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Polyethylene glycol as a green chemical solvent

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Abstract

Polyethylene glycol (PEG) is an industrial commodity produced for applications foremost in the medial and personal care business. This review focuses on the much less explored application of using PEG as a chemical solvent. This review highlights some of the successful chemical synthesis strategies to illustrate the advantages of using PEG as an environmentally friendly reaction medium. These advantages include its ability to (a) dissolve a wide range of chemicals including mineral salts, (b) serve as a catalyst because of its acid/base functionalities, (c) complex metal cations, and (d) engage in redox chemistry. New developments of combining PEG with other green solvents and/or functionalizing PEGs are covered as well. The present state of physicochemical studies of PEG as a solvent is also provided and clearly shows the need for future research in this area to further promote the effective use of PEG as a medium for chemistry.

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Introduction

Global production of polyethylene glycol (PEG, H-[O$-$CH$_2$$-CH_2$]$_n$-OH) has been steadily increasing and is currently approaching 600,000 tons a year to supply market needs for medical, personal care and industry applications [1]. PEGs are also increasingly at the center of laboratory research activities. At the time of writing this review, typing 'PEG' in the SciFinder® search engine resulted in 392,000 hits, with recent annual hits near 20,000. Clearly, PEGs are used in a large variety of research fields. Many of these SciFinder® hits concern chemical and health care applications, such as paints, ointments, and cremes, where PEG is a minor ingredient, that is, an additive. Another large domain of hits concerns chemicals that were purposely functionalized with PEG. The synthetic strategies for 'PEGylating' chemicals have been reviewed [2,3]. These PEGylated chemicals expand their application portfolio. As for a few chemical applications, functionalized PEGs have been used as corrosion inhibitors [4] and as task-specific ionic liquids (ILs) [5]. As far as medical applications, there is a very rich body of literature concerning the development of PEGylated therapeutics that has been reviewed a number of times [6–8]. Because PEG is highly water-soluble, biocompatible, non-toxic, biochemically stable, and low cost, it has been the most commonly used polymer to covalently couple drugs for the purpose of drug delivery [6,9]. With respect to cancer drug development, the goal is to improve tumor penetration of anticancer drugs [10] by enveloping these with PEG, which also reduces the negative side effects of the drugs to the patients [11]. However, while the PEGylation has helped to increase the circulation time of these drugs in the blood by escaping the uptake by the reticuloendothelial system, once inside the tumor cells the PEGylated drugs unfortunately do show significantly inhibited gene expression, a dilemma termed as the 'PEG dilemma' [12].

This review focuses on PEG as a chemical solvent, which is an application of PEG where it is the main component. Therefore, the vast area of research about PEG as an additive is not the subject of this review. Furthermore, this review will only touch on those PEGylated chemicals that might serve as chemical solvents as well. The organization of this review is as follows. To start, a description of the need for chemical solvents in the context of green chemistry will be presented. Next, specific aspects of PEG as a solvent in chemical synthesis and heterogeneous catalysis will be highlighted. Other solvent systems involving PEG, such as deep eutectic solvents and PEGylated molecules, will be inspected next. It will become self-evident from the summarized successes that there is a need to improve our present molecular-level understanding of PEG as a solvent, in particular within the context of chemical interfaces. Therefore, the present state of physicochemical characterization of PEG will be presented. Finally, the review will be concluded by summarizing the key insights, as well as by providing an outlook for future interface research directions.

PEG as a solvent in general and a green solvent in particular

Chemical synthesis involves the breaking and/or formation of chemical bonds. In many cases, two or more reactants need to be brought into contact so that they can react with each other. This task can be accomplished by the use of a suitable chemical solvent that is capable of dissolving all reactants so that the reaction can take place in the solution phase. Depending on the reaction, the product may either precipitate out of the solution or stay dissolved in the solution. The precipitated product can be filtered off. The dissolved product is either extracted into another solvent, which then needs to be removed later on, or the solvent is boiled off, which includes the case of distillation if the product has also a comparably low boiling point. Traditional chemical solvents are therefore rather volatile, which contributes to making them flammable. The volatility also exposes the chemical worker to these solvents some of which may also be toxic. Exposure mitigation strategies such as using a fume hood are then needed to reduce exposure to acceptable levels.

It is rarely the case that a chemical reaction is quantitative with a 100% yield of product. Therefore, the obtained product contains impurities, which could be unreacted reactants, side products or a myriad of other impurities that may have been already present in the reactants or that may have been inadvertently introduced during handling of the involved chemicals. Purification steps such as extraction, recrystallization or column chromatography all require chemical solvents too. Furthermore, many of the analysis techniques, such as gas or liquid chromatography or NMR spectroscopy, also require the use of solvents. Thus, organic solvents are ubiquitous in the chemical and pharmaceutical industries.

Unfortunately, as already indicated, many organic solvents are hazardous for human health and the environment. Thus, one of the principles of Green Chemistry calls for avoiding problematic solvents or replacing them with innocuous ones [13]. Widely recognized replacement solvent options exist, but all solvent options have their drawbacks, and none can be universally used for all applications. For example, water and aqueous solutions cannot be used with solutes that react with water or are hydrophobic. Fluorinated solvents may be nonflammable, but their manufacturing is problematic and may contribute to the reduction of the atmospheric ozone layer. Supercritical carbon dioxide is very benign but requires high-pressure equipment and is not a suitable solvent for highly polar or ionic compounds. ILs can dissolve a wide range of chemicals and possess a negligible vapor pressure, which allows for product separtion by distillation or extraction, but many ILs are corrosive, and their toxicity to human health and environment is presently not well established [14].

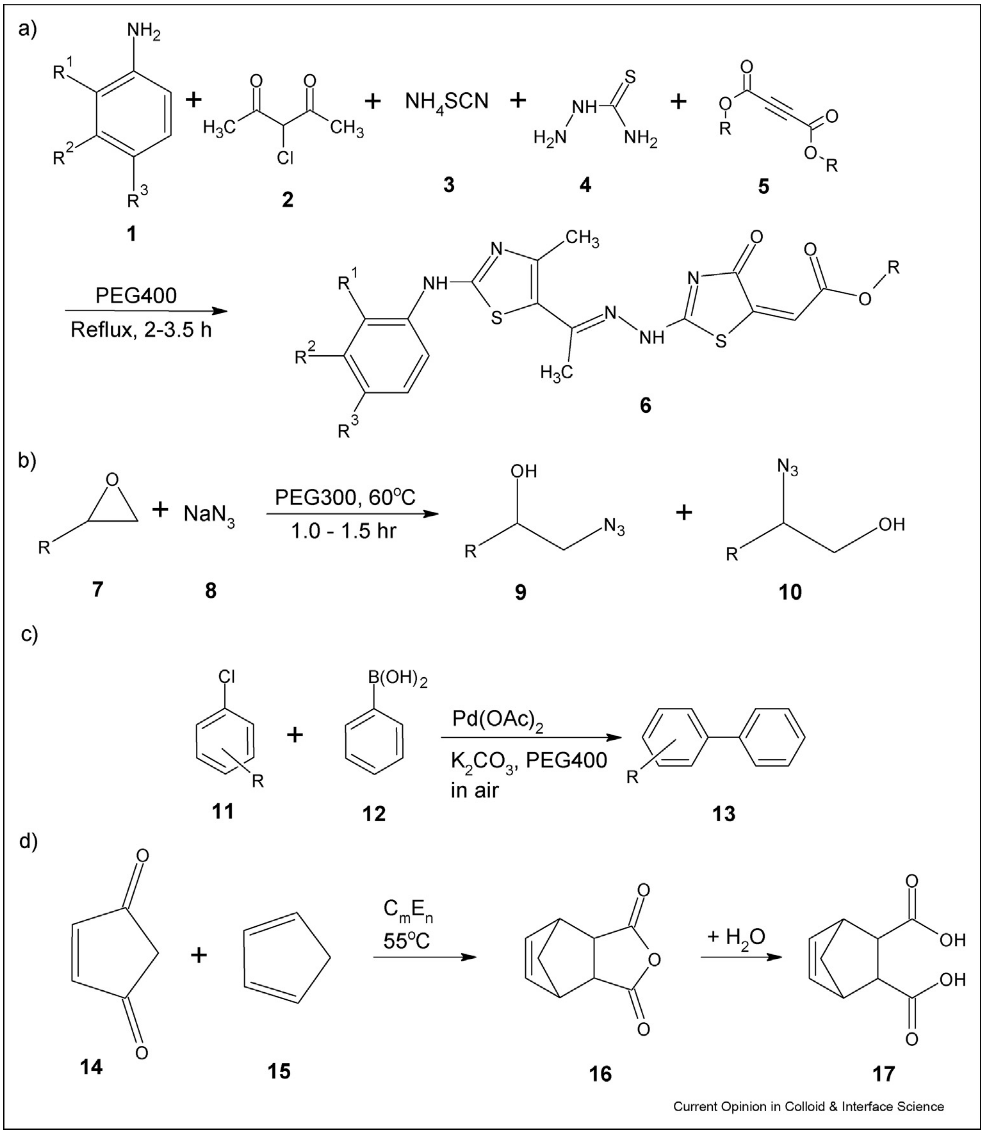
PEG has emerged over the past two decades as another viable green solvent option. Industrially produced PEG is polydisperse with the average molar mass indicated as part of the product name, such as PEG 400, where 400 g/mol is the average molar mass. PEGs are commercially available up to an average molar mass of 20,000, while those of higher molar mass are sold as polyethylene oxide (PEO). In this review, we are generally only concerned with low molar mass PEGs ($<1000\ \mathrm{g\cdot mol^{-1}}$) that are liquid at room temperature, an obvious prerogative for considering PEG as a solvent. Some aspects and solvent properties of PEGs and ILs are similar. Both are rather viscous liquid solvents. The volatility of both is low, which reduces solvent exposure to workers by inhalation. Both also readily absorb water from the atmosphere, making water the primary impurity. As will be shown in more detail, PEG is also like ILs capable of dissolving a variety of substances, including some mineral salts. The solvent properties of ILs can be tailored by different cation and anion combinations or the introduction of functional groups to the cation structure. By comparison, the solvent properties of PEGs are less dramatically changing with the increase of average molecular weight unless one considers also PEGylated chemicals as potential solvents. The latter will be explored in Section 5. The advantages of PEG as a solvent are that it is non-toxic, harmless to the environment and biodegradable [15]. PEG is also less expensive than ILs given that it is already produced industrially in large quantities. The following sections will highlight some of the many achievements to date of using PEG successfully and advantageously in chemical synthesis. Overall, our intent is to illustrate the need for physicochemical investigations to further improve the understanding of PEG and related compounds as chemical solvents and thus assist future developments of using PEG as a chemical solvent.

PEG as a reaction medium

PEG has been explored as a solvent for organic synthesis for more than two decades. Early work has been reviewed in 2005 [16–18]. Since then, much progress has been made, and more reviews have come about [19–22]. Three reviews on PEG as a reaction medium were published in 2020 alone [23–25]. Kardooni and Kiasat [23], as well as Soni et al. [25] provide excellent overviews of organic synthesis reactions that have been accomplished using PEG as a solvent, while the review by Campos specifically focuses on the synthesis of nitrogen-containing heterocycles [24]. This subsection intends to accentuate strengths and limitations of PEG as a solvent in organic synthesis and will only pick exemplary reports in the literature to illustrate these aspects. This will then set the basis for the subsequent sections that will highlight other success areas of PEG and PEG-related compounds as solvents in chemistry.

One strength of PEG as a chemical solvent is its ability to dissolve a wide range of compounds. Visak et al. [26] noted that PEG400 outperforms several ILs as a solvent for the high-value compounds thymol, ferulic acid, caffeic acid, and vanillic acid noting PEG's high polarity and proton donor/acceptor ability as contributing factors. They also note that PEGs may change their polarity from polar to nonpolar by changing their structural conformation from ordered helical structure to random coil-like structure, which makes benzene completely miscible in PEG200, PEG400, and PEG600 [26]. On the one hand, with the ability of PEG to dissolve a wide range of chemical compounds, it is conceivable to bring in contact reactants of disparate polarity using PEG as the reaction medium. On the other hand, reaction products might stay dissolved in the PEG reaction medium and could be difficult to isolate. The chance for the product to precipitate out of the PEG solvent solution increases with the molar weight of the product. Indeed, PEG has been a very effective solvent for the formation of a large product from multi-reactant

Figure 1



Example reactions in PEG (a–c) and in PEG-based nonionic surfactant C_mE_n (d). (**a**) One-pot multicomponent synthesis reported by Sujatha and Vedula [27], (**b**) epoxide ring opening reaction [23], (**c**) palladium catalyzed ligand-free Suzuki coupling in PEG400 under aerobic conditions [28,29], **(d)** Diels Alder cycloaddition. PEG, polyethylene glycol.

components in ‘one-pot’ multicomponent reactions. One impressive example of a one-pot multicomponent reaction was recently reported by Sujatha and Vedula [27] and is shown in Figure 1a.

Thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene) acetates were obtained in a one-pot reaction from substituted aniline (**1**), 3-chloroacetylacetone (**2**), ammoniumthiocynate (**3**), thiosemicarbazide (**4**), and dialkylacetylene dicarboxylate (**5**). After diluting the final reaction mixture into ice-cold water, the product precipitated out of the solution and was obtained by filtration [27]. Clearly, it is highly desirable to obtain such complex molecules in one synthesis step as opposed to a series of individual reaction steps as this saves not only a lot of time and reagents but also increases the overall product yield because each product isolation and purification step leads to unavoidable product loss. The example reaction shown in Figure 1a illustrates several additional aspects of successfully using PEG as a solvent in organic synthesis that will next be discussed one by one.

As is the case in many other one-pot multicomponent reactions, ring structures are formed during the reaction, liberating small molecules in the process, such as water, during condensation reactions. Consequently, the resulting product not only possesses a much larger molar weight than the individual reactant components but is also less polar. The lower polarity makes the product less soluble in the PEG solvent, which, if possible, can be further accentuated by adding a polar co-solvent, such as water. Condensation reactions such as the Biginelli condensation reaction or the Knoevenagel condensation reaction are indeed quite common for using PEG as a solvent, as can be seen in the review by Kardooni and Kiasat [23]. Water is very soluble in PEG at room temperature. The water liberated from a condensation reaction is thus more likely to interact with the PEG solvent and diffuse away from the product, thus further shifting the chemical equilibrium toward the product side. As could be shown in a study of water in the IL 1-ethyl-3-methylimidazolium methanesulfonate, it is not even necessary that the water be strongly bound to the solvent medium to effectively remove it from the condensation product molecule and thus prevent the reverse hydrolysis reaction [30].

The next aspect exemplified in the reaction of Figure 1a is that the PEG not only acts as the solvent medium but may also catalyze the reaction. The intermediates generated during condensation reactions are formed through accepting and/or donating protons. PEG can serve in both ways, as a proton acceptor as well as a proton donor. This makes PEG an acid-base catalyst as, in fact, shown by Sujatha and Vedula [27] in their proposed reaction mechanism of the reaction in Figure 1a.

Finally, it is noteworthy that the reactant ammonium-thioscyanate in Scheme 1 is a salt. Salts are typically not very soluble in conventional organic solvents because charged species cannot be supported well in a solvent medium of low polarity. However, PEG is capable of dissolving various mineral salts, some even to a surprisingly high concentration on the order of 1 mol·L^{-1} [31]. This has been attributed for quite some time to the ability of PEG to form PEG-metal complexes similar to crown ethers, which is why PEGs and crown ethers have both been used as a phase transfer catalyst [16]. This leaves the anion bare, that is, not ion-paired or part of a complex, and ready to react. This increased anion availability has recently been recognized as an important aspect in the facilitation of epoxide (**7**) ring opening reactions with sodium azide (**8**) to yield azidohydrins (**9** and **10**) as shown in Figure 1b [23]. The ability of PEG to at least partially dissolve inorganic solutes, complexed and/or as dissolved ion pairs, appears to be crucial for a number of organic synthesis reactions that require inorganic catalysts. Perusing the catalyst entries provided in the review by Kardooni and Kiasat [23], these include a wide variety of inorganic substances such as I_2, NH_4Cl, $NaHSO_4{\cdot}H_2O$, Na_2CO_3, K_2CO_3, $Mg(ClO_4)_2$, $BaCl_2$, $KAl(SO_4)_2{\cdot}12H_2O$, $Cu(OTf)_2$, $PdCl_2$, $SnCl_2{\cdot}H_2O$, $Fe(HSO_4)_3$, KH_2PO_4, $Yb(OPf)_3$, $CeCl_3$, $FePO_4$, $SiCl_4$, $ZrCl_4$, $Hf(NPf_2)_4$, and $H_3PMo_{12}O_{40}$. The salts with high ion charge are likely less soluble in the PEG [31] and are probably present as a solid phase.

The dynamic processes that occur at solid catalyst — PEG solution interphases have not been explored to the best of our knowledge. One organic synthesis area where this aspect is particularly important is cross-coupling reactions, which are catalyzed by transition metals, foremost palladium. In these reactions, the palladium that is initially introduced either homogeneously as a salt, such as palladium chloride or palladium acetate, or heterogeneously on a support material undergoes redox changes to form palladium metal that may be present as a suspended colloid [32,33]. The mechanistical details of the catalytic steps are difficult to elucidate and remain the subject of debate [33]. PEG has been very successfully used as a solvent for cross-coupling reactions as three reviews on this subject demonstrate [21,22,34]. PEG appears to play more than just the role of chemical solvent but is part of the redox chemistry to reduce Pd(II) to Pd (0) by oxidation of the hydroxyl end group [22]. Interestingly, the *in-situ* generated Pd (0) does not oxidize to palladium oxide, which would deactivate the catalyst. This allowed Han et al. [28,29] to let substituted aryl chlorides (**11**) couple with phenyl boronic acid (**12**) to form various biaryls (**13**) without using an inert gas environment but in the open air as shown in Figure 1c. The authors of these reaction studies did not attempt to recover the expensive catalyst. Recovery of the catalyst is generally more difficult in homogeneous catalysis than heterogeneous catalysis where the catalyst is either an insoluble solid, such as nickel powder [36] or fixated onto a support material. Recovery of the catalyst is in favorable cases easily achieved by filtration [37], centrifugation [38], or the use of an external magnet [39]. Various solid materials have been explored as catalyst support for coupling reactions in PEG, including modified multi-walled carbon nanotubes [38], functionalized magnetic nanoporous MCM-41 [37,39,40], and boehmite nanoparticles [41]. Within this context, it should be noted that high molar weight PEGs have been used as support material by PEGylating catalysts, such as various palladium complexes, functionalized ferrocene or aryl iodides (see review by Pires et al. [22]). These PEGylated catalysts have been mostly used in conjunction with some solvent other than PEG and thus do not technically fall under the scope of this review. However, in the case of PEG-SANM nanocomposite [42], PEG-$HClO_4$ [43], and PEG-OSO_3H [44], it is remarkable that these PEG supported catalysts allowed for solvent-free organic synthesis reaction.

Another advantage of using PEG as a reaction medium is that it is very suitable for microwave assisted organic synthesis. Some first reports appeared as early as 2001 using microwave assisted heating for Suzuki [45], Sonogashira [46], and Heck [47] coupling reactions in PEG. After these early reports, microwave-assisted synthesis in PEG was carried out to successfully obtain selenides and tellurides [48], 2,3-diarylimidazo [1,2-*a*] pyridines [49], oximes [50], N-methyliminodiacetic acid boronates [51], 4-thiomethyl-1,3-dioxolan-2-ones [52], and 4,7-dihydrotetrazolo [1, 5-a] pyrimidines [53].

To close this section, some directions of organic synthesis in PEG are highlighted that are presently less explored but appear to be very valuable for society. The primary types of catalysts used for coupling reactions are palladium based. However, palladium is rather expensive. In this light, it is remarkable that Qi et al. were able to achieve the Sonogashira coupling of aryl iodides using the much less expensive metal manganese [54]. Next, the work by Roy et al. to sequester carbon dioxide in the presence of PEG-600 should be mentioned in light of growing concerns over climate change induced by anthropogenic carbon dioxide in the atmosphere [55]. Finally, PEG has recently been successfully used as the reaction medium for the synthesis of metal-organic frameworks (MOFs) [56], thus crossing into the realm of inorganic synthesis. PEG may play an important role here as a solvent because of its abovementioned ability to dissolve to varying degrees mineral salts. The synthesis of MOFs in PEG may further be promoted when using microwave irradiation [57].

In summary, it is evident that PEG can be advantageously used as a green solvent alternative for a wide variety of organic synthesis reactions. PEG is capable of dissolving a wide range of compounds, including some salts allowing them to come in contact during the reaction medium, which made it a particularly successful solvent for multi-component, one-pot synthesis reactions. PEG's polar character, low vapor pressure, and high boiling point allow its use as a reaction medium in microwave-assisted synthesis. In many cases, PEG has been found to not only play the role as reaction medium but also to participate as part of the reaction and thus catalyze the reaction.

PEG in mixed solvent systems

This section focuses on mixed solvents that include PEG as one of the components. The binary solvent system of water and PEG has already sprung forth in Section 3 because some reactions liberate water as a side product, and some studies have compared the effect of present water on the synthesis outcome. For example, the mixed PEG-water system has also been used successfully as a reaction medium for the reaction shown in Figure 1c [35]. Other examples of successfully using water-PEG mixed solvent systems include the cyanation of aryl halides under microwave irradiation [58], cross-coupling of aryl iodides with alkynes [59,60], the synthesis of functionalized isoxazole substituted pyrroles [61] and carboxylate derivatives [62], and the synthesis of thiazoloquinoline scaffolds [63].

Water and lower molecular weight PEGs are completely miscible at room temperature. However, at elevated temperatures, liquid–liquid phase separation occurs. The consulate temperature decreases with the increasing average molar weight of the PEG. Combined with either a second polymer or a salt, these systems are referred to as aqueous biphasic systems (ABSs) and have been used for decades to recover and purify biomolecules because both liquid phases are water-rich and thus compatible for biomolecules [64]. These PEG-based ABSs have recently found renewed interest in combination with various ILs as a salt component to broaden the range of hydrophilicity/hydrophobicity in the respective equilibrium phases. In particular, the choice of the IL anion has a profound effect on the system's ability to form a polymer/salt ABS where anions of high hydrogen bond basicities enhance ABS formation, while the opposite is true for anions that are weak hydrogen bond acceptors [65].

Another major research area where mixtures of PEGs and ILs are explored as a beneficial solvent medium is electrochemistry. Water as a solvent in electrochemistry is limited by the range of voltages that can be applied without breaking down water in an electrolysis reaction to form oxygen and hydrogen. Molten salts overcome this limitation but require high temperatures. In a review written in a personal style by Wilkes [66], it can be seen that efforts to develop molten salt systems with much lower melting points began as early as the 1960s. The initial focus was placed on chloroaluminates with organic cations, which are liquid at room temperature. Ultimately the term ‘ionic liquid’ was coined to distinguish these from the general phrase ‘molten salts’. Unfortunately, chloroaluminates are also reactive with water. Thus, many anion combinations were tested. While these may not have improved the electrochemical performance compared to chloroaluminates, these tests sprung forward the seminal field of ILs as chemical solvents. Nevertheless, the search for (inexpensive) ILs suitable for electrochemistry continued, and in 2003, Abbot et al. [67] published their research on developing various eutectic mixtures of inexpensive organic salts, in particular choline chloride, and a second component such as urea. As these eutectic mixtures achieve melting temperatures below room temperature, Abbot coined the phrase deep eutectic solvents (DES). Martins et al. [68] recently proposed a more rigorous definition: “DES are eutectic mixtures for which the eutectic point temperature should be lower to that of an ideal liquid mixture”. Choline chloride continues to be one of the more common components of DES in combination with ethylene glycol oligomers or polydisperse PEGs [69–76]. There are also recent reports on DES consisting of PEG and hydroxide salts, as well as organic salts [77]. These types of DES are successfully used as a medium for chemical synthesis [78,79] and separations [80,81], including the extraction of amino acids [82] and sulfur [83]. Chen et al. [84] developed superbase-derived eutectic solvents using ethylene glycol for CO_2 capture and note as a cautionary remark that these DES possess high volatility in contrast to many other DES.

The other major electrochemical application that drives the exploration of combining PEG with ILs stems from the development of fuel cells. Here, PEO as a solid polymer electrolyte has found prominent use as solid polymer electrolyte rechargeable batteries [85,86]. Similar can be said for solar cells [87] that were further developed using PEGs [88,89], as well as DES with PEGs and ILs [90,91]. The ions from the IL and/or other salts are playing primarily the role of hydrogen bond acceptor partner in these electrochemical applications of IL-PEG DESs, while PEG is primarily playing the role of hydrogen bond donor (although the ether groups are certainly hydrogen bond acceptors as well) [89].

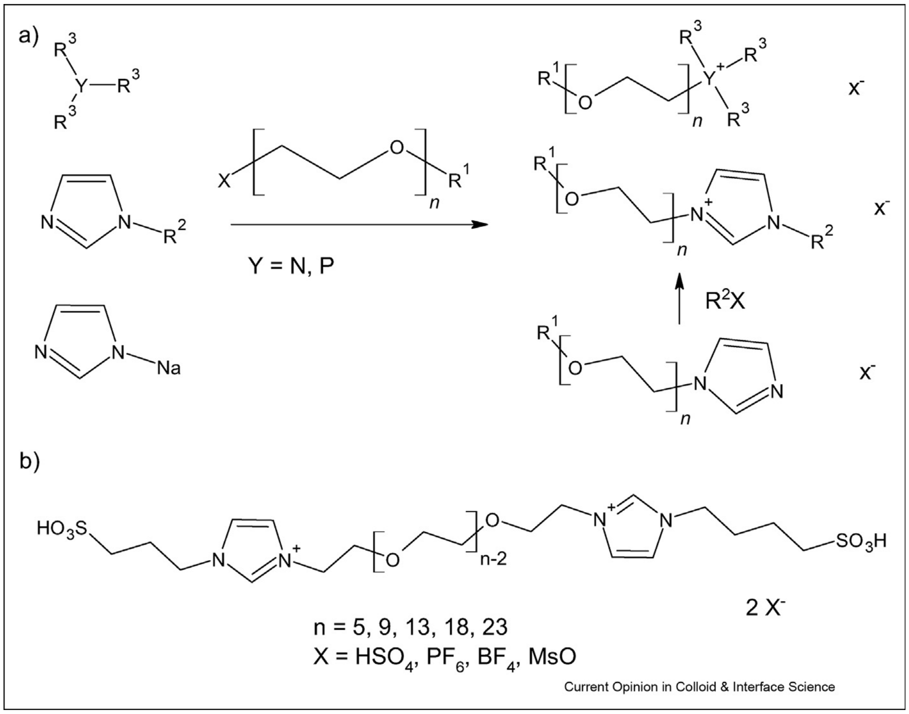
In closing this section, it can be seen that mixing PEGs with other constituents is another possibility of creating attractive green solvent media. In the next subsection, researchers have gone even one step further by chemically attaching ILs or other chemicals to PEG, that is, by PEGylation.

Solvents derived from PEGylation

We have pointed out already in prior Sections 1 and 2 that PEG has been repeatedly used as a building block to chemically attach other molecules such as drugs [6] or catalysts [92]. While these and other applications of PEGylated chemicals such as lubricants, for example, [93] are all very exciting, the focus of this review is on PEG as a solvent. Therefore, this review will focus on PEGylated chemicals that can serve as chemical solvents. There are mainly two groups of PEGylated solvents, PEGylated ILs and PEG-related nonionic surfactants. The former group of PEGylated solvents has only recently been conceived as designer solvents. The latter group consists of molecules that are longstanding industrial chemicals produced in large quantities and used as detergents and emulsifiers. Unlike PEG, PEG-based nonionic surfactants are presently not widely used as solvents in chemistry. PEGylated ILs will be discussed first before turning to PEG-based nonionic surfactants. An excellent review by Cecchini et al. [94] describes the state of the art of PEGylated ILs as solvents up to the publication year of 2014. Here, we are highlighting some of the principal tenets and new developments of PEGylated ILs.

Figure 2a shows general schemes for synthesizing PEGylated ILs. Interestingly, PEG mixtures of up to PEG6000 have been used even though PEGs of the average molar weight of 1000 $g{\cdot}mol^{-1}$ and higher are solid at room temperature. However, these PEGylated ILs form glasses with glass transition temperatures well below room temperature. As one can see from Figure 2a, the main types of PEGylated ILs are either synthesized from tertiary amines/phosphines or an N-substituted imidazole by reacting with a PEG that is functionalized to have a good leaving group X. The obtained anion X^- may then be substituted by another anion Z through methathesis with HZ or KZ. The opportunity to further functionalize these PEGylated ILs by choice of $R^1 - R^3$ is retained. Thus, in conjunction with the choice of anion, the properties of the PEGylated ILs can be further tailored for specific purposes, as is true for ILs in general. For example, the PEGylated IL PEG-DAIL shown in Figure 2b is not only a diprotic acid making the IL especially suitable for acid-catalyzed reactions but also displays advantageous phase behavior. Organic solvents become miscible in PEG-DAIL at high temperatures so that chemical synthesis can be conducted at temperatures above the miscibility temperature, while separations can be achieved at temperatures below the miscibility temperature [94].

Figure 2



a) General synthesis routes to PEGylated ILs, (**b**) thermoregulated acidic PEG DAIL. IL, ionic liquids; PEG, polyethylene glycol.

As summarized by Cecchini et al. PEGylated solvents have been used for the same type of chemical synthesis reactions as described in Section 2 for PEGs, in particular metal-catalyzed reactions and one-pot multicomponent reactions [95]. For these reactions, the PEG moiety adds the above-discussed advantages of stronger, crown ether-type chelating interactions with metals and metal ions, as well as serving as a redox partner. These properties help generate and stabilize metal nanoparticles during metal-catalyzed reactions and prevent metal catalyst leaching [94]. Another advantage of PEGylating ILs is that some of these have been shown to be biodegradable [95,96].

More recent developments of using PEGylated ILs include the following. PEGylated ILs have been shown to possess high efficiency in capturing iodine, which is important for developing a reliable method of removing radioactive iodine from the environment [97]. PEGylated ILs are increasingly evaluated as a medium for electrochemical applications, including electrochemical deposition [98] and rechargeable batteries [99], where it has been found that the mobility of the PEGylated IL cation is larger than the lithium cation. It should be mentioned that Chai et al. [100] used PEGylated viologens in a non-aqueous redox flow battery design that resulted in extended cyclability. With respect to biological systems, an imidazolium-based IL functionalized by methyl capped PEG and tert-butanol increased enzyme activity 2—4 fold compared with regular ILs [101]. A PEGylated quaternary ammonium salt was found to cross membranes 2—3 fold faster than any of the non-PEGylated ILs examined in the study [102]. A DNA binding agent was synthesized in a one-pot synthesis using the biodegradable PEG-bonded triethylammonium L-prolinate ([PEG-TEA]LP) [95]. Finally, proteins were efficiently extracted from a PEGylated IL — water system [103].

PEG-based nonionic surfactants are discussed next. These display similar advantages as PEGs with respect to physical and chemical properties, liquid at room temperature, negligible vapor pressure, nonflammability, excellent toxicological and biodegradability profile, and low material costs. Potentially, an even wider range of substances might be soluble in PEG-based nonionic surfactants compared to PEG itself because of their amphiphilic structure. Some mineral salts are also soluble in PEG-based nonionic surfactants, albeit somewhat less than PEG [31]. These solubility characteristics may allow reactants of disparate polarity to be brought in contact within a single phase. The author is taking the liberty here to include some work from his lab that illustrates these potentialities in the hope to encourage others to further explore PEG-based nonionic surfactants as a chemical solvent. Specifically, the

Diels–Alder cycloaddition reaction shown in Figure 1d was successfully conducted.

The reaction was carried out in two PEG-based nonionic surfactant formulations, that is, C_mE_n-type, with m being in both cases a 50/50 mixture of 8 and 10. The composition for n was chromatographically determined to be for one surfactant an average value of n = 5 with a mole fraction of 0.75 of n > 3, and for the other surfactant, the average value was n = 2. Both surfactants are hygroscopic with a saturation value of 2.5 ± 0.5 mass % as determined by Karl Fischer titration. Reaction products of Scheme 1 were analyzed by ^{1}H NMR spectroscopy. In a typical procedure, 0.2 g of maleic anhydride (**14**) was dissolved in 1.6 mL of surfactant and then mixed with 0.2 mL of cylopentadiene (**15**), freshly distilled from dicyclopentadiene, in a centrifuge tube at a water bath-controlled temperature of 55 °C. The reaction mixture was immediately allowed to cool first to room temperature then to 0 °C in an ice bath. When a few crystals formed on the bottom of the tube, the tube was centrifuged for several minutes and then returned to the ice bath, which would accelerate crystal formation. For obtaining cis-5-norbornene-endo-2,3-dicarboxylic anhydride (**16**), the crystals were collected in a Buchner funnel through vacuum filtration and washed with cold pure water until foaming in the filtrate ceased. The crystals were dried in a desiccator lined with anhydrous $CaCl_2$. For obtaining cis-norbornene-5,6-endo-dicarboxylic acid (**17**), 5 ml of water was added to the centrifuge tube and quickly mixed to allow the surfactant to dissolve into the water. The tube was centrifuged and the aqueous layer carefully decanted. The separation process was repeated until no surfactant remained in the product as observed by the absence of an oily appearance of the water and the waxy appearance of the crystals. The crystals were dried in a desiccator lined with anhydrous $CaCl_2$.

Many Diels–Alder reactions involve reactants that are quite disparate in polarity. Indeed, standard teaching laboratory procedures for the Diels–Alder reaction in Scheme 1 often use a mixed solvent of hexane and ethyl acetate [104], and even in ILs, the reaction was observed to be bi-phasic [105]. We observed that the reaction mixture was single-phased in both surfactants and produced spectroscopically pure cis-5-norbornene-endo-2,3-dicarboxylic anhydride (**16**) after the surfactant had been removed from the crystallized product by vacuum filtration with water (see supplementary material). The overall yield of the isolated product was for both surfactants only about 20% mainly due to loss of product during filtration. When the surfactant was removed by repeated extraction with water (longer contact time of water with the crystalline product), the product hydrolyzed completely to cis-norbornene-5,6-endo-dicarboxylic acid (**17**) in 89% overall yield of the isolated product for the surfactant with n = 5 and 45% yield for surfactant with n = 2. The lower yield obtained with the shorter surfactant is mainly because of its lower water solubility, requiring a larger number of extractions.

It is perhaps an unanticipated result by itself that crystallization can occur in a rather viscous solvent. This greatly facilitates the removal of the surfactant solvent from the reaction mixture. Unlike ILs, recovering and recycling the surfactant solvent, although desirable from a point of view of consering materials, is much less of a concern due to the biodegradability and the low costs of the surfactant solvent. Given the amphiphilic nature of the surfactant solvent, product recovery from the

Table 1

Thermophysical properties [with reference] of PEGs at 298.15 K an ambient pressure.

PEG	200	300	400	600
Density/g·cm^{-3}	1.12036 [111]	1.12165 [112]	1.12239 [113]	1.1214 [114]
Viscosity/mPa·s	49.45 [115]	68.67 [116]	92.797 [117]	135.73 [114]
Refractive index	1.4542 [109]	1.4607 [116]	1.4650 [113]	1.4637 [118]
Speed of sound/m·s^{-1}	1608.4 [111]	1562.50 [119]	1592.8 [113]	
Molar heat capacity/J·K^{-1}·mol^{-1}	416.3 [120]	609.4 [121]	772.5 [122][a]	
Dielectric constant	19.69 [109]	14.45 [123]	11 [123]	10.71 [123]

[a] Value obtained by interpolation.

surfactant solvent may generally prove to be difficult for reactions where the product does not crystallize. Future research is needed to explore for which applications nonionic liquid surfactants can be used advantageously as a new class of green solvents.

Physicochemical studies

Thermophysical properties

Despite the successes described in Section 3 using PEG as a solvent for chemical synthesis, there is a dearth of physicochemical studies on PEG with a specific focus to understand it better as a chemical solvent. The present situation is similar to what the state of ILs research was by the end of the 1990s. Organic chemists had shown many times success of using ILs advantageously as a solvent medium, but physicochemical studies to help this enterprise were lacking. However, one difference in this comparison is that PEG has been around for many decades. Therefore, some basic thermophysical properties of PEGs have been reported in the literature, oftentimes as part of binary systems with compounds that are miscible over the entire composition range. Some of these studies on binary systems involve ILs or other compounds to form DESs [90,106]. Horowitz et al. [107] noted that even for ethylene glycol oligomers, thermophysical data are scarce or entirely absent for pentaethylene glycol and higher ethylene glycol oligomers.

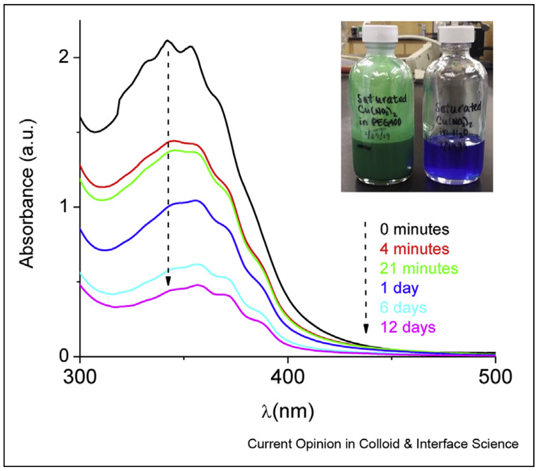
Table 1 summarizes some basic thermophysical properties for some PEG solvents and the literature from which they were taken. Densities, refractive index, and speed of sound do not vary much overall between the different PEGs. Viscosities and molar heat capacities increase with increasing molar weight as expected because intermolecular interactions and degrees of freedom both increase as well. The dielectric constant decreases with an increasing number of ethylene oxide repeat units, which are less polar than the terminal hydroxy functional groups. In addition to the thermophysical properties listed in Table 1, other physicochemical properties have been reported for neat PEGs. The vapor pressure of PEGs at 95 °C reduces by nearly an order of magnitude from 9.9 Pa for PEG200 to 0.2 Pa for PEG600, which are similarly low vapor pressures as for some common ILs [108]. The electrical conductivity of PEG200 was reported as 5.72 $\mu S\cdot cm^{-1}$, a small but non-negligible number [109]. The temperature dependence of the self−diffusion coefficient of PEG200 was shown to follow closely the Arrhenius law over the temperature range of 293−353 K, where the self−diffusion coefficient increased from about 0.2×10^{-10} $m^2\cdot s^{-1}$ to nearly 6×10^{-10} $m^2\cdot s^{-1}$, respectively [110].

PEG-water binary system

A novel description of the phase behavior of PEG400 with water is provided by Derkaoui et al. [124] where they show a new local scale demixing area involving micelles and spread gels. These authors point out that 'the physicochemical behavior of polyethylene glycols in aqueous solutions is still very puzzling' [124]. This is despite the fact that the all-in gauche structure of PEG's was studied as early as 1936 as summarized by Kan-Jen Liu [125]. An authoritative review on the phase behavior of PEGs with water, similar to one published for the PEG-based nonionic surfactants [126], is to the best of our knowledge missing. The author is only aware of a review on the phase behavior of PEGs with some ILs [26].

Although a review by Branca et al. [127] on experimental spectroscopic findings focuses on neat and aqueous high molar weight PEG systems, some of their summarizing conclusions may likely apply to lower molar weight PEGs as well. In the liquid state, the polyethoxy chain takes on a rather random conformational configuration, while in aqueous solution the polyethoxy chains tend to assume a helical trans-gauche-trans structure similar to the crystalline state. The added water is hydrogen bonding not only to the terminal OH groups but also to the ether oxygens that can accept up to two hydrogen bonds. This leads to a swelling of the PEG when water is added. The swelling is temperature-dependent as the hydration number decreases with increasing temperature. However, it remains unclear if PEG is aggregating in dilute concentrations. Interestingly, the interactions of PEG with D_2O compared with H_2O are sufficiently different to cause conformational changes of the PEG structure raising caution for experimental techniques that rely on isotopic substitution. Ensing et al. [128] showed that the water solubility of polyoxoethylene in contrast to

Figure 3



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UV−vis spectra of a sample of PEG400 saturated with $Cu(NO_3)_2$ after dilution with two volume portions of water. The feature near 350 nm is decaying slowly in time. The inset shows $Cu(NO_3)_2$ saturated in PEG400 (left bottle) and water (right bottle). PEG, polyethylene glycol.

polyoxymethylene, which is water insoluble, is not only due to steric effects, as is commonly believed, but also more likely due to the higher partial charge on the oxygen atoms leading to stronger inductive effects in polyoxoethylenes. Ensing et al. [128] arrived at this insight in part by using MD simulations, which were, as is often the case in other MD simulation studies, done on methyl capped PEGs for which first force fields were developed in the late 1990s [129,130]. Force fields specifically for PEGs were developed later but were optimized only in an aqueous solution [131,132], which may not reflect well the behavior of the neat PEG. Finally, one study by Singh and Pandey should be mentioned that does indeed focus on PEG and aqueous PEG solutions as a solvent medium where they used fluorescence spectroscopic probes to show that PEG preferentially solvates a betaine dye [130].

Salt solubility

As mentioned in prior sections, PEG is capable of complexing metal cations similar to crown ethers. This ability of PEG to interact strongly with metal cations sets also the basis of PEOs as solid polymer electrolyte material [133]. Thus, even though organic solvents are typically not good solvents for mineral salts, it may not be too surprising that PEG200 can dissolve some mineral salts such as KBr up to molar concentrations [31]. To this effect, the author wishes to share here some interesting observations made during an unpublished study in the author's lab determining the solubility of copper (II) nitrate in PEG400. After adding $Cu(NO_3)_2{\cdot}3H_2O$ in excess to PEG200, nitrogen gas was bubbled through the initially blue mixture overnight to remove the water content that was introduced by the crystal water of the copper (II) nitrate trihydrate. The picture shown in the inset of Figure 3 shows the resulting green suspension, a prominent difference in color and appearance compared with the dark blue clear saturated aqueous solution of copper (II) nitrate also shown in the inset of Figure 3. The suspension would persist for weeks until, finally, particles settled and a clear dark green liquid layer developed on top. Some of the liquid was extracted with a syringe and filtered through a 45-micron membrane for further inspection by UV–vis spectrophotometry. The copper (II) nitrate PEG solution was too concentrated. When diluting one part of copper (II) nitrate with two parts of water, the sample became noticeably warmer and the color temporarily changed to blue before turning to a pale green. Interestingly, this green color was visually observed to gradually fade away over days. The disappearance of color in time was thus monitored by UV–vis spectrophotometry in a repeated experiment shown in Figure 3. Instead of the typical nitrate feature near 306 nm, a broad feature centered near 350 nm with fine structure is observed possibly indicating the presence of individual vibronic transitions. The spectral feature decays first sharply during the first minutes and then increasingly slower in time such that it remains visible even after 12 days. A slight shift to longer wavelengths in time is also indicated. The temporal signal decay cannot be fit well by an exponential or biexponential function. Apparently, there are several processes involved that gradually change the coordination of the copper (II) ion in time as soon as the water has been introduced as a competing ligand. The copper (II) ion is initially likely coordinated with the oxygen atoms of the ethylene oxide backbone. The ease by which water can penetrate and exchange as a ligand may depend on the size of the ethylene oxide oligomer, faster with lower oligomers, slower with larger oligomers, which would explain the different timescales observed. However, more studies are needed to further understand these surprisingly slow processes. For example, one should not discount the possibility of ion-pairing in these complex chemical equilibria.

One experimental technique that could shed light on the coordination structure of ions dissolved in PEG is X-ray absorption spectroscopy. There are a number of relevant reports from studies of polymer electrolytes available in the literature even though the samples were typically prepared with PEO as a film of solid amorphous material. Given that these studies have been conducted several decades ago and may easily be overlooked, their main findings are summarized here.

Initial work focused on RbI, RbSCN [134], KI [135], and CaI_2 [136]. For Rb^+, four oxygen atoms were found to be coordinated that were split into two short and two long bonds in the case of RbI [134]. While there was evidence of RbI ion pairing, Ca^{2+} was found to be exclusively surrounded by 10 oxygen atoms and no iodine atoms [136]. For KI, it was shown that increasing temperature reduces the oxygen coordination number in PEO-KI [135]. A series of papers followed focusing on polymer electrolytes with the transition metal salts of $CuCl_2$ and $CuBr_2$ [137,138]; $CoCl_2$, $CoBr_2$ [138–142]; $ZnCl_2$, $ZnBr_2$, and ZnI_2 [138,141–149]; and $NiBr_2$ [138,143,149,150]. Some of these studies included lower molecular weight PEG as (part of) the matrix material [143,149]. The coordination number of Cu^{2+} and Zn^{2+} tends to overall stay at four with two Br and two O atoms as nearest neighbors. For Co^{2+}, the coordination number was found to be between 6 and 7, while Ni^{2+} actually shows coordination numbers up to 10 [138]. With decreasing salt content, the coordination to O increases relative to the halide [137,149], but in the case of $CuCl_2$, some halide remains in the first coordination shell even at very low salt concentration [137]. The addition of LiBr increases the Br^- coordination number and shifts equilibrium toward MBr_3^- and MBr_4^{2-}

complex ions at the expense of reduced O coordination [140,144,145]. The metal-to-oxygen bond distances remain either constant upon the addition of Li^+ or only change by a few 0.01 Å, which is hardly above the measurement uncertainty [137,139,144,149,151,152]. In summary, these prior works on solid electrolytes show the level of structural detail that can be expected if X-ray absorption spectroscopy were to be used for studying the coordination of ions dissolved in PEG solution.

Conclusions and outlook

After more than two decades of exploratory research, it can be safely stated that PEG is now recognized as an attractive green solvent alternative. It is especially effective as reaction media for multi-component one-pot synthesis reactions, metal-catalyzed reactions, fabrication of metal-organic frameworks, and combined with co-solvents, including ILs, for electrochemistry. Moreover, PEG is a suitable medium for microwave heating. A better understanding of PEG as a solvent is needed to further promote these green chemical synthesis research efforts. Some exemplary research areas that would seem to be of particular interest to the readership of *This Journal* include the following

(a) Phase behavior investigations could provide important insights on how to improve synthesis product recovery. Components of particular interest include ethyl acetate, water, and various salts. Ethyl acetate is frequently used as an extraction solvent. Water is often added after the completion of a reaction to force precipitation of the product. Possibly, schemes could be devised to incorporate product separation and purification with ABSs. Understanding how the presence of salts that are frequently used, for example, as catalysts, affects the phase behavior is important given the non-negligible solubility of mineral salts in neat PEG. Furthermore, there are new developments of combining green solvents with PEG as one of the components. DES are just one example of that. Phase behavior studies of these mixed solvents are present only in their infancy.

(b) Heterogeneous catalysis is increasingly used in synthesis with PEG as a reaction medium. Heterogeneous catalysis schemes include catalysts immobilized on high surface area materials where confinement effects will play a role. The interactions and mechanistic details at these interfaces in the presence of PEG are essentially unexplored [153].

(c) Solvation of solutes in PEG is largely unknown because the focus of solvation studies with PEG have focused on PEG as a solute rather than the solvent. For example, while PEG does not possess a nonpolar aliphatic tail in its structure compared to nonionic surfactants, it may still possibly aggregate in the presence of other components. The complex interactions of PEG with metal cations and how this affects solvation of the counter anion is in this regard one specific unresolved detail.

Results of these types of investigations are likely to not only advance the field of PEG as a chemical solvent but also many other fields because PEGs and PEGylated chemicals are used in a wide array of applications as indicated in Section 1.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cocis.2021.101537.

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