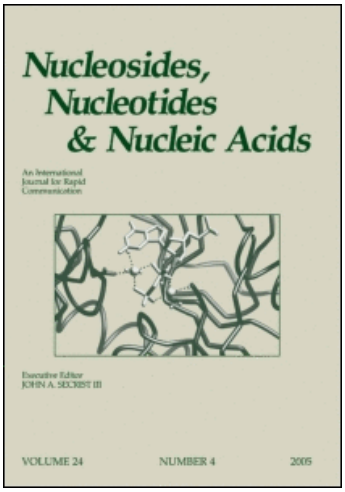

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The Pro-Oligonucleotide Approach: Chimeric Dodecamers Bearing Six Bioreversible Protecting Groups

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THE PRO-OLIGONUCLEOTIDE APPROACH: CHIMERIC DODECAMERS BEARING SIX BIOREVERSIBLE PROTECTING GROUPS.

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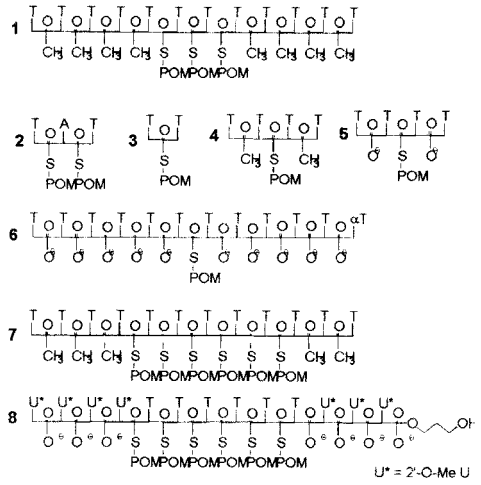
ABSTRACT : Chimeric dodecamers prooligo bearing a 6 POM gap were fully hydrolyzed in total CEM cell extract with half-lives of about 30 h.

We have already shown that the phosphate negative charges of mononucleotide could be temporarily masked with bioreversible pivaloyloxymethyl (POM) or S-acylthioethyl (SATE) protecting groups, in order to intracellularly deliver the first metabolite (*i.e.* the monophosphate nucleoside) [1].This approach was extended to oligonucleotide to yield the pro-oligonucleotides (pro-oligo). Thus we have shown that dodecathymidines bearing three central bioreversible protecting groups (POM or Me-SATE) and methylphosphonate flanks could release, in total CEM cell extract (TCE), the three charged oligos by a carboxyesterase mediated mechanism [2,3]. In order to elicit human RNase H activity a 5 or 6 phosphodiester window is required in chimeric oligos [4]. However since prooligo with a 3 POM gap has shown a decreasing rate of hydrolysis for the last hydrolysis[2]. The question that arises is « Could we fully hydrolyze a chimeric 6 POM gap pro-oligo by a mechanism mediated by carboxyesterases? »

For this purpose, we studied in TCE, the influence of the neighborhood (charged or neutral) on the rate of hydrolysis by carboxyesterases of a POM bioreversible group.



Pro-oligo	HPLC RT* (min.)	$t_{1/2}$ in TCE (first hydrolysis) (h)	$t_{1/2}$ of fully unmasked oligo (h)
1	51.0	0.1	9.6
2	46.7	0.4	4.8
3	44.0	2.2	
4	42.3	2.1	
5	36.4	5.6	
6	31.5	22	
7	59.0	1.4	31
8	51.0	0.1	30

Half-lives of prooligo **1** to **8** in total CEM cell extract. *RT on C_{18} column

Our data shown that half-lives seem reverse connected with HPLC retention time (*i.e.* $t_{1/2}$ is high when RT is low). During the monitoring by HPLC of the incubation in TCE of **7** and **8**, we noticed that each hydrolysis proceeded with its own rate and could be very different from one to another. These data could be explain by the change of lipophilicity of the substrate compound due to the removal of POM groups. Hence when optimal of lipophilicity (*i. e.* optimal substrate ability) is arisen the rate of hydrolysis is the highest. A last POM group could be hydrolyzed (pro-oligo **6**) and a 6 gap could be fully unmasked ($t_{1/2}$ 30 to 31h). Furthermore, it is expected that hydrolysis will be much more rapid in intact cells (*i.e. in vivo*). Thus a dodecamer chimeric prooligo bearing a 6 POM gap is compatible with our pro-oligonucleotide approach.

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