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MINIREVIEW

n-Butanol: An Ecologically and Economically Viable Extraction Solvent for Isolating Polar Products from Aqueous Solutions

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Klaus Hafner in memoriam

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Abstract: Water is the solvent of choice in terms of greenness and sustainability. However, it can be difficult to isolate very polar products from water. Here, we discuss the use of *n*-butanol as a solvent to extract polar compounds from aqueous solution. *n*-Butanol produces high yields and can also be sourced sustainably from biomass, which makes it attractive from a climate perspective. The reason for its high efficiency is that the wet *n*-butanol phase is a nanomaterial that incorporates little pockets of water that can stabilize the polar solute. Thus, the environment remains very water-like, and the presence of hydrophobic groups can tip the equilibrium towards the *n*-butanol phase. We also discuss a simple estimate whether *n*-butanol will be an efficient extraction solvent for the compound of interest based on common public databases. This should help to guide practicing organic chemists during the solvent selection process.

1. Introduction

Meeting the ambitious climate goals is a global challenge that requires the replacement of chemical production processes based on fossil fuels by more sustainable green solutions. One particular focus in that regard has to be the choice of solvent, as it is usually one of the main contributors to the climate balance of a reaction.^[1] To address this challenge, the toolbox of practicing organic chemists not only includes a plethora of modern reagents and catalysts, but also a variety of techniques for isolating the desired products.^[2]

Water is the best solvent in terms of greenness and sustainability, but its use comes with several challenges, including the extraction of reaction products. In a standard procedure, the reaction is quenched with water followed by extraction using such solvents as ethyl acetate or ether in a separatory funnel. Quite often the extraction step needs to be repeated several times for raising the final yield, but nowadays this is ecologically and economically suboptimal. This assessment pertains irrespective of the nature of the reagent or man-made catalyst or enzyme. Early suggestions for maintaining environmentally sound procedures were made decades ago.^[3]

More recently, general rules for green procedures in organic chemistry have been issued, which also touch on the solvent choice.^[4] When the desired product is fairly soluble in water, efficient extraction constitutes an acute problem. Ethyl acetate or ethereal solvents such as diethyl ether or tetrahydrofuran are not ideal for extracting polar compounds, and halo-alkanes cannot be used for environmental reasons. Guidelines for choosing solvents on an acceptable ecological level have been proposed by several groups.^[4] Metrics and various guides have also been suggested by pharmaceutical researchers and process engineers, including solvent choice in enzyme-catalyzed transformations.^[4-5]

The present mini-review focuses on the use of *n*-butanol as a renewable biogenic extraction solvent for isolating polar products. Thus, emerging modern solvents like ionic liquids,^[6] or supercritical carbon dioxide^[7] are not treated here. The same applies to deep eutectic solvents, which are a new class of ionic liquids that constitute a mixture of different Lewis or Brønsted acids and bases.^[8] Historically, *n*-butanol has been used on a number of occasions as an extractant for very hydrophilic compounds such as acids, but this solvent seems to have fallen out of favor over time^[9] even though it leads to high yields and selectivity compared to other solvents.^[10] Recently, the Reetz group faced the problem of isolating a water-soluble compound produced in an enantioselective enzymatic transformation.^[11] In a one-step enzymatic cascade reaction transforming cyclohexane into chiral cyclohexane-1,2-diol, quantitative conversion was indicated by an analytical method, but upon performing three extraction steps with ethyl acetate, a poor yield was observed. We speculated that the product is too water-soluble. Fortunately, upon turning to *n*-butanol, an almost quantitative yield of cyclohexane-1,2-diol was obtained.^[11] Previously, *n*-butanol had been used only sporadically as an extraction solvent in organic chemistry,^[10, 12] which is surprising given its positive rating as a green solvent and its low toxicity and safety issues.^[5b, 5c, 5f, 13] Therefore, it seems worthwhile to point out several advantages of this solvent, including its sustainable production means and its unique nanostructure that makes it an excellent choice for the extraction of polar compounds.

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Following our very promising experience with *n*-butanol and discussions with Gerhard König, at that time member of the Theory Department of the Max-Planck Institute in Mülheim, a theoretical project was initiated which led to a recent publication.^[14] In this study we pointed out that one of the main challenges in finding a suitable green substitute for any solvent is to predict which alternative is best for a given compound. It was concluded that solvent selection guides should be supplemented by solubility data for a diverse set of molecules in the recommended solvents,^[14] in order to easily find the best solvent. When experimental solubility or distribution coefficient data are not available, modern computational chemistry methods can fill this gap with relatively high accuracy, particularly if quantum-mechanical (QM) calculations are used to further improve the accuracy of the predictions.^[15] The resulting relative solvent affinities can help to guide the choice of the practicing organic chemist.

2. *n*-Butanol as a Solvent

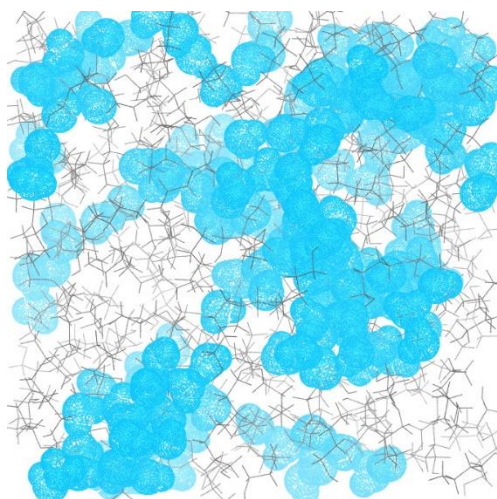


Figure 1. The wet *n*-butanol phase during extractions from water is an almost equimolar mixture of *n*-butanol and water. This snapshot from molecular dynamics simulations shows the inverted micelles of water (cyan mesh) inside of *n*-butanol (grey lines). These inverted micelles provide a very water-like environment for hydrophilic molecules.

2.1. The Structure of Wet *n*-Butanol

n-Butanol is the shortest linear alcohol that is able to form a separate phase when mixed with water at ambient conditions.^[16] It is therefore suitable for liquid-liquid extraction from water. However, due to the mutual solubility of *n*-butanol and water, the *n*-butanol phase during extraction is not pure, but saturated with water. This so-called wet *n*-butanol phase exhibits an almost equimolar mixture of the two components, with a mole fraction of water of 0.4883 at 25°C.^[17] Wet *n*-butanol therefore has different properties than pure *n*-butanol, and those differences are mostly governed by its nanostructure. The hydroxyl group of *n*-butanol can serve both as a hydrogen bond donor and acceptor, while the short aliphatic chain can create a more hydrophobic environment. The structure of pure *n*-butanol is characterised by cyclic and linear networks of the hydroxyl groups, where five or more *n*-

butanol molecules interact with each other.^[18] In wet *n*-butanol, the water molecules aggregate in inverted micelles (Figure 1), which provide small pockets of aqueous environment. The presence of inverted micelles is analogous to the ones that were observed in other alcohols, like *n*-octanol,^[19] but, due to the higher water content of wet *n*-butanol, its effect on the solubility of polar compounds is more pronounced.

Our computational study showed how molecules of different sizes and polarities interact with the wet *n*-butanol phase.^[14] While there is a small entropic penalty for transferring very polar molecules from the water phase to the restricted volume of the inverted micelles (with diameters of about 6 to 9.5 Å),^[14] the interactions with the aliphatic tail of *n*-butanol can oftentimes overcome those costs if the solute contains apolar groups. Out of the partition coefficients that were evaluated in the study, only water itself, methanol and the amino acid serine exhibited a higher affinity for water, while the rest of the molecules favoured the wet *n*-butanol phase.^[14] Examples of polar molecules that favour the wet *n*-butanol phase over aqueous solution are acetic acid, diethylamide, adenosine triphosphate, acetamide, cyclohexane-1,2-diol, as well as large organic compounds like progesterone derivatives.^[14, 20]

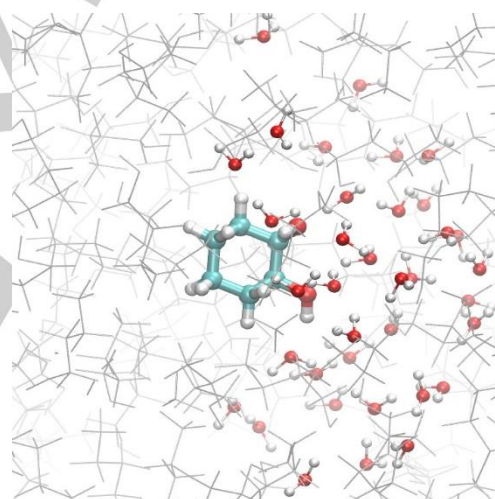


Figure 2. Stabilization of polar compounds in the wet *n*-butanol phase by interactions with water clusters. In this snapshot from a molecular dynamics simulation, the polar part of cyclohexane-1,2-diol (center) is solvated by a water cluster, while the less polar part interacts with *n*-butanol (grey lines). Thus, both polar and hydrophobic interactions can be maintained at the same time in the wet *n*-butanol phase.

Figure 2 shows a snapshot from a molecular dynamics (MD) simulation of cyclohexane-1,2-diol in the wet *n*-butanol phase. Here, the polar part of the solute interacts with an inverted micelle via hydrogen bonds, while the less polar aliphatic ring interacts with *n*-butanol via dispersion, thus forming both hydrophilic and hydrophobic interactions simultaneously. In addition, *n*-butanol itself can also form hydrogen bonds with the solute. This advantage can be used to extract a wide range of polar compounds with *n*-butanol. For more hydrophobic compounds it can be beneficial to employ *n*-octanol, which can also be sourced sustainably and has a lower water content. Therefore, *n*-octanol

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exhibits a different size distribution of its inverted micelles.^[14, 19a] Importantly, the nanostructure of wet alcohols can also be tuned with additives,^[21] which can be used to optimize the yield. Depending on the compound of interest, the pH of the aqueous solution can also play an important role for the efficiency of the extraction process.^[10, 12e] Finally, the nanostructure of *n*-butanol can also lead to an increased selectivity of the extraction process.^[10]

2.2. Bio-butanol as a Sustainable Solution for Extraction

One major advantage of *n*-butanol as a solvent is the possibility to produce it sustainably from biomass.^[22] The acetone–butanol–ethanol fermentation to produce *n*-butanol is actually one of the oldest biotechnological techniques and has been used on an industrial scale since World War I.^[23] In addition, major efforts have been invested in recent years to optimize the production of so-called bio-butanol as a green alternative to diesel for combustion engines. Bio-butanol can reduce the greenhouse gas emissions by 60% relative to diesel,^[24] and higher savings are possible if it is used as a solvent. Compared to the employment of *n*-butanol as a biofuel, which requires high purities of about 99%, the use as an extractant from water can tolerate much higher water contents, as the wet *n*-butanol phase will be saturated with water in any case. Therefore, distillation or high-level purification steps are not necessary for this application, which can lead to significant savings in terms of energy, costs, and ecological footprint.^[25] At the end-of-life, *n*-butanol is currently either released or incinerated for energy recovery,^[26] but with decreasing costs for the recovery step^[27] its recycling becomes a more viable option. Notably, an increased demand of *n*-butanol for the use as a solvent can also help to support the blossoming biofuel industry in its early stages.^[28]

2.3. Conditions that Make *n*-Butanol a Suitable Extractant

The best way to determine whether *n*-butanol is likely to be a suitable extractant for the molecule of interest from water is to estimate its distribution coefficient P_{buoh} according to Nernst's law.^[29] The distribution coefficient gives the ratio of the concentrations of the compound in the two phases at chemical equilibrium. The P_{buoh} value is larger than 1 if the concentration of the molecule is higher in the *n*-butanol phase than in aqueous solution. Thus, high P_{buoh} values correspond to high extraction yields. In order to reach a yield of at least 99% with one extraction step with equal volumes of water and wet *n*-butanol, the P_{buoh} value has to be higher than 99. To reach a 99% yield with two extraction steps requires a P_{buoh} value that is higher than 9. And for three extraction steps to yield more than 99% of the molecule of interest, the distribution coefficient has to be higher than 3.65. Taking the decadic logarithm of those distribution coefficients, a $\log P_{\text{buoh}}$ value of at least between 0.56 and 2 is required to reach a yield of 99% (depending on the extraction volume and the number of extraction steps, with continuous extraction requiring lower $\log P_{\text{buoh}}$ values to reach the desired yield).

Ideally, the $\log P_{\text{buoh}}$ values would be determined experimentally for a series of molecules and then collected in a database. But, so far, relatively few partitioning experiments have been conducted for *n*-butanol and water.^[20, 30] Alternatively, modern computer simulation techniques can be used to estimate the

$\log P_{\text{buoh}}$ based on the free energy of transfer between the two phases. In our computational study,^[14] we calculated the $\log P_{\text{buoh}}$ values of 15 different compounds. Experimental $\log P_{\text{buoh}}$ values were only available for six of these compounds, but the simulations reproduced the experimental values with a remarkably small mean error of 0.05. This included the blind prediction of the $\log P_{\text{buoh}}$ of cis-cyclohexane-1,2-diol, where the deviation between simulated and experimental values was only 0.02.

Other publications further support the appropriateness of our theoretical study.^[14] Kashefolgheta et al. tested the cross-solvation free energies of *n*-butanol with 24 other compounds, yielding errors below 1.2 kcal/mol in all cases with an analogous protocol.^[31] And different force fields for *n*-butanol were also tested by Cerar et al. based on experimental X-ray scattering data, where the simulations correctly reproduced the basic features of the peaks, exhibiting good qualitative agreement.^[18c] Liquid-liquid equilibria based on quantum-chemical calculations with COSMO-RS were also reported with errors of 0.24% relative to experimental data.^[32] COSMO-RS was also employed to select solvents for the extraction of food aromas.^[33] This indicates that computational methods can be a very useful tool for solvent selection. Notably, computer simulations offer the additional benefits that they can be easily automatized and hardly produce any waste as long as the required electricity can be sourced sustainably.

As a fast, preliminary test to see whether *n*-butanol might be a suitable solvent, it is also possible to extrapolate from $\log P$ data of similar solvents. The most common distribution coefficient in this regard is *n*-octanol/water (P_{ooh}), which is often used as a measure for solubility and membrane permeation in drug design.^[34] Determining the $\log P_{\text{ooh}}$ values is also a regulatory requirement for the registration of chemicals to assess their potential impact on the environment.^[35] Therefore, a wide range of experimental and estimated values of the $\log P$ of *n*-octanol/water can be found in public databases such as PubChem.^[36] Given the wealth of experimental reference data, the determination of $\log P_{\text{ooh}}$ values is also a suitable target for machine learning algorithms for cases where no experimental data is available.^[37] Thus, organic chemists can make use of the resources that were developed for drug design to guide their extraction solvent selection.

In our theoretical study,^[14] we proposed a linear relationship between the $\log P$ of *n*-butanol and that of *n*-octanol, as both solvents are linear chain alcohols that exhibit inverse micelles of water in their wet phase. Based on the 15 compounds from the theoretical study, $\log P_{\text{buoh}} \approx 0.69 \log P_{\text{ooh}} + 0.31$. Remarkably, this simple equation based on pure computation was recently confirmed in a study by Hanson et al. that included 173 experimental values.^[30] While the slopes of the two regressions are within the experimental standard deviations, the intercept of the experimental study is higher by a value of 0.22. However, this small difference could be explained by the presence of several outliers in the experimental $\log P_{\text{ooh}}$ data. We, therefore, consider the level of agreement between the theoretical prediction and experiment to be absolutely remarkable.

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3. Conclusions and Perspectives

Given the global challenge of climate change, it is the civic responsibility of every organic chemist to find greener solutions to address the needs of modern society. One particular challenge is the adequate choice of solvents, with water as the gold standard in terms of greenness. Unfortunately, traditional extraction solvents such as ethyl acetate cannot always be avoided for the extraction of organic products after an aqueous workup, which means that more research is necessary for reasons of sustainability. However, the situation is completely different when wanting to extract polar products from an aqueous medium. In such cases, ethyl acetate and other conventional solvents can indeed be avoided. As already reported in our experimental study,^[11] and emphasized here again, *n*-butanol appears to be well suited as an extraction solvent for isolating fairly water-

soluble products. This applies to enzyme-catalyzed transformations and to reactions induced by man-made reagents and catalysts as well. We hope that this mini-review will inspire organic chemists as well as protein engineers to consider *n*-butanol in future studies more so than in the past, fueled by the desire to achieve green chemistry.

Manfred T. Reetz is an organic chemist who pioneered, inter alia, the concept of directed evolution of stereo- and regioselective enzymes as ecologically and economically viable catalysts. He worked at several universities in Germany, USA and China, the longest stay being at the Max-Planck-Institut für Kohlenforschung in Mülheim 1991-2011, which he restructured with the establishment of five independent departments.



Gerhard König works in the area of computational chemistry and biophysics. He obtained his doctoral degree at the University of Vienna in 2010 under the guidance of Prof. Stefan Boresch. He then underwent postdoctoral training with Dr. Bernard R. Brooks at the NIH, Prof. Walter Thiel at the Max-Planck-Institut für Kohlenforschung, Prof. Darrin York at Rutgers University, and Prof. Sereina Riniker at ETH Zürich. Since 2020 he is a Senior Research Fellow at the Centre for Enzyme Innovation of the University of Portsmouth.



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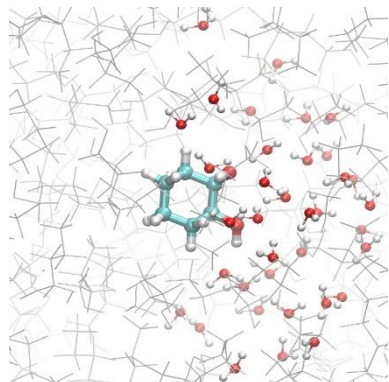
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Keywords: Sustainable chemical processes • Enzymatic reactions • Extraction solvent selection • Wet *n*-butanol

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Water is the green solvent of choice for many reactions, but it can be challenging to extract polar compounds from aqueous solution. This problem can often be addressed with *n*-butanol, which can be produced sustainably from biomass. The wet *n*-butanol phase is a nanomaterial where polar compounds can be accommodated in inverse micelles of water. Ways to determine *a priori* whether *n*-butanol is a suitable extractant are also discussed.

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