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Strong Hydration and Salt Association Complicate Nucleotide Oligomer Analysis by Mass Spectrometry

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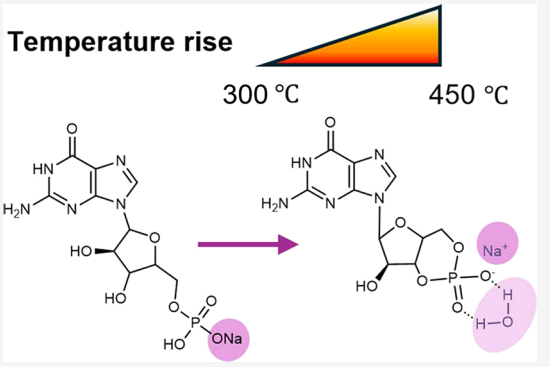
ABSTRACT: The abiotic synthesis of nucleotide oligomers via wet−dry cycling may have provided a source of nucleic acids necessary for the origin of primitive forms of life. Mass spectrometry (MS) is an important analytical tool used to investigate such oligomers, but the products are surprisingly complex because of water molecules and salt ions adsorbed to ionic and polar groups on the molecules. There are also aggregates of monomers stabilized by noncovalent forces, and differentiating between covalent polymers and noncovalent aggregates remains a subject of technical debate. This study addresses methods for identifying peaks in mass spectra by investigating the adsorption of water and sodium during the ionization of uridine monophosphate and 3′,5′-cyclic guanosine monophosphate (UMP and cGMP). Using ^{18}O-labeled water and increasing the temperature of the heated capillary inlet, we demonstrated that hydrogen-bonded water molecules persist even under high temperatures up to 450 °C. Furthermore, we identified the salt enrichment effect, where increasing chain length leads to a binomial accumulation of sodium ions even in an acidic (pH 2.5) environment. By employing field-asymmetric ion mobility MS, we successfully deconvoluted isobaric ions, distinguishing between massive noncovalent UMP 35-mer aggregates and true covalent 36-mer UMP polymers. These results confirm that water and salt involvement are intrinsic to the MS signature of nucleotide monomers and oligomers. Our findings provide a rigorous analytical framework for validating prebiotic polymerization and highlight the necessity of advanced separation techniques in the characterization of nucleic acid polymers synthesized nonenzymatically on the prebiotic Earth.



INTRODUCTION

In origin of life (OOL) research, wet−dry cycling in acidic conditions (pH 2−3) and elevated temperature (80 °C) promotes the formation of nucleotide oligomer chains from the free acid form of nucleotide monomers. Three different analytical methods support this claim. Rajamani et al.[1] showed that the oligomers were recognized by two enzymes used to end-label RNA for gel electrophoresis. The labeled oligomers were mostly 25−75 nucleotides long, with some approaching 100. The oligomers also produced millisecond ionic current blockades as they translocated through the hemolysin nanopore, closely resembling the blockades caused by known RNA homopolymers.[2] Single-stranded RNA and DNA are the only linear biopolymers that can pass through the 2 nm diameter pore and cause such blockades.

Atomic force microscopy (AFM) can also reveal polymers. If nucleic acids are exposed to freshly cleaved mica surfaces, they adhere strongly to the atomically smooth mineral surface and can be readily resolved by tapping mode AFM. To test whether polymers could be observed following wet−dry cycling, dilute mononucleotide solutions were exposed to wet−dry cycles on mica surfaces which were then flushed with water to remove excess solutes. Long polymers were apparent with thicknesses characteristic of nucleic acids.[3] More recently, 3′,5′-cyclic guanosine monophosphoric acid (cGMP), has been established to be an activated nucleotide able to initiate phosphodiester bonds (PDE) and chain elongation.[4−6]

In a previous publication, we used mass spectrometry to monitor the formation of nucleotide oligomers driven by wet−dry cycling.[7] Multiple techniques including high-resolution mass spectrometry (HR-MS), nanopore sequencing, ^{31}P-nuclear magnetic resonance (^{31}P NMR), and Fourier transform infrared spectroscopy (FTIR) were also used to provide complementary structural evidence. Nevertheless, a concern has been raised regarding false positive results caused by aggregate species composed of noncovalently bonded nucleotide monomers. Additionally, the concern also suggested that adsorbed water molecules were completely removed when analyte molecules were exposed to the high temperature of the

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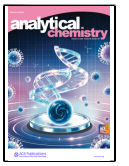

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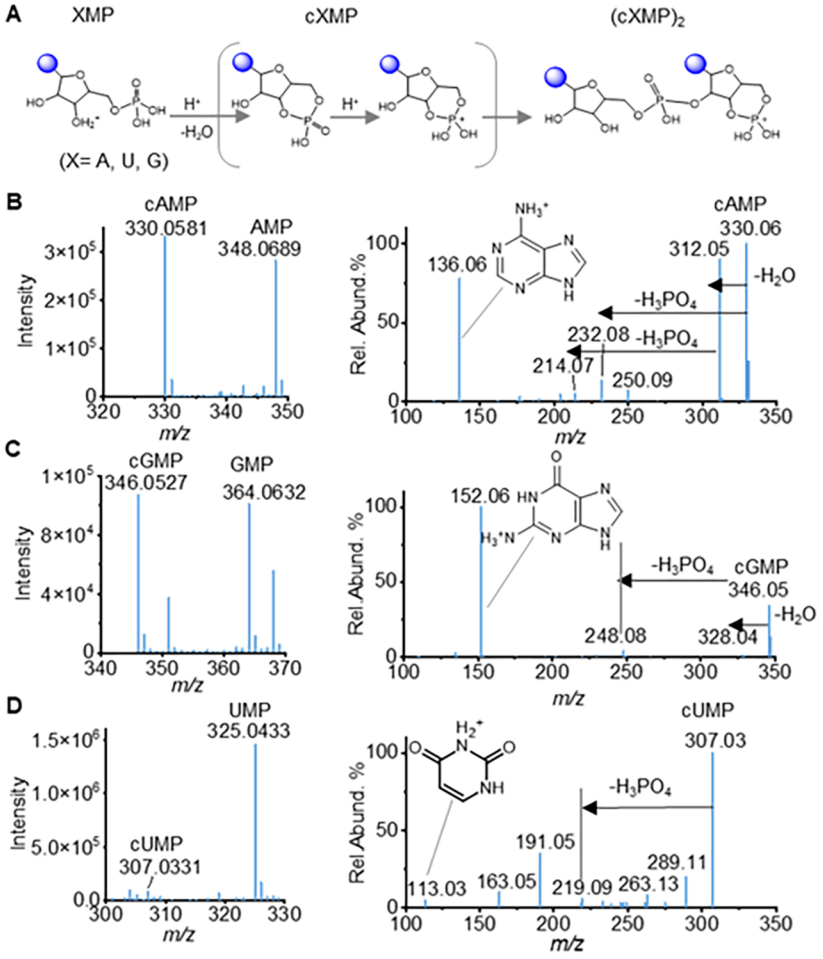

Figure 1. Synthesis of phosphodiester bonds linking mononucleotides. (A) Cyclic nucleotide monomers are formed from mononucleotides by an acid-catalyzed dehydration (condensation) reaction. The cyclic nucleotides can then link by forming a phosphodiester bond. Continuation of the reaction with additional cyclic nucleotides results in oligomers. Blue spheres represent nucleobases. (B) The presence of cAMP, (C) cGMP, and (D) cUMP can be detected by high-resolution mass spectrometry after wet−dry cycling and confirmed by tandem mass spectrometry.

MS inlet capillary during the electrospray ionization step of ESI mass spectrometry.

We present here new mass spectrometric evidence not only to confirm the strong physical adsorption of water molecules but also the increased sodium ion enrichment expected in longer nucleotide chains. These experimental results make it essential to consider water and salt involvement when assigning the nucleotide oligomer peaks. Conventional MS alone cannot distinguish isobaric ions that share the same m/z value, whereas high-field asymmetric waveform ion mobility spectrometry (FAIMS) provides an additional gas-phase separation based on differences in field-dependent ion mobility and can therefore help resolve covalent oligomers from noncovalent aggregates before mass analysis.[8] We therefore employed FAIMS to examine covalently linked polymers and partially polymerized aggregates formed during wet−dry cycling. This observation led us to propose a novel mechanism for polymerization based on the presence of cyclic nucleotides among the products of wet−dry cycling.

EXPERIMENTAL METHODS

Mass spectrometry is typically performed to analyze pure compounds, but the compounds we are investigating are the result of exposing mononucleotides to cycles of wetting and drying that simulate conditions in hydrothermal fields such as Yellowstone National Park today. This results in a complex mixture of short oligomers and aggregates, together with adsorbed sodium ions and water molecules. A high-resolution mass spectrum therefore displays hundreds of separate peaks. Our approach to identifying individual peaks in the spectrum is to compare experimental and theoretical peaks that represent various combinations of a specific oligomer with a certain number of adsorbed sodium ions and water molecules, and an assumed value of z, the ionic charge on the oligomer. If we find a near-perfect match, it is taken as a reasonable initial identification of the nature of the oligomer. We can then use additional analytical methods to test whether the oligomer is present in the mixture. We must also test whether simple aggregates of monomers can be matched to theoretical peaks by the same procedure.

The calculation assumes that variable numbers of sodium ions and water molecules add to the molecular mass of a given oligomer, therefore one of the aims of this report was to demonstrate that water and sodium are present. Because of the complex composition of compounds resulting from wet−dry cycling, we focused on two mononucleotides that had adsorbed water molecules and sodium ions. Uridine 5′-monophosphoric acid (UMP) incorporates a pyrimidine nucleobase, and cyclic guanosine monophosphoric acid (cGMP) incorporates a purine base. cGMP has a demonstrated ability to form phosphodiester (PDE) bonds that link it into dimers and longer oligomers. Both nucleotides were purchased from Sigma-Aldrich, and 10 mM stock solutions were prepared at room temperature in RNase- and DNase-free ultrapure water (Thermo Fisher Scientific). Sodium ion residues in solutions were removed by filtering through an ion-exchange resin that replaced sodium for hydrogen ions (Bio-Rad

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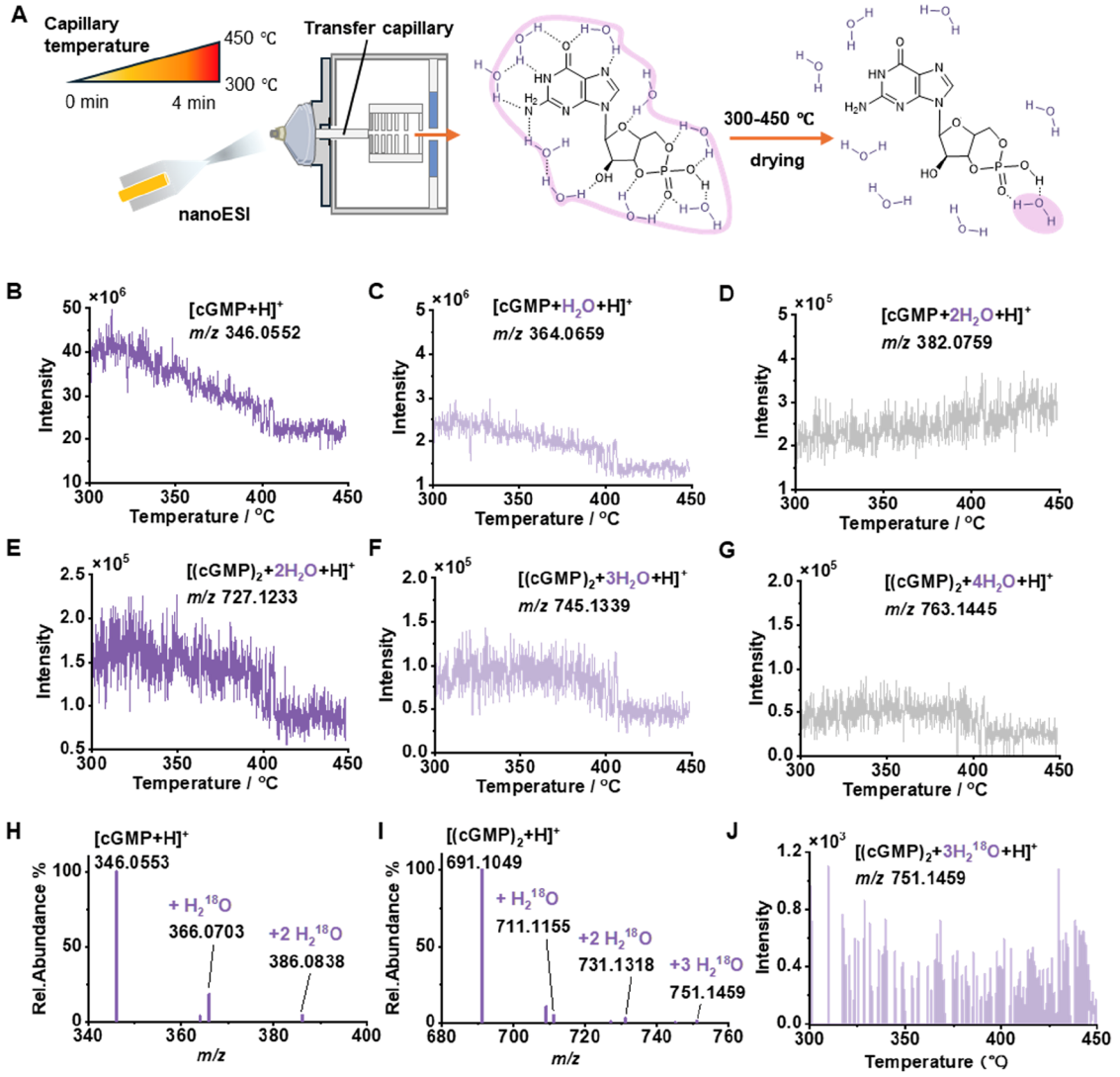

Figure 2. Water molecules remain adsorbed to nucleotides even at high temperatures. (A) Diagram of nESI-MS and the programmed increase of capillary temperature from 300 to 450 °C. A cyclic GMP embedded in a water cage cannot be fully dehydrated even as temperature increases from 300 to 450 °C because of the strong hydrogen bonding between phosphate and water molecules. (B–D) The ion intensities of single cGMP molecules carrying 0, 1, and 2 water molecules. If adsorbed water was entirely lost, the intensity of the hydrated peaks would decrease to zero. Although the intensities decrease by about half, they never disappear, indicating that adsorbed water remains. Surprisingly, the intensity of the bare ions also decreases by half, perhaps due to chemical changes caused by the temperature increase. (E–G) The ion intensities of cGMP dimer carrying 2, 3, and 4 water molecules. (H, I) The relative abundance of monomers and dimers of cGMP that were present in water labeled with ^{18}O. (J) Temperature dependence of the $[(cGMP)_2+3H_2{}^{18}O+H]^+$ ion intensity. The peaks at *m/z* 346 and 691 correspond to the bare nucleotides, and the presence of adsorbed water molecules with ^{18}O confirms that water molecules remain attached even though they were exposed to elevated temperatures.

Laboratories). Samples for mass spectrometry were prepared from the solutions of nucleotides described above. The solution pH was adjusted to 2.5 (with HCl). A 100 μL aliquot of cGMP or UMP solution was transferred onto a quartz glass slide containing a shallow well and dried on a thermostat-controlled hot plate at 85 °C. The samples were visibly dry after a few minutes, and the slides were maintained at that temperature for 30 min to promote condensation reactions. Products were resuspended in 100 μL RNase- and DNase-free ultrapure water at room temperature and then exposed to the next round of wet–dry cycling.

The nanoelectrospray ionization method (nESI) was employed to deliver wet–dry cycling products into the mass spectrometer (MS, Orbitrap Elite, Thermo Fisher Scientific, San Jose, CA). The nESI tip was made of a borosilicate glass capillary (OD: 1.5 mm, ID: 0.86 mm, length: 10 cm) and fabricated by a micropipette puller (Sutter Instrument Co., Novato, CA). Information about the final emitter geometries and their effects on the observed multimer and Na-adduct distributions is provided in the Supporting Information (Table S1 and Figures S2 and S3). Key parameters can be accessed from the Supporting Information of the previous publication.[7] A stainless-steel needle connected with a high-voltage source was then inserted from the back end of the tip and dipped into the loaded sample solution. When a +1.8 kV high voltage was applied to the needle, the strong electric field at the nESI sprayer tip triggered the spraying process, and small amounts of the resulting microdroplets entered the MS for ion signal monitoring. The MS capillary temperature was set at 300 °C; S-lens voltage at 55 V, and maximum injection time set at 400 ms.

We also tested whether a given peak was an oligomer or aggregate by using an FAIMS device (Ultra-FAIMS, Owlstone Medical Ltd., U.K.) to couple with the MS inlet and separate isobaric ions. Two critical parameters, drift field (DF) and compensation field (CF), were tuned from a range of 100 to 400 Td, and −3.0 to +3.0 Td, respectively, to achieve an optimized separation of aggregates from true oligomers.

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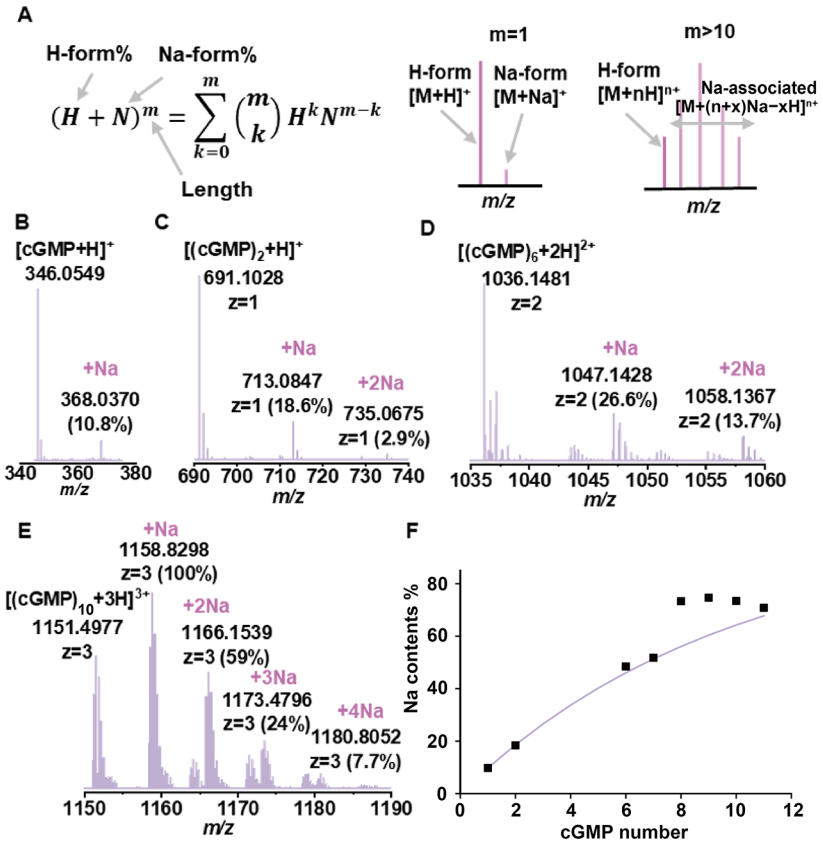

Figure 3. Sodium association with increasing cGMP multimer size. (A) Binomial model based on the monomer H-form/Na-form distribution and schematic representation of H-form and Na-associated species. (B–E) Representative mass spectra of the cGMP monomer, dimer, 6-mer, and 10-mer showing Na-associated species. (F) Experimental Na-associated fractions (black squares) compared with the binomial prediction (purple line) as a function of cGMP multimer size.

RESULTS

Formation of Cyclic Nucleotide Monophosphate Through Wet–Dry Cycling Procedure

In our previous study, we subjected native nucleotide monophosphate to wet–dry cycling and reported systematic chain-length distributions and their evolution over successive cycles.[7] It was hypothesized that the cyclic nucleotide monophosphate (cXMP) is the active intermediate that triggers the stepwise ring-opening chain formation (Figure 1A). The results presented here used three wet–dry cycles of the acidic forms of AMP, GMP, and UMP solutions at pH 2.5. After the last round of drying process, the solid residues were reconstituted with ultrapure water for the nESI-MS test. We observed that cXMP is synthesized from the three mononucleotides with estimated yields of 55%, 56%, and 5%, respectively. The response-factor measurement used to correct the cGMP yield is shown in Figure S1. A tandem mass spectrometry experiment (MS/MS) confirmed the identities of the cXMP ions (Figure 1B–D).

Persistence of Water Molecules Bound to Nucleotides

To investigate the water molecule persistence on nucleotides, we used 3′,5′-cyclic guanosine monophosphate (cGMP) as the model initiator. Samples analyzed in Figures 2 and 3 were prepared using the same three-cycle wet–dry procedure described above. cGMP is chosen because several previous publications observed its polymerization under the conditions of pH = 2.0, continuous drying, and a temperature of 80 °C.[4−6,9] When the nESI emitter sprays the cGMP solution into the mass spectrometer (MS), the sprayed microdroplets enter the MS inlet with a temperature increasing from 300 to 450 °C. One might expect that any water molecules surrounding cGMP should be fully removed creating a completely dry cGMP molecule. However, the persistence of strong hydrogen bonding still allows some water molecules to remain (Figure 2A).

As shown in Figure 2B–D, there were strong ions at levels of 2×10^7, 1×10^6, and 2×10^5 which represent the species of $[cGMP+H]^+$ (m/z 346.0552), $[cGMP+H_2O+H]^+$ (m/z 364.0659), and $[cGMP+2H_2O+H]^+$ (m/z 382.0759) even at a temperature of 450 °C. The $[cGMP+H_2O+H]^+$ is presumably due to cGMP hydrolysis. The $[cGMP+2H_2O+H]^+$ at m/z 382.0759 has no other possibility except that the cGMP is noncovalently bonded with two water molecules or GMP with one additional water. Likewise, for cGMP aggregate dimer, more water molecules can be characterized by ions of m/z 727.1233 ($[(cGMP)_2+2H_2O+H]^+$), m/z 745.1339 ($[(cGMP)_2+3H_2O+H]^+$), and m/z 763.1445 ($[(cGMP)_2+4H_2O+H]^+$). Even if two cGMP have been condensed to form the GMP dimer, there are still additional 1–3 water molecules that adhere to the chain (Figure 2E–G). These results indicate that the physical adsorption of water complicates MS peak assignment in differentiating aggregated monomers from true polymers. There may also be incomplete polymerization in which partially aggregated monomers are combined with polymers.

We employed ^{18}O-labeled water ($H_2{}^{18}O$) to further verify its physical adsorption onto nucleotides. As shown in Figure 2H

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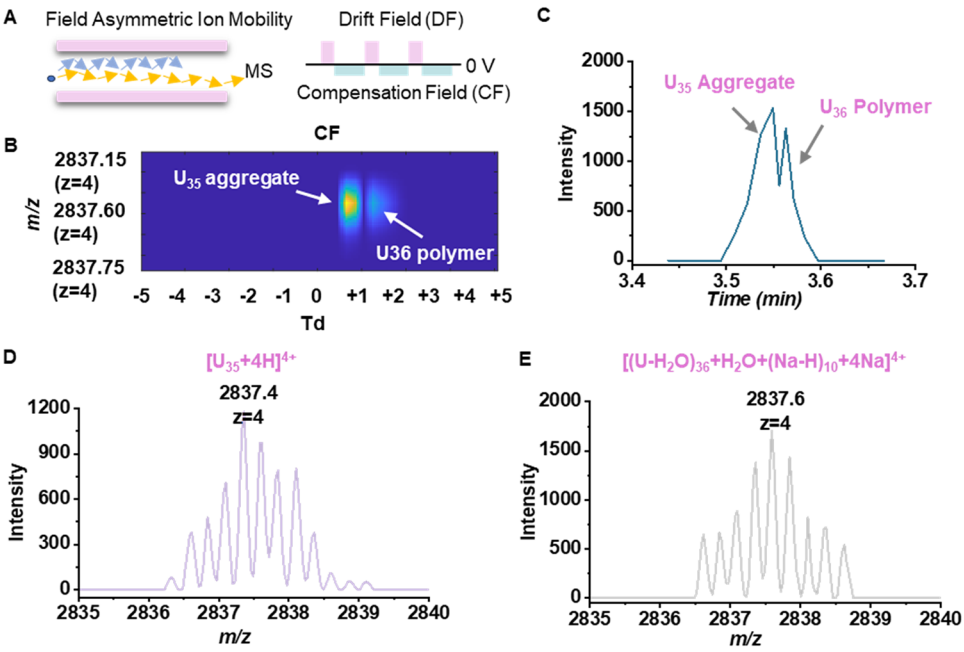

Figure 4. Differentiation of U_{35} aggregates and U_{36} polymers by FAIMS. (A) Diagram of the FAIMS core principle and parameters for separating isobaric ions; (B) FAIMS recognition of U_{35} aggregate and U_{36} polymer which have different adductions and inseparable m/z value; (C) Partial separation of U_{35} aggregate and U_{36} polymer characterized by extracted ion chromatogram; (D, E) the isotope distribution patterns of U_{35} aggregate and U_{36} polymer.

and 2I, the monomer and dimer carrying one additional $H_2{}^{18}O$ account for 4.1% and 1.1%, respectively. The ion intensity of $[(cGMP)_2+3H_2{}^{18}O+H]^+$ remained 6×10^2 at the temperature of 450 °C (Figure 2J). The water content will gradually accumulate with a further increase of chain length. This result further supports the necessity of including water molecules into the assignment of mass peaks.

Enhanced Salt Enrichment in Longer Nucleotide Chains

It is known that the acidic form (H^+-form) of nucleotide monomers should be more reactive than the sodiated form (Na^+-form).[4−6,10] Both hydration and sodium association occur in the wet−dry products. Figure 3 focuses on sodium-associated species to illustrate the effect of chain length on salt association. However, using H^+-form monomers still cannot guarantee a clean mass spectrum of nucleotide species in a polymerization experiment. Even after ion-exchange desalting and acidification, a small fraction of Na-associated cGMP remained detectable. The monomer H^+/Na^+ distribution gives a Na-association probability, p_{Na}, of approximately 0.098. Assuming independent and equivalent association sites, the probability of observing k Na^+ ions in an n-mer follows a binomial distribution, $P(k) = \binom{n}{k} p_{Na}^{k} (1 - p_{Na})^{n-k}$ (Figure 3A). Representative spectra illustrate the increasing number of Na-associated states from the monomer and dimer to the 6- and 10-mers (Figure 3B−E). The corresponding fraction containing at least one Na^+ is $1 - (1 - p_{Na})^n$, and the experimental values across multiple multimer sizes are compared with this prediction in Figure 3F. Therefore, we emphasize that the salt ions must be taken into consideration for mass assignment even if only the H^+-form monomer is used and the polymerization experiment is conducted at pH 2.5. Different emitter geometries reproduced the main cGMP-derived multimer families, with shifts in multimer and Na-adduct patterns at their respective stable spray voltages (Figure S3).

Differentiation between Aggregated Prepolymers and True Polymers

Given the complexity of the possible composition, we employed FAIMS to separate those multiply charged isobaric ions. FAIMS provides differential-mobility separation but does not directly yield CCS values, so structural assignment still relies on the measured m/z, charge state, and isotope distribution.[11] Isobaric species with varied conformations have different traveling trajectories under sweeping drift field (DF) and compensation field (CF) (Figure 4A). Taking the ion at a nominal m/z of 2837 (z = 4) as an example, two isobaric species were successfully recognized in the two-dimensional (2D) image composed of m/z (y axis) and CF (x axis) (Figure 4B), although the two isobaric ions were still overlaid in the additional CF dimension (Figure 4C). By averaging the relatively pure part of the time window from the twin peaks, the separate mass spectrum of each species can be obtained. We hypothesized that a certain multiply charged ion is putatively composed of monomer number, salt numbers, water numbers, and charge numbers. The identities of the two peaks were assigned as $[(UMP)_{35}+4H]^{4+}$, and $[(UMP\text{-}H_2O)_{36}+H_2O+(Na-H)_{10}+4Na]^{4+}$, which are aggregates of 35 UMP monomers (Figure 4D), and a polymer made of 36 UMP monomers (Figure 4E). The simultaneous presence of water and sodium adducts in the U36 species is consistent with the hydration and salt-association effects examined separately in Figures 2 and 3. This result not only justified our hypothesized composition types involving water and salt but also supports the presence of covalently linked polymers formed during wet−dry cycling.

Previous studies have shown that nucleotide oligomerization under wet−dry conditions depends strongly on the reaction environment, particularly the acidity and thermal history.[12,13]

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Related studies under different drying conditions and nucleotide chemistries further show that oligomer formation can persist across a broader range of temperatures and ionic environments.[3,10] These observations support the broader relevance of wet−dry chemistry while also indicating that the detailed product distribution is condition dependent. Such wet−dry settings have been widely used as experimental analogues of fluctuating terrestrial hydrothermal environments.[14]

CONCLUSION

It became clear during this study that the products of wet−dry cycling of mononucleotides are far more complex than simple mixtures of monomers and oligomers. The other components include varying numbers of water molecules and sodium ions adsorbed by oligomers, and hydrolytic degradation products such as purines and nucleosides, as well as cyclic nucleotides. In addition, there are aggregates of monomers stabilized by noncovalent forces. These aggregates may arise during the preparative wet−dry process and the subsequent nESI evaporation step. The first dehydration step occurs as part of the preparative wet−dry cycling and the second occurs as the spray process produces microdroplets from the reconstituted solution. Rapid evaporation of aqueous microdroplets has been reported to favor dehydration and condensation reactions.[15,16] Microdroplet environments can also enhance molecular aggregation.[17] These effects may contribute to noncovalent nucleotide association during nESI. Aggregates are unlikely to occur in other analytical methods like gel electrophoresis or HPLC in which the mononucleotides are maintained in solution during analysis.

The results reported here confirm that oligomers are synthesized when mononucleotides are exposed to wet−dry cycling. We also presented evidence that adsorbed water and salt ions must be considered when analyzing mass spectra of nucleotide polymers because of persistent water adsorption and increasing enrichment of salts in longer strands of polymers. The aggregated mononucleotides can be differentiated from true polymers by the FAIMS mass spectrometry method. Cyclic mononucleotides were present after wet−dry cycling, and it is possible that they serve as reactive intermediates for nucleotide polymerization into oligomers.

Considering the complex mixture of products synthesized by wet−dry cycling, we recommend for future studies that samples undergo pretreatments using separation techniques to simplify the composition. For instance, the liquid chromatography step of LCMS allows individual products to be identified, and nanopore sequencing can provide base sequences of single-stranded nucleic acids, both DNA and RNA.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.analchem.6c03667.

Positive-mode response comparison between cGMP and GMP; Effect of nESI emitter geometry on observed multimer and sodium-adduct distributions (PDF)

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Notes

The authors declare no competing financial interest.

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