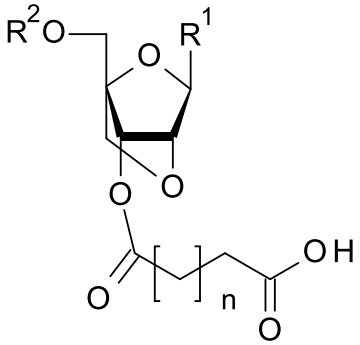
and the oligonucleotide is then synthesized by sequentially coupling monomers to the solid support-bound synthon. This iterative elongation eventually results in a final oligonucleotide compound which it is cleaved from the support and, if necessary further worked up to produce the final oligonucleotide compound.

In a further development linker molecules attached to the solid support have been introduced for carrying out the oligonucleotide synthesis more efficiently, particularly on the automated process synthesizers nowadays used. For instance the Int. Patent Publication WO 2005/049621 or WO 2006/029023 discloses such linker compounds. Oligonucleotide elongation usually starts from an O-dimethoxytrityl (O-DMT) on the linker molecule.

However, in the synthesis of LNA oligonucleotides, it was found in that to a certain extent the first coupling on the linker molecule failed, resulting in final oligonucleotides with a substantial amount of (N-1) impurities, i.e. oligonucleotides with one lacking nucleoside at the 3'-end.

Object of the present disclosure therefore was to reduce the amount of 3`-end (N-1) impurities to a great extent, as such impurities can hardly be removed by state-of-the-art chromatographic purification methods and cause thereof a substantial loss in yield, e.g. by tight fraction pooling in the preparative chromatography step and/or an unsatisfying impurity profile in the isolated LNA oligonucleotide.

In one aspect, there is provided LNA-dicarboxylic acid derivatives of the formula I



I

or salts thereof,

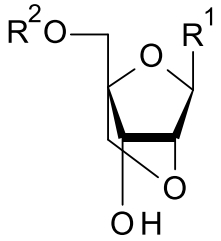
wherein

R^1 is a nucleobase or a modified nucleobase

R^2 is a hydroxy protecting group and

n is an integer from 1 to 5.

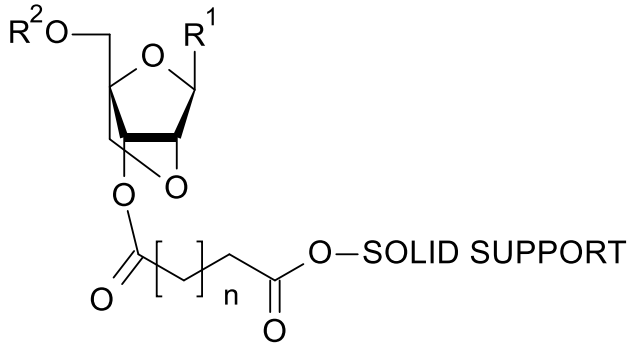
In another aspect, there is provided a process for the preparation of LNA-dicarboxylic acid derivatives of formula I comprising the reaction of an LNA alcohol of formula II



II

wherein R^1 and R^2 are as above, with a C_{2-6}-dicarboxylic acid anhydride, in the presence of a base and an organic solvent to form the LNA-dicarboxylic acid derivatives of formula I.

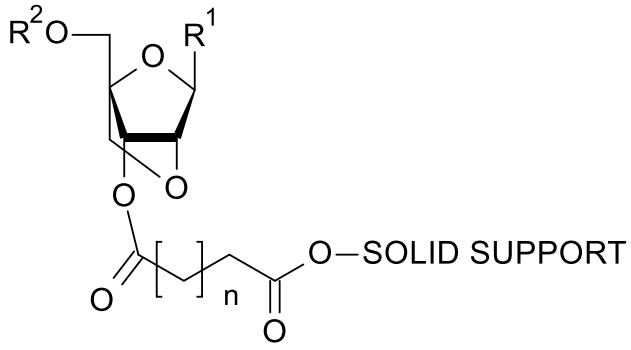
In another aspect, there is provided use of the LNA-dicarboxylic acid derivatives of the formula I as defined herein, for the preparation of a preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis.

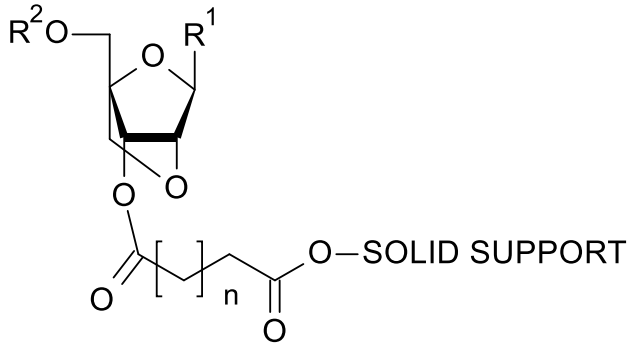
In another aspect, there is provided a preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis.

In another aspect, there is provided use of the preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis as start material in oligonucleotide synthesis.

It was found that with LNA-dicarboxylic acid derivatives of the formula I as described above, which can be attached to a solid resin (Int. Patent Publication WO 1992/006103) and act as pre-loaded resin the N-1 failures can be reduced to great extent.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "C_{1-6}-alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms, and in a more particular embodiment 1 to 4 carbon atoms. Typical examples include methyl, ethyl, propyl, isopropyl, n-butyl, *i*-butyl, sec-butyl, or *t*-butyl, preferably methyl or ethyl.

The term "C_{1-6}-alkyoxy" denotes a C_{1-6}-alkyl group, more preferably a C_{1-4}-alkyl group, as defined above attached to an oxygen atom. Typical examples include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, i-butoxy, t-butoxy, preferably methoxy or ethoxy.