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Offline oxygen isotope analysis of organic compounds with high N:O

Glendon B. Hunsinger*, William M. Hagopian and A. Hope Jahren
University of Hawaii-Manoa, School of Ocean and Earth Science & Technology, Dept. of Geology and Geophysics, Honolulu, HI 98622, USA

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Although the advantages of online δ^{18}O analysis of organic compounds make its broad application desirable, researchers have encountered NO$^+$ isobaric interference with CO$^+$ at *m/z* 30 (e.g. $^{14}N^{16}O^+$, $^{12}C^{18}O^+$) when analyzing nitrogenous substrates. If the δ^{18}O value of inter-laboratory standards for substrates with high N:O value could be confirmed offline, these materials could be analyzed periodically and used to evaluate δ^{18}O data produced online for nitrogenous unknowns. To this end, we present an offline method based on modifications of the methods of Schimmelmann and Deniro (*Anal. Chem.* 1985; 57: 2644) and Sauer and Sternberg (*Anal. Chem.* 1994; 66: 2409), whereby all the N_2 from the gas products of a chlorinated pyrolysis was eliminated, resulting in purified CO_2 for analysis via a dual-inlet isotope ratio mass spectrometry system. We evaluated our method by comparing observed δ^{18}O values with previously published or inter-laboratory calibrated δ^{18}O values for five nitrogen-free working reference materials; finding isotopic agreement to within ±0.2‰ for SIGMA® cellulose, IAEA-CH3 cellulose ($C_6H_{10}O_5$) and IAEA-CH6 sucrose ($C_{12}H_{22}O_{11}$), and within ±1.8‰ for IAEA-601 and IAEA-602 benzoic acids ($C_7H_6O_2$). We also compared the δ^{18}O values of IAEA-CH3 cellulose and IAEA-CH6 sucrose that was nitrogen-'doped' with adenine ($C_5H_5N_5$), imidazole ($C_3H_4N_2$) and 2-aminopyrimidine ($C_4H_5N_3$) with the undoped δ^{18}O values for the same substrates; yielding isotopic agreement to within ±0.7‰. Finally, we provide an independent analysis of the δ^{18}O value of IAEA-600 caffeine ($C_8H_{10}N_4O_2$), previously characterized using online systems exclusively, and discuss the reasons for an average 1.4‰ enrichment in δ^{18}O observed offline relative to the consensus online δ^{18}O value. Copyright © 2010 John Wiley & Sons, Ltd.

Oxygen stable isotope analysis of organic compounds has been a valuable tool for earth science, ecology, biochemistry and other disciplines for over 60 years (e.g. Urey[1]). Rittenberg and Ponticorvo[2] published the first vacuum-line method for the δ^{18}O analysis of ^{18}O-labeled organic substrates via chlorinated pyrolysis. Their mercuric chloride technique,[2] and the nickel technique of Thompson and Gray,[3] were the standard methods for determining the δ^{18}O value of C, H, O compounds up to the 1990s, including those compounds with low N or S content.[4,5] More recently, rapid and precise online techniques using high-temperature conversion (HTC) coupled with isotope ratio mass spectrometry (IRMS) instruments have dramatically advanced and increased the applications of δ^{18}O measurements.[6–10] The expansion of δ^{18}O analysis into novel fields (e.g., forensics,[11] biomedical,[12] food adulteration[13] and toxicology[14]) has required application of the technique to increasingly complex chemical substrates.

Although the advantages of online δ^{18}O analysis (i.e. dual isotope analysis, rapid and precise measurements on large sample sets) favor the extensive application of this methodology, researchers have encountered difficulties with standardization[7–9,15–17] and NO$^+$ interference[8–10,15,17–20] when analyzing substrates containing nitrogen. This is because the N_2 produced during the online HTC of a nitrogenous compound reacts with oxygen in the ion source, and the resultant NO$^+$ ion creates isobaric interference with the CO$^+$ ion at *m/z* 30 (e.g. $^{14}N^{16}O^+$, $^{12}C^{18}O^+$). The interference may alter the online δ^{18}O values by as much as 6‰ for substrates with N:O mass ratios above 0.3.[10] Users have attempted to eliminate this nitrogen interference using several online approaches including N_2 peak diversion, He dilution, increased gas chromatographic (GC) separation of N_2 and CO, and variable background subtraction.[9,10,12,15,20]

While each laboratory may maintain internal reference materials to help correct for interference, the widespread adoption of online δ^{18}O analysis for nitrogenous organic substrates is ultimately hampered by a lack of suitably δ^{18}O-calibrated reference materials. Currently, IAEA-600 caffeine is the only certified N-bearing organic reference material with a consensus value (glutamic acids failed exclusion tests), and the online interferences discussed above resulted in inconsistencies and elevated measures of uncertainty among laboratories.[17] Our goal was to perfect an offline method to completely eliminate N from nitrogenous organics, while isolating the O in these compounds as unfractionated CO_2, for analysis on the dual inlet of an IRMS system. In particular, we wished to establish a technique that

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*Correspondence to: G. B. Hunsinger, University of Hawaii-Manoa, School of Ocean and Earth Science & Technology, Dept. of Geology and Geophysics, Honolulu, HI 98622, USA.
E-mail: gbhunsin@soest.hawaii.edu

can be used to produce reference values for compounds with relatively high N:O mass ratios (e.g. alkaloids, nitro-organic explosives).

We formulated a cohesive, optimized offline method based on modifications of the techniques developed by Schimmelmann and Deniro[4] and Sauer and Sternberg,[21] whereby all N_2 from the gas products of a chlorinated pyrolysis was eliminated, resulting in purified CO_2 for analysis via a dual-inlet IRMS system. We evaluated our method in two ways: (1) we compared the $\delta^{18}O$ value of five nitrogen-free working reference materials: cellulose (SIGMA® and IAEA-CH3), sucrose (IAEA-CH6), and benzoic acids (IAEA-601 and IAEA-602) obtained using this method, with previously published or inter-laboratory calibrated $\delta^{18}O$ values of the same materials; (2) we compared the $\delta^{18}O$ values of cellulose (IAEA-CH3) and sucrose (IAEA-CH6) that were nitrogen-'doped' with the $\delta^{18}O$ value that we observed in part (1) above. We also provide an independent analysis of the $\delta^{18}O$ value of IAEA-600 caffeine ($C_8H_{10}N_4O_2$), which had previously been characterized exclusively using online HTC systems.

EXPERIMENTAL

Vacuum line methods

This work combined and modified the offline techniques of Schimmelman and DeNiro[4] and Sauer and Sternberg;[21] converting all the oxygen in an organic substrate into gas suitable for introduction into the high-precision dual inlet of an IRMS system. The initial thermal decomposition is performed using mercuric chloride ($HgCl_2$) as a reagent, which produces hydrogen cloride (HCl) gas as a product. Schimmelman and DeNiro[4] removed this HCl via reaction with isoquinoline; we have replaced this toxic portion of the procedure with the zinc (Zn) reaction established by Sauer and Sternberg[21] which produces $ZnCl_2$, thus allowing for separate and complete HCl removal from each individual sample. The result is a reliable and accurate, albeit lengthy and involved, method for isolating O as CO_2 and eliminating N_2 from nitrogenous organic samples. An illustration of the fate of O and N as a substrate is converted into CO_2 during this process is shown in Fig. 1.

All glass (quartz) used in the reactions was subject to rigorous cleaning in order to remove impurities and eliminate potential reactive surfaces. In brief, quartz tubes were heated to 550°C for 6 h in a muffle furnace, rinsed with distilled-deionized (DDI) water, soaked overnight in hydrochloric acid, triple rinsed with DDI, rinsed with 100% ethanol, and heated to 550°C for 6 h, then held under vacuum in a desiccator until use.[22] The nickel (Ni) reagent was prepared from high-purity nickel hydroxide followed by reduction to fine Ni powder under hydrogen atmosphere according to the method of Schimmelmann and DeNiro:[4]

$$Ni(OH)_2 + H_2 \rightarrow Ni^0 + 2H_2O \qquad (1)$$

Quartz ampules (15.5 cm lengths of 9 mm o.d.) were loaded with 10.8 ± 0.2 mg of $Ni(OH)_2$ and the contents were directly reduced at 275°C for ~54 h resulting in 6.5 ± 0.5 mg of powered Ni product; cutting the reaction time of Schimmelmann and DeNiro[4] in half. These quartz ampules were kept under vacuum until later use for the disproportionation of CO to CO_2, thereby preserving the reactive capacity and avoiding steps that could result in contact with ambient air or water vapor.

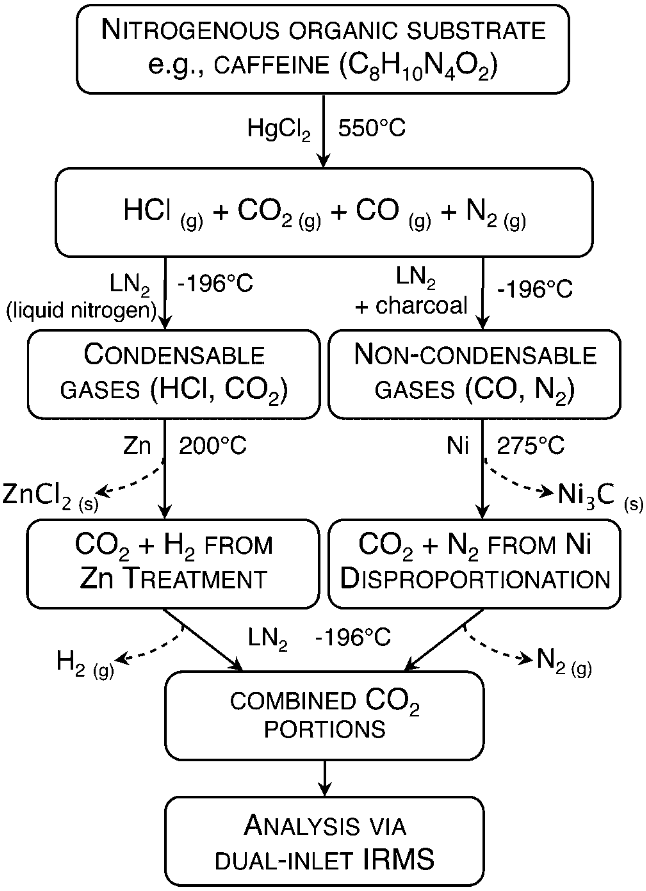

Figure 1. Diagram illustrating the separate fate of O and N from the example nitrogenous organic compound caffeine ($C_8H_{10}N_4O_2$) during our offline procedure.

Eight quartz ampules were typically processed as a single batch and were loaded with an amount of sample consistent with a theoretical yield of 45 ± 5.0 µmol of CO_2 (~3 mg of substrate[23]) from pyrolysis; reducing the quantity of substrate by 70% compared with that of Schimmelmann and DeNiro.[4] After the addition of 190 ± 10 mg of $HgCl_2$,[23] the quartz ampules were heated under vacuum at 100°C for 2 h using immersion heaters in order to remove any absorbed water vapor or water of hydration. The samples were then pyrolyzed at 550°C for 6 h[21] producing condensable (HCl, CO_2) and non-condensable gases (CO, N_2). The pyrolysis products were passed through an ethanol slush (−70°C) as an added precaution against volatile contaminants. The HCl and CO_2 products were condensed into a quartz ampule containing Zn, while CO and N_2 were sorbed onto 10 to 20 mg of activated charcoal (Anasorb CSC, lot#2000; SKC Inc., Eighty Four, PA, USA) under liquid nitrogen (LN_2) within the previously prepared Ni ampules. The charcoal had been pre-conditioned by heating under vacuum to glowing red for 3.5 min, while the Zn was heated for 1 min, in order to remove contaminants and oxides. This physical

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separation of condensable and non-condensable gas fractions marked a departure from the traditional method of Schimmelman and DeNiro,[4] which used common-bath reaction with isoquinoline to remove HCl. The HCl was removed from condensable gases via reaction with Zn at 200°C for 2 h:

$$Zn + 2HCl \rightarrow ZnCl_2 + H_2 \qquad (2)$$

while the CO_2 fraction remains unaffected. The other quartz ampule (containing non-condensable gases) was subject to a CO disproportion reaction at 275°C for 96 h via reduced Ni:

$$2CO + 3Ni \rightarrow CO_2 + Ni_3C \qquad (3)$$

while the N_2 fraction remains unaffected. The CO_2 contents of both ampules were further purified using an ethanol slush (−70°C), measured manometrically to determine yield, and condensed into one 6-mm Pyrex ampule for analysis on the dual inlet of the IRMS system. We estimated the oxygen yield as percentage CO_2 recovered, with an uncertainty of ±1.2% based on manometer calibration. The process blanks of each step and the N-doping reagent blanks did not produce measurable CO_2 quantities. Unless specifically noted, statements of statistical significance refer to the 95% confidence interval ($p \leq 0.05$); statistical tests were conducted using Microsoft Excel analysis toolpak.

Dual-Inlet IRMS measurement and calibration

The $\delta^{18}O$ analyses reported here were performed on an Isoprime IRMS instrument (Micromass, Manchester, UK) configured with a dual inlet. Sample and reference gases were introduced into the ion source at equal pressures yielding 4×10^{-9} amp major ion beam intensity. Normalization of the sample $\delta^{18}O$ value to the VPDB scale was based on the carbonate reference materials NBS-18 and NBS-19, and one internally calibrated calcite material. The $\delta^{18}O_{VPDB}$ value of CO_2 generated by digestion of these carbonates with 100% orthophosphoric acid (H_3PO_4) at 25°C for 16 h[24] was calculated using an acid fractionation factor $\alpha = 1.0103$.[25] The data were then transferred to the VSMOW-SLAP scale using the revised expression of Coplen *et al.*:[8,26]

$$\delta^{18}O_{VSMOW\text{-}SLAP} = 1.03092 * \delta^{18}O_{VPDB} + 30.92 \qquad (4)$$

Due to discrepancies discussed later in the text regarding benzoic acid reference materials, direct calibration to the VSMOW-SLAP scale was precluded; thus carbonate CO_2 was utilized. The CO_2 reference gases were analyzed in tandem with the CO_2 generated from the samples using the offline methods described above. The standard error in the $\delta^{18}O$ value conferred via the dual-inlet IRMS instrument was ±0.02‰. All the δ-values are reported in per mil with reference to the VSMOW-SLAP scale.

RESULTS AND DISCUSSION

Nitrogen-free reference materials

Initial experiments were performed on three C, H, O organic substrates: (1) SIGMA® and IAEA-CH3 cellulose ($C_6H_{10}O_5$); (2) IAEA-CH6 sucrose ($C_{12}H_{22}O_{11}$); and (3) IAEA-601 and IAEA-602 benzoic acids ($C_7H_6O_2$) (Table 1). A comparison of the $\delta^{18}O$ values gained using the method described here with published and inter-laboratory consensus values indicated agreement across a range in $\delta^{18}O$ value of approximately 50‰ (Fig. 2). A regression of the observed vs. referenced data yielded $R^2 = 0.99$. Student's t-test and covariance test of the resulting slope (from Fig. 2) vs. a slope of 1 revealed no significant difference from a 1:1 relationship for these data.

The average difference between consensus and our observed values for SIGMA® cellulose, IAEA-CH3 (cellulose) and IAEA-CH6 (sucrose) was 0.2‰ ($n = 48$). The average CO_2 yield for SIGMA® cellulose and IAEA-CH3 (cellulose) was 96.3% ($n = 12$, standard deviation (s.d.) = 5.1) and 93.6% ($n = 24$, s.d. = 5.1), respectively. However, yields <100% are unavoidable during cellulose analysis, due to hygroscopicity (i.e., when weighed the substrate contains water that is removed under vacuum prior to

Table 1. Measured mean carbon dioxide yield, observed and reported mean $\delta^{18}O$ values for undoped and nitrogen-doped materials. ADN = adenine, IMZ = imidazole and APY = 2-aminopyrimidine

Material(s)	Formula(s)	Type	ID[*]	n[#]	Observed CO_2 yield [%]	Observed $\delta^{18}O$ [‰]	Reported $\delta^{18}O$[**] [‰]	$\Delta\delta^{18}O$[***] [‰]
SIGMA®	$C_6H_{10}O_5$	Cellulose	SIG	12	96.3 (5.1)[##]	29.2 (0.6)	29.3 (0.3)	0.1
IAEA-CH3	$C_6H_{10}O_5$	Cellulose	CE0	24	93.6 (5.1)	32.0 (0.6)	31.9 (0.5)	-0.1
IAEA-CH3 + ADN	$C_6H_{10}O_5 + C_5H_5N_5$	N-doping	CE1	9	94.9 (1.0)	31.9 (0.2)	31.9 (0.5)	-0.1
IAEA-CH3 + IMZ	$C_6H_{10}O_5 + C_3H_4N_2$	N-doping	CE2	3	95.1 (0.1)	32.5 (0.3)	31.9 (0.5)	-0.7
IAEA-CH3 + APY	$C_6H_{10}O_5 + C_4H_5N_3$	N-doping	CE3	4	97.6 (5.0)	32.3 (0.7)	31.9 (0.5)	-0.5
IAEA-CH6	$C_{12}H_{22}O_{11}$	Sucrose	SU0	12	98.8 (1.9)	36.2 (0.6)	36.4 (0.6)	0.2
IAEA-CH6 + ADN	$C_{12}H_{22}O_{11} + C_5H_5N_5$	N-doping	SU1	8	100.4 (0.8)	36.0 (0.3)	36.4 (0.6)	0.4
IAEA-CH6 + IMZ	$C_{12}H_{22}O_{11} + C_3H_4N_2$	N-doping	SU2	4	101.3 (0.4)	36.0 (0.7)	36.4 (0.6)	0.4
IAEA-CH6 + APY	$C_{12}H_{22}O_{11}$	N-doping	SU3	4	101.1 (0.2)	36.2 (0.2)	36.4 (0.6)	0.2
IAEA-600	$C_8H_{10}N_4O_2$	Caffeine	CAF	4	99.2 (1.8)	-2.1 (0.5)	-3.5 (0.5)	-1.4
IAEA-601	$C_7H_6O_2$	Benzoic Acid	BZ1	3	92.7 (3.3)	24.9 (0.2)	23.1 (0.2)	-1.8
IAEA-602	$C_7H_6O_2$	Benzoic Acid	BZ2	3	93.3 (2.2)	72.9 (0.9)	71.3 (0.4)	-1.6

[*] As per Fig. 2.
[**] reference value citations: SIGMA®[21]; IAEA-CH3;[27–29] IAEA-CH6;[6,10] IAEA-600, -601, -602.[17]
[***] $\Delta\delta^{18}O = \delta^{18}O_{this\ study} - \delta^{18}O_{reported}$ using mean values.
[#] Number of determinations
[##] Standard deviation of mean shown in parentheses.

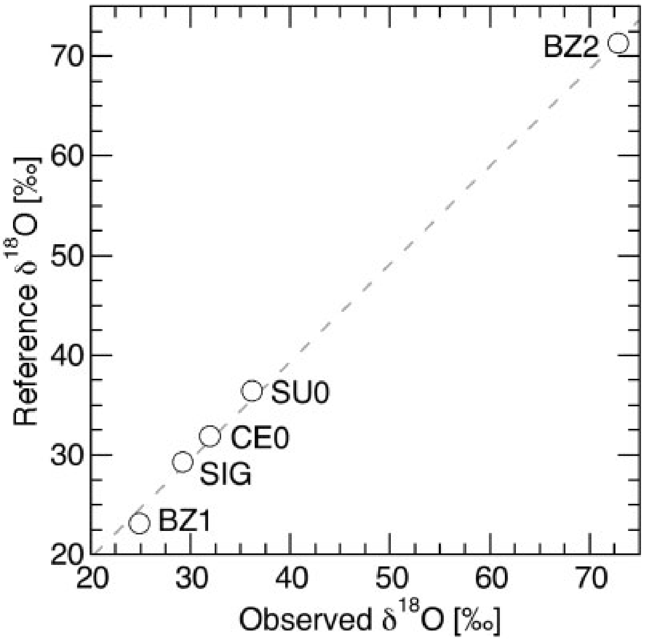

Figure 2. Offline $\delta^{18}O_{VSMOW-SLAP}$ values vs. previously published δ^{18}O values for nitrogen-free substrates IAEA-601 benzoic acid (BZ1), SIGMA® cellulose (SIG), IAEA-CH3 cellulose (CE0), IAEA-CH6 sucrose (SU0), IAEA-602 benzoic acid (BZ2). Error bars representing measurement uncertainty did not exceed the size of the data symbols.

pyrolysis).[3,4,21,26–28] These CO_2 recoveries surpassed previous yields for $HgCl_2$ pyrolysis[4] and agreed with prior work using Ni pyrolysis.[3] The average CO_2 yield for IAEA-CH6 sucrose was 98.8% ($n = 12$, s.d. = 1.9; Table 1) and was not significantly different from 100%. The overall measure of precision showed no significant difference between inter-comparison consensus precision and deviation observed in our experiments.

The IAEA-601 and IAEA-602 benzoic acids showed a significant difference from referenced values, with offsets of 1.8‰ ($n = 3$) and 1.6‰ ($n = 3$), respectively (Table 1). Prior work has suggested that volatile compounds (e.g., benzoic acid, benzophenone) decompose differentially under $HgCl_2$ pyrolysis;[30] thus, researchers have preferably utilized the decarboxylation method.[22] We observed the following aspects, which resulted in lowered CO_2 recoveries (<93%) and affected the observed δ^{18}O values of benzoic acids: (1) electrostatic substrate adhered to ampule walls and partially decomposed during ampule 'necking' with a torch, (2) variable losses of substrate during the water removal step (100°C, under vacuum) due to volatilization, and (3) carbonaceous deposits upon pyrolysis may have created a reactive surface for carbon oxides. Nonetheless, the remarkably consistent offset in δ^{18}O values between the offline and online techniques highlights the potential for reproducibility using the offline technique, even across disparate substrates and a broad range of δ-values. With these analyses we established a nitrogen-free δ^{18}O value in an organic substrate using our offline method, one that we can test against the same materials doped with nitrogen.

Nitrogen-doped reference materials

In order to simulate the N:O mass ratios observed in nitro-organic explosives and other N-bearing organic substrates, we analyzed IAEA-CH3 cellulose and IAEA-CH6 sucrose reference materials to which we had added the following nitrogenous compounds: adenine (ADN; $C_5H_5N_5$), imidazole (IMZ; $C_3H_4N_2$) and 2-aminopyrimidine (APY; $C_4H_5N_3$). We chose this suite of compounds to encompass chemical structure diversity and doped the standards up to a maximum N:O mass ratio = 2.5 (23% N by weight (wt %), based on total mixture). We modeled this approach on previous offline experiments which successfully produced equivalent δ^{18}O values in doped and undoped materials up to a maximum N:O = 0.2 (3.7 wt % N, based on total mixture).[4] We note that online techniques have revealed disagreement between δ^{18}O values for APY-doped vs. undoped beet sucrose by up to 6‰,[10] further illustrating the need for successful elimination of N interference. If our offline technique successfully eliminated N interferences, we would expect the δ^{18}O value of N-doped reference materials to be the same as the δ^{18}O values of undoped reference materials, and this was indeed the case (Table 1, Fig. 3). The regression of doped vs. undoped materials showed no significant difference from a 1:1 relationship using both t-test and covariance tests. The CO_2 yields in N-doped IAEA-CH3 cellulose and IAEA-CH6 sucrose were 95.9% and 100.9%, respectively, and did not differ by more than 2.3% from the average for undoped materials.

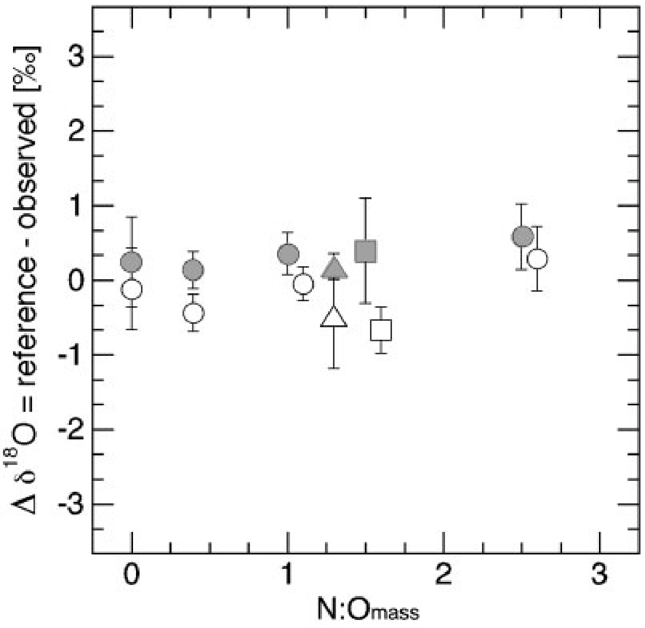

Figure 3. Offline $\delta^{18}O_{VSMOW-SLAP}$ values for nitrogen-doped IAEA-CH3 cellulose (open symbols) and IAEA-CH6 sucrose (filled symbols) with doping agents adenine ($C_5H_5N_5$, circles), imidazole ($C_3H_4N_2$, squares) and 2-aminopyrimidine ($C_4H_5N_3$, triangles) across the range N:O = 0 to 2.5 (0 to 23 wt % N).

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Nitrogen-bearing reference material IAEA-600 caffeine

We performed offline analysis of the N-containing reference material IAEA-600 caffeine ($C_8H_{10}N_4O_2$; N:O = 1.8; 28.9 wt % N) in order to independently determine the $\delta^{18}O$ value, which had previously been characterized using online HTC systems. Our average $\delta^{18}O$ value was −2.1‰ ($n = 4$;s.d. = 0.5) while online values for IAEA-600 caffeine varied from –3.2 to −4.4‰.[17] Therefore, our offline method resulted in a $\delta^{18}O$ value 1.4‰ higher, on average, than that from online methods, suggesting that N interference gives rise to an ^{18}O-depletion effect online. Brand *et al.*[17] suggested that during the HTC of caffeine, NO^+ produced on the filament may cause interference at *m*/*z* 30, or $(CN)_x$ precursors may elute slowly from the GC column, causing unpredictable consequences for $\delta^{18}O$ determinations. For our offline analysis, separate yield calculations indicated that CO_2 produced during the initial $HgCl_2$ pyrolysis and recovered after the Zn treatment averaged 66.0% ($n = 18$; s.d. = 1.1), while the Ni disproportionation reaction produced CO_2 yields ranging from 9.5 to 38.2% (average = 26.1; s.d. = 9.3). The most important factors necessary to maximize yield from the Ni-disproportionation reaction were complete sorption of CO and N_2 onto charcoal, Ni batch purity, excess Ni (>0.4 mg/μmol of CO), and the avoidance of Ni contact with air after reduction. Based on sample runs that optimized these factors (i.e. quantitative theoretical yields), we propose that the $\delta^{18}O$ reference value of IAEA-600 caffeine be established as −2.1‰, or (at very least) re-evaluated, in light of our analysis yielding 99.2% ($n = 4$;s.d. = 1.8) CO_2 recovery using this offline procedure.

CONCLUSIONS

The observation of N interference during the online analysis of nitrogenous organic compounds is a long-standing concern. We have confirmed this effect by showing that a 99.2 ± 1.8% CO_2 yield ($n = 4$; not significantly different from 100%) via offline analysis of caffeine ($C_8H_{10}N_4O_2$) resulted in a $\delta^{18}O$ value that is 1.2‰ above the nearest published value using HTC.[17] Researchers have argued that interference from N_2 skews oxygen isotope composition towards lower $\delta^{18}O$ values during online HTC analysis by demonstrating that dilution or diversion of the N_2 peak increased $\delta^{18}O$ values by approximately 0.6‰.[20] Our results suggested that although online dilution and diversion modifications may decrease nitrogen interference they do not completely eliminate the issue. Due to chromatographic peak tailing of the N_2 and related N-oxides emanating from the HTC system the interference is still present. The offline method we have described and tested is not subject to these effects because the involved reactions are not performed under highly reducing conditions, the reaction temperatures are relatively low, quantifiable conversion (i.e., 100% CO_2 yield) is confirmed, and the final CO_2 product is purified and introduced to the IRMS system as a pure gas. Using our offline technique, reference values could be determined for inter-laboratory standards of new substrates with high N:O values, such as nitro-organic explosives PETN, TNT and RDX with N:O = 0.3, 0.4 and 0.9, respectively. These reference materials, in turn, can be analyzed periodically during online analyses of the $\delta^{18}O$ values of nitrogenous or nitro-organic unknowns, and considered when correcting and validating data produced online.

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