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Differentiation of Isotopically Labeled Nucleotides Using Fast Atom Bombardment Tandem Mass Spectrometry

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The positional isotope exchange reaction has proven to be a valuable tool in elucidating mechanistic pathways for enzyme-catalyzed reactions involving phosphoryl transfer. Several examples of the analysis of phosphorylated nucleotides by fast atom bombardment ionization mass spectrometry have been reported; however, the small number and low relative abundance of structurally significant fragment ions make structure elucidation difficult. Recently, we reported that the dissociation reactions of organo-alkali-metal ion complexes are influenced by the alkali-metal binding site, and this effect can enhance the relative abundance of structurally significant fragment ions in the collision-induced dissociation spectrum. In the present studies the $[M + Na]^+$ ions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]uridine triphosphate formed by fast atom bombardment ionization and analyzed by using tandem mass spectrometry are examined to determine the position of ^{18}O atoms in the molecule.

The positional isotope exchange (PIX) technique has proven to be a valuable tool in elucidating mechanistic pathways for enzyme-catalyzed reactions (*1*). The PIX technique has been used with reactions involving phosphoryl transfer in nucleotides followed by analysis with ^{31}P NMR or derivitization (to enhance volatility) followed by electron impact ionization mass spectrometry. Several studies on the analysis and structure elucidation of nucleotides and nucleosides using mass spectrometry have been reported. For example, field desorption (FD) (*2, 3*), desorption chemical ionization (DCI) (*4*), thermospray (*5*), and liquid ionization (*6*) have been successfully used for the analysis of nonderivatized nucleosides and nucleotides. More recently impressive results on polar, nonvolatile organic molecules have been demonstrated using a group of particle-induced desorption ionization techniques, e.g., secondary ion mass spectrometry (SIMS) (*7, 8*), ^{252}Cf plasma desorption mass spectrometry (PDMS) (*9–11*), laser desorption (LD) (*12*), and fast atom bombardment mass spectrometry (FAB-MS) (*13–24*).

Although several studies concerning the analysis and structure elucidation of phosphorylated nucleotides using FAB ionization have been reported, the number and abundance of structurally significant fragment ions are low in the FAB mass spectrum. For this reason, several workers have proposed the use of tandem mass spectrometry (TMS) in combination with FAB ionization for structural characterization of polar organic molecules (*25–29*). Owing to the large number of reaction channels available to the collisionally activated ion, the abundance of structurally significant fragment ions in a FAB-TMS spectrum is low (*25*). One factor to consider in the case of FAB ionization of nucleoties is the greater sensitivity for the negative ion spectrum. This is undoubtedly a result of the extent of dissociation of the acidic phosphate groups in the liquid matrix prior to particle bombardment (*30*). The lowest energy dissociation reaction available to the collisionally activated ion $[M - H]^-$ is electron detachment; consequently, it would be preferable to analyze the nucleotide by positive ion FAB ionization. Conversely, the phosphate groups of the nucleotide have relatively high alkali metal ion affinities and even trace impurities of sodium give rise to abundant $[M + Na]^+$ ions and only weak $[M + H]^+$ ions.

Molecules such as peptides, sugars, nucleotides, etc. contain highly polar functional groups which have different proton and alkali metal ion affinities. It follows, therefore, that the binding sites of protons and alkali metal ions to the organic molecule may differ. In the event that protonation and cationization (via alkali metal ions) occur at different sites in the organic molecule, the types of fragment ions obtained and the relative abundances of those ions may differ substantially for the $[M + H]^+$ and $[M + Na]^+$ ions. Recently, we showed that the collision-induced dissociation reactions of organo-alkali-metal ion complexes of peptides are influenced by the alkali metal ion binding site (*31*). In this study it was also demonstrated that the relative abundance of structurally significant fragment ions was enhanced in the FAB-TMS spectrum of $[M + Na]^+$ ions (*31*).

In the present study, the dissociation reactions of the $[M + Na]^+$ ions of nucleotides to determine the position of oxygen-18 (^{18}O) atoms will be examined. First, the proposed mechanism for the PIX reaction will be described with particular reference to exchange of ^{18}O into the $\alpha\beta$ bridging position of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]uridine triphosphate (UTP). Second, the position of the ^{18}O atoms will be determined by analyzing the FAB-TMS spectrum for the $[M + Na]^+$ ions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP before and after the PIX reaction is performed.

EXPERIMENTAL SECTION

The labeled potassium dihydrogen phosphate ($KH_2P^{18}O_4$) used in the synthesis of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]uridine triphosphate (UTP) was prepared by following the procedure of Risely and Van Etten (*32*). All other chemicals necessary for the synthesis and positional isotope exchange reaction of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP were purchased from Sigma Chemical Co. Dithiothreitol (no. 15,040-0) and dithioerythritol (no. 16,176-4) used as the fast atom bombardment matrix were purchased from Aldrich Chemical Co.

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Synthesis of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]Uridine Triphosphate. A mixture of 200 mg of $KH_2P^{18}O_4$, 1 mL of 1 M sodium acetate (pH 4.8), and 1.5 mL of an aqueous potassium cyanate (KOCN) solution (800 mg in 2 mL of H_2O) is incubated at 30 °C for 25 min. The pH of the solution is adjusted every 5 min to 6.5 by using acetic acid. After the incubation period, the remaining KOCN solution is added and incubated for five additional minutes. This solution is then added to 500 μmol of uridine monophosphate (UMP), 100 μmol of adenosine diphosphate (ADP), 25 mmol of Tris buffer (pH 7), 700 μmol of Mg^{2+}, 150 units of carbamate kinase, 12 units of nucleoside monophosphate kinase, and 12 units of nucleoside diphosphate kinase. Owing to the pH dependence on the formation of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP, the reaction is monitored at 15-min intervals by anion exchange HPLC. Once the formation of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP is complete, the reaction is quenched by lowering the pH to 3 by using 10 M HCl. The [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP is then purified on a DEAE column and a 0–500 mM triethylamine (TEA)/bicarbonate (HCO_3^-) buffer gradient elution scheme. The TEA/HCO_3^- buffer is used to minimize contamination of the sample by sodium or other alkali metals. The UTP was collected and dried to a solid residue.

Positional Isotope Exchange Reaction. The positional isotope exchange (PIX) reaction was performed by adding 5 μmol of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP, 10 μmol of glucose-1-phosphate, 1 mmol of Mg^{2+}, 0.05 unit of UDPG-pyrophosphorylase, and 25 mmol of Tris buffer (pH 7.5) in a volume of 500 mL. The reaction mixture is allowed to equilibrate for 24 h and quenched by lowering the solution pH to 2 using 10 M HCl. The quenched solution was passed through an Amicon PM 10 membrane to remove protein; the [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP was collected from the filtrate by raising the pH of the filtrate to 8 prior to separation by chromatography with a DEAE column (0–500 mM TEA/HCO_3^- gradient elution). The UTP samples were collected and dried to a solid residue.

Fast Atom Bombardment Tandem Mass Spectrometry. The studies reported here were performed with a Kratos MS-50 triple analyzer (*33*), in the fast atom bombardment (FAB) ionization mode. The FAB ion source used for these studies is the standard Kratos system, equipped with an ION TECH 11-NF saddle field atom gun. Xenon was used for the bombarding fast atom beam. Typical operating conditions were beam energies of 6–7 keV and an anode current of 1 mA.

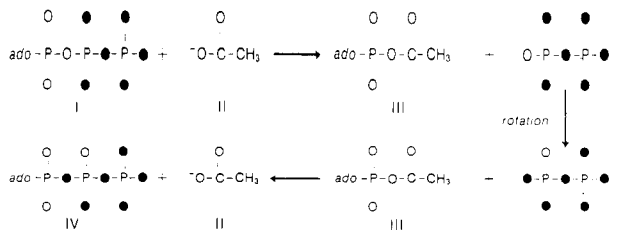
Collision-induced dissociation (CID) studies were performed in the mass-analyzed ion kinetic energy (MIKE) scan mode (*34*), with helium target gas and an incident ion energy of 8 keV (*33*). All CID spectra were recorded with a collision gas pressure corresponding to a 50% attenuation of the molecular ion beam. To improve the signal-to-noise ratio all CID spectra were signal averaged (eight scans at a rate of 20 s/scan) by using a Nicolet Instrument Corp. 1170 (Model 172/2) signal averager. Hard copies of the spectra were plotted on a Houston graphics 2000 X-Y recorder.

The solutions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP and [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP samples were prepared for FAB-MS by dissolving ca. 2 mg of the solid sample in 500 μL of distilled-deionized water. Typically 4 μL of this solution was placed on a brass probe tip and air-dried. To this sample was added approximately 2 μL of a 4:1 mixture of dithiothreitol and dithioerythritol as the liquid matrix.

RESULTS AND DISCUSSION

In an earlier paper FAB-MS was used to monitor the positional isotope exchange (PIX) reaction of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]adenosine triphosphate (ATP) shown in Scheme I (*24*). In this study incorporation of ^{18}O at the $\alpha\beta$ position was followed by enzymatic degradation of the ATP and AMP followed by FAB-MS analysis. The PIX reaction was performed by use of acetyl-CoA synthetase in the presence of acetate anion. Nucleophilic attack of the acetate anion at the α-P of ATP causes the pyrophosphate group to be cleaved. Upon equilibration of the PIX reaction mixture there is a 67% probability (assuming free rotation of the β-phosphoryl group) for incorporation of ^{18}O at the $\alpha\beta$ bridging position (see Scheme I). Using hexokinase, adenylate kinase, and glucose,

Scheme I



I adenosine triphosphate-[β-$^{18}O_2$, $\beta\gamma$-^{18}O, γ-$^{18}O_3$]
II acetate anion
III acetyl adenylate
IV adenosine triphosphate-[$\alpha\beta$-^{18}O, β-^{18}O, $\beta\gamma$-^{18}O,γ-$^{18}O_3$]

adenosine monophosphate (AMP) is formed via cleavage of the β- and γ-phosphoryl groups of ATP. Exchange of ^{18}O into the $\alpha\beta$ bridging position of the ATP shifts the mass of the resulting AMP by two (2) mass units. By enzymatically stopping the PIX reaction at specific times, the percent of ^{18}O exchange was determined by using FAB mass spectrometry (*24*).

A procedure similar to that used for the ATP studies could not be used for [$^{18}O_6$]uridine triphosphate (UTP) because enzymatic cleavage of the β- and γ-phosphoryl groups of uridine triphosphate (UTP) is not catalyzed by hexokinase and adenylate kinase. Also, direct FAB-MS analysis is not possible due to the low relative abundance for the monophosphate fragment ion in the $[M - H]^-$ mass spectrum of UTP ionized by FAB.

Several workers have proposed the use of tandem mass spectrometry (TMS) in combination with FAB ionization for the structure elucidation of polar organic molecules (*25–29*). However, to determine the extent of PIX for ^{18}O incorporation at the $\alpha\beta$ bridging position of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP, specific reaction channels must be observed in the corresponding FAB-TMS spectrum. The most useful reaction channels involve cleavage of the $\beta\gamma$-pyrophosphate (i.e., neutral loss of $H_3P_2O_6$ and $H_3P_2O_7$, see Figure 1A,B).

Although our earlier work on ATP was performed in the negative ion mode (*24*), the fragment ions necessary to elucidate the position of ^{18}O incorporation are not observed in the FAB-TMS spectrum of the $[M - H]^-$ ions of UTP (*35*). The number and relative abundance of fragment ions in a negative ion FAB-TMS spectrum are poor since the electron affinity of $[M - H]^-$ ions is lower than the dissociation energy. The specific fragment ions required to follow ^{18}O exchange into the $\alpha\beta$ bridging position may be observed in the FAB-TMS spectrum of the $[M + H]^+$ ions of UTP, but residual sodium present in the samples of UTP greatly reduces the yield for $[M + H]^+$ ions. That is, the $[M + Na]^+$ ion is the most abundant ion observed in the molecular ion region of the normal FAB mass spectrum. Without extensive purification on each sample, FAB-TMS analysis of the $[M + H]^+$ ions of UTP cannot be performed.

In the present study, the $[M + Na]^+$ ions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP and [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP (positional isomers, see Figure 1A,B) are formed by using FAB ionization analyzed by using tandem mass spectrometry (TMS). For convenience we have tabulated the mass, relative abundance, and structural assignment of the major CID product ions (see Figures 2–5), observed in the $[M + Na]^+$ ion FAB-TMS spectra of all UTP samples examined.

In the FAB-TMS spectrum of the $[M + Na]^+$ ions of unlabeled UTP (m/z 506, Figure 2) strong signals are observed at m/z 345 and m/z 329 which correspond to loss of $H_3P_2O_6$ and $H_3P_2O_7$, respectively. Assuming that these ions arise by cleavage of the $\alpha\beta$-pyrophosphate, it should be possible to follow the PIX reaction by observing a mass shift of the fragment ion at m/z 345.

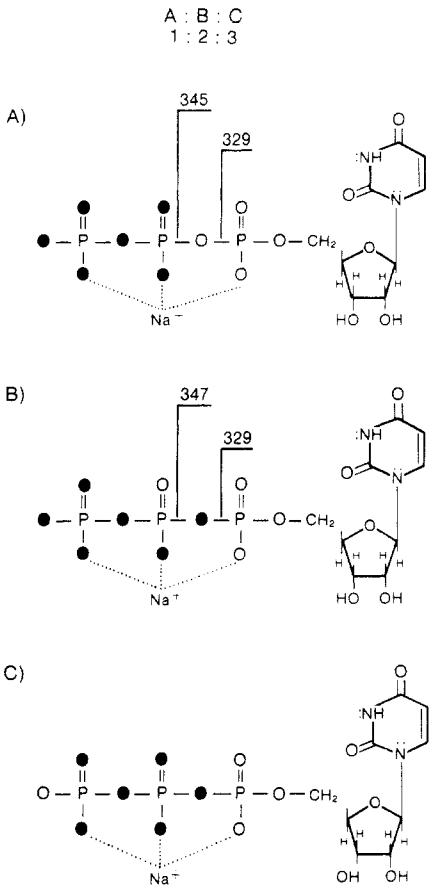


Figure 1. Proposed origin of fragment ions observed in the FAB-TMS spectrum of the $[M + Na]^+$ ions of (A) $[\beta\text{-}^{18}O_2,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP, (B) $[\alpha\beta\text{-}^{18}O,\beta\text{-}^{18}O,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP, and (C) $[\alpha\beta\text{-}^{18}O,\beta\text{-}^{18}O,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP due to "flipping". After the PIX reaction, a 1:2:3 ratio exists for the structures shown above (see text for details).

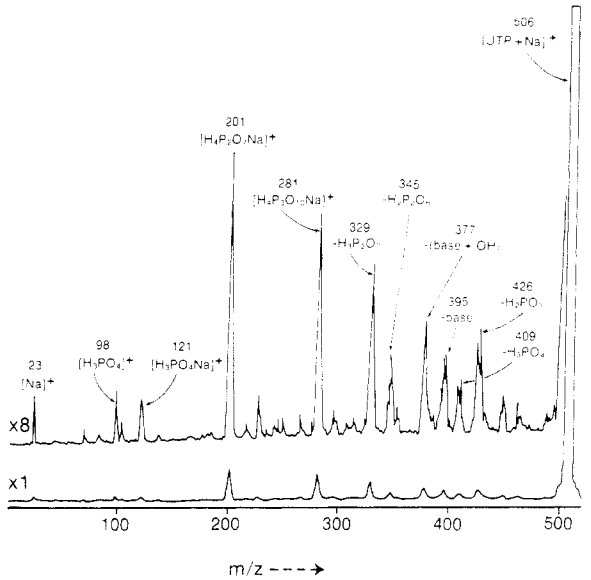


Figure 2. CID spectrum of the $[M + Na]^+$ ions of uridine triphosphate (UTP) (m/z 506).

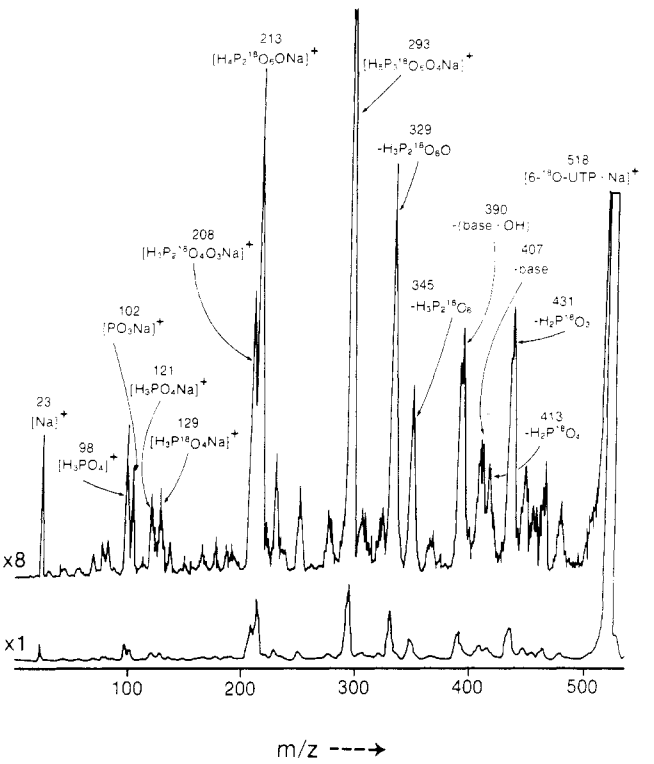


Figure 3. CID spectrum of the $[M + Na]^+$ ions of $[\beta\text{-}^{18}O_2,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP ($m/z$ 518) before the positional isotope exchange (PIX) reaction is performed.

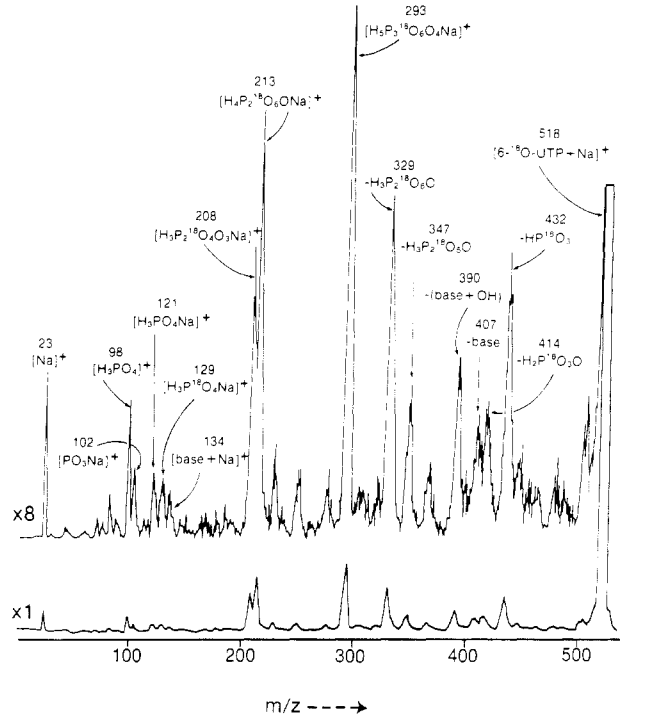


Figure 4. CID spectrum of the $[M + Na]^+$ ions of $[\alpha\beta\text{-}^{18}O,\beta\text{-}^{18}O,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP ($m/z$ 518) after the positional isotope exchange (PIX) reaction is performed.

In the FAB-TMS spectrum of the $[M + Na]^+$ ions of a synthetic sample of $[\beta\text{-}^{18}O_2,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP ($m/z$ 518, Figure 3) fragment ions at m/z 345 and 329 are observed which correspond to loss of $H_3P_2{}^{18}O_6$ and $H_3P_2{}^{18}O_6O$, respectively. The occurrence of these fragments ions is consistent with ^{16}O being located at the $\alpha\beta$ bridging position (see Figure 1A).

Following the PIX reaction, the fragment ion at m/z 345 should shift to higher mass due to the incorporation of ^{18}O at the $\alpha\beta$ bridging position. Indeed, the FAB-TMS spectrum of the $[M + Na]^+$ ions of $[\alpha\beta\text{-}^{18}O,\beta\text{-}^{18}O,\beta\gamma\text{-}^{18}O,\gamma\text{-}^{18}O_3]$UTP ($m/z$ 518, Figure 4) contains fragment ions at m/z 347 and m/z 329 corresponding to the loss of $H_3P_2{}^{18}O_5O$ and $H_3P_2{}^{18}O_6O$, respectively. The presence of these fragment ions indicates that ^{18}O has been incorporated at the $\alpha\beta$ bridging position.

Three additional significant fragment ions observed in the FAB-TMS spectrum of the $[M + Na]^+$ ions of unlabeled UTP are m/z 121, 201, and 281 which correspond to H_3PO_4Na,

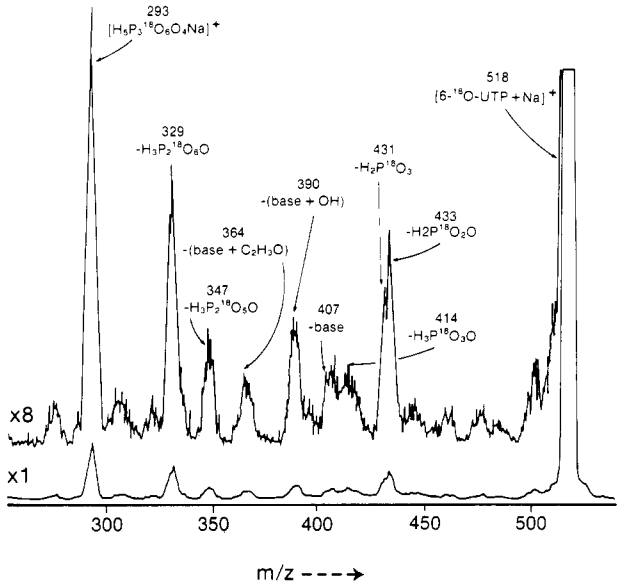
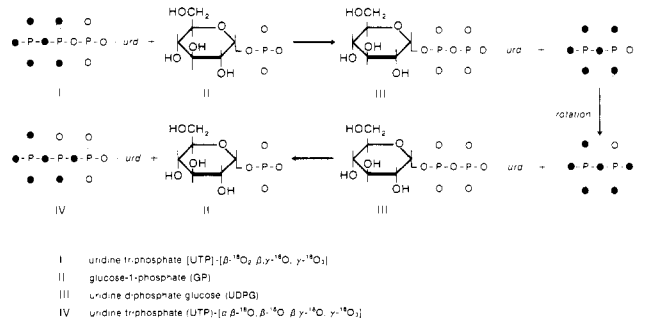


Figure 5. Narrow scan (m/z 250–518) CID spectrum of the [M + Na]$^+$ ions of [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP (m/z 518) after the positional isotope exchange (PIX) reaction is performed.

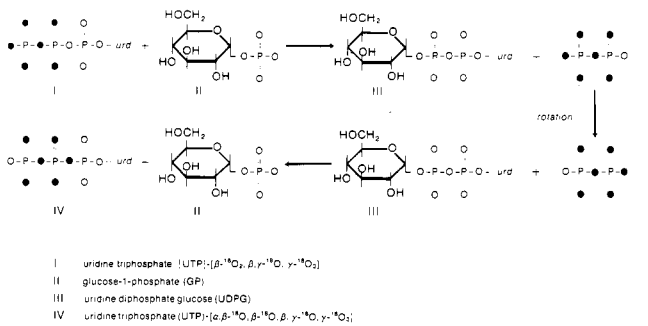
$H_4P_2O_7Na$, and $H_4P_3O_{10}Na$, respectively. It is interesting to note that these fragment ions account for ca. 45% of the total fragment ion yield in the CID spectrum. The relative abundance of these fragment ions suggests a strong interaction of the Na^+ ion with the phosphate chain of the molecule. Recently, we reported that the dissociation reactions of organo-alkali-metal ion complexes are influenced by the alkali-metal binding site, enhancing the structurally significant fragment ions formed (*31*). It seems feasible, therefore, that the attachment of the sodium ion to the phosphate portion of UTP gives rise to structurally significant fragment ions which are not observed in the FAB-TMS spectrum for the [M + H]$^+$ or [M − H]$^-$ ions (*35*). Additional fragment ions are observed in the FAB-TMS spectrum of the [M + Na]$^+$ ions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP which clearly indicate the interaction site of the Na^+ ion with the nucleotide. For example, the ions at m/z 293, 213, and 208 correspond to $H_5P_3{}^{18}O_6O_4Na$, $H_4P_2{}^{18}O_6ONa$, and $H_3P_2{}^{18}O_4O_3Na$, and the ions at m/z 129, 121, and 102 correspond to $H_3P^{18}O_4Na$, H_3PO_4Na and, PO_3Na. These ions account for ca. 53% of the total product ion yield, again suggesting a strong interaction of the Na^+ ion with the phosphate chain of the molecule.

In the narrow scan FAB-TMS spectrum (Figure 5), fragment ions are observed at m/z 433, 431, and 414 which correspond to loss of $H_2P^{18}O_2O$, $H_2P^{18}O_3$, and $H_3P^{18}O_3O$, respectively. The fragment ion at m/z 414 is observed in the wide scan FAB-TMS spectrum of the [M + Na]$^+$ ions of [β-$^{18}O_2$,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP (Figure 3); however, the fragment ions at m/z 433 and m/z 431 are not completely resolved in the broad band spectrum and are reported as m/z 432. The poor resolution of the broad band spectrum is due to the limited number of data points taken (1024 points) for the full MIKE scan (i.e., 0–535 V, or 0.52 V/channel). If the previously described PIX reaction mechanism is correct (i.e., cleavage of the terminal $\beta\gamma$-pyrophosphate group and free rotation of the β-phosphoryl group followed by re-formation of the triphosphate nucleotide; see Scheme II), the fragment ions at m/z 433 and m/z 414 should not be observed. These fragment ions indicate that ^{16}O is present at the γ-phosphate (see Figure 1C) vis-a-vis the α- and β-phosphate groups as shown in Figure 1B. Therefore, an additional mechanism must exist such that cleavage of the terminal pyrophosphate leads to free rotation or "flipping" perpendicular to the $\beta\gamma$ bridging oxygen. This causes a γ-^{18}O atom to be exchanged into the $\alpha\beta$ bridging

Scheme II



Scheme III



position (see Scheme III), leaving and ^{16}O atom in the γ-phosphate group. Cleavage of the γ-phosphate group at this point would lead to formation of the fragment ion at m/z 433 and cleavage of the γ-phosphate with the $\beta\gamma$-oxygen leads to formation of the fragment ion at m/z 414.

Of the six outer oxygen atoms present in the cleaved pyrophosphate group of [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP there are five ^{18}O atoms present. Three ^{18}O atoms are originally present at the γ-phosphate and two ^{18}O atoms are present at the β-phosphate; the ^{16}O is originally present at the β-phosphate. After equilibration of the PIX reaction mixture a 3:2:1 ratio for ^{18}O incorporation from the α-phosphate over the β-phosphate group over no incorporation (i.e., starting material re-formed) should exist (see Figure 1 for details). Therefore a 3:3 ratio for the relative abundance of the fragment ions at m/z 433 and m/z 431 (in the FAB-TMS spectrum of the [M + Na]$^+$ ions of [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP) should be observed if the "flipping" mechanism occurs since the original starting material yields a fragment ion at m/z 431. Investigation of the narrow scan FAB-TMS spectrum of the [M + Na]$^+$ ions of [$\alpha\beta$-^{18}O,β-^{18}O,$\beta\gamma$-^{18}O,γ-$^{18}O_3$]UTP gives a ratio of ca. 2.9:2.1 ratio for the fragment ions at m/z 433 and m/z 431. Owing to this additional reaction mechanism for PIX, there is an 83% probability of ^{18}O incorporation into the $\alpha\beta$ bridging position. Therefore, the observed high percent of incorporation of ^{18}O at the $\alpha\beta$ bridging position in the PIX reaction would be expected (*24*).

This study further illustrates the utility of alkali-metal ion attachment to specific sites of a complex organic molecule to enhance structural information. A particularly difficult problem in mass spectrometry is to identify structural isomers, or in this specific case the identification of isotopically labeled positional isomers. The specific fragment ions required to determine (qualitative and quantitative) the incorporation of ^{18}O into the $\alpha\beta$ bridging position are shown to arise as a direct result of attachment of Na^+ to the phosphoryl functional group. It is possible that this interaction will allow the determination of the PIX reaction from the $\beta\gamma$ bridge position to a β nonbridge position (i.e., kinase reactions) since neutral loss of the γ-phosphate group (i.e., H_2PO_4) is observed. Therefore, these data provide information on the kinetics and reaction mechanisms of the PIX reaction.

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Osmium Isotopic Ratio Measurements by Inductively Coupled Plasma Source Mass Spectrometry

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The isotopic composition of nanogram quantities of osmium was measured by using an inductively coupled plasma source mass spectrometer. Sensitivity was enhanced a factor of ≈100 by the use of an osmium tetraoxide vapor generator rather than nebulization of solution. For samples ≤5 ng, the ratios $^{190}Os/^{192}Os$, $^{189}Os/^{192}Os$, and $^{188}Os/^{192}Os$ were determined to better than ±0.5% ($1\sigma_m$) precision. For the minor isotopes, the ratios $^{187}Os/^{192}Os$ and $^{186}Os/^{192}Os$ were determined to ±1%, and $^{184}Os/^{192}Os$ (4×10^{-4}) was determined to ≈10%. Isotope ratios for common osmium are reported.

The ability to measure the isotopic composition of nanogram or smaller quantities of osmium is necessary for the development of the ^{187}Re–^{187}Os dating technique for geological samples and would provide a sensitive method of measuring osmium concentrations in rocks or other materials by isotope dilution. Such measurements have been hampered by the difficulties in isolating osmium from samples and finding suitable mass spectrometric techniques. It has been shown that osmium isotopic measurements can be made with an ion microprobe (*1*, *2*). However osmium isotopic assay by ion microprobes requires extensive sample preparation. The collected spectra are subject to polyatomic ion interferences, and the equipment is expensive and not widely available. Measurements have also been made with the laser microprobe mass analyzer (LAMMA) (*3*), but in addition to having the same problems as the ion probe, interpretation of LAMMA spectra was complicated by severe nonlinearities in the detector system. Recently there have been reports of osmium isotopic ratio measurements by resonance ionization mass spectrometry (*4*) and accelerator mass spectrometry (*5*). As part of a project to measure the ^{187}Re half-life (4.35×10^{10} years) (*6*), we investigated inductively coupled plasma source mass spectrometry (ICP-MS) (*7*) as a tool for making such measurements.

In ICP-MS, samples are usually liquids, which are introduced into the plasma by means of a nebulizer and spray chamber. Even though this process is only ≈1% efficient, the

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