{\ln \alpha_{op}} \quad (3)$$

Results and Discussion

We began our investigations by screening a wide range of chiral guests to determine which classes could be extracted in an enantioselective manner with these hosts. Overall, high selectivities towards 1,2-amino alcohols were observed, whereas amino acids or amines were extracted as racemates. (S)-VANOL **PA2** extracted phenylalaninol **7** with 8% *ee* and a good α_{op} of 1.5, whereas (S)-VAPOL **PA1** extracted linear 1,2-amino alcohols **9**, **12** and **15** with 10, 11, and 5% *ee* and α_{op} values of 1.3, 1.9, and 1.6, respectively (Scheme 1). *Para*-substituted 1,2-amino alcohols **18** and **21** could be extracted with similar selectivities to the unsubstituted **9**, whereas no selectivity was achieved in

Scheme 1. ELLE screening of chiral substrate classes with (S)-VAPOL PA1 and (S)-VANOL PA2. Conditions: 2 mM guest solution (H₂O, pH 5 phosphate buffer) vs. 1 mM host solution (CHCl₃), 6 °C. Determination of the ee, distribution, and α_{op} was by reverse-phase HPLC of aqueous-phase aliquots.

the extractions of *O*-methyl phenylglycinol **19** and *N*-isopropyl phenylglycinol **20** with either host. These findings underline the importance of the presence of both the free amine and free alcohol moieties of the guest. The best results were obtained with cyclic 1,2-amino alcohols. Indeed, when a racemic mixture of *trans*-1-amino-2-indanol (**8**) dissolved in a pH 5 phosphate buffer solution was placed in contact with a chloroform solution containing PA1 and left to stir at 6 °C until equilibrium was reached, (1*S*,2*S*)-*trans*-1-amino-2-indanol [(*S*)-**8**] was extracted preferentially with an impressive ee of 37% and α_{op} of 7.2. The use of PA2 resulted in 12% ee and a α_{op} of 1.8 under the same conditions. In the case of *cis*-1-amino-2-indanol (**8'**), good selectivity was also obtained (8% ee, α_{op} = 1.3) with PA1. In all cases, the (*S*)-enantiomer of the host preferentially extracted the (*S*)-enantiomer of the amino alcohol.

This level of selectivity has, to our knowledge, never been achieved before with cyclic 1,2-amino alcohols. To the synthetic chemist, the selectivities reported herein may initially appear relatively low. They are actually highly interesting as the use of multistage countercurrent extraction enables the full separation of the racemate based on these values. We have already demonstrated this possibility in the past with a different host-guest couple using a cascade of six centrifugal contactor separators in series and another one for the back extraction of the product.^[18]

Encouraged by these results we studied the effect of the extraction parameters, as temperature, solvent, and pH are known to have marked effects on the efficiency of the process. Starting with temperature, we measured the selectivity of the ELLE of **8** over a 2–90 °C range.^[20] Although an optimum was observed at 2 °C for (*S*)-VAPOL PA1, yielding impressively high selectivities with 38% ee and an α_{op} of 7.3, the process proved surprisingly robust towards changes in temperature with ee values remaining stable over the 2–40 °C range (38–36% ee; Scheme 2a) and only dropping significantly above this point (25% ee at 60 °C). When the solvent was switched to trichlorotoluene, which is a less efficient solvent for the extraction but which allowed us to probe a wider temperature range, the ee dropped by only 4% when heating from 6 °C to 90 °C (16% and 12% ee, respectively). With PA2, we found a similar robustness, with ee values remaining stable over the 2–40 °C range. Operational selectivities also dropped less than expected (Scheme 2b), from 7.3 at 2 °C to 1.8 at 60 °C (2.7 at 40 °C) when using PA1, and dropping slightly from 1.8 at 6 °C to 1.2 at 40 °C when using PA2. This high temperature stability allows some design flexibility when adapting this ELLE process to large-scale mixing separation devices, which could potentially be run at room temperature while retaining good α_{op} (6.3 at 18 °C), thereby avoiding the need for cooling and its inherent cost.

We then turned our attention to the pH dependency of the ELLE of **8** (Scheme 3). Both hosts showed similar behaviors with an optimal pH of around 5. Selectivities dropped significantly at more acidic or basic pH. Interestingly, in the case of PA1, the operational selectivity of the extraction proved remarkably stable in a ± 0.5 pH unit window centered around pH 5, which is unusual for such a system^[21] (Scheme 3a). Such

Scheme 2. Temperature screening for the ELLE of **8** with **PA1** and **PA2**. Conditions: 2 mM guest solution (H_2O , pH 5 phosphate buffer) vs. 1 mM host solution, 16 h. Determination of the *ee*, distribution, and α_{op} by reverse-phase HPLC of aqueous phase aliquots.

behavior renders the system more robust towards small local variations in pH. It should be noted that although α_{op} remains stable at around pH 5, the distributions vary greatly (Scheme 3c) as the pH varies probably because of a combination of variations in complex stability and solubility.

The effect of the host phase solvent was next studied (Scheme 4). Chloroform proved optimal for both hosts in terms of *ee* and α_{op} ; other haloalkane-based solvents resulted in lower selectivities, whereas aromatic solvents, both halogenated and not, gave relatively unfavorable results.^[22]

With optimal conditions in hand, we next investigated the scalability of the process. In addition to a good distribution and operational selectivity, the ability to dynamically recover the guest from the host is of vital importance. To measure this, we employed a U-tube (Figure 3), based on a modified design by Cram,^[18a,21] which is a good procedure to establish the capability of the host to release the enriched guest into a receiving phase. In addition, it will demonstrate that the host can selectively transport the desired enantiomer in a catalytic fashion between the feeding and receiving phase with multiple turnovers. A blank extraction, run at pH 5 for 24 hours in the absence of host, showed that no background leaching of guest from the feeding to the receiving phase occurred, indicating that all observed extraction would be due to transport by the

Scheme 3. pH screening for the ELLE of **8** with **PA1** and **PA2**. Conditions: 2 mM guest solution (H_2O , phosphate buffer) vs. 1 mM host solution (CHCl_3), 6°C , 16 h. Determination of the *ee*, distribution, and α_{op} by reverse-phase HPLC of aqueous phase aliquots.

host. When a U-Tube extractor composed of a 20 mM feeding phase and a 0.5 mM host solution was run, an *ee* of 41% could be observed after 10 minutes in the receiving phase, which remained stable over one hour. As the feeding phase became depleted in one enantiomer, the host increasingly transported the second enantiomer, resulting in a slow erosion of the *ee* of the receiving phase, reaching 30% after two hours and dropping to 14% after four. At the end of the run, 10 turnovers were reached. Overall these results clearly indicated that the enantioselective extraction process was catalytic and can

be scaled up. We have previously established that large-scale racemate separation can be performed highly efficiently in countercurrent flow by using a number of centrifugal mixing separation devices^[18,23] in series to enhance the *ee* at each step, according to the Fenske equation. The high α_{op} would allow such a process to be run with as few as 5 or 6 stages, with a final *ee* of up to 99% in the final stage, as we reported in the case of 3,5-dinitrobenzoyl-(*R,S*)-leucine.^[18]

To gain a better understanding of the origin of the remarkable selectivity in the extraction of *trans*-1-amino-2-indanol (**8**) by using VAPOL phosphoric acid (**PA1**), DFT energy minimizations were carried out. The geometries of **PA1**⊃(*S,S*)-**8** and **PA1**⊃(*R,R*)-**8** were optimized at the B3LYP/6-31G++(d,p) level of theory by using an IEFPCM CHCl₃ solvation model (Figure 4).^[18,24] The hydrogen-bond lengths in the structure

Figure 4. DFT energy-minimized structures [B3LYP/6-31G++(d,p)] for the diastereomeric complexes **PA1**⊃(*S,S*)-**8** (left) and **PA1**⊃(*R,R*)-**8**.

with (*S,S*)-**8** (N...O = 2.60 Å; O...O = 2.70 Å) are slightly shorter than those found in the structure with the (*R,R*)-enantiomer (N...O = 2.61 Å; O...O = 2.72 Å). Furthermore, where the (*S,S*)-guest nicely points outwards from the binding pocket offered by the phosphoric acid, there appears to be some steric repulsion between the (*R,R*)-guest and the phenanthrene moiety of the host. The Gibbs free energy calculated for **PA1**⊃(*S,S*)-**8** is 3.8 kJ mol^{−1} lower than for **PA1**⊃(*R,R*)-**8**, which is in line with experiment [that is, selective extraction of the (*S,S*)-enantiomer; see above]. This steric interaction is absent in the structures calculated for **PA2** (see the Supporting Information), which corroborates with the lower *ee* in the extraction experiments.

Conclusions

In summary, we have investigated the efficiency of VAPOL- and VANOL-based phosphoric acids as chiral hosts for the enantioselective liquid–liquid extraction of a range of 1,2-amino alcohols. These previously unexplored hosts proved to be good selectors for several 1,2-amino alcohols, offering a particularly cost-efficient process for their resolution, owing to the relatively easy synthetic availability of these phosphoric acids and the high selectivity reached. In particular, (*S*)-VANOL **PA2** allows for the resolution of phenylalaninol (**7**) whereas (*S*)-VAPOL **PA1** proved particularly efficient for the ELLE of *trans*-1-amino-2-indanol (**8**), yielding an *ee* of 37% and impressive operational selectivity of 7.2. DFT calculations have been used to elucidate the origin of the remarkable selectivity, showing clear preference for binding of one of the enantiomers. The extraction

Figure 3. U-Tube model reactor. Conditions: Host phase = **PA1** in chloroform (0.5 mM, 10 mL), feeding phase = **8** in H₂O (20.0 mM pH 5 phosphate buffer), receiving phase = aq. HCl (5 mL, pH 2), 6°C Determination of the *ee*, distribution, and α_{op} was by reverse-phase HPLC of aqueous phase aliquots.

process proved also to be highly robust, tolerating small variations in the optimal conditions with little or no impact on its efficiency. The U-tube experiments showed the catalytic nature of the extraction process, as well as the feasibility of an efficient back-extraction. In view of the high operational selectivity, this process could be easily scaled up by using as few as 5 or 6 stages.

Experimental Section

To a vial with a stirring bar, a solution of the racemic guest (0.4 mL, 2.0 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, indicated pH) was added to a solution of the host in CHCl₃ (0.4 mL, 1.0 mM). After capping the vial, the mixture was cooled to the indicated temperature and stirred at 900 rpm for 16 h. The phases were allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot was injected into a reverse-phase HPLC for determination of the *ee*, distribution, and α_{op} . All extraction experiments were carried out in triplicate and with a simultaneous blank reaction (concentration of host = 0.0 mM).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amino alcohols • chiral resolution • extraction • host–guest systems • phosphoric acids

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