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DIALKYL ALUMINIUM CHLORIDE: A REAGENT FOR REMOVAL OF TRITYL GROUP FROM TRITYL ETHERS OF DEOXYNUCLEOSIDES, DEOXYNUCLEOTIDES, AND OLIGODEOXYNUCLEOTIDES

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Summary: Detritylation of N-acyl-5'-O-tritylated deoxynucleosides, deoxynucleotides, and oligodeoxynucleotides have been quantitatively achieved in minutes at room temperature by using diethylaluminium chloride or diisobutylaluminium chloride. Reactions take place in unpolar solvents in homogeneous phase under completely aprotic conditions.

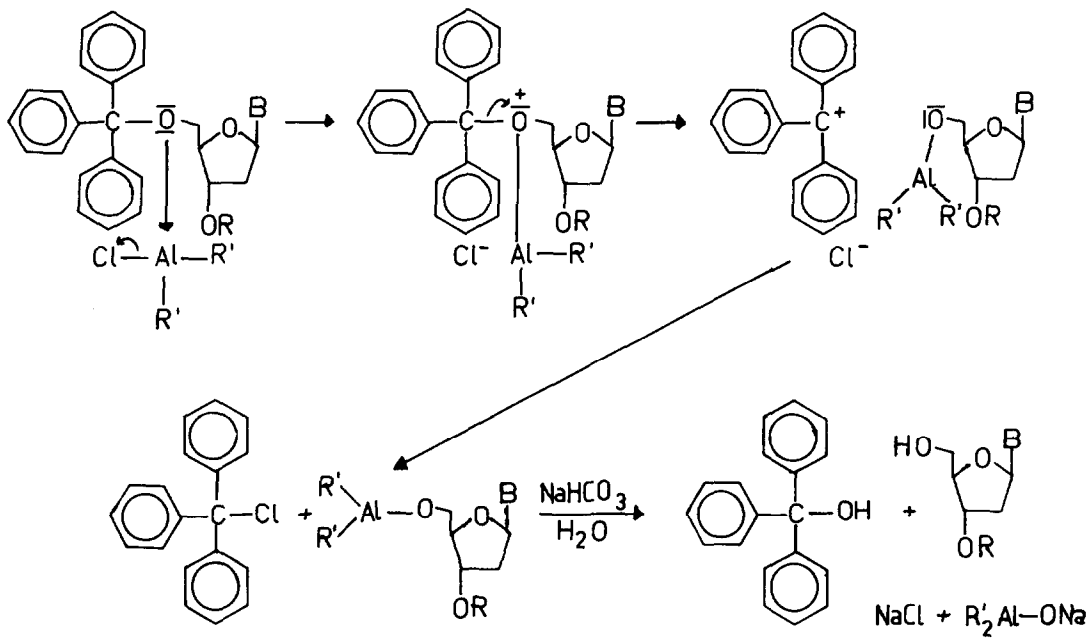
The trityl (triphenylmethyl) group, as a protection of 5'-OH-function of the nucleoside moiety, is most desirable as tritylethers are stable in slightly acidic, basic and other reaction conditions in use for oligodeoxynucleotide synthesis[1]. However, this desirable group, as a protection of 5'-OH, does not find wide application, because very drastic conditions using protic acids were required for its removal from nucleosides where cleavage is accompanied by depurination. Zincbromide in methylene chloride[2] or nitromethane[3] has been used recently for detritylation without cleavage of the glycosidic bond.

A drawback, however, of the Lewis acid $ZnBr_2$ is its low solubility in nonpolar aprotic solvents. In nitromethane the maximal concentration which can be obtained is 0.1 M[3], in methylene chloride $ZnBr_2$ has only a very low solubility so that reactions take place in heterogeneous phase[2]. This is particular disadvantageous if $ZnBr_2$ should be used for the detritylation during oligonucleotide synthesis performed on polymeric carriers, because in this case high concentration of reagent has to be employed. Therefore co-solvents have been introduced such as methanol[1, 2] or even water[4]. This opens the possibility that hydrobromic acid is being formed which will cleave the N-glycosidic linkage of N-acylated deoxynucleosides. Thus the advantage of using a Lewis acid instead of the direct use of a protic acid is lost.

We therefore like to report in this communication a solution to this problem by the use of dialkylaluminium chlorides for detritylation in homogeneous phase under nonpolar and completely aprotic conditions. Diisobutyl-

aluminium chloride in toluene and diethylaluminium chloride in hexane have been found to remove trityl groups from 5'-tritylether of deoxynucleoside, deoxynucleotide and oligodeoxynucleotide dissolved in dry methylene chloride having various protecting groups for $-NH_2$ and 3'-OH without any depurination or side reaction with the other protecting group(s) present in the molecule. Of all the various protected nucleosides used, only 5'-O-trityl-3'-O-levulinyl deoxythymidine under the reaction condition used was found to give after complete detritylation the desired 2'-deoxy-3'-O-levulinylthymidine (55%) and the hemiketal (28%) derived from free 5'-OH and C=O of levulinyl moiety (shown by PMR). In all cases detritylation was quantitative in 2 to 10 minutes at room temperature.

The mechanism of this reaction could probably be as shown in Scheme 1, whereas B is thymine or N-acylated adenine, guanine, cytosine,



R' is H, acyl or silyl protecting group, phosphodiester or phosphotriester group or an oligonucleotide chain, R'' being ethyl or isobutyl. During dropwise addition of the dialkylaluminium chloride a yellow colour of the trityl cation appears due to a reaction of Tr-Cl with the excess of R_2Al-Cl forming $Tr^+ R_2AlCl_2^-$ (this could be demonstrated in an appropriate model reaction). The back reaction is not likely to occur under these conditions because the 5'-OH is blocked. Coloration is a good indicator that reaction conditions

Table 1: Detritylation with diethylaluminium chloride (A) and diisobutylaluminium chloride (B)

Product	Solvent per mmole (ml)	Equivalents of reagent ( )	Time in min	Deprotection[3] in %	Isolated Yield after Chromatography in %
(Tr)T_d[1]	CH_2Cl_2 (25)	10 (B)	10	100	
(Tr)tl^4C_d	CH_2Cl_2 (30)	10 (B)	10	100	
(Tr)bz^6A_d	CH_2Cl_2 (30)	12 (B)	10	100	
(Tr)bz^6A_d(tBuBz)	CH_2Cl_2 (30)	15 (B)	10	100	
(Tr)an^4C_d(tBuBz)	CH_2Cl_2 (30)	15 (B)	10	100	
(Tr)ib^2G_dp(ClPh)	CH_2Cl_2 (50)	20 (B)	10	100	
(Tr)T_d(Lev)[2]	CH_2Cl_2 (20)	10-15 (B)	10	100	
(Tr)T_d	CH_2Cl_2 (20)	15 (A)	2	100	
(Tr)tl^4C_d	CH_2Cl_2 (20)	10 (A)	2	100	
(Tr)ib^2G_d	CH_2Cl_2 (100)	10 (A)	2	100	
(Tr)bz^6A_d(tBuBz)	CH_2Cl_2 (60)	15-20 (A)	3	100	85
(Tr)an^4C_d(tBuBz)	CH_2Cl_2 (60)	10 (A)	3	100	85
(Tr)T_d(tBuPh$_2$Si)	CH_2Cl_2 (50)	10 (A)	3	100	80
(Tr)T_dp(ClPh, TCE)	CH_2Cl_2 (30)	10 (A)	3	100	70
(Tr)T_d(Lev)[2]	CH_2Cl_2 (30)	10 (A)	3	100	
(Tr)bz^6A_dp(ClPh)tl^4C_d	CH_2Cl_2 (45)	10 (A)	3	100	
(Tr)T_dp(ClPh)tl^4C_d	CH_2Cl_2 (50)	10 (A)	3	100	
(Tr)ib^2G_d(ClPh)bz^6A_d	CH_2Cl_2 (100)	10 (A)	3	100	

1) With respect to the abbreviations used see lit. 1 and 6.

2) It results a product mixture: 3'-O-levulinyl deoxy thymidine (55-60%) and cyclic hemiketal (23-28%) characterized by pmr.

3) Complete detritylation has been demonstrated by tlc on silica gel.

are suitable for detritylation. During work up using extraction with an excess of aqueous sodium or triethylammonium bicarbonate the 5'-OH function is liberated while hydrochloric acid is (simultaneously) neutralized. Thus the sensitive nucleotidic material is either in an unpolar, aprotic milieu or comes into contact with non-acidic aqueous environment.

Reaction conditions when detritylating different nucleotidic compounds are summarized in Table 1. Under the experimental conditions 4-monomethoxytrityl and 4,4-dimethoxytrityl ethers of deoxynucleosides such as (MMTr)T_d and (DMTr)ib^2G_d have also been deprotected quantitatively without any side reactions. Furthermore deoxynucleotides bearing the unusual methyl phosphonate internucleotidic linkage have also been detritylated without any problems using this method. We therefore feel confident that this is a

method of general value not only restricted to the use in oligonucleotide chemistry.

The application of this method is very advantageous for oligonucleotide synthesis on polymeric carriers as high concentrations of reagent can be obtained in either unpolar or polar aprotic solvents while maintaining homogenous reaction conditions[7, 8].

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8. In this case after a thorough wash-out of the excess of dialkylaluminium chloride with CH_2Cl_2 the dialkylaluminium bond to the 5'-O has to be cleaved by a treatment with n-butanol/pyridine, followed by a wash with CH_2Cl_2.

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