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(RESEARCH ARTICLE)

# Catalysis and specificity of the polycondensation of aminopropyltrimethoxysilane on nucleic acids

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## Abstract

The polycondensation of a silane derivative such as aminopropyltrimethoxysilane (ATMS) in the presence of nucleic acids has never been investigated. Our group has previously demonstrated that in chloroform ATMS hydrolysis and polycondensation were faster when the reaction were carried out in the presence of double stranded DNA (146 bp). The results showed that the kinetics of ATMS hydrolysis was affected by the base type used, a fast hydrolysis reaction rate being observed with nucleotide molecules containing adenosine group, and that in the absence of water the amino group of deoxyadenosine units, and not the hydroxylic group of the sucrose residue, can react with ATMS methoxy groups. The present work was initiated aiming at providing a better understanding of this effect. It was observed that the polymerization degree of oligodeoxyadenylate has a clear impact on the kinetic of reaction this effect being as much important as the polymerization degree of the oligodeoxyadenylate was high. Structural investigation by molecular modeling showed that this enhanced reactivity can be explained by conformational effects. Altogether, these results are accounted for assuming that DNA can act as a specific template for ATMS polycondensation, in organic medium such as chloroform, opening the way to possible DNA encapsulation, and a new way for DNA chemical modification in organic solvent.

**Keywords:** Aminopropyltrimethoxysilane Templated Polycondensation; Nucleic Acids; Specific Catalysis.

## 1 Introduction

Oligonucleotides have been seldom investigated as catalyst for simple organic reaction [1], but rather as catalyst for biological systems (RNA and DNA ligation, hydrolytic cleavages, photorepair of DNA, reactions of peptides…) [2]. DNA synthesis has been mostly studied in the case of biological processes applied to nucleic acid templated synthesis such as replication of genetic information, or transcription of DNA into RNA [3,4,5]. Template step polymerization, as introduced by Szwarc [6] in 1954, of an alkoxysilane derivative (Aminopropyltrimethoxysilane (ATMS)) on nucleic acids, has been demonstrated in a previous paper [1]. The hydrolysis and the step polymerization of ATMS have been investigated by $^{1}H$ and $^{29}Si$ NMR in the presence and the absence of ds-DNA in chloroform. The ATMS reaction was also studied in presence of different DNA bases, nucleosides and nucleotides in order to clarify the influence of the nucleic acid structure. The reaction of ATMS in the presence of DNA was explained by its reactivity with deoxyadenosine units. This unexpected reactivity of adenine based units deserves a specific investigation, and the presentpaper reports efforts to address such templated mechanism.

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## 2 Experimental Section

Chemical components. Deuterated chloroform ($CDCl_3$) used as such in all experiments was purchased from Eurisotop (France). Aminopropyltrimethoxysilane (ATMS) purchased from ABCR (Karlsruhe, Germany) was distilled before use.

ds-DNA. DNA fragments were prepared from calf thymus. Chromatin was extracted in low ionic strength buffer after micrococcal nuclease digestion of nuclei. After removal of linker histones, 146 bp DNA was obtained by controlled digestion with micrococcal nuclease. After precipitation in cold 2-propanol, DNA pellets were dried under vacuum and stored at -80 °C.

Oligonucleotides. Homo-oligonucleotides composed of 20 residues of deoxyadenosine (oligo-$dA_{20}$), deoxycytidine (oligo-$dC_{20}$), deoxyguanosine (oligo-$dG_{20}$) or deoxythymidine (oligo-$dT_{20}$) as well as the homo-oligonucleotide composed of 15 residues and 6 residues of deoxyadenosine (Oligo-$dA_{15}$ and oligo-$dA_6$) were purchased from Sigma-Aldrich (France). Homooligonucleotides A of 15 bases for UV visible spectroscopy were purchased from Eurogentec. The 200 µM stock solutions were lyophilized and the residue was dissolved in deuterated chloroform ($CDCl_3$).

UV-visible experiments. In this study, the spectrometer used for UV visible spectrometry was a Cary 50 (200 nm-750 nm).

NMR experiments. All NMR samples were prepared in deuterated chloroform used as such ($CDCl_3$). $^1$H NMR experiments were performed on a Bruker Avance 600 MHz NMR spectrometer equipped with a cryoprobe. NMR spectra were collected in $CDCl_3$ at 293K using 60 µl sample volume in sealed 1.7 mm diameter capillary tubes.

Molecular modeling. Molecular mechanic method using Energy-minimized structure was applied by MMFF94s force field using 9000 steps to reach a convergence of 10-7.

## 3 Results and discussion

### 3.1 Enhancement of ATMS reaction in chloroform by various oligonucleotides (anhydrous conditions)

In order to confirm the impact of the nucleotide type on the methanol production reaction rate in the ATMS-DNA system, experiments were carried out using homo-oligonucleotides composed of 20 residues of deoxyadenosine (oligo-$dA_{20}$), deoxycytidine (oligo-$dC_{20}$), deoxyguanosine (oligo-$dG_{20}$) or deoxythymidine (oligo-$dT_{20}$).

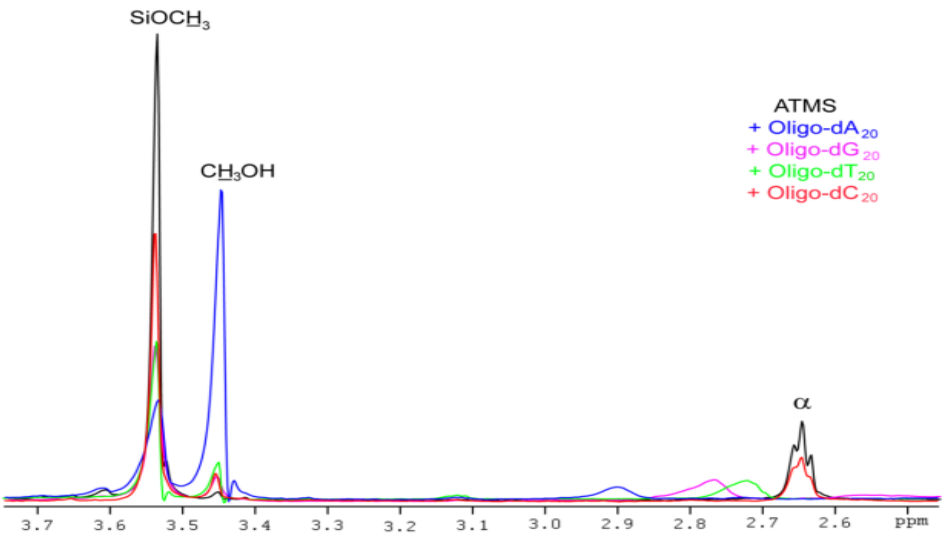



**Figure 1** $^1$H NMR spectra at 600 MHz of ATMS, alone (in black, inthe presence of oligo-$dA_{20}$ (in blue), oligo-$dG_{20}$ (in purple), oligo-$dT_{20}$ (in green), and oligo-$dC_{20}$ (in red), recorded after 20 min reaction time. These experiments were performed with a molar ratio ATMS/nucleotide units 1/1, [ATMS] = 2mM, [oligo-$X_{20}$] = 100 µM, no added water, in $CDCl_3$ at room temperature.

For the different experiments, $^1$H NMR spectra have been recorded at 20 minutes of reaction time after ATMS addition in $CDCl_3$ measuring the concentration of the methanol generated during reaction duration. Water concentration was low (if any) and kept constant during all experiments, since the same new type of sample containing the same adventitious water amount lower than 0.005% (mole/mole) was used and the oligonucleotides were lyophilized before use. A clear difference in methanol formation reaction rates was observed using ATMS without or with different homo-oligonucleotides. After 20 min of reaction time, the methanol production rate in the presence of oligo-$dA_{20}$ is clearly higher (64% mole/mole of initial ATMS methoxy groups) than the one observed with the others homo-oligonucleotides (≤16%) (Figure 1).

It was observed that 3h after ATMS addition, the methanol formation reaction was complete in the presence of oligo-$dA_{20}$ whereas with the other homo-oligonucleotides, reaction reached 55%. Finally, after 16 h of reaction, consecutive to ATMS addition, the methanol formation yield for ATMS alone was only 40% whereas it was 100 % with oligo-$dG_{20}$ and oligo-$dT_{20}$ and quasi-complete with oligo-$dC_{20}$ (95% of the total methoxy groups). A shift and a broadening of ATMS resonance peaks during the methanol formation reaction were observed (an example is shown with the Hα of ATMS in Figure 1) and, at the end of the reaction, the ATMS methoxy resonance peaks at 3.54 ppm disappeared completely. Methanol production witnesses the condensation of ATMS, and UV-visible spectroscopy can provide some additional informations. It is known that a single strand DNA gives a UV absorption with a maximum at around 260 nm wavelength. This absorption is not modified by the glycosidic and phosphate moieties. It is also known that dsDNA has an absorption intensity lower than that of the corresponding ssDNA [7].Thus a spectroscopic investigation was carried out comparing the spectrum in chloroform of oligo$A_{15}$ (0.48 mg/mL) without and with introduction of ATMS (one ATMS molecule for one base) (Figure 2). Such experiment shows that the absorption at 260 nm of the oligo$A_{15}$ is strongly decreasing upon ATMS introduction, after 200 mn of reaction time. This decrease of the absorption band characteristic of the Oligo$A_{15}$ is the result of the reaction with ATMS, and shows that the role of ATMS is not simply producing interactions with DNA.

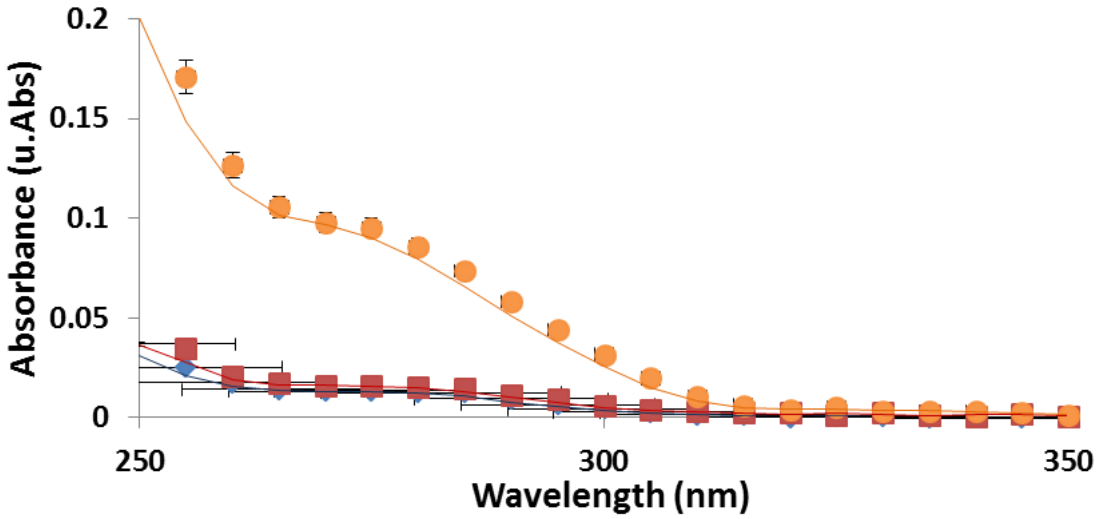



**Figure 2** Study of the UV spectrum of oligonucleotide $dA_{15}$ (0.01 mg/mL) in chloroform in the absence (orange round symbols) and in the presence of ATMS around 0.01 mg/mL , showing UV spectrum modification of oligonucleotide by ATMS interaction after 200 min reaction time (red square symbols) and 22 hours reaction time (blue diamond symbols).

To give an additional evidence of the condensation reaction, a HSQC NMR experiment was carried out. Taking into account the fast reaction kinetic in the presence of oligo $dA_{20}$, and the duration of a HSQC NMR sequence recording, oligo $dC_{20}$ (instead of oligo $dA_{20}$) was used in the ATMS/chloroform mixture for NMR (Figure 3).

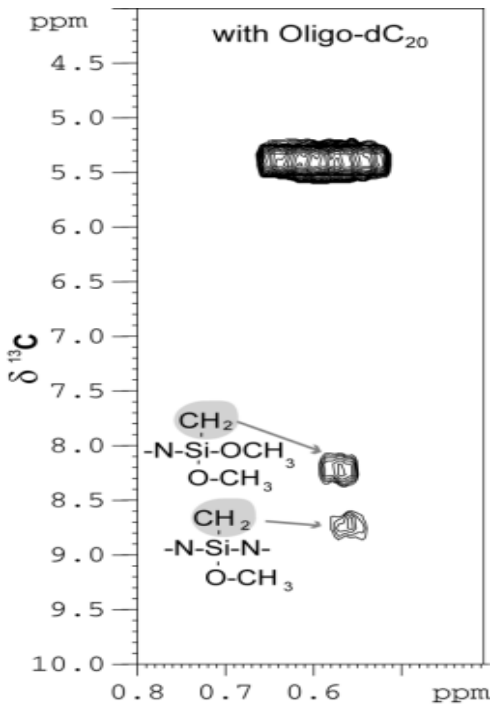


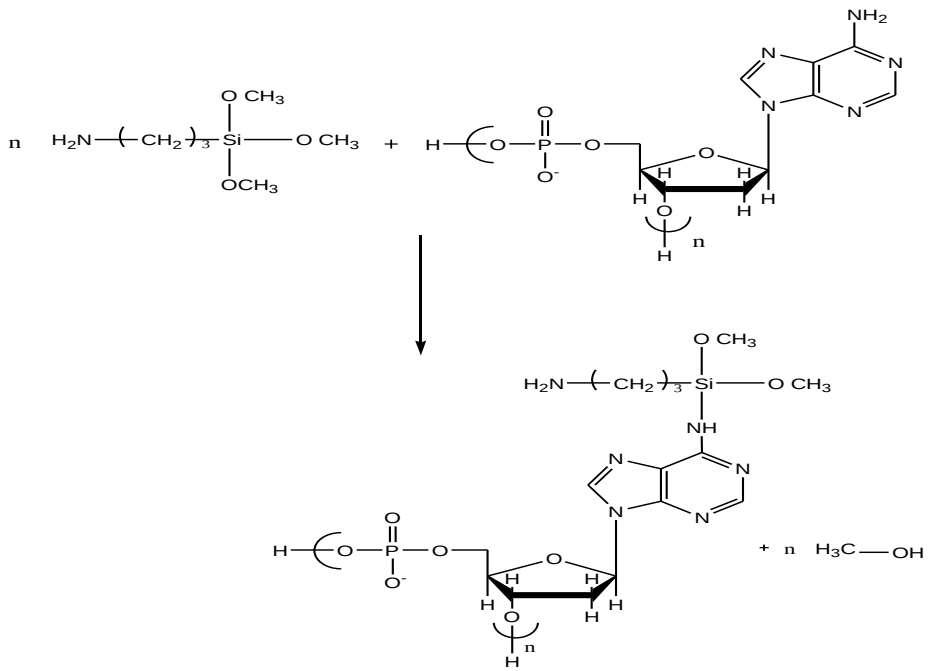

**Figure 3** HSQC NMR spectra of the -CH2-Si group (main peak δ $^{13}$C = 5.7 ppm) of the ATMS polycondensation products obtained after polycondensation with Oligo-$dC_{20}$ without water addition [ATMS] = 2mM, [oligo-$dC_{20}$] = 100µM.

In the presence of oligo-$dC_{20}$, the -$CH_2$-Si group of ATMS can be used as marker of the polycondensation reaction, as shown on Figure 3. The main peak at 5.7 ppm ($\delta^{13}$C) corresponds to the residual unreacted monomer, a second peak at 8.2 ppm corresponds to a $CH_2$-Si linked to two residual methoxy groups and one N-$(CH_2)_3$-Si- group. The peak at 8.7 ppm corresponds to the same methylene group linked to a silicon atom connected to two -N-Si groups. These assignments are in agreement with the theoretical calculated chemical shifts obtained with ChemDraw Ultra software. This information brought by NMR spectroscopy was obtained with oligo-$dC_{20}$ which is less reactive than oligo-$dA_{20}$ and allows obtaining HSQC spectra before gelation. This experiment supports the assumption that, in the absence of water, the reaction between this oligonucleotide and ATMS produced silazane bonds.

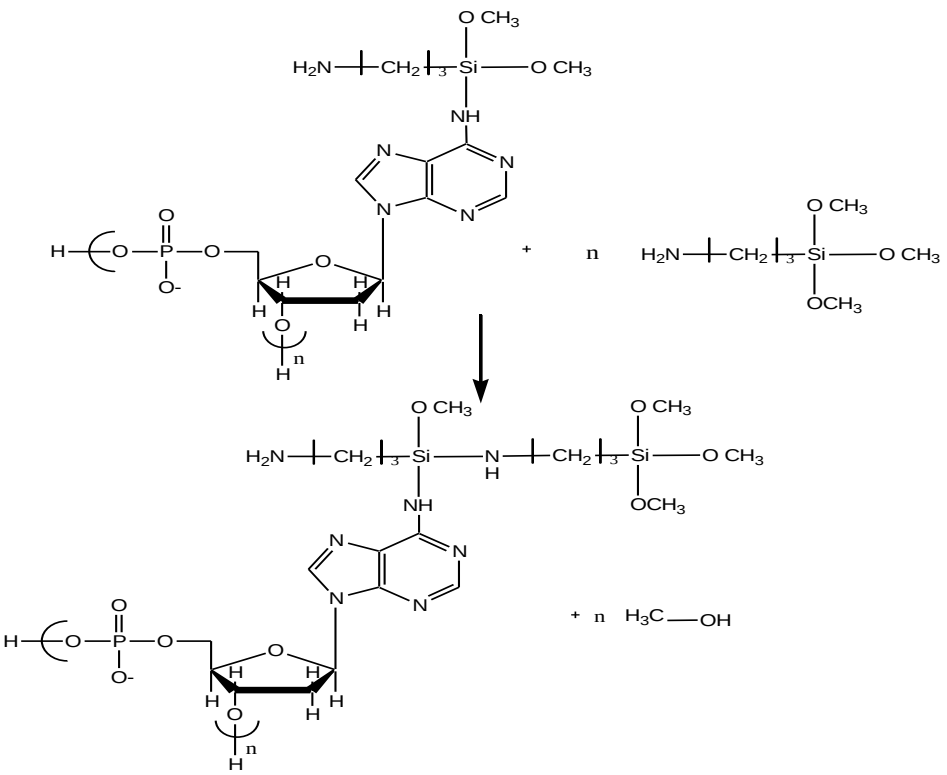
These data showed that homo-oligonucleotides and ds-DNA were able to enhance methanol production (by the aminolysis of methoxysilyl bonds of ATMS) as shown on reaction scheme 1, and crosslinking according to reaction scheme 2. The sensitivity of the silicon-to-nitrogen bonds to hydrolysis when water is present regenerates the initial oligonucleotide and the silanol group which can undergo further condensation. The importance of the nucleotide base type in the reaction mechanism and the involvement of an interaction of ATMS with the nucleotides is also confirmed. The main reaction paths leading to these results are discussed in the section below.

### 3.2 Effect of homo-oligodeoxyadenylate on ATMS aminolysis in anhydrous conditions

To get further insight into the effect of nucleic acids on the methanol production from ATMS, a kinetic study was carried out using one nucleotide or homo-oligonucleotides with different sizes. According to the above data, desoxyadenylate is the best nucleotide to promote the formation of methanol from ATMS and then the highest polycondensation rate.



**Scheme 1** Proposed scheme for the reaction the amino group of adenosine monophosphate units of the oligodeoxyadenylate with ATMS (functionalization of nucleotide).



**Scheme 2** Proposed scheme for the reaction of ATMS amino group with the product of the reaction of ATMS with nucleotide (possibility of branching and crosslinking).

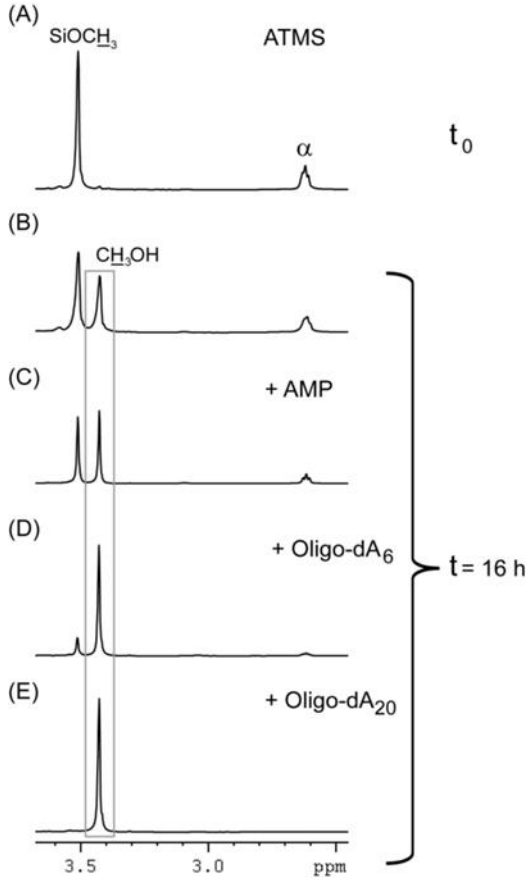



**Figure 4** $^1$H NMR spectra of 2mM ATMS alone (A) at initial condition, reaction (B) after 16h without oligomer addition or (C) with dAMP, (D) with oligo-dA$_6$, (E) with oligo-dA$_{20}$, respectively. The experiments were carried out in anhydrous $CDCl_3$ at room temperature with a molar ratio [ATMS]/[base] = 1/1.

Reactions involving dAMP and homo-oligodeoxyadenylate of 6 or 20 residues were compared using $^1$H NMR spectra. For ATMS alone (Figure 4A and 4B), the methanol formation observed after 16 h (40%) could be explained by the occurrence of self aminolysis occurring in the medium. With the addition of dAMP and the two oligomers (oligo-dA$_6$ and oligo-dA$_{20}$), a clear difference in kinetics was observed, as shown by the intensity of the $SiOCH_3$ peak. Noteworthy, the methanol formation was increased from 50% to 84% for dAMP and oligo-dA$_6$, (respectively Figure 4 C- D). This is confirmed by the fact that increasing the size of oligonucleotides from 6 to 20 units, also significantly enhanced methanol formation rate (Figure 4D- E). After 16 h, methanol formation reaction with oligo-dA$_6$ was not complete (84%, Figure 4D) whereas after only 3h with oligo-dA$_{20}$ the reaction was quantitative. The modification of the aminolysis reaction rate was only due to the oligomer polymerization degree, a parameter the influence of which indicates both a cooperative and a template effect.

The high values of methanol production in the absence of added water (Figure. 4D-E) shows that more than one methoxysilane function of ATMS can react with an amino group, despite the stoichiometric 1/1 (mol/mol) conditions. The mechanism leading to such result is worth being discussed. At this stage, two assumptions can be set forward: either the alkylamino group of ATMS can also react with the methoxysilane functions, or the second hydrogen function borne by the amine adenosine base can also participate to the condensation reaction producing silazane function and a methanol molecule. The fact that ATMS alone in anhydrous conditions gives homocondensation (Figures 4A and 4B supports the first hypothesis, even if this reaction can proceed through an equilibrium. The presence of a proton donating species such as methanol molecules (produced by the initial reaction) can help to proceed up to the formation of some crosslinked material. About the second afore assumption, it must be noticed that this reaction of a molecule with the DNA macromolecule functionalized by the reaction with ATMS can lead to a gel production reaction (scheme 2). Indeed, the same reaction can be observed between a methoxysilane function borne by DNA (after a reaction with an ATMS molecule) and the second hydrogen atom borne by an amino group somewhere else on a functionalized DNA macromolecule. However, steric hindrance could decrease the reactivity of this second hydrogen atom and consequently prevents crosslinking through this mechanism. It is clear that both routes discussed above can lead to gel production, but the first reactivity scheme is in good agreement with the experimental results (Figure 4B).

Quite clearly, these experiments show that ATMS has a better reactivity with dAMP than with other nucleotides. The interaction of ATMS with adenine and cytosine bases, the best and the worst efficient for aminolysis, respectively, have been then studied by molecular modeling in attempt to explain the differences of reactivity.

## 4 Molecular modeling of the induced aminolysis reaction on ATMS by adenyle or other groups

Minimizing energy of interaction of ATMS-dAMP and ATMS-dCMP couples unambiguously shows that ATMS-dCMP is more stable than ATMS-dAMP (-1.646.1 kJ/mol *vs* -1,285.98 kJ/mol).

Such a difference informs on the stability of the association but alone cannot explain the reactivity preference of dAMP to achieve the ATMS aminolysis. Indeed, taking into account experimental data, dAMP exhibits an approximately 6 fold higher methanol production rate than that of dCMP.

Such enhancement with a theoretical lower stabilization argues for a specific conformation effect, associated with a decreased of activation energy, i.e. a template effect of dAMP towards ATMS compared to dCMP. Lower stability of ATMS-dAMP supports the fact that aminolysis induced by dAMP is kinetically more favored, increasing the rate compared to ATMS-dCMP.

About the conformations, examination of the ATMS-dAMP/dCMP interaction modeling reveals some no negligible difference. A short distance (0.985 Å) allowing hydrogen bonding between oxygen of a side methoxy group from ATMS and the primary amine of the AMP base is calculated (Figure 5A). In ATMS-dCMP, a slightly higher intermolecular distance (1.001 Å) (Figure 5B) decreases hydrogen bonding strength between the aforementioned groups.

## 5 Discussion

These results must be discussed at different levels to the light of already published data.It has been reported that cytosine exhibits a quite similar proton affinity than adenine [8,9,10]. Moreover, it has been demonstrated that polysiloxanes own a no negligible proton affinity (189.2-203.4 kcal.mol$^{-1}$ [11]) strengthened in the case of Si-O-$CH_3$ by methyl substitution.

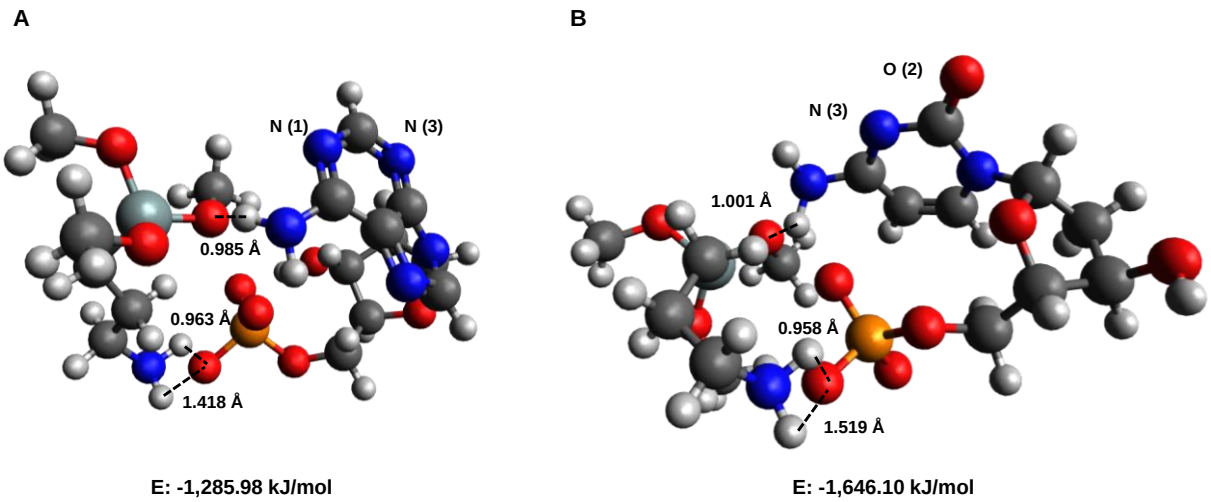



**Figure 5** Energy-minimized using MMFF94s molecular mechanical method of ATMS monomer interacting with (A) adenine and (B) cytosine.

This structural analysis suggests that the reaction of the dAMP primary amino group with a methoxy group of ATMS is favored. Considering dCMP, such process appeared less favored since in the model shown the amine hydrogen atoms of ATMS can form one hydrogen bond with one oxygen atom (0.958-1.519 Å)(Figure 5B). Literature reports that in dAMP the nitrogen atoms N3 and N1 of primary amine exhibits the best proton affinity (230.9 and 224.4 kcal.mol$^{-1}$, respectively), while close values are obtained for nitrogen N3 and oxygen O2 (234.4 and 231.9 kcal.mol$^{-1}$, respectively) of dCMP (Figure 5). This weak difference between dAMP and dCMP in the proton affinity of the endocyclic nitrogen atoms cannot justify the large difference of their reaction rates with ATMS, in the absence of the conformational effect shown above. A possible assumption may involve two or more oligomers leading to a cooperative catalysis of the

process. Experimental data clearly show that the presence of oligo-$dA_6$ instead of dAMP monomer, with the same ATMS/base molar ratio accelerates the methanol production. It was difficult to accurately describe the occurring process by computation data, because of the size of the oligo-$dA_6$. However, according to the semi-helical structure of oligo-$dA_6$ resulting from MM2 computation (data not shown), oligo-$dA_6$ could serve as multivalent scaffold when an ATMS molecule is docked in the inner rim. When several molecules are complexed, the proximity leads to an already increased rate of methanol production and follows a reaction path in agreement with the template effect observed for dAMP. Similar hypothesis can be formulated for oligo-$dA_{20}$.

In summary, the interpretations of the results are based on (i) an increased statistically methanolysis (multivalence versus 1 ATMS) and (ii) the strongly enhanced methanolysis rate due to more optimized conformation of ATMS monomer with the nucleotide. Such macromolecular configuration can potentially support the methoxysilyl reaction of several ATMS molecule simultaneously.

The presence of free methanol molecules exhibiting a Lewis acid feature, undoubtedly can accelerate siloxane cleavage reaction, as previously reported [12] and follows a reaction path similar to the template effect observed for dAMP. The enhancing effect of the polymerization degree is accounted for, oligo-$dA_{20}$ presenting an extended structure which favors the reaction. It was previously demonstrated that Si-O bond, even when methyl substituted siloxane are present, can be effectively cleaved in anhydrous conditions provided that an adequately proton transfer reaction occurred.[10] This is in tune with the fact that the helical structure is not the best conformation for this aminolysis reaction, but rather an extended conformation.

In the context of the interactions of DNA with methoxysilane functions, it is clear from the above studies that not only interactions are detected but also reactions. It is necessary to discuss the mechanism leading to the production of methanol according to a template effect, to the light of known literature. Since in some instances reported above there was not enough water producing a polymer chain of polyaminopropylsiloxane, as discussed above (section 2.1., HSQC experiment and the high value of methanol production in the absence of added water) it must be concluded that, due to the interaction, an amine group can react with methoxysilane functions producing methanol and a silazane bond. The methoxysilane functions on the same silicon atom can react with an amino group, either on the same unit forming a ring due to an intramolecular reaction, or belonging to another adenosine unit giving rise to a polymolecular structure [13]. From the results reported herein it is quite complicated to determine whether the two possibilities can simultaneously occured. It is worth recalling that cyclisation reaction is a strong tendency of such monomers in the presence of water due to silanol functions [14].

It is well known that the alkoxysilyl functions behave to some extent as carbon–based esters, and consequently can react with amine [15]. An aminolysis mechanism was also proposed to explain the adhesion promoted by (3-aminopropyl) triethoxysilane on a polycarbonate. Similarly, evidences in the literature were provided showing that (3-aminopropyl) dimethylethoxysilane can react by both ethoxy and aminopropyl moieties with the surface hydroxyl groups of silica substrate, a process in which the aminopropyl group was shown playing a catalytic role [16].

The work described here shows how the catalytic role of amino functions can play: the amino moiety reacts with silicon ester Si-O-C function, giving rise to the corresponding alcohol molecule, and due to the high reactivity of silazane function with water (if present), hydrolysis takes place, which regenerates the initial amine group and gives the corresponding silanol function. Besides the polymerization degree effect mentioned above, the catalytic effect is explained by the fact that when adenosine units are present, the aminolysis reaction is faster than the direct hydrolysis of the a lkoxysilyl function, as shown by the conformation effect described in this study. It is worth recalling that the specificity of the polydeoxyadenylate is demonstrated by the comparison of the results of methanol production starting from hydrated 2'deoxyadenosine + 1 mole of water (see ref. 1) with the experiment involving oligo-dA20 giving complete methanol formation within 3 h (Figure 2). In the reference [17], the development of DNA chemistry in organic solvents using low or minimal water content was made possible, and our work goes one step further using DNA for a template reaction in chloroform.

## 6 Conclusion

The catalysed hydrolysis and polycondensation of ATMS have been studied in chloroform in the presence of ds-DNA as well as in the presence of different bases of DNA, nucleoside, nucleotides and homo-oligonucleotides. These reactions can lead to microgels based on silazane bonds. A promoting effect on aminolysis and polycondensation reactions has been observed in the presence of ds-DNA, nucleotides and homo-oligonucleotides. A difference of reaction rate has been shown between the different homo-oligonucleotides indicating a specificity of the mechanism with the nature of the nucleotides, the homopolymer of deoxyadenylate being the best template. The template effect has been evidenced by

comparison of the different base types of homo-oligonucleotides. Condensation higher experiments showed polymerization rate effects not only with ds-DNA but also with of homo-oligonucleotides. The polymerization degree of the poly-A nucleic acid induced the higher reaction rates. Combined with the DNA solubility enhancement, the high reactivity of adenine-based nucleic acid units gives hopes to be able to encapsulate DNA in chloroform with polyATMS. These findings represent a first key milestone which paves the way to the use of polyATMS for DNA complexation and encapsulation.

Our results clearly show that it is possible to use DNA-templated synthesis in pure organic solvent without water, such as chloroform, thanks to the interaction and reaction between the deoxyadenosine based monomer units of DNA and the alkoxysilane based monomer, solubilizing DNA in the reaction medium, opening new procedures for DNA-based chemistry.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

If two or more authors have contributed in the manuscript, the conflict of interest statement must be inserted here.

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