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Beyond Phase Equilibria: Selecting Suitable Solvent Systems for Reactive Extraction of Carboxylic Acids

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Keywords

reactive extraction, liquid–liquid extraction, carboxylic acids, solvent selection, process implementation

Abstract

Reactive extraction is an attractive separation technology that can replace energy-intensive water evaporation steps in the industrial production of carboxylic acids. We systematically review the current literature on the extraction of low-value bioproducts and thereby identify the reduced availability of predictive models, limited selectivity, and challenging phase separation as possible bottlenecks in the industrial implementation of reactive extraction. Furthermore, we discuss requirements and strategies for closing the material cycles for batch and continuous processes. With these challenges in mind, we analyze the most widely used extractants (trioctylamine, trioctylphosphine oxide, and tributyl phosphate) in combination with common diluents (e.g., long-chain alcohols and alkanes) in terms of their ability to meet process needs. We illustrate the subordinate role of equilibrium constants in overall process design while emphasizing the potential for flexible reactive extraction systems tailored to process requirements.

1. INTRODUCTION

Bio-based platform chemicals play a crucial role in the shift toward a circular economy (1). They can substitute for fossil fuel–based resources in the chemical industry as drop-in solutions or as novel materials (1–3). Furthermore, they have a better carbon footprint than their petrochemical counterparts (4). Nonetheless, economic process implementation is challenging (5); the market share of bio-based polymers from 2020 to 2023 was only 8% (2, 6). A primary impediment to the implementation of bio-based production processes for bulk chemicals is low profit margins (6). Due to high substrate costs in relation to low selling prices, high-yield fermentations and effective downstream processes are inevitable (7). Ideal substrates are cheaper than glucose and do not compete with the food industry (8). For purification, high recovery rates, low energy consumption, and minimal waste production in the overall process are valuable (9). By combining these factors, ethanol has become the most dominant representative of bio-based bulk chemicals, with a production capacity ranging from 79 million metric tons per annum (MMt/a) (10) to 102 MMt/a and a market price of US$0.74/kg in 2024 in Europe (see **https://www.chemanalyst.com**). The low boiling point of ethanol allows it to be purified by distillation with overhead product recovery (10), an established, scalable unit operation that is robust toward impurities resulting from the use of cheap complex substrates (11).

Amino acids also have large production volumes. A well-known example is L-glutamic acid, which has a production capacity of 2.9 MMt/a (10). Amino acids are purified by more complex unit operations, such as ion exchange (12). However, as stated by Ewing et al. (10), they are used predominantly for nutrition and animal feed and can be sold at higher market prices, above $2/kg (see **https://www.chemanalyst.com**), enabling a more extensive production process.

Carboxylic acids are another group of biotechnologically produced platform chemicals. Due to their functional groups, they offer a wide variety of applications, ranging from polymer manufacturing (13, 14) to acrylate, ester, vinylester, and ketone synthesis (15, 16). In comparison to ethanol production, the microbial conversion of glucose to carboxylic acids offers a more efficient substrate use, which in turn promises an economically feasible production process (10). However, because of their higher boiling points, carboxylic acids cannot be purified by distillation with overhead product recovery. Therefore, downstream processing accounts for much of the production cost (17, 18). Because the market price of carboxylic acids ranges from $0.90/kg to $2/kg (see **https://www.chemanalyst.com**), these high downstream processing costs can limit market entry; as a result, only a few carboxylic acids, such as citric, lactic, and itaconic acid, are produced in large quantities by bioconversion (19–21).

Well-established unit operations are used for purification. For example, in itaconic acid production, the target compound is produced at a low fermentation pH, concentrated by water evaporation, and subjected to multiple crystallization steps for purification (7, 21). However, large amounts of water need to be removed by evaporation prior to crystallization, increasing the energy demand and carbon footprint of the overall process (22, 23) and raising energy costs (7). For highly soluble acids such as citric and lactic acids (24), direct crystallization is not feasible (25). Therefore, they are commonly concentrated by precipitation with calcium salts and subsequent acidification with sulfuric acid (19, 20). This process option, however, results in equimolar amounts of calcium sulfate, which can pose a problem for disposal (26). The challenge of developing efficient production processes for carboxylic acids is mirrored in succinic acid production (17). Whereas in 2014 the manufacturers Myriant, BioAmber, Succinity, and Reverida were planning or operating succinic acid production plants with a total capacity of 64 kilotons per annum (kt/a) (27), none of them are active in 2024, as the process had difficulty competing with fossil fuel–based synthesis (5). Thus, in order to access the full potential of carboxylic acids, we must implement different, efficient downstream processing unit operations with a high recovery rate, low energy demand, a reduced carbon footprint, and limited waste production.

ISPR: in situ product removal

In the literature, liquid–liquid extraction is viewed as a promising energy-efficient separation step (5, 28). To efficiently capture and concentrate highly polar target compounds such as lactic acid, extractants like tertiary amines or phosphine oxides are added to the solvent phase (29). By complexation with the target compound, these extractants increase its solubility in the organic phase and can capture polar products from highly diluted solutions (24, 30). As a result, reactive extraction could replace evaporation or precipitation as the first capture step. Furthermore, the wide variety of extractants and diluents (31) theoretically offers the possibility of tailoring the extraction system to overall process needs, such as distribution coefficient and selectivity (31), phase separation (32), and biocompatibility (33). Additionally, reactive extraction can be used for in situ product removal (ISPR) (34–38). However, while reactive extraction is already the state of the art for metal purification (39), and some patents on reactive extraction of carboxylic acids are available (40, 41), commercial biotechnological processes using reactive extraction for the production of bulk chemicals are rare.

This review aims to systematically identify the bottlenecks in the industrial implementation of reactive extraction of carboxylic acids, using an extraction systems database. We provide a comprehensive overview of the target compounds, extractants, and diluents investigated in the literature and discuss their potential for industrial application. Furthermore, our classification of papers into research fields enables the identification of possible research gaps.

As physical extraction is already established in the chemical industry for the purification of small molecules such as butadiene and toluene (42, 43), we compare its principles and findings and, if suitable, transfer them to reactive extraction of carboxylic acids. Where applicable, we draw connections to reactive extraction in metal recycling, where the product price is much higher but the extraction mechanism and the physical properties of the systems are similar. This review aims to bridge the gap between academic research and industrial applications for reactive extraction of carboxylic acids and to identify relevant research fields.

2. LITERATURE SCREENING AND THE ROLE OF REACTIVE EXTRACTION IN RESEARCH

To represent the research landscape for physical and reactive extraction of low-value products between 1950 and 2024, we conducted a systematic literature screening on the topic "extraction" using Elsevier's online platform Scopus (see **https://www.scopus.com/search/form.uri?display=basic#basic**).

2.1. Database Creation

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To obtain a comprehensive overview of the extraction of bio-based platform chemicals with a focus on carboxylic acids, we performed multiple search queries. We then sorted the literature obtained from each search query by hand to eliminate off-topic results (see **Supplemental Appendix A.1**). We found a total of 431 suitable publications by using the following searches:

1. Title screening. We searched for "extraction" within publication titles to gain an overall impression of physical and reactive extraction of biomolecules ($n = 285$).
2. Platform chemical query. We searched for extraction of well-known platform chemicals such as lactic, acetic, succinic, and fumaric acids. This query reveals a bias regarding target compounds but provides more information on reactive extraction systems used for carboxylic acids ($n = 35$).

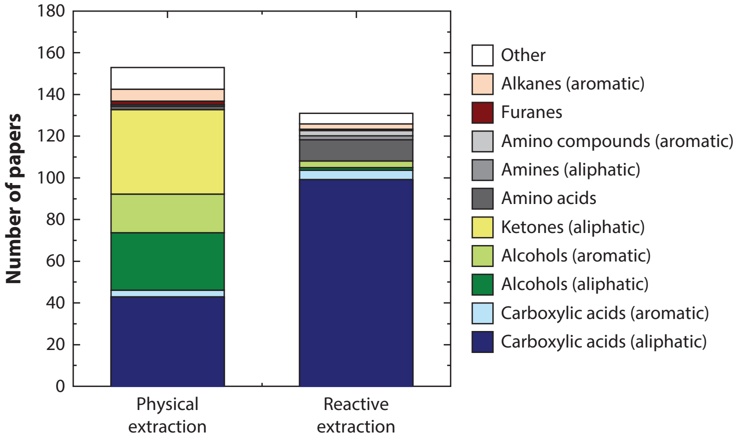

Figure 1

Literature between 1950 and 2024 on extraction of bio-based platform molecules. Data are from title screening (search for "extraction" in publication titles; *n* = 285).

3. Extraction of acids query. We searched for extraction and acids in general. Similar to the platform chemical query, this query shows a bias regarding target compound distribution but provides more information on extraction systems (*n* = 56).
4. Reactive extraction of acids query. We searched for reactive extraction and carboxylic acids. The results show a bias regarding target compound distribution and extraction mechanisms but also provide an impression of the use of reactive extraction systems for carboxylic acids (*n* = 55).

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For comprehensive information on the search queries, see **Supplemental Appendix A.1**. Below, we analyze the database with regard to the distribution of physical and reactive extraction in the literature, the target compounds used for data curation, the extraction systems applied, and their research focus. Depending on the analysis to be made, we employ different search queries. As most publications investigate several transfer components, extractants, and diluents, we normalized the number of mentions for one component or a component group to the number of publications (**Figure 1**) (**Supplemental Appendix A.2**).

2.2. Representation of Physical and Reactive Extraction in the Literature

We used title screening to obtain the distribution of publications on physical and reactive extraction and the representation of target compounds (**Figure 1**). Among the publications we identified as related to the extraction of bio-based platform chemicals, 53.9% are on physical extraction and 46.1% are on reactive extraction. These extraction systems differ depending on their target compound distribution. In physical extraction, primarily alcohols, ketones, and carboxylic acids are of interest (**Table 1**). As acetone and succinic acid are represented in the standard test systems for physical extraction to simplify standardized apparatus design and implementation (44), they contribute to a large share of the publications.

In contrast to the product spectrum in physical extraction, carboxylic acids make up 82.3% of all compounds investigated in reactive extraction. Among the carboxylic acids, lactic, acetic, propionic, citric, and succinic acids are the most frequently mentioned target compounds for reactive extraction (**Table 1**). The high representation of acetic acid in both physical and reactive extraction can be linked to its large market volume of 15 MMt/a (45) and its manufacturing via chemical

Table 1 The most frequently investigated target compounds for physical and reactive extraction

	Main production route (48)	Production rate in MMt/a^{a} (year)	Literature share (%)^{b}	$K_{D,octanol}$ (52)
Physical extraction				
Acetone	Chemical	8.8 (2022)	32.0	0.58
Acetic acid	Chemical	15 (2022)	18.3	0.68
Ethanol	Bio-based	102 (2022)	9.8	0.50
Phenol	Chemical	11 (2023)	7.2	28.84
Succinic acid	Chemical (51)	0.07 (2022)	6.5	0.26
Reactive extraction				
Lactic acid	Bio-based (20)	1.7 (2023)	13.7	0.19
Acetic acid	Chemical	15 (2022)	12.2	0.68
Propionic acid	Chemical	0.40 (2022)	12.2	2.14
Citric acid	Bio-based (19)	2.8 (2022)	10.7	0.76 (53)
Succinic acid	Chemical (51)	0.07 (2022)	6.1	0.26
Butyric acid	Chemical	0.22 (2022)	6.1	6.17

[a] Worldwide. MMt/a stands for million metric tons per annum. Data are from **https://www.chemanalyst.com**.

[b] Percentage of publications mentioning the selected target compound. Data are from title screening (search for “extraction” in publication titles; *n* = 284).

(46) and biotechnological (47) routes. Of all the compounds listed in **Table 1**, only ethanol and lactic and citric acids are produced predominantly by biotechnological conversion (8, 19, 20). All other compounds are manufactured by chemical means (48). However, bio-based synthesis of the other compounds within the table is feasible, as their microbial synthesis has been demonstrated in the literature (see **Supplemental Appendix A.1**).

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All of the compounds in **Table 1** have high water solubility as well as highly hydrophilic properties, reflected in the octanol–water partition coefficient ($K_{D,octanol}$). As a result, physical extraction often demonstrates a limited distribution coefficient (44). While the limited distribution coefficient can be partially compensated for by the use of multistage extraction columns with regard to product recovery (49), the concentration factor for capturing these molecules is limited. The low distribution coefficient emphasizes the relevance of reactive extraction for the purification of polar compounds. Purely on the basis of the high distribution coefficients compared with those of physical extraction (24, 50) as well as the abundant data from the literature (**Figure 1**), the implementation of reactive extraction for the purification of these molecules seems achievable and could provide economic benefits. Below, we discuss the obstacles to industrial implementation of reactive extraction for purifying carboxylic acids and connect them to the capabilities and characteristics of commonly used reactive extraction systems.

3. REACTIVE EXTRACTION OF CARBOXYLIC ACIDS: CURRENT STATUS

The literature describes various reactive extraction systems containing at least one extractant and diluent (29). Long-chain amines, phosphine oxides, and phosphates are common extractants, while diluents range from highly polar solvents like 1-butanol to alkanes like dodecane (29). In this section, we quantify the distribution of these systems within the literature and discuss the mechanistic differences in complex formation of the target molecule with the most relevant extractants. Lastly, we analyze the main research areas in reactive extraction and correlate them with the more established physical extraction methods. Our goal is to develop a basis for understanding the challenges in reactive extraction and identifying potential solutions in subsequent sections.

TOA: trioctylamine

TBP: tributylphosphate

TOPO: trioctylphosphine oxide

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3.1. Extraction Systems in the Literature

To identify the most frequently used extractants in the literature, we expanded the database described in Section 2.2 by incorporating three additional search queries focused on reactive extraction (Section 2.1), thereby creating a more comprehensive overview of reactive extraction systems. The target compound distribution for reactive extraction remains similar (see **Supplemental Appendix A.3**). However, to focus solely on the extraction of carboxylic acids, we excluded other target compounds from the evaluation. To account for the screening bias when using different search requests, **Figure 2** displays each search query individually along with a total analysis. All compounds are listed in **Supplemental Appendix A.1**.

In all search queries, tertiary amines are the most dominant extractant group and are mentioned in half (49.9%) of all publications. Among them, trioctylamine (TOA) is the most frequently represented, appearing in 30.7% of all publications. Phosphate-based extractants are the second most commonly mentioned extractant group; among them, tributylphosphate (TBP) and trioctylphosphine oxide (TOPO) are the most prominent representatives, appearing in 11.4% and 7.2% of publications, respectively. **Figure 2*b*** shows the diluents used in the literature. Alcohols and alkanes represent a large proportion of diluents; 39.8% are long-chain alcohols and another 31.2% are alkanes. Alkanes are often mixed with alcohols or ketones as modifiers for increased solubility of the acid–extractant complex (54). **Table 2** lists the most common diluents.

3.2. Reactive Extraction Mechanism

Complex formation of the target compound with the extractant affects yield, selectivity, physical properties, and organic-phase regeneration and differs depending on the choice of extractant and diluent (31, 36, 64, 65). In this section, we discuss the extraction mechanisms and complex forms resolved in the literature for the most common extractants: TOA, TOPO, and TBP. For a comprehensive overview of extraction mechanisms and their modeling, see the review by Sprakel & Schuur (29).

TOPO and TBP extract target compounds via physical solvation and formation of hydrogen bonds (66–68). As a result, they extract solely undissociated compounds (69) (**Figure 3*b***). However, TOA can be protonated at the liquid–liquid interface at low pH values (70) (**Figure 3*c*,*d***). The apparent basicity of TOA depends primarily on diluent choice (70–72), extractant concentration (73), and pH value (70, 74–76). Thus, the transfer of compounds into the organic phase by TOA can occur via three routes: (*a*) ion-pair bonding with the protonated form of TOA, (*b*) hydrogen bonding with the unprotonated form of TOA, or (*c*) physical solvation by the diluent (73, 75, 77, 78). Independently of the transfer mechanism into the organic phase, TOA can form hydrogen bonds (64) (**Figure 3*c***) as well as ion-pair bonds (79) (**Figure 3*d***) with carboxylic acids. As a result of these overlapping extraction mechanisms, TOA can extract not only fully protonated acid but also, to some extent, its dissociated form (75, 79), resulting in a more extensive potential pH range for extraction compared with that of TOPO and TBP (70) (**Figure 3*c*,*d***). All three extraction agents can coextract water (80–82). With regard to TBP and TOPO, water competes with carboxylic acids for hydrogen bonding with the extractant and can, therefore, be displaced by the carboxylic acid (80). TOA coextracts water in proportion to the diluent's ability to solubilize water, resulting in carboxylic acid–amine complexes with a certain hydration number (81, 82). When the carboxylic acid is extracted, the pH value increases as a result of the removal of the molecule. Extraction stalls if a pH value is reached where, in the case of TOPO or TPB, no fully

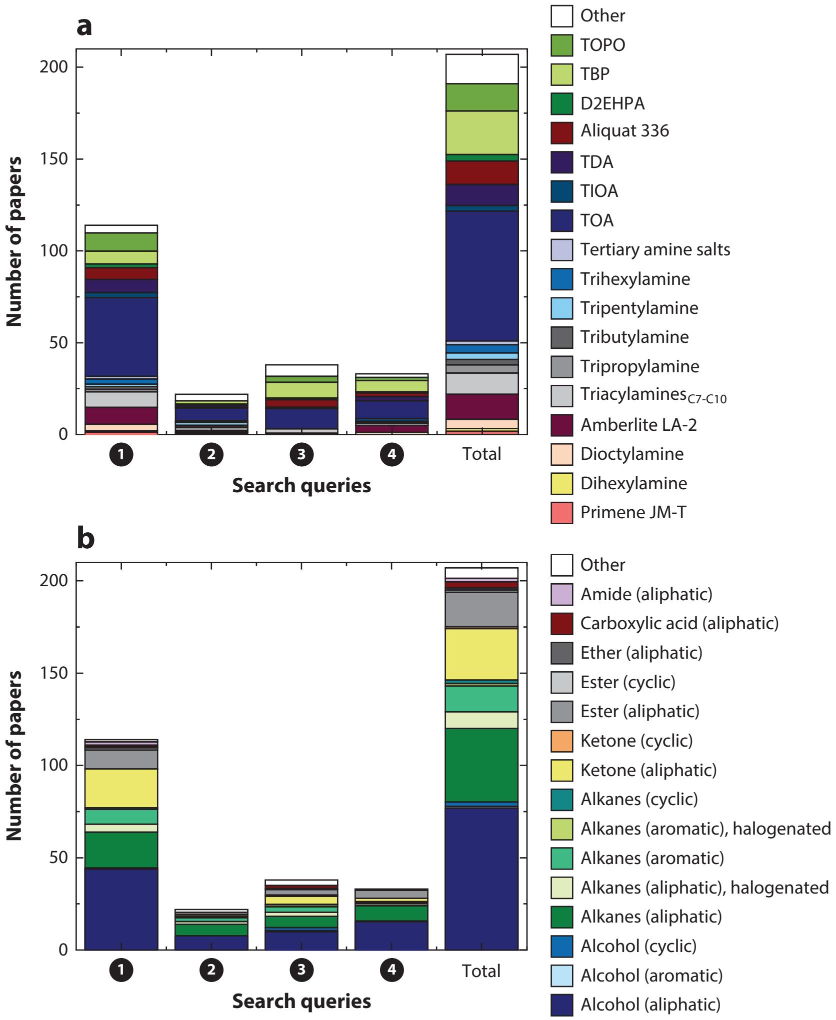

Figure 2

(*a*) Extractants and (*b*) diluents used in the literature for purification of carboxylic acids. Commonly used abbreviations of extractants are listed within the graph. Data are from title screening (①; $n = 114$), the platform chemical query (②; $n = 22$), the extraction of acids query (③; $n = 38$), and the reactive extraction of acids query (④; $n = 33$). Overall data can be found in **Supplemental Appendix A.1**. Abbreviations: Amberlite LA-2, a long-chain secondary amine; D2EHPA, bis(2-ethylhexyl) phosphate; Primene JM-T, dimethylheptadecan-1-amine; TBP, tributylphosphate; TDA, tridodecylamine; TIOA, tri-isooctylamine; TOA, trioctylamine; TOPO, trioctylphosphine oxide.

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protonated carboxylic acid is present (66, 83). In the case of TOA, extraction continues until it is limited by the availability of protonated TOA (75) (**Figure 3*c*,*d***).

3.3. Influence of Diluents

Aside from extractants, diluents influence the yield and selectivity of carboxylic acid extraction as a result of their interaction with the carboxylic acid–extractant complex (64), their influence on complex solubility (31), and physical solvation of the carboxylic acid (50). They can be separated

Table 2 The most commonly mentioned diluents for reactive extraction of carboxylic acids in the literature

Compound	Total literature (% of publications)	Solubility in water (g/L) at 25°C	Dynamic viscosity (mPa·s) at 25°C
1-Octanol	48.9	0.54 (56)	7.288 (61)
1-Decanol	27.8	0.04 (56)	10.9 (61)
Methyl isobutyl ketone	25.8	19 (57)	0.57 (62)
Toluene	15.2	0.52 (58)	0.56 (61)
n-Heptane	14.7	0.0034 (57)	0.58 (62)
n-Hexane	12.6	0.0029 (58)	0.44 (62)
Kerosene	12.1	None	0.737–3.153 (63)
Dodecane	10.5	None	1.81 (62)
1-Hexanol	10.0	5.9 (56)	4.43 (62)
1-Butanol	7.4	80 (56)	2.54 (61)
Chloroform	7.4	7.95 (59)	0.538 (62)
Isoamyl alcohol	7.4	26.7 (60)	3.74 (62)
Butyl acetate	6.3	8.33 (57)	0.685 (61)

[a] Percentage of all publications on reactive extraction within the literature database; data are from the title screening (query 1 in Section 2.1; $n = 114$), the platform chemical query (query 2; $n = 22$), the extraction of acids query (query 3; $n = 38$), and the reactive extraction of acids query (query 4; $n = 33$).

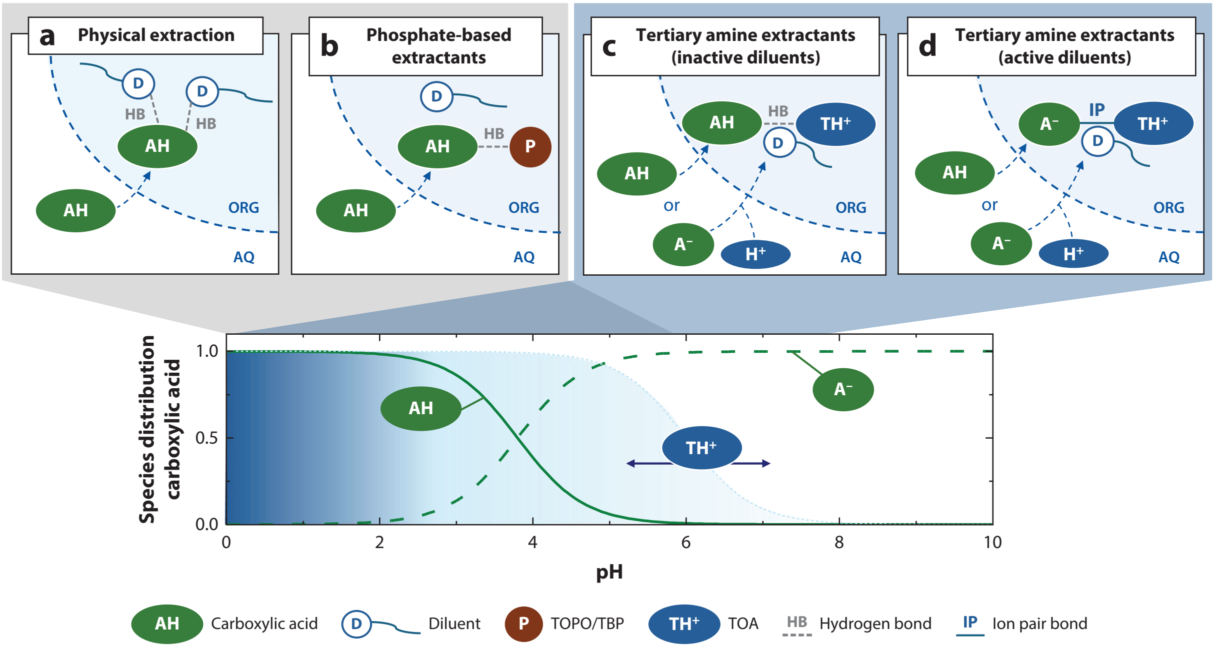

Figure 3

Schematic overview of (*a*) physical extraction and (*b*–*d*) reactive extraction with different extractants: (*b*) phosphate-based extractants, (*c*) tertiary amine extractants with inactive diluents, and (*d*) tertiary amine extractants with active diluents. Abbreviations: AQ, aqueous phase; ORG, organic phase; TBP, tributylphosphate; TOA, trioctylamine; TOPO, trioctylphosphine oxide. Figure based on References 29, 75, and 79.

into active and inactive diluents, and their effect differs depending on the extraction mechanism (29). For TOPO and TBP, active diluents can increase equilibrium constants because they improve the physical solvation of the target compound in the organic phase (50). However, in some cases, an increase in TOPO concentration in the organic phase leads to a decrease in extraction efficiency, as the alcohol diluent can compete with the carboxylic acid as a proton donor (50, 84, 85). Inactive diluents, like alkanes, are preferable in this case (50, 68). In contrast, the use of an inactive diluent with TOA can lead to limited distribution coefficients, reduced complex solubility, and third-phase formation, as TOA forms preferably highly polar ion-pair complexes (64, 79, 82, 86, 87). Active diluents promote and stabilize the formation of ion-pair bonds between TOA and the carboxylic acid (64, 79). This increased ion-pair formation is reflected partly by the enthalpy change for complex formation, as summarized in **Supplemental Appendix A.4** (64).

FTIR: Fourier transform infrared

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3.4. Complex Stoichiometry

As described in Sections 3.2 and 3.3, complexation in the organic phase depends on the interplay among the target compound, diluent, and extractant. However, the overall extraction efficiency is governed not only by complex formation between the target compound and the extractant but also by overlapping physical extraction, an abundance of different complex stoichiometries, and subsequent agglomerate formation of multiple complexes within the organic phase. These different complex forms are only partially distinguishable.

For phosphor-based extractants, physical extraction and hydrogen pair formation play equal and overlapping roles in extracting carboxylic acids (50). Similar to polar diluents, TOPO and TBP act as proton acceptors in hydrogen bond formation, while carboxylic acids act as proton donors (66, 67, 88). Thus, physical extraction and reactive extraction by hydrogen bonds are not easily distinguishable, and their combination can lead to increased apparent complex stoichiometries (89). Furthermore, the distribution coefficient of carboxylic acids can increase with higher loadings of the organic phase on the basis of changes in polarity due to extraction, contributing to an apparent stoichiometry higher than 1:1 (89).

In extraction with TOA, complex formation by ion-pair bonds can be distinguished from hydrogen bonds, for example, by Fourier transform infrared (FTIR) spectroscopy of the organic phase or by titration calorimetry, facilitating the evaluation of different complex forms in the organic phase (64, 90). In active diluents, carboxylic acids are bound by ion-pair bonds with TOA until all of the TOA molecules are occupied (79). Furthermore, when dicarboxylic acids are used as target compounds, complexes of 1:2 stoichiometries can occur (79, 90). In contrast, overloading of a carboxylic acid–extractant ratio up to 2.5:1 is possible if the amine–acid complex is supplemented with more carboxylic acid molecules hydrogen-bonded to the molecules already bound in the complex (30, 90). Additionally, agglomerates of multiple complexes can form, leading to a considerable increase in the distribution coefficient at higher loadings when inactive diluents are used (30, 70).

3.5. Current Research Focus

Numerous publications containing equilibrium data on the reactive extraction of carboxylic acids are available (**Figures 1** and **2**), and process concepts ranging from batch (32) to continuous processes (24) are well-established. Nonetheless, full process implementations in technical equipment such as extraction columns (91) or mixer-settlers (92) are rare (24, 93). In contrast, extensive data sets on the operation of technical devices (94, 95) and holistic approaches to process simulation (96, 97) are available for physical extraction. Therefore, to systematically identify technical bottlenecks in the industrial implementation of reactive extraction, we categorized the

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COSMO-RS: conductor-like screening model for real solvents

UNIFAC: universal quasichemical functional group activity coefficient

literature within the database (see the four search queries in Section 2.1) by research topic (see **Supplemental Appendices A.1** and **A.5**). By comparing the resulting distribution of research fields with physical extraction, which is already well-established in the petrochemical industry (42), we identified potentially relevant research areas for the industrial implementation of reactive extraction. To obtain a general overview, we considered all of the target compounds in data evaluation for physical extraction. However, as this review aims to identify the bottlenecks in the implementation of reactive extraction for carboxylic acid purification, we considered only publications concerning carboxylic acids for reactive extraction. **Figure 4** depicts the distribution of these categories for reactive and physical extraction.

The greatest differences between reactive and physical extraction lie in phase equilibria and apparatus implementation. For reactive extraction, 43.0% of publications focus on phase equilibria in pure systems with or without stoichiometric modeling. In contrast, for physical extraction, only 13.2% of publications focus on equilibrium determination but 51.6% concern apparatus implementation and modeling thereof. Consequently, reactive extraction research is deficient in terms of apparatus implementation and related scale-up considerations. Furthermore, while both types of extraction are similar in terms of phase equilibria and their correlation with thermodynamic models, physical extraction offers a broader availability of predictive models, such as conductor-like screening models for real solvents (COSMO-RS) or universal quasichemical functional group activity coefficients (UNIFAC). Although these predictive models have limitations (98), they can be combined with fluid-phase properties and implemented in process simulations to screen for extraction systems while accounting for the overall requirements of the process (96, 97). This combination enables a holistic process design early in development. In particular, given the broad variability of reactive extraction systems, a preliminary screening that considers process implications can offer great potential. Lastly, research on both reactive and physical extraction shows limited use of complex systems, demonstrating that data on selectivity for reactive and physical extraction are scarce. However, given the complexity of fermentation broth (31, 99), research on the behavior of bio-based systems with regard to yield, selectivity, and phase separation for apparatus implementation can be decisive for the implementation of economic processes (100). In summary, an increased understanding of extraction mechanisms for reliable phase equilibria, the implementation and modeling of technical devices, and the influence of impurities on extraction and fluid dynamic behavior can facilitate a comprehensive process design for the industrial application of reactive extraction in the purification of carboxylic acids.

4. CHALLENGES IN REACTIVE EXTRACTION

Section 3.5 illustrates the research gap between physical and reactive extraction regarding process-related topics such as predictive modeling, selectivity, and apparatus implementation. In the following subsections, we discuss the challenges in these areas and compare them with approaches from physical extraction. We also draw parallels to the better-established reactive extraction of metals where applicable (39). With reference to Section 3.1, we evaluate the capability of the most common reactive extraction systems to address these challenges and identify promising combinations of extractants and diluents.

4.1. Prediction and Description of Phase Equilibria

As stated in Section 3.5, model-based prediction of phase equilibria can be implemented in process simulations to allow solvent selection based on overall process considerations (96–98). However, predicting phase equilibria in reactive extraction for the purification of carboxylic acids remains challenging. Whereas in physical extraction a three-component matrix can be used to describe the

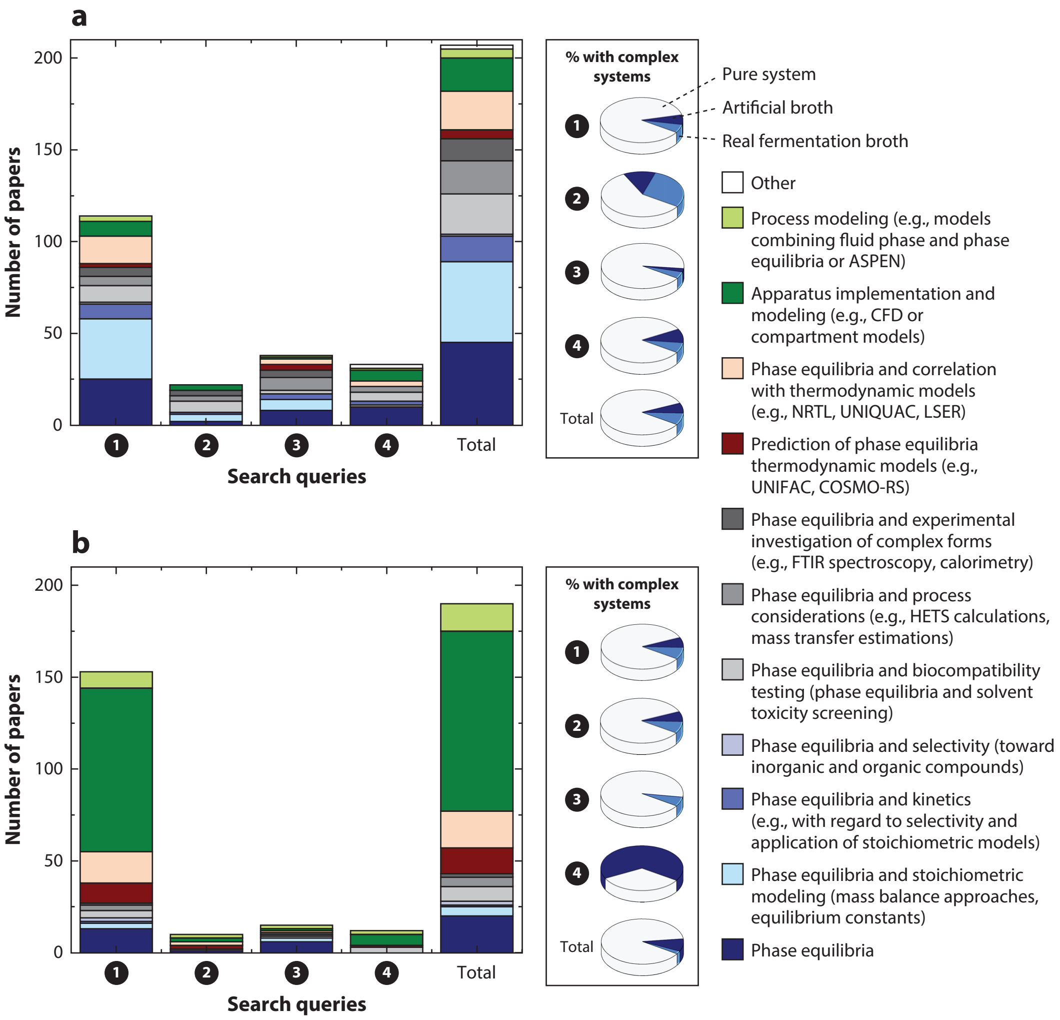

Figure 4

Literature data, categorized by research focus, for (*a*) reactive extraction and (*b*) physical extraction. Data are from title screening (①; $n_{\text{reactive}} = 114$, $n_{\text{physical}} = 153$), the platform chemical query (②; $n_{\text{reactive}} = 22$, $n_{\text{physical}} = 10$), the extraction of acids query (③; $n_{\text{reactive}} = 38$, $n_{\text{physical}} = 15$), and the reactive extraction of acids query (④; $n_{\text{reactive}} = 33$, $n_{\text{physical}} = 12$). Panel *a* includes only carboxylic acids. Panel *b* includes all target compounds. The pie charts present the percentage of database publications that investigate pure systems, real fermentation broth, or artificial fermentation broth. For the overall data, see **Supplemental Appendix A.1**. Abbreviations: ASPEN, software package (Aspen Technology, Inc., Bedford, MA); CFD, computational fluid dynamics; COSMO-RS, conductor-like screening model for real solvents; FTIR, Fourier transform infrared; HETS, height equivalent to a theoretical stage; LSER, linear solvation energy relation; NRTL, nonrandom two-liquid; UNIFAC, universal quasichemical functional group activity coefficient; UNIQUAC, universal quasichemical.

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system comprising the organic phase, target compound, and water, reactive extraction requires the additional considerations of extractant and pH. Furthermore, electrolytes and by-products commonly found in fermentation broth (31) complicate modeling (98). Consequently, the implementation of predictive models based on group contribution methods, such as UNIFAC (101), or on quantum chemical methods, such as COSMO-RS (102), is challenging for reactive extraction systems.

LSER: linear solvation energy relation

While we have not identified a purely predictive approach to the modeling of reactive extraction, thermodynamic factors derived from the UNIFAC Dortmund model (103) have been combined with linear solvation energy relations (LSERs) (104), and the resulting model was parameterized with experimental data (105, 106). Whereas this approach leads to accurate results, the use of LSERs by themselves already yields good agreement with experimental data (107–109).

In general, these thermodynamic models are rarely applied to reactive extraction. However, many stoichiometric models based on the mass action law have been published (30, 82, 110–112). In these models, extraction of the undissociated acid in different complex stoichiometries is assumed (30). Heterogeneous models use an equilibrium constant describing the ratio of the target compound concentration in the organic phase to the concentration of the target compound in the aqueous phase (30, 73). In homogeneous models, the physically solubilized target compound in the organic phase is related to the complex concentration in order to obtain an equilibrium constant (113, 114). The mass action law can also be used to describe the loading of TOA based on Langmuir saturation equations (115). While these stoichiometric models are easy to apply, they ignore the physical interactions between components, rendering them less realistic (30, 116). Furthermore, while they have the greatest potential in process (111) and apparatus (36, 113) modeling, stoichiometric models are frequently used to decipher reactive extraction mechanism and complex formation. While this type of modeling yields good results with regard to data fitting (117), the complex forms need to be validated experimentally, such as by FTIR spectroscopy (30). Another way to obtain mechanistic insights is molecular modeling based on quantum mechanical concepts, such as density functional theory (64).

Mass action law models rarely take TOA protonation into account (30, 113, 114). However, because, among the complex solubility and dissociation constants of the target species, TOA protonation determines selectivity and pH range (73, 116, 118), relative basicity models based on TOA protonation have been developed (73, 119). In order to parameterize apparent basicity models, TOA protonation is determined via extraction of HCl, under the assumption that the Henderson–Hasselbalch equation is valid (73, 120). One can then develop a model that is based on a linear relationship between the pK_a of the acid and the apparent basicity of TOA and that takes into account organic-phase hydrophobicity (119). This approach is easy to apply and yields good results. Furthermore, it has the potential to describe the competitive extraction of inorganic anions and carboxylic acids (31). Nonetheless, the parameters obtained are not descriptive, as hydrophobicity and pK_a-related constants are combined (119). Furthermore, this approach neglects changes in extraction efficiencies due to changes in organic phase polarity at different organic phase loadings (121). However, Schunk & Maurer (77, 78, 116, 118) and Ziegenfuß & Maurer (122) have presented a more extensive approach combining mass balancing, TOA protonation, and changes in activities to describe multicompound extraction and changes in extraction efficiency due to loading. As with homogeneous models based purely on mass balances, they consider the physical solubility of the target compound in the organic phase based on activity coefficients. They also take into account the physical solubilities of TOA and diluent in water. On the basis of different complex stoichiometries for each compound, Schunk & Maurer (116, 118) model the co-extraction of inorganic salts, depending on the composition of the organic phase. The compound concentrations of the two equilibrated phases are calculated by minimizing the Gibbs energy of the isothermal two-phase systems based on feed composition. While these models provide deep and accurate mechanistic insights and are able to display changes in selectivity, parameterization by experiments cannot be avoided.

Table 3 summarizes these different approaches to modeling reactive extraction. Generally, predicting reactive extraction efficiencies is highly challenging because of the complexity of the multicomponent mixtures. Such prediction is even more challenging when using real

Table 3 Modeling approaches for reactive extraction in the literature

Approach	Model type	Predictive versus correlated[a]	Accuracy	Literature (%)[b]	Reference
Predictive thermodynamic models	Group contribution methods	Predictive	Good within one substance group	1.7	106
NRTL	Simple thermodynamic model	Correlated	Good within one substance group	1.3	123
LSER[c]	Simple thermodynamic equations based on solubilization	Correlated	Good within one substance group	9.3	107
Stoichiometric modeling	Mass balance with equilibrium constants	Correlated	Good	20.3	30
Langmuir isotherm	Adsorption isotherm	Correlated	Good within one substance group	0.4	115
Molecular modeling	Molecular interaction based on DFT	Predictive but needs validation by FTIR/calorimetry	Good, with mechanistic insights	0.8	64
Relative basicity	Protonation of TOA	Correlated	Good within one substance group	1.3	115
Stoichiometric modeling with activity coefficients	Mass balance with activities and equilibrium constants	Correlated	Good with mechanistic insights	0.8	116

[a] Correlated to experimental data.

[b] Percentage of all papers on reactive extraction within the literature database. Data are from title screening (query 1 in Section 2.1; $n = 114$), the platform chemical query (query 2; $n = 22$), the extraction of acids query (query 3; $n = 38$), and the reactive extraction of acids query (query 4; $n = 33$).

[c] Partially with Hildebrand–Hansen solubility parameters.

Abbreviations: DFT, density functional theory; FTIR, Fourier transform infrared; LSER, linear solvation energy relation; NRTL, nonrandom two-liquid; TOA, trioctylamine.

fermentation broth, where not all compounds may be identified (100). As a result, experimental data may be necessary to obtain reliable information. One way to reduce experimental work could be to implement robotic platforms and combine their results with those of simple thermodynamic models based on complex solubility, such as LSER (107, 108).

4.2. Selectivity for Side Compounds from Microbial Production

Reactive extraction is commonly used as the initial capturing step after cell removal in biotechnological downstream processes (35). As the target compound is usually present extracellularly, no cell disruption is necessary (124), but by-products and medium components in addition to the target compound are present in the aqueous phase (124, 125). While only a few papers within the database explicitly cover the influence of impurities within the feed (**Figure 4**), the impact of these impurities on reactive extraction is not negligible (31, 126). We discuss this topic in the following subsections.

4.2.1. Inorganic compounds. Carboxylic acid production is often initiated after a growth phase if a specific nutrient, usually nitrogen, is limited (24, 127). Other nutrients are only partially used and remain within the fermentation broth for downstream processing (31). Adjuvants for pH adjustment are also present (7, 127, 128). In carboxylic acid fermentation, the product acidifies the fermentation broth (127). Thus, especially for fermentation at neutral pH, equimolar quantities

D2EHPA: bis(2-ethylhexyl) phosphoric acid

of base (e.g., sodium hydroxide) need to be added in order to maintain the desired fermentation pH. Furthermore, when ammonium salts are used as a nitrogen source, ammonium is incorporated in its NH_3 form, releasing one proton and thereby requiring even more base to maintain the fermentation pH (127, 129). However, as described in Section 3.2, for high extraction yields the pH value must be reduced for downstream processing (75, 127). The reduction in pH causes the fermentation medium to have high ionic strength, which influences yields in the subsequent reactive extraction (31) either by changing the activity of the target compound within the aqueous phase or by coextracting salt ions into the organic phase (31, 76, 116, 118).

In the case of small, polyvalent ions, a change in the activity of the target compound due to high ionic strength leads to an increase of the extraction coefficient by salting out (130, 131). Baral et al. (131), among others, have demonstrated this effect. However, because they did not investigate ion coextraction, this effect might also overlap with the simultaneous extraction of ions from the aqueous phase. Ion coextraction depends heavily on the reactive extractants and diluents used. TOPO is frequently used in metal extraction for purification of metal salts (132). In addition, when combined with salting-out effects (133) or ionic liquids (134), TBP can extract metal salts.

Figure 2 illustrates the use of other phosphate-based extractants, such as bis(2-ethylhexyl) phosphoric acid (D2EHPA), for reactive extraction. In contrast to TOPO and TBP, D2EHPA contains a free hydroxy group that can efficiently form chelates to extract cations such as manganese, zinc, and sodium (135, 136). Therefore, the possibility of cation coextraction cannot be excluded when using phosphate-based extraction agents to remove carboxylic acids from aqueous solutions. As the literature on this topic is sparse, further research will be necessary to characterize the interactions among carboxylic acids, anions, and phosphate-based extraction agents with regard to yield and selectivity.

The literature offers more information about TOA. Because of its ability to protonate at the liquid–liquid interface (70), TOA can coextract the anions of inorganic acids, such as hydrochloric, sulfuric, and phosphoric acids, with high affinity (31, 75, 120). As stated above, if the fermentation is conducted at a neutral pH, an acid needs to be used to lower the pH for efficient purification. Depending on the type of anion, this addition results in competitive extraction of carboxylic and inorganic acids, lowering yields (31, 137) and reducing mass transfer rates (76), depending on the type of salt. This effect can be partly compensated for by using more TOA (126); however, the extraction of a strong, inorganic acid causes the pH value to increase steeply (75) (Section 3.2). As a result, even more inorganic acid is necessary for pH adjustment and full extraction of the carboxylic acid. The subsequent transfer of the inorganic acid to back-extraction may also increase the amount of adjuvant needed for back-extraction. Therefore, purification of a fermentation broth with an initially high pH value seems infeasible with the use of TOA.

However, some fermentations, such as itaconic acid fermentations, can be efficiently conducted at lower pH values (127, 128) such as 3.5 or 3.6. The ability of TOA to extract both the protonated and deprotonated forms of carboxylic acids enables high extraction yields without the need to adjust the pH (34, 128) (**Figure 3**). To further limit the coextraction of inorganic acids present in the medium, one can reduce TOA protonation either by increasing the TOA concentration within the organic phase (126) or by using less polar diluents (73). Because the influence of salt type on the extraction coefficient differs depending on the type of anion, as well as on the combination of anion and cation (31, 77, 78), a combination of less polar reactive extraction systems and the use of salts in the fermentation medium with low influence on extraction yield, such as phosphate salts (86, 126), could minimize anion coextractions when using TOA. However, according to data from Schunk & Maurer (116, 118), total selectivity cannot be obtained. In light of their greater selectivity, phosphate-based extractants like TOPO and TBP are recommended instead.

4.2.2. Organic by-products. Aside from inorganic anions and cations, the fermentation broth may contain the carbon source and organic by-products (124). While sugar extraction can be neglected (24, 126), by-products can pose challenges in process implementation. Although metabolic engineering can minimize side products, it is limited, among other factors, by the knowledge of relevant pathways and the need to close the redox balance of the target compound production (138). Therefore, molecules such as carboxylic acids, alcohols, or ketones may be present in the fermentation broth. In succinic acid fermentations, for example, possible by-products are ethanol, pyruvate, acetate, formic acid, propionic acid, and lactic acid (31, 76, 86). The separation of carboxylic acids by reactive extraction depends largely on the differences in their pK_a values. The more the pK_a values of the products differ, the more selective extraction can be (31, 86). However, most carboxylic acids, such as lactic and succinic acids, have pK_a values ranging from 3.8 to 4.2 (139, 140), leading to a challenging separation problem. In addition, alcohols can be coextracted by physical solvation (33), and selectivity is not easily obtained.

As a result, some by-products will likely be coextracted and led through the purification sequence. Depending on the subsequent steps, they may be separated by other material properties, such as their solubility (124). However, additional unit operations could increase the production price (7, 25). In combination with increased substrate use for by-product formation and, therefore, decreased yields, metabolic engineering for reduced by-product formation plays a vital role in establishing efficient processes (141).

4.3. Phase Separation and Implementation in Apparatuses

The largest research gap between physical and reactive extraction lies in the implementation of reactive extraction in apparatuses (Section 3.5). For physical extraction, coalescence has been studied extensively in settling experiments (92). For reactive extraction, however, data on both coalescence and apparatus implementation are limited. **Table 4** lists some publications on reactive extraction in technical devices.

Table 4 demonstrates the dominant use of devices requiring no dispersion of the two liquid phases, such as membrane contactors, micropipeline systems, and thin layer extraction. In one case, a dispersion-based apparatus was used, but phase separation was controlled with colloidal aphrons. Membrane contactors are particularly frequently used. In contrast to conventional technical devices, the number of theoretical stages is limited, and mass transfer may occur more often than in mixer-settlers or columns (151, 152). The abundance of dispersion-free apparatuses within the literature implicates possible complications with phase separation in reactive extraction systems. Few data systematically compare the settling times of physical and reactive extraction systems based on one target compound and one diluent. However, a general comparison of the settling times in reactive and physical extraction (92, 153), and the fact that centrifugal steps are frequently applied after reactive extraction (128), suggests that reactive extraction systems might show impaired phase separation.

Phase separation is governed by coalescence. A comprehensive review on coalescence by Kamp et al. (154) describes coalescence in a simplified manner that can be applied to reactive extraction systems of bio-based molecules. The continuous phase is usually fermentation broth. The dispersed phase consists of the reactive extraction system. To discuss the possible factors influencing phase separation in reactive extraction and to identify advantageous reactive extraction systems, we transfer the principles of coalescence in physical extraction to reactive extraction, based on the main physical properties of the organic and aqueous phases.

Changes in interfacial tension can pose a challenge in phase separation in reactive extraction systems. For example, a decrease in interfacial tension leads to greater deformation of drops when

Table 4 Publications on reactive extraction in apparatuses

Extractant	Diluent	Transfer component	Device	Reference
TOA	1-Octanol	Lactic acid	Membrane contactor	142
TOA	1-Octanol	Succinic acid	Colloidal liquid aphrons	143
TOA	1-Octanol	Lactic/pyruvic acid mix	Thin layer extraction	144
TOA	2-Octanol	3-Hydroxypropionic acid	Membrane contactor	36
TOA	1-Decanol	3-Hydroxypropionic acid	Membrane contactor	36
TOA	1-Decanol	Lactic acid	Membrane contactor	9
TOA	1-Decanol	Lactic acid	Membrane contactor	24
TOA	IPM	Itaconic acid	Direct contact[a]	34
Alamine 336	Shellsol A	Citric acid	Pulsed plate column	93
TIOA	Toluene	Citric acid	Mixer-settler	145
TIOA	Oleyl alcohol	Butyric acid	Direct contact[b]	37
Aliquat336	1-Octanol	Acetic acid	Membrane contactor	146
Aliquat336	1-Octanol	Propionic acid	Membrane contactor	146
Aliquat336	1-Octanol	Butyric acid	Membrane contactor	146
Aliquat336	1-Octanol	Valeric acid	Membrane contactor	146
Aliquat336	1-Octanol	Caproic acid	Membrane contactor	146
TOPO	Mineral oil	Caproic acid	Membrane contactor	147
TOPO	Kerosene	Lactic acid	Membrane contactor	66
TBP	Kerosene	Butyric acid	Impinging jet reactor	148
TBP	Kerosene	Phenol	Micropipeline system	149
D2EHPA	Kerosene	L-Phenylalanine	Membrane contactor	150

[a] In shake flasks.

[b] In stirred cells.

Abbreviations: alamine 336, trialkylamine (C8–10); Aliquat336, quaternary ammonium salt, mainly C8; D2EHPA, bis(2-ethylhexyl) phosphoric acid; IPM, isopropyl myristate; TBP, tributylphosphate; TIOA, tri-isooctylamine; TOA, trioctylamine; TOPO, trioctylphosphine oxide.

they come into contact with one another. This greater deformation increases the area for film drainage between these drops, which often leads to longer drainage times (154). If nonpolar diluents such as toluene or aliphatic alkanes are used, then TOA, TOPO, and TBP act as surface-active molecules, decreasing interfacial tension (155–157) (**Figure 5*a***). However, active, polar diluents (**Figure 2**), which demonstrate low interfacial tension with water in a binary system (158), are frequently used. Therefore, the effect of the reduction in interfacial tension might be overlaid by the surface activity of an active diluent. Data from metal and ion extraction indicate that target compound–extractant complexes can also be surface active (39, 156).

Figure 5*b* displays the interfacial tension over the loading of the organic phase for a standard test system for reactive extraction (isododecanol–D2EHPA–$ZnSO_4$–water) (159) and for a toluene–TOA–HCl–water system (120, 156). Both systems show a strong decrease in interfacial tension with increasing complex formation. Although we found no data on complexes with carboxylic acids in the literature, it is likely that, in the case of TOA, they behave the same as metal complexes as a result of similar ion-pair formation. However, one of the standard test systems for physical extraction (1-butanol–succinic acid–water) shows much lower interfacial tension (44), and according to Henschke (160), the influence of interfacial tension on actual settling times is low. Consequently, interfacial tension alone might not be the bottleneck in the coalescence of reactive extraction systems.

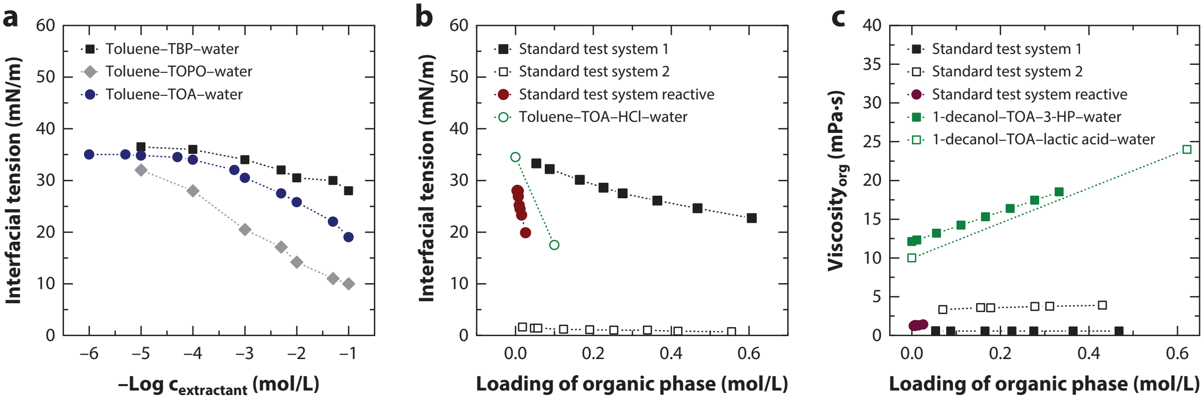

Figure 5

Physical properties of reactive and physical extraction systems. (*a*) Interfacial tension in toluene–TOA–water (156), toluene–TOPO–water (157), and toluene–TBP–water (157) systems depends on the extractant concentration. (*b*) Interfacial tension in standard test system 1 (toluene–acetone–water) (44), standard test system 2 (1-butanol–succinic acid–water) (44), the standard test system for reactive extraction (isododecane–D2EHPA–$ZnSO_4$–water) (159), and a toluene–TOA–HCl–water system (156) depends on the concentration of the target compound within the organic phase. For toluene–TOA–HCl–water, full extraction of HCl was assumed, as 0.1 M HCl and 0.1 M TOA were used (120). (*c*) Viscosity of the organic phase for standard test systems 1 and 2, the standard test system for reactive extraction (1-decanol–TOA–3-hydroxypropionic acid–water) (36), and a 1-decanol–TOA–lactic acid–water system (113). Abbreviations: D2EHPA, bis(2-ethylhexyl) phosphoric acid; TBP, tributylphosphate; TOA, trioctylamine; TOPO, trioctylphosphine oxide.

Increased viscosity of the aqueous phase can also decrease coalescence, as it leads to an increase in drainage time and a smaller drop size distribution in mixing (154). High viscosity of the organic phase decreases inner movement within the drop and, therefore, reduces the velocity of the droplet and the force with which the droplets collide (154). The viscosity of the continuous phase, however, is supposed to have a greater effect (160). Few data are available on the viscosity of aqueous phases after reactive extraction of carboxylic acids, but the viscosity of wine (1.225–1.505 mPa·s) offers an estimation (161). While this is only a slight increase compared with that of water, reactive extraction systems show much higher viscosity than organic phases for physical extraction or for metal extraction (36, 44, 113, 159) (**Figure 5*c***), and viscosity increases further upon the formation of carboxylic acid–extractant complexes (36, 113). Therefore, the viscosity of both phases might hinder phase separation and impose mass transfer limitation in diffusion-controlled extraction equipment like membrane contactors. As a result, further research on tuning the viscosity in reactive extraction systems is needed.

Furthermore, surface potential can play a large role in phase separation. According to the theory (162) presented by Derjaguin, Landau, Verwey, and Overbeek, organic droplets can repulse one another as a result of their surface potential, thereby avoiding coalescence (154). As TOA can protonate at the liquid–liquid interface (see Section 3.2), it can act as an anionic surfactant. As a result, it raises the surface potential (163) and thus may hinder coalescence (164). The surface potential can be influenced by, for example, pH, the addition of salts to the medium, and the presence of other surface-active compounds (154).

All in all, the abundance of polar and highly viscous diluents such as 1-decanol, in combination with the presence of surface-active compounds in the organic phase and from fermentation broth, can make the transfer from the lab scale to a technical device tedious (**Table 4**). This is mirrored in the systems used for each technical device. While active C8–C10 chain alcohols are used as diluents for membrane contactors, dispersion-based systems requiring subsequent phase separation are used primarily with diluents with no to low polarity, such as toluene, Shellsol A, oleyl alcohol,

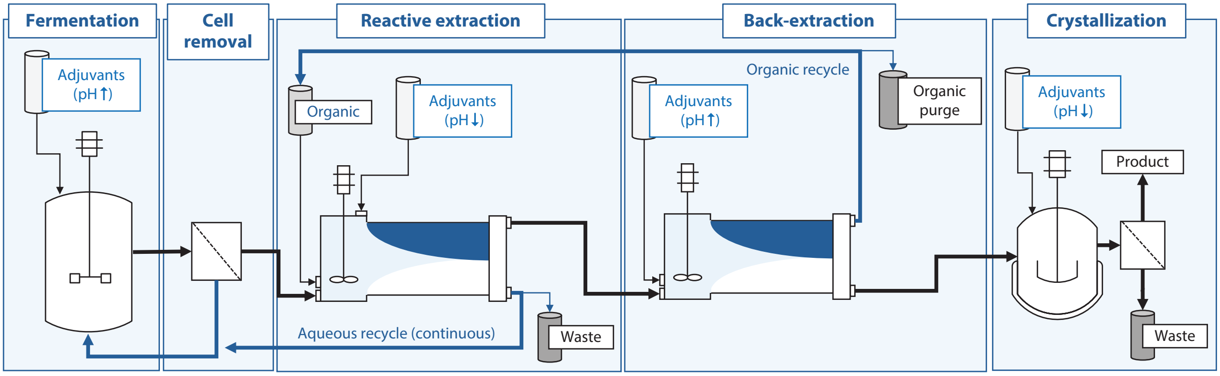

Figure 6

Overview of potential process design options in the literature. Figure based on data from References 9, 35, 65, and 167–169.

kerosene, and isopropyl myristate (34, 37, 93, 145, 148). Thus, nonpolar diluents might be helpful with the use of conventional apparatuses with high mass transfer, such as mixer-settlers or extraction columns. However, the selection of extractants might be more challenging; both TOPO and TOA show impaired phase separation (66, 128), which could be due to their high surface activity (**Figure 5*a*,*b***) and viscosity (**Figure 5*c***). As a result, further research on suitable combinations of extractant, diluent, and target compound is needed with regard to phase separation.

5. CLOSING MATERIAL CYCLES

As stated in Section 4.2, reactive extraction is generally employed as the first capturing step after fermentation. After reactive extraction, the carboxylic acid needs to be recovered from the organic phase for further processing. **Figure 6** displays a separation sequence using reactive extraction for purification of batch (35) or continuous (24) fermentation. After cell removal and a pH shift, in accordance with the pH value of the fermentation broth (see Section 4.2) (75, 127), carboxylic acid is extracted into the organic phase. The depleted fermentation broth is discarded in batch processing or recycled back to fermentation in a continuous process (24, 35). The organic phase is regenerated, and the target compound is extracted back into the aqueous phase via a chemical or a pH shift (165). The organic phase can thus be reintroduced into the process (**Figure 6**). After back-extraction, the target compound is ideally present at high concentrations and can be crystallized from the aqueous phase via cooling or a combination of cooling and pH-shift crystallization (7, 35, 65). Concentration by distillation is also possible (166).

In this section, we discuss the closing of aqueous and organic material cycles, as well as the recycling and disposal of purge streams. In addition, multiple pH shifts are required, resulting in the accumulation of corresponding adjuvant salts (**Figure 6**). We evaluate the ways to reduce this salt accumulation through suitable selection, implementation, and connection of unit operations.

5.1. Back-Extraction and Recycling of the Organic Phase

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For an economic process, efficient closure of the organic phase cycle is mandatory (81, 170) (see **Supplemental Appendix A.7**). Back-extraction should also be able to concentrate the product for further processing without interfering with subsequent processing steps (35). However, when evaluating the literature database for back-extraction, we found that only 13.6% of papers related to reactive extraction investigated the recovery of the organic phase by itself or in combination with reactive extraction (**Figure 7**). Physical extraction uses primarily distillation of the volatile target

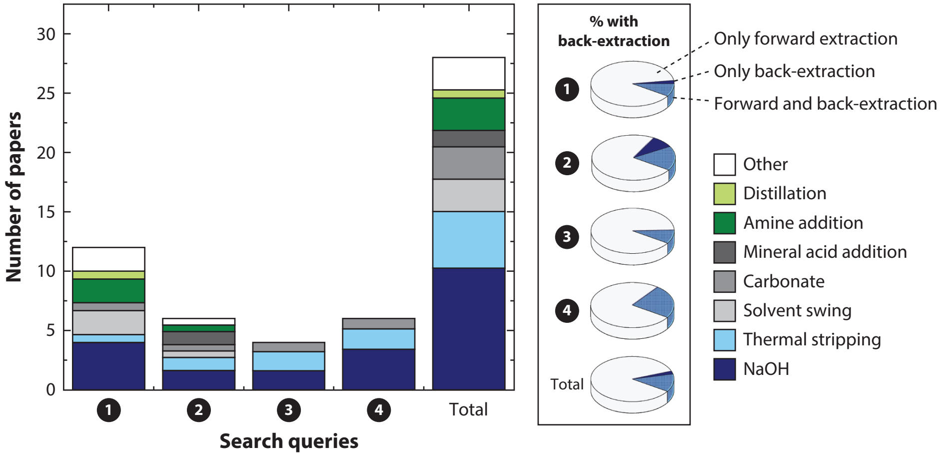

Figure 7

Organic phase regeneration after carboxylic acid extraction. Data are from title screening (①; $n = 113$), the platform chemical query (②; $n = 22$), the extraction of acids query (③; $n = 38$), and the reactive extraction of acids query (④; $n = 33$). Pie charts present the percentage of papers investigating back-extraction within the database. Back-extractions for closing mass balances were not considered.

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compound or the solvent (91) (see **Supplemental Appendix A.8**). For low-volatility carboxylic acids, however, this is rarely an option (65, 165), and other process variants (listed in **Table 5**) are required (65).

Of the publications in our database, 53.6% report a pH shift with sodium hydroxide to a pH value where no extraction occurs (**Figure 7**) and the acid is thus transferred back into the aqueous phase (35). This approach results in high recovery (32, 35) and is equally applicable to TOA, TOPO, and TBP (24, 99, 173). Therefore, the addition of sodium hydroxide is often used to close mass balances at the lab scale (9, 174). The medium to high pH after back-extraction results in a fully deprotonated carboxylic acid; however, protonation is necessary for subsequent crystallization (7, 175). Thus, at least equimolar amounts of inorganic acids must be added, and the salt formed from the anion of the inorganic acid and the corresponding cation of the base accumulates and may reduce yields in the subsequent crystallization step (7, 9). This salt accumulation can be addressed via electrochemical pH-shift back-extraction and crystallization within an electrolytic cell (9, 176). **Figure 8** illustrates the principle. The electrolytic cell comprises two electrodes in an electrolyte solution separated by a membrane. After reactive extraction, the organic phase is led into a cathode chamber, where water is reduced to hydrogen gas and hydroxide ions. The

Table 5 Options in the literature for back-extraction

Back-extraction	Adjuvants	Product[a]	Organic[a]	Reference(s)
pH shift	Base	A^-, concentrated in NaOH	Recovered	9, 66
Solvent swing	Antisolvent	HA, at solubility limit	Solvent mix	64, 171
Temperature and solvent swing	Antisolvent	HA, at solubility limit	Solvent mix	64, 171
Amine complexation	Short-chain amine	HA-A, crystalline	Recovered	168, 172
Carbonate addition	Carbonate salts	HA-S	Recovered	169
Inorganic acid addition	Acid	HA, at solubility limit	With inorganic acid	167

[a] State after recovery.

Abbreviations: A^-, dissociated form of the acid; HA, protonated form of the acid; HA-A, amine–acid complex; HA-S, carboxylic acid salt.

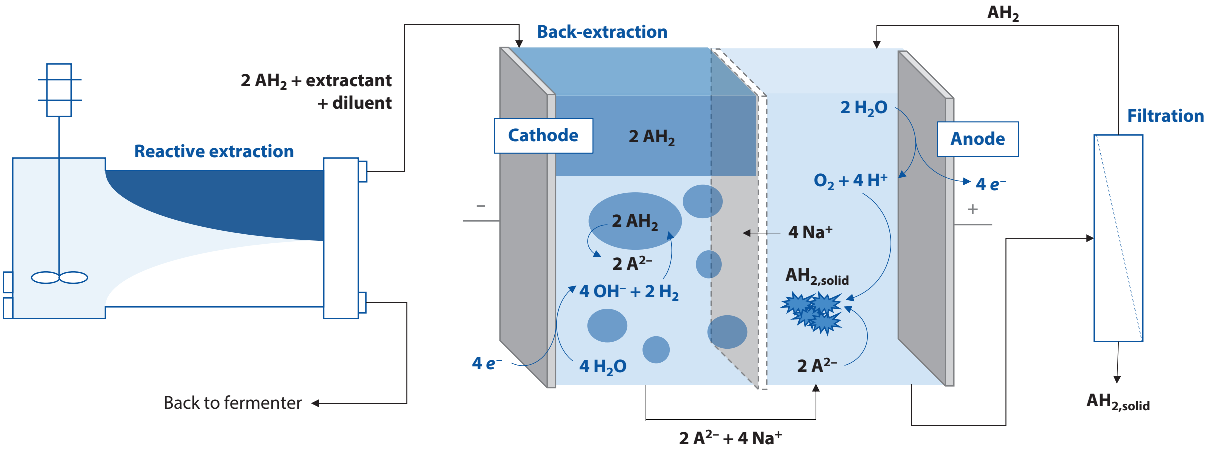

Figure 8

Electrochemical pH shift for back-extraction without salt accumulation (9).

pH value is increased, and back-extraction occurs. The alkaline solution is then led into an anode chamber, where water is oxidized to produce oxygen gas and hydrogen ions, thereby lowering the pH value and leading to pH-shift crystallization of the carboxylic acid. The permeation of sodium ions through the membrane ensures conductivity. This electrochemical pH shift enables the recycling of sodium ions and prevents salt accumulation within the system (9, 176). The crystals are removed by filtration, and the acidified solution is led back into the anode chamber. Although this approach has been demonstrated within a full process (24), scale-up of the electrolytic cells requires ion exchange membranes that tolerate direct solvent contact without scaling or fouling over the long term.

A solvent or temperature swing, or a combination of both, is reported in 39.3% of the research papers on reactive extraction in our database (**Figure 9**). A solvent swing involves either the introduction of a liquid antisolvent (e.g., pentane) or a gaseous antisolvent (e.g., ethane) or the removal of a diluent by distillation (65, 165). In contrast to back-extraction using a pH shift, this method is

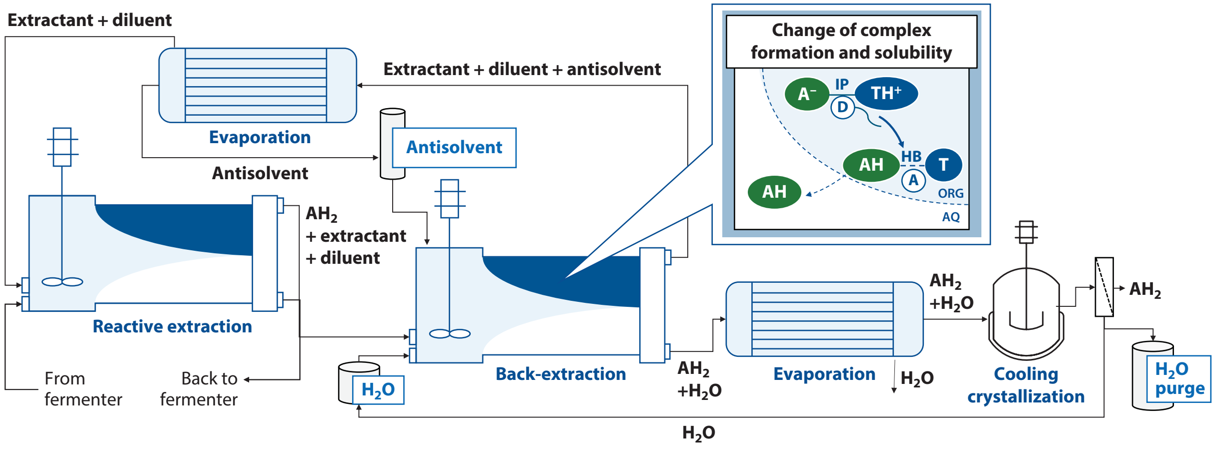

Figure 9

Antisolvent back-extraction, as described by Sprakel et al. (65).

promising for TOA because of its extraction mechanism via ion-pair bonds. The addition of inactive diluents changes the interaction between acid and extractant, introduces hydrogen bonding (64), and can reduce binding enthalpy or complex solubility (64, 65). For TOPO, extraction already occurs via hydrogen bonding and functions effectively in nonpolar diluents. Therefore, the addition of an antisolvent would not lead to full recovery (65). The acid is transferred back into the aqueous phase in its protonated form, and full recovery is possible at high antisolvent-to-solvent ratios (65). As the product concentration within the aqueous phase after back-extraction is limited to the solubility limit of the protonated acid, a subsequent concentration step is necessary to obtain the fully crystalline acid (7, 64). The remaining solvent–antisolvent mixture can be separated and recycled by distillation or, when the antisolvent is a gas, by pressure release. Because a gaseous antisolvent needs to be pressurized in order to be fed back into the process, the investment costs of compressors are substantial (65). The total energy requirement, however, is calculated to be 13 MJ/kg of pure acid, which is less than half of the energy needed for solvent distillation. Therefore, from an economic and environmental perspective, this process option is promising (65). The process economics of a solvent swing can be further enhanced through combination with a temperature swing, which would lead to increased acid recovery in systems with TOPO as an extractant (65, 165). Other options for back-extraction are the addition of short-chain amines, carbonates, and inorganic acids into an aqueous phase (for details, see **Supplemental Appendix A.9**).

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Comparing all options listed in **Table 5** illustrates the need for adjuvants in back-extraction. These adjuvants can influence subsequent crystallization or the recovery of the organic phase and present one major obstacle to process design. Regarding the feasibility of subsequent unit operations, the combined solvent and temperature swing offer a highly promising approach, as the carboxylic acid is already present in its fully protonated form, requiring little to no mineral acid addition (7, 21). However, as full recovery efficiencies have been demonstrated only for tertiary amines, electrochemical pH-shift electrolysis coupled to crystallization (9, 176) may be applicable to a wider range of reactive extraction systems.

5.2. Recycling of the Aqueous Fermentation Broth in In Situ Product Removal Applications

Reactive extraction can be used for ISPR (34, 37, 38). The basic idea is to couple reactive extraction directly to microbial conversion (24). ISPR can be implemented as depicted in **Figure 6**, where the cells are retained within the fermenter by a membrane unit and the cell-free fermentation broth is fed to reactive extraction. Another option is to couple cell retention and extraction using a membrane contactor (24). Furthermore, an organic solvent can be added directly to the fermenter (34, 177). Although the direct addition of the solvent eliminates membrane use, emulsions stabilized by cells at the liquid–liquid interface may form, complicating process control and pH adjustment for fermentation and extraction (177).

In all cases, the product is consistently removed and the product titer is kept below an inhibitory concentration (178). Therefore, the production phase is extended, the amount of substrate necessary for cell maintenance is reduced as a result of lower product toxicity, and the same amount of biomass can yield more product, boosting the overall substrate yield (178). Furthermore, the water footprint of the process is reduced because less aqueous phase needs to be discarded per gram of carboxylic acid produced. In contrast to the sequential processing of batch fermentations, which requires predominantly high yields, high selectivity, and good phase separation (see Sections 4.2 and 4.3), different considerations are necessary when implementing ISPR because the conditions for fermentation and purification must be aligned. Unlike in batch processing, the depleted fermentation broth remains within the process, reducing the need for high extraction efficiency for sufficient overall process yields (24). However, if the volume flow of fermentation broth to reactive

Supplemental Material >

extraction remains constant, the distribution coefficient constrains the maximum separation rate of the extraction equipment (see **Supplemental Appendix A.6**). In this case, a low distribution coefficient will lead to an increased product concentration within the fermenter, which can negatively influence fermentation performance (178). Consequently, very low distribution coefficients are not desirable. Yet, lactic acid fermentations in particular are regulated at high pH values such as 6 (9). Thus, a direct coupling of reactive extraction to fermentation cannot be realized, as extraction yields would be too low. As the addition of a mineral acid would lead to its accumulation within the process, electrochemical pH-shift electrolysis is recommended in order to attain adequate extraction levels while preventing salt accumulation (9). If fermentations are conducted at a lower pH value, residual carboxylic acid is still extractable from the fermentation broth and a direct coupling of reactive extraction to the fermenter is feasible (34). Furthermore, biocompatibility of the organic phase is vital for all reactor concepts.

Organisms will be in contact with the solvent, either directly in a biphasic system or as a result of the solubility of the solvent within the aqueous phase. Therefore, the solvent should not influence the organism's productivity, viability, or metabolism (179, 180). The literature distinguishes between phase and molecular toxicity in terms of solvent effects. Molecular toxicity can occur in all ISPR process options because of the reactive extraction solvent's solubility in water (**Table 2**). A cross-solubilized solvent degrades and inactivates proteins associated with the cell surface and can be integrated into the lipophilic parts of the cell membrane, affecting its permeability (180). If the cells are in direct contact with the organic phase, then the organic phase can block nutrient transport and disrupt the cell wall, possibly leading to the extraction of intracellular compounds (181) and thereby inducing phase toxicity. While phase toxicity can be severe, both phase and molecular toxicity lead to reduced productivity and cell death (24, 34). A possible indicator of good biocompatibility is a high log$P$ value, which leads to low cross-solubility and, thus, a low concentration of the solvent in the aqueous phase (180). Although this trend has also been observed in simultaneous testing of molecular and phase toxicity (182), this concept must be applied cautiously, as the functional groups of the solvents also influence biocompatibility (24).

Polar, readily water-soluble diluents such as 1-butanol or 1-hexanol are widely used (**Figure 2**). However, the biocompatibility of these diluents is severely limited (24, 182). Esters like isopropyl myristate (34, 182) or alcohols with a longer chain length, such as 1-decanol, are more promising (24, 113). Furthermore, alkanes, such as kerosene, hexadecane, isooctane, oleyl alcohol, and Shellsol TD, offer high biocompatibility (33) and low cross-solubility (**Table 2**). As TOA can be challenging to use alongside these diluents because of complex solvation (31), phosphate-based extractants might be more suitable, depending on the apparatus.

Extractants themselves can also influence biocompatibility. TOA and TOPO show high phase toxicity (33, 34) and can also influence biological activity via molecular toxicity (24, 183). However, ISPR operations using a membrane contactor are still feasible with these extractants (24, 147). TBP can affect mammalian cell lines (184), and as a result of its high cross-solubility (0.4 g/L) it can be assumed to have limited biocompatibility (185).

Therefore, in ISPR operations that incorporate reactive extraction systems, the use of membranes for cell retention—either as membrane contactors or as microfiltration units—becomes essential. Since the synergy between the distribution coefficient and apparatus type determines the maximum achievable productivity, these elements need to be properly aligned with the solvent's biocompatibility. Additionally, phase separation must be taken into account when using mixer-settlers or columns for reactive extraction (see Section 4.3). Given these criteria, nonpolar diluents with low cross-solubility and low viscosity, such as alkanes, are appropriate. The evaluation of TOPO or TOA usage should be based on the solubility of the carboxylic acid–extractant complex within the organic phase.

5.3. Disposal of Aqueous and Organic Waste Streams

The abovementioned integrated process concept not only enhances substrate conversion but also results in reduced waste streams, as both the fermentation broth and the organic phase are recycled within the system. Nevertheless, purge streams are essential to maintain stable process performance (186), making disposal an ongoing concern. Although minimizing the purge stream size is economically preferable, waste disposal or recycling must be practically feasible. Additionally, the choice of solvents is influenced not only by process viability but also by health and safety regulations.

With the regenerated organic phase, back-extraction can be performed multiple times (99), but a small purge stream prevails (186). The organic waste stream's composition depends on the back-extraction procedure and may include extractants, solvents, inorganic compounds, antisolvent, and some carboxylic acids. The organic solvent stream can be either purified and reused, via additional distillation steps (187), or disposed of in a hazardous waste incineration plant (187, 188). During incineration, alkanes are reduced to carbon and ash, the latter consisting mainly of inorganic compounds (189).

Extractants containing nitrogen and phosphate groups, however, are converted into their acidic gases. Halogenated and sulfonated diluents also pose problems and could require subsequent unit operations after incineration, such as the use of a caustic scrubber to remove toxic acids (189). As these additional process steps are correlated with increased operating and capital costs, it could complicate the implementation of reactive extraction. Furthermore, the de novo synthesis of solvents requires energy and is costly (187). As a result, distillation might be an option for organic-phase recovery, increasing circularity within these processes. However, its feasibility depends on the extractant, diluent, and impurities within the organic phase (187).

The process concept demonstrated in Section 5 creates two aqueous waste streams. One originates from fermentation, and its quantity depends on whether the operation is in batch or continuous mode (see Section 5.2). This purge stream includes components not extracted into the organic phase, such as traces of the organic and inorganic impurities discussed above (see Section 4.2). The second waste stream accumulates after crystallization and contains mainly the target compound in its concentrated form and possibly some impurities (see Section 4.2). Incineration is often not a viable way to treat aqueous purge streams because of their high water content (187, 190). Consequently, conventional treatment methods for industrial wastewater must be employed to ensure that the water meets the necessary purity level before being released into the environment (191, 192). Industrial wastewater treatment typically involves a combination of physical, chemical, and biological methods. Cross-solved organics present significant challenges for biological methods in particular because these compounds are often highly toxic to microorganisms, rendering biological treatment impractical (see Section 5.2) (193). In such cases, activated charcoal can remove hydrocarbons as well as more polar diluents from the aqueous phase (194, 195).

With regard to the commonly used diluents listed in **Table 2**, an organic phase composed of long-chain alkanes can easily be incinerated (187), has a low cross-solubility in the aqueous phase (**Table 2**), and can be removed from the aqueous phase by adsorption (195). Additionally, although long-chain alkanes (GHS08, H304) are toxic, their low water solubility and low vapor pressure make them safe to use along with adequate protection equipment (196, 197). In contrast, methyl isobutyl ketone, which is used in approximately 25.8% of the reactive extraction papers in our database, is classified as carcinogenic, mutagenic, and reprotoxic (GHS02, H351), and its high solubility in water challenges work safety as well as disposal of the aqueous phase. However, some active diluents, such as long-chain alcohols (C10–C12), have a low cross-solubility and are not as acutely toxic as alkanes. Therefore, aside from extraction performance (e.g., yield, selectivity), several important practical challenges must be taken into account during process development.

6. PROCESS ECONOMICS

In addition to the feasibility challenges described in Sections 4 and 5, process economics are decisive for process implementation. As stated in Section 1, we do not know of any industrial application of reactive extraction for the purification of carboxylic acids. However, some techno-economic comparisons between extraction and other purification strategies have been reported. The following subsections discuss these data.

6.1. Techno-Economic Evaluation of Reactive Extraction of Carboxylic Acids

Some studies focus on the overall process (198–200), whereas others simply compare different purification strategies (201, 202). As the overall process benefits from consideration of both fermentation and purification (7, 141), **Figure 10** displays only the selling or production prices derived from the overall processes using different purification strategies (198–200).

Fermentation is generally performed in batch or fed-batch mode (198–200). Reactive extraction of citric acid and itaconic acid employs TOA in 1-octanol and ethyl oleate, respectively. For reactive extraction of lactic acid, the literature focuses primarily on comparing downstream processing options without taking fermentation into account (201, 202). As a result, **Figure 10** depicts lactic acid purification by physical extraction using methyl isobutyl ketone (200). For citric acid, reactive extraction demonstrates favorable process economics, with a realistic selling price of \$0.73/kg (198), but it performs worse than adsorption (199) or precipitation (200) for itaconic or lactic acid.

Nonetheless, as shown in **Figure 10**, the selling price or processing costs vary greatly depending on the process conditions. The effects of different fermentation pH values, titers, and yields on

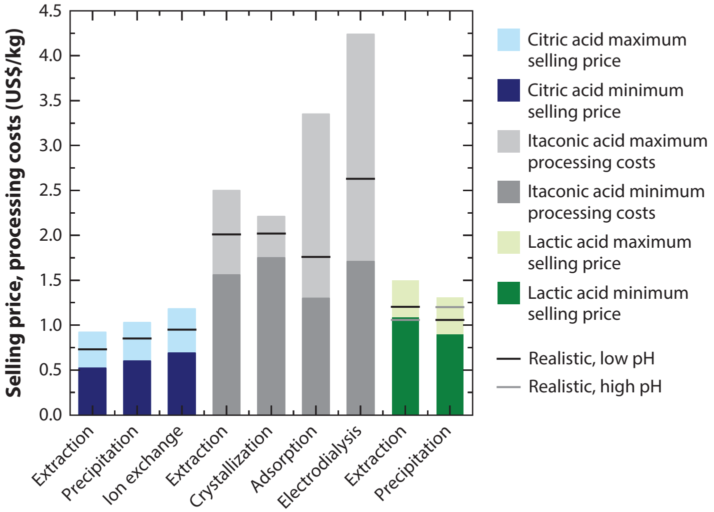

Figure 10

Techno-economic analysis of different purification options. Shaded areas indicate the possible price range, depending on cultivation conditions. Data for the citric acid selling price are from Wang et al. (198), who describe purification based on precipitation with $Ca(OH)_2$, solvent extraction with TOA in 1-octanol, and ion exchange using a cation resin. Data for itaconic acid production price are from Magalhães et al. (199), who compare crystallization, fixed-bed column adsorption by a Purolite PFA-300 resin, reactive extraction with TOA in ethyl oleate, and electrodialysis. Lactic acid selling price data are from Marchesan et al. (200), who use calcium precipitation and extraction with MIBK, with $Mg(OH)_2$ and HCl for pH adjustment. Abbreviations: MIBK, methyl isobutyl ketone; TOA, trioctylamine.

the process economics of lactic acid purification have been investigated via a holistic approach to bioprocess design (200). While extraction results in a lower production price at low fermentation pH values, precipitation has greater potential at high fermentation pH values (200). In citric and itaconic acid production, fermentation has been conducted only at low pH values, mitigating pH adjustment and the possible coextraction of inorganic anions (Section 4.2).

While in both cases fermentation costs still affect process economics, changes in downstream processes have a greater influence (198, 199). If the acids are purified by reactive extraction, then the cost of the organic phase is the most decisive factor for process economics (198, 199), demonstrating the necessity of efficient organic-phase recycling (see Section 5.1). Similar effects apply if ion exchange resins or electrodialysis is used for purification, as the resin and membrane use cycle are the key cost drivers (198, 199). For precipitation of citric acid, electricity costs are dominant (198), whereas for crystallization of itaconic acid, equipment costs have the greatest influence on production costs (199).

In summary, the economic feasibility of purification options depends not only on the target molecule but also on the fermentation parameters and operating conditions for downstream processing. For reactive extraction, the use of efficient, easily recyclable solvent systems is vital. Furthermore, to evaluate the full potential of reactive extraction, we need holistic approaches to process design that take fermentation strategies and solvent selection into account.

6.2. On the Economy of Scale

Another crucial factor in process economics is production scale. In general, biotechnological processes obey the economy of scale (4, 203). Orjuela et al. (203) propose an increase in the production capacity of succinic acid from 12,000 to 55,000 Mt/a, which would decrease production costs by 10% to 15%. Assuming a fermentation time of 3 days (204), the production capacity would correspond to a fermentation capacity of roughly 6,000 m^3. These suggestions are similar to those by Bobier et al. (4), who propose a total facility capacity of 2,000–5,000 m^3 using fermenters with a working volume of 150–400 m^3. According to these authors, production costs could be reduced by 50% (4). These assumptions are mirrored in the current production scale of lactic acid. For example, Corbion owns a production facility with a capacity of 125,000 Mt/a (205); in contrast, succinic acid facilities (now out of operation) were smaller by a factor of 10 (5).

However, a review of the literature reveals some limitations regarding scale. In particular, scale-up of fermentation can be challenging. As a result of nonideal mixing (206, 207), large-scale bioreactors contain gradients in oxygen transfer (206, 207), product accumulation (208), and heat transfer (207). These properties can change during fermentation. For example, if a fed-batch fermentation starts at 40 m^3, the filling volume can rise to 90 m^3, increasing the mixing time from 50 to more than 150 s (209). The industrial-scale fermenters described in the literature range from 19 to 600 m^3 (206, 207, 210–212) because the effect of varying cultivation conditions changes depending on the microbes (210); fungal cultivation tends to occur at the largest scale (210). Scale-up of extraction-based nonbiotechnological processes is more frequently realized on a large scale. The chemical industry uses primarily physical extraction in extraction columns (213). In 1968, the butadiene process at BASF SE already had a capacity of 70,000–80,000 Mt/a (42), and in 2014, the TPC Group had production facilities with a capacity of 272,000 Mt/a (214). For reactive extraction in the metallurgical industry, mixer-settlers operate in production facilities with a capacity of, for example, 250,000 Mt of copper per year (215; see **https://fcx.com/operations/south-america**).

In summary, both fermentation and extraction can run at economically feasible scales. However, efficient fermentation scale-up could be an obstacle to breaking the cost barrier in bio-based processes (4).

6.3. Evaluation and Scale-Up of Continuous Processes

As discussed in Section 4.2, continuous processes with ISPR can significantly enhance the overall process economics. For example, data from a study by Heerema et al. (152) on phenol fermentation using physical extraction with 1-octanol indicate that transitioning from a batch to a continuous process can reduce production costs by 68%. However, a limitation of the process proposed by Heerema et al. is the low mass transfer efficiency through the membrane module, especially in highly viscous systems (Section 4.3). Reactive extraction could improve process performance by increasing the driving force for mass transfer in membrane contactors, which is attributable to the high partition coefficients of reactive solvents (152, 216). Additionally, as noted in Section 4.2, TOA can broaden the operational pH range as a result of its overlapping extraction mechanisms. Despite these advantages, scaling up fermentation with ISPR presents significant challenges, and to date no industrial-scale processes have been reported.

For direct addition of an organic phase into fermenters, newly developed fermenters with a working volume of 12,000 L are available (see **https://dab.bio/technology-fermenter**). In contrast, perfusion-based bioreactors for pharmaceutical applications currently operate at scales up to 500 L (217). Therefore, the development of large-scale reactors tailored for ISPR is a pressing need.

7. CONCLUSION AND OUTLOOK

Biotechnologically produced platform chemicals are becoming increasingly important in the chemical industry (2, 6). To fully harness the potential of a bio-based circular economy, it is essential to reduce the carbon footprint and waste generated by biotechnological manufacturing processes while ensuring that they remain economically viable (22, 23). Current methods, such as distillation and precipitation (19–21), could be replaced with more efficient, cost-effective, and energy-saving technologies, such as adsorption or extraction (28). These alternative methods may also facilitate the production of novel molecules on an industrial scale. While the use of reactive extraction will depend on the product properties and process parameters, it can contribute to the transition to a bio-based economy.

On the basis of a comprehensive analysis of data from the literature, we have identified predictive modeling, selectivity, and implementation in apparatuses as bottlenecks in reactive extraction with extractants such as TOA, TOPO, and TBP. Furthermore, we find that the combination of back-extraction and subsequent unit operations, biocompatibility, and solvent toxicity limits overall process implementation. In particular, organic-phase recovery is vital for improved process economics. By connecting the most frequently used reactive extraction systems with these requirements, this review challenges the use of reactive extraction systems such as TOA with alcohol diluents and emphasizes the relevance of less polar diluents, such as alkanes or long-chain alcohols. Because the solubility of carboxylic acid–TOA complexes within these diluents can be impaired, phosphate-based extractants using extraction via hydrogen bonds can be employed instead. However, the lower distribution coefficients and narrower pH range of TOPO or TBP versus TOA may be a disadvantage in ISPR fermentation, where increased distribution coefficients at high pH values can be beneficial.

To tailor these diverse reactive extraction systems to these different process requirements, predictive modeling of extraction efficiency and selectivity could be combined with holistic process models considering fluid-phase properties. Such holistic process models have already been implemented for physical extraction (96, 97) and enable the early selection of solvents based on overall process requirements.

For process implementation and control, these models could be combined with visual online analytics for model-predictive control of extraction (49). Particularly in the field of biotechnology with varying feed streams, they could facilitate extraction column operation and thus be decisive for process feasibility. Overall, while reactive extraction systems show promise for purifying bio-based carboxylic acids, addressing the research gaps identified in this review will be crucial for unlocking their full potential and advancing a bio-based circular economy.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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