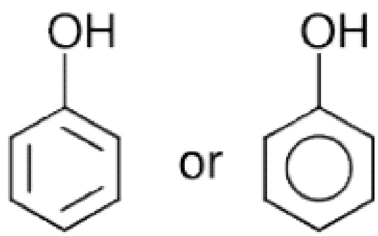
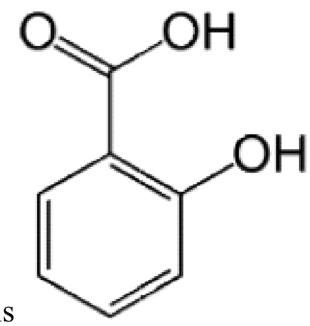
UNIT III (SEM –II)

In organic chemistry, **phenols**, sometimes called **phenolics**, are a class of chemical compounds consisting of one or more hydroxyl groups (−O H) bonded directly to an aromatic hydrocarbon group.[1] The simplest is phenol, C_6H_5OH. Phenolic compounds are classified as simple phenols or polyphenols based on the number of phenol units in the molecule.



Phenol – the simplest of the phenols



Chemical structure of salicylic acid, the active metabolite of aspirin

Phenols are both synthesized industrially and produced by plants and microorganisms.[2]

Properties

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Acidity

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Phenols are more acidic than typical alcohols. The acidity of the hydroxyl group in phenols is commonly intermediate between that of aliphatic alcohols and carboxylic acids (their pK_a is usually between 10 and 12). Deprotonation of a phenol forms a corresponding negative **phenolate ion** or **phenoxide ion**, and the corresponding salts are called **phenolates** or **phenoxides** (**aryloxides** according to the IUPAC Gold Book).[citation needed]

Condensation with aldehydes and ketones

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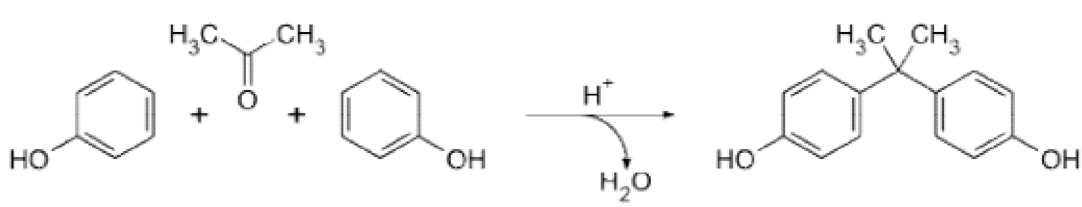
Phenols are susceptible to Electrophilic aromatic substitutions. Condensation with formaldehyde gives resinous materials, famously Bakelite.[citation needed]

Another industrial-scale electrophilic aromatic substitution is the production of bisphenol A, which is produced by the condensation with acetone.[3]



C-Alkylation with alkenes

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Phenol is readily alkylated at the ortho positions using alkenes in the presence of a Lewis acid such as aluminium phenoxide:[citation needed]

$CH_2{=}CR_2 + C_6H_5OH \rightarrow R_2CHCH_2\text{-}2\text{-}C_6H_4OH$

More than 100,000 tons of tert-butyl phenols are produced annually (year: 2000) in this way, using isobutylene ($CH_2{=}CMe_2$) as the alkylating agent. Especially important is 2,6-ditert-butylphenol, a versatile antioxidant.[3]

Other reactions

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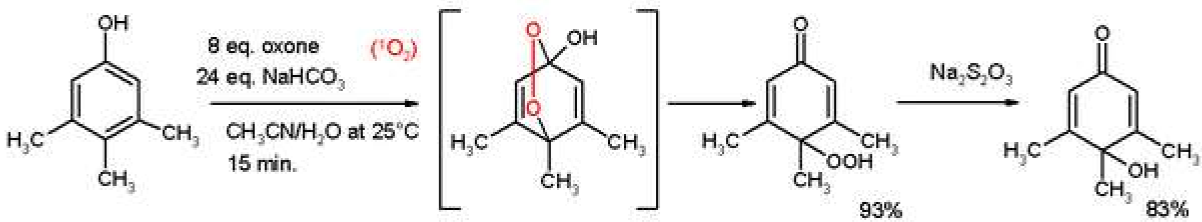
Phenols undergo esterification. Phenol esters are active esters, being prone to hydrolysis. Phenols are reactive species toward oxidation. Oxidative cleavage, for instance cleavage of 1,2-dihydroxybenzene to the monomethylester of 2,4 hexadienedioic acid with oxygen, copper chloride in pyridine[4] Oxidative de-aromatization to quinones also known as the Teuber reaction.[5] and oxone.[6] In reaction depicted below 3,4,5-trimethylphenol reacts with singlet oxygen generated from oxone/sodium carbonate in an acetonitrile/water mixture to a para-peroxyquinole. This hydroperoxide is reduced to the quinole with sodium thiosulfate.



Phenols are oxidized to hydroquinones in the Elbs persulfate oxidation.

Reaction of naphtols and hydrazines and sodium bisulfite in the Bucherer carbazole synthesis.

Synthesis

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Many phenols of commercial interest are prepared by elaboration of phenol or cresols. They are typically produced by the alkylation of benzene/toluene with propylene to form cumene then O
$_2$ is added with H
$_2$SO
$_4$ to form phenol (Hock process). In addition to the reactions above, many other more specialized reactions produce phenols:

- rearrangement of esters in the Fries rearrangement[7][8]
- rearrangement of *N*-phenylhydroxylamines in the Bamberger rearrangement[9][10]
- dealkylation of phenolic ethers
- reduction of quinones

- replacement of an aromatic amine by an hydroxyl group with water and sodium bisulfide in the Bucherer reaction[11]
- thermal decomposition of aryl diazonium salts, the salts are converted to phenol[12]
- by the oxidation of aryl silanes—an aromatic variation of the Fleming-Tamao oxidation[13]
- catalytic synthesis from aryl bromides and iodides using nitrous oxide[14]

Classification

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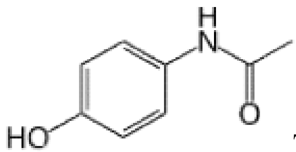

The best-selling drug in the U.S., Acetaminophen, also known as Paracetamol, is a phenol.

There are various classification schemes.[15]:2 A commonly used scheme is based on the number of carbons and was devised by Jeffrey Harborne and Simmonds in 1964 and published in 1980:[15]:2[16]

Phenol	the parent compound, used as a disinfectant and for chemical synthesis
Bisphenol A	and other bisphenols produced from ketones and phenol / cresol
BHT	(butylated hydroxytoluene) - a fat-soluble antioxidant and food additive
4-Nonylphenol	a breakdown product of detergents and nonoxynol-9
Orthophenyl phenol	a fungicide used for waxing citrus fruits
Picric acid	(trinitrophenol) - an explosive material
Phenolphthalein	pH indicator
Xylenol	used in antiseptics & disinfectants

Drugs and bioactive natural products

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More than 371 drugs approved by the FDA between the years of 1951 and 2020 contain either a phenol or a phenolic ether (a phenol with an alkyl), with nearly every class of small molecule drugs being represented, and natural products making up a large portion of this list.[17]

tyrosine	one of the 20 standard amino acids
L-DOPA	dopamine prodrug used to treat Parkinson's disease
propofol	short-acting intravenous anesthetic agent
vitamin K hydroquinone	blood-clotting agent that converts
levothyroxine (L-thyroxine)	Top-selling drug to treat thyroid hormone deficiency.

amoxicillin	Top-selling antibiotic
estradiol	the major female sex hormone

In organic chemistry, **ethers** are a class of compounds that contain an ether group—an oxygen atom bonded to two organyl groups (e.g., alkyl or aryl). They have the general formula R−O−R′, where R and R′ represent the organyl groups. Ethers can again be classified into two varieties: if the organyl groups are the same on both sides of the oxygen atom, then it is a simple or symmetrical ether, whereas if they are different, the ethers are called mixed or unsymmetrical ethers.[1] A typical example of the first group is the solvent and anaesthetic diethyl ether, commonly referred to simply as "ether" ($CH_3-CH_2-O-CH_2-CH_3$). Ethers are common in organic chemistry and even more prevalent in biochemistry, as they are common linkages in carbohydrates and lignin.[2]

Structure and bonding

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Ethers feature bent C−O−C linkages. In dimethyl ether, the bond angle is 111° and C–O distances are 141 pm.[3] The barrier to rotation about the C–O bonds is low. The bonding of oxygen in ethers, alcohols, and water is similar. In the language of valence bond theory, the hybridization at oxygen is sp^3.

Oxygen is more electronegative than carbon, thus the alpha hydrogens of ethers are more acidic than those of simple hydrocarbons. They are far less acidic than alpha hydrogens of carbonyl groups (such as in ketones or aldehydes), however.

Ethers can be symmetrical of the type ROR or unsymmetrical of the type ROR'. Examples of the former are dimethyl ether, diethyl ether, dipropyl ether etc. Illustrative unsymmetrical ethers are anisole (methoxybenzene) and dimethoxyethane.

Vinyl- and acetylenic ethers

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Vinyl- and acetylenic ethers are far less common than alkyl or aryl ethers. Vinylethers, often called enol ethers, are important intermediates in organic synthesis. Acetylenic ethers are especially rare. Di-tert-butoxyacetylene is the most common example of this rare class of compounds.

Nomenclature

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In the IUPAC Nomenclature system, ethers are named using the general formula *"alkoxyalkane"*, for example $CH_3–CH_2–O–CH_3$ is methoxyethane. If the ether is part of a more-complex molecule, it is described as an alkoxy substituent, so $–OCH_3$ would be considered a *"methoxy-"* group. The simpler alkyl radical is written in front, so $CH_3–O–CH_2CH_3$ would be given as *methoxy*(CH_3O)*ethane*(CH_2CH_3).

Trivial name

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IUPAC rules are often not followed for simple ethers. The trivial names for simple ethers (i.e., those with none or few other functional groups) are a composite of the two substituents followed by "ether". For example, ethyl methyl ether ($CH_3OC_2H_5$), diphenylether ($C_6H_5OC_6H_5$). As for other organic compounds, very common ethers acquired names before rules for nomenclature were formalized. Diethyl ether is simply called ether, but was once called *sweet oil of vitriol*. Methyl phenyl ether is anisole, because it was originally found in aniseed. The aromatic ethers include furans. Acetals (α-alkoxy ethers R–CH(–OR)–O–R) are another class of ethers with characteristic properties.

Polyethers

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Polyethers are generally polymers containing ether linkages in their main chain. The term polyol generally refers to polyether polyols with one or more functional end-groups such as a hydroxyl group. The term "oxide" or other terms are used for high molar mass polymer when end-groups no longer affect polymer properties.

Crown ethers are cyclic polyethers. Some toxins produced by dinoflagellates such as brevetoxin and ciguatoxin are extremely large and are known as *cyclic* or *ladder* polyethers.

Aliphatic polyethers

Name of the polymers with low to medium molar mass	Name of the polymers with high molar mass	Preparation	Repeating unit	Examples of trade names
Paraformaldehyde	Polyoxymethylene (POM) or polyacetal or polyformaldehyde	Step-growth polymerisation of formaldehyde	$–CH_2O–$	Delrin from DuPont
Polyethylene glycol (PEG)	Polyethylene oxide (PEO) or polyoxyethylene (POE)	Ring-opening polymerization of ethylene oxide	$–CH_2CH_2O–$	Carbowax from Dow
Polypropylene glycol (PPG)	Polypropylene oxide (PPOX) or polyoxypropylene (POP)	anionic ring-opening polymerization of propylene oxide	$–CH_2CH(CH_3)O–$	Arcol from Covestro
Polytetramethylene glycol (PTMG) or Polytetramethylene ether glycol	Polytetrahydrofuran (PTHF)	Acid-catalyzed ring-opening polymerization of tetrahydrofuran	$-CH_2CH_2CH_2CH_2O-$	Terathane from Invista and PolyTHF from BASF

(PTMEG)

The phenyl ether polymers are a class of aromatic polyethers containing aromatic cycles in their main chain: polyphenyl ether (PPE) and poly(*p*-phenylene oxide) (PPO).

Related compounds

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Many classes of compounds with C–O–C linkages are not considered ethers: Esters (R–C(=O)–O–R′), hemiacetals (R–CH(–OH)–O–R′), carboxylic acid anhydrides (RC(=O)–O–C(=O)R′).

There are compounds which, instead of C in the C−O−C linkage, contain heavier group 14 chemical elements (e.g., Si, Ge, Sn, Pb). Such compounds are considered ethers as well. Examples of such ethers are silyl enol ethers $R_3Si{-}O{-}CR{=}CR_2$ (containing the Si−O−C linkage), disiloxane $H_3Si{-}O{-}SiH_3$ (the other name of this compound is disilyl ether, containing the Si−O−Si linkage) and stannoxanes $R_3Sn{-}O{-}SnR_3$ (containing the Sn−O−Sn linkage).

Physical properties

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Ethers have boiling points similar to those of the analogous alkanes. Simple ethers are generally colorless.

Selected data about some alkyl ethers

Ether	Structure	m.p. (°C)	b.p. (°C)	Solubility in 1 liter of H_2O	Dipole moment (D)
Dimethyl ether	CH_3–O–CH_3	−138.5	−23.0	70 g	1.30
Diethyl ether	CH_3CH_2–O–CH_2CH_3	−116.3	34.4	69 g	1.14
Tetrahydrofuran	$O(CH_2)_4$	−108.4	66.0	Miscible	1.74
Dioxane	$O(C_2H_4)_2O$	11.8	101.3	Miscible	0.45

Reactions

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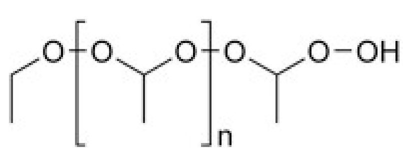

Structure of the polymeric diethyl ether peroxide

The C-O bonds that comprise simple ethers are strong. They are unreactive toward all but the strongest bases. Although generally of low chemical reactivity, they are more reactive than alkanes.

Specialized ethers such as epoxides, ketals, and acetals are unrepresentative classes of ethers and are discussed in separate articles. Important reactions are listed below.[4]

Cleavage

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See also: Ether cleavage

Although ethers resist hydrolysis, they are cleaved by hydrobromic acid and hydroiodic acid. Hydrogen chloride cleaves ethers only slowly. Methyl ethers typically afford methyl halides:

$$ROCH_3 + HBr \rightarrow CH_3Br + ROH$$

These reactions proceed via onium intermediates, i.e. $[RO(H)CH_3]^+Br^-$.

Some ethers undergo rapid cleavage with boron tribromide (even aluminium chloride is used in some cases) to give the alkyl bromide.[5] Depending on the substituents, some ethers can be cleaved with a variety of reagents, e.g. strong base.

Despite these difficulties the chemical paper pulping processes are based on cleavage of ether bonds in the lignin.

Peroxide formation

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When stored in the presence of air or oxygen, ethers tend to form explosive peroxides, such as diethyl ether hydroperoxide. The reaction is accelerated by light, metal catalysts, and aldehydes. In addition to avoiding storage conditions likely to form peroxides, it is recommended, when an ether is used as a solvent, not to distill it to dryness, as any peroxides that may have formed, being less volatile than the original ether, will become concentrated in the last few drops of liquid. The presence of peroxide in old samples of ethers may be detected by shaking them with freshly prepared solution of a ferrous sulfate followed by addition of KSCN. Appearance of blood red color indicates presence of peroxides. The dangerous properties of ether peroxides are the reason that diethyl ether and other peroxide forming ethers like tetrahydrofuran (THF) or ethylene glycol dimethyl ether (1,2-dimethoxyethane) are avoided in industrial processes.

Lewis bases

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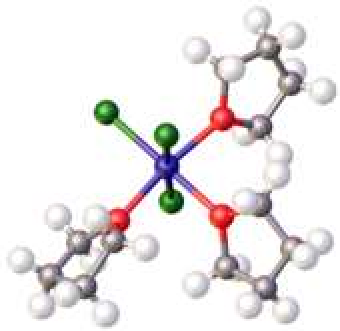 Structure of VCl3(thf)3.[6]

Vanadium, V
Chlorine, Cl
Carbon, C
Hydrogen, H
Nitrogen, N

Ethers serve as Lewis bases. For instance, diethyl ether forms a complex with boron trifluoride, i.e. borane diethyl etherate ($BF_3 \cdot O(CH_2CH_3)_2$). Ethers also coordinate to the Mg center in Grignard reagents. Tetrahydrofuran is more basic than acyclic ethers. It forms with many complexes.

Alpha-halogenation

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This reactivity is similar to the tendency of ethers with alpha hydrogen atoms to form peroxides. Reaction with chlorine produces alpha-chloroethers.

Synthesis

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Dehydration of alcohols

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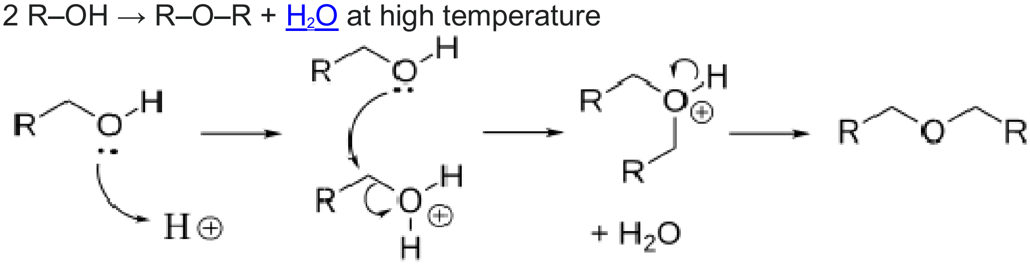
The dehydration of alcohols affords ethers:[7]

2 R–OH → R–O–R + H_2O at high temperature



This direct nucleophilic substitution reaction requires elevated temperatures (about 125 °C). The reaction is catalyzed by acids, usually sulfuric acid. The method is effective for generating symmetrical ethers, but not unsymmetrical ethers, since either OH can be protonated, which would give a mixture of products. Diethyl ether is produced from ethanol by this method. Cyclic ethers are readily generated by this approach. Elimination reactions compete with dehydration of the alcohol:

R–CH_2–CH_2(OH) → R–CH=CH_2 + H_2O

The dehydration route often requires conditions incompatible with delicate molecules. Several milder methods exist to produce ethers.

Electrophilic addition of alcohols to alkenes

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Alcohols add to electrophilically activated alkenes. The method is atom-economical:

$R_2C=CR_2$ + R–OH → R_2CH–C(–O–R)–R_2

Acid catalysis is required for this reaction. Commericially important ethers prepared in this way are derived from isobutene or isoamylene, which protonate to give relatively stable carbocations. Using ethanol and methanol with these two alkenes, four fuel-grade ethers are produced: methyl tert-butyl ether (MTBE), methyl tert-amyl ether (TAME), ethyl tert-butyl ether (ETBE), and ethyl tert-amyl ether (TAEE).[4]

Solid acid catalysts are typically used to promote this reaction.

Epoxides

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Main article: epoxide

Epoxides are typically prepared by oxidation of alkenes. The most important epoxide in terms of industrial scale is ethylene oxide, which is produced by oxidation of ethylene with oxygen. Other epoxides are produced by one of two routes:

- By the oxidation of alkenes with a peroxyacid such as *m*-CPBA.
- By the base intramolecular nucleophilic substitution of a halohydrin.

Many ethers, ethoxylates and crown ethers, are produced from epoxides.

Williamson and Ullmann ether syntheses

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Nucleophilic displacement of alkyl halides by alkoxides

R–ONa + R′–X → R–O–R′ + NaX

This reaction, the Williamson ether synthesis, involves treatment of a parent alcohol with a strong base to form the alkoxide, followed by addition of an appropriate aliphatic compound bearing a suitable leaving group (R–X). Although popular in textbooks, the method is usually impractical on scale because it cogenerates significant waste.

Suitable leaving groups (X) include iodide, bromide, or sulfonates. This method usually does not work well for aryl halides (e.g. bromobenzene, see Ullmann condensation below). Likewise, this method only gives the best yields for primary halides. Secondary and tertiary halides are prone to undergo E2 elimination on exposure to the basic alkoxide anion used in the reaction due to steric hindrance from the large alkyl groups.

In a related reaction, alkyl halides undergo nucleophilic displacement by phenoxides. The R–X cannot be used to react with the alcohol. However phenols can be used to replace the alcohol while maintaining the alkyl halide. Since phenols are acidic, they readily react with a strong base like sodium hydroxide to form phenoxide ions. The phenoxide ion will then substitute the –X group in the alkyl halide, forming an ether with an aryl group attached to it in a reaction with an S_N2 mechanism.

$C_6H_5OH + OH^- \rightarrow C_6H_5–O^- + H_2O$
$C_6H_5–O^- + R–X \rightarrow C_6H_5OR$

The Ullmann condensation is similar to the Williamson method except that the substrate is an aryl halide. Such reactions generally require a catalyst, such as copper.[8]

Important ethers

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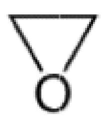
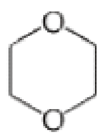
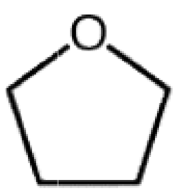
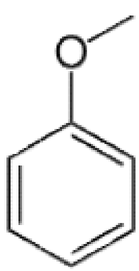
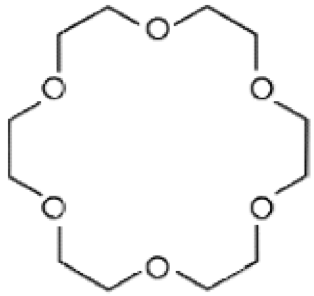
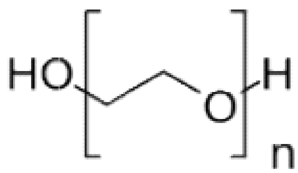
	Ethylene oxide	A cyclic ether. Also the simplest epoxide.
	Dimethyl ether	A colourless gas that is used as an aerosol spray propellant. A potential renewable alternative fuel for diesel engines with a cetane rating as high as 56–57.
	Diethyl ether	A colourless liquid with sweet odour. A common low boiling solvent (b.p. 34.6 °C) and an

		early anaesthetic. Used as starting fluid for diesel engines. Also used as a refrigerant and in the manufacture of smokeless gunpowder, along with use in perfumery.
	Dimethoxyethane (DME)	A water miscible solvent often found in lithium batteries (b.p. 85 °C):
	Dioxane	A cyclic ether and high-boiling solvent (b.p. 101.1 °C).
	Tetrahydrofuran (THF)	A cyclic ether, one of the most polar simple ethers that is used as a solvent.
	Anisole (methoxybenzene)	An **aryl ether** and a major constituent of the essential oil of anise seed.

	Crown ethers	Cyclic polyethers that are used as phase transfer catalysts.
	Polyethylene glycol (PEG)	A linear polyether, e.g. used in cosmetics and pharmaceuticals.
	Polypropylene glycol	A linear polyether, e.g. used in polyurethanes.
	Platelet-activating factor	An ether lipid, an example with an ether on sn-1, an ester on sn-2, and an inorganic ether on sn-3 of the glyceryl scaffold.