

Oxa acids via air oxidation of PEGs in aqueous systems

Dr Andreas Meudt and Dr Jörg Jung of Archimica introduce an economic and environmentally friendly approach to a unique class of compounds

Oxa acids are high-technology materials that are available in two series with the general structures given in Figure 1. In most cases, R is methyl (CH₃) in the mono-acid series. These materials have unique properties and are used in various applications in pharmaceuticals, nanotechnology, cosmetics and chemistry.

Archimica makes many oxa acids at a commercial or pilot plant scale, including 3,6-dioxa-heptanoic acid, 3,6,9-trioxa-decanoic acid, 3,6,9-trioxa-undecanoic acid, diglycolic acid, polyglycol-diacid and 3,6-dioxa-octanedioic acid. It can also make others on request and scale them to plant equipment.

The most remarkable characteristics of oxa acids are: a combination of a chemically inert hydrophilic chain with a reactive carboxylic acid moiety; outstanding complexing properties for metal ions; very good biodegradability; being low in toxicity and non-irritant; excellent heat stability; good water solubility; and, a very broad liquid range, due to low melting points and high boiling points. Those properties can be fine-tuned by a proper adjustment of the chain length and/or choosing appropriate materials from the mono- or diacid series.

Applications

One of the main applications for oxa acids is **pharmaceuticals**. Here, polyethylene glycols (PEGs) are widely used in peptide modification with the goal of enhancing the bioavailability and stability of proteins.¹⁻⁵ This is commonly known as PEGylation. The term refers to the covalent coupling of PEG to peptides, which is achieved by various coupling agents, including triazines, sulphonates and various 'active esters'.

The target of all those reagents is to attach an electrophilic centre to the PEG backbone, which can react with the nucleophilic parts of peptides (generally amino functions) or APIs in order to create a stable covalent bond. However, those techniques rarely give satisfactory results, due to incomplete conversion, the difficulty of removing toxic by-products or low selectivities if more than one reactive site is present in the peptide or API.

Oxa acids now offer an alternative approach. The carboxylic acid function can act directly as an electrophile after suitable activation. Archimica's coupling reagent T3P, which is known to give high selectivities in many reactions and which produces only non-toxic by-products, is often used in this coupling.⁶

PEG chains introduced via this route contain an additional oxygen atom, therefore this method is referred to as oxaPEGylation (Figure 2). A more detailed article on this very promising new technology will be forthcoming shortly.

Nanotechnology is a relatively new field and deals by definition with extremely small particles. Due to the high surface

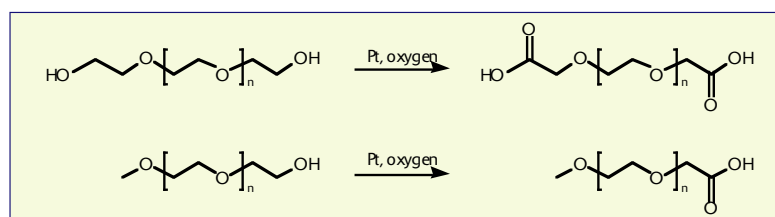
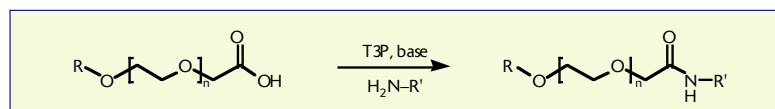
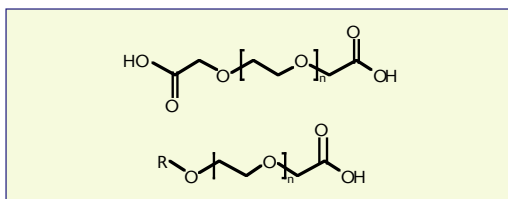


Figure 2 - (top)
OxaPEGylation of peptides or APIs with oxa acids & T3P as coupling agent

Figure 3 - (above)
Preparation of oxa acids via oxidation

energy, those particles tend to agglomerate strongly as soon as they are formed. This can be avoided by suitable additives that stabilise dispersions either by steric or electronic effects.

With oxa acids, both effects generally apply, resulting in very stable dispersions, even at low additive concentration, in many systems. This can be explained by the excellent complexing properties of oxa acids, which leads to strong interactions to certain surfaces.

Oxa acids are often used in **chemical & process applications**, because they form very stable and highly water-soluble complexes with metal ions. Due to those properties, oxa acids can be used for special phase transfer catalysis application ('open crown ethers') and also to avoid the unwanted precipitation of metal ions from aqueous solutions. Unlike many other complexing agents, such as EDTA, they are easily biodegradable which is important for large-scale use in aqueous systems.

Synthesis of oxa acids

The synthesis of oxa acids can be achieved via two different routes, both starting from PEG or PEG monoethers. One approach is the reaction of the starting materials with haloacetic acid or derivatives and base, resulting in chain-elongated products.⁷⁻¹⁰

The obvious disadvantage of this approach is the formation of molar amounts of salt. Due to the highly hydrophilic nature and the very good water solubility of all oxa acids, the separation of the formed salt is very difficult to achieve and not economically viable in a technical process.

As a consequence, the resulting products can only be used in applications which can tolerate the high salt content. However, high levels of salt interfere with most of the applications described above, which greatly limits the use of oxa acids produced via this route.

The second route to oxa acids uses the same starting materials as described above, but the products are formed by oxidation, leading to materials with the same number of carbon atoms and not to chain-elongated products.

The literature provides many methods and reagents for oxidations from primary alcohols to carboxylic acids, including compounds of Cr(VI), manganese or hypervalent iodine, plus bleach, under various conditions.¹¹⁻¹⁵ However, all of these methods create large amounts of inorganic by-products that cannot be separated easily and are often toxic.

From an economic and environmental point of view, the best oxidant would clearly be oxygen, since water is the only unavoidable by-product. Reactions using oxygen for the conversion of primary alcohols to carboxylic acids are described in the literature, generally using platinum as catalyst and water as solvent.¹⁶⁻¹⁷ However, basic conditions are often required, again resulting in the formation of an undesirable salt loading.

After suitable optimisation, this route proved to work also for the oxidation of PEGs and monomethylated PEGs in a neutral medium without the addition of bases, providing oxa acids free of inorganic impurities. If the conditions for the oxidation reaction, i.e. temperature, oxygen amount and catalyst, are chosen properly, the formation of decomposition products from ether cleavage and over-oxidation can be largely suppressed, providing pure materials as aqueous solution.

The subsequent separation of water by simple distillation provides the desired products. With this method, a wide range of oxa acids is accessible, only limited by the availability of the starting materials.

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