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International Journal of Mass Spectrometry 185/186/187 (1999) 393–399

International Journal of Mass Spectrometry

Ring versus oxygen protonation in metastable ion decompositions of protonated isopropyl phenyl ether

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Received 5 June 1998; accepted 5 August 1998

Abstract

Protonated alkyl phenyl ethers possess more than one stable tautomer. A debate has arisen over whether only one of them gives rise to the principal dissociation pathway observed in their mass-analyzed ion kinetic energy (MIKE) spectra. Alkene loss constitutes the major (often the exclusive) metastable ion decomposition, yielding protonated phenol ions. A hydron deposited by chemical ionization exchanges with some of the alkyl hydrogens (but none of the ring hydrogens) prior to fragmentation. Previously published MIKE spectra have shown that $[(CD_3)_2CHOPh]D^+$ gives only *m*/*z* 97 ($C_6H_5D_2O^+$), but that $[(CD_3)_2CHOPh]H^+$ gives a mixture of *m*/*z* 96 ($C_6H_6DO^+$) and *m*/*z* 97. Exchange must arise via ion-neutral complexes that result from *O*-protonated ions, $(CD_3)_2CHO(H)Ph^+$. Current controversy centers around the contribution of ring-protonated ions to the production of unexchanged fragment ions. Here we determine the mole fractions of ring-protonated (*X*) and *O*-protonated (1 − *X*) parent ions using *m*/*z* 95:*m*/*z* 96:*m*/*z* 97 MIKE ion abundance ratios from H_2O and D_2O CI of $(CH_3)_2CHOPh$, $CH_3(CD_3)CHOPh$, and $(CD_3)_2CHOPh$. Data from the first two compounds give unbiased assessments of *X* and four other relative rate constants that are obtained using a steady-state kinetic model that gives a set of five equations in five unknowns. The values calculated from the data predict an *m*/*z* 96:*m*/*z* 97 ratio of 4.7 for $[(CD_3)_2CHOPh]H^+$ that turns out to be the same ratio as is measured experimentally. This validation of the data analysis corroborates the value of $X \leq 0.01$ extracted from the experimental results. The contribution of ring-protonated parent ions to the MIKE spectra of chemically ionized isopropyl phenyl ether is therefore negligible. (Int J Mass Spectrom 185/186/187 (1999) 393–399) © 1999 Elsevier Science B.V.

Keywords: Chemical ionization; Isotopic exchange; Mass-analyzed kinetic energy (MIKE) spectroscopy; Mechanism; Steady state kinetics

1. Introduction

Phenyl ethers and their derivatives constitute a major class of industrially manufactured compounds, ranging from pharmaceuticals (e.g. gemfibrozil or tamoxifen) to polymer intermediates such as phenyl glycidyl ether (PGE, a derivative of propyl phenyl ether). This class includes molecules that present potentially serious environmental pollution hazards, insofar as they mimic hormones (as does tamoxifen) or modify DNA (as does PGE). Mass spectrometry offers one of the best ways to characterize xenobiotics, their derivatives, and the compounds they form with biological macromolecules. The phenoxy group

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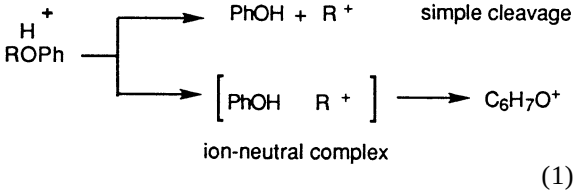
Dedicated to M.T. Bowers on the occasion of his 60th birthday.

PII S1387-3806(98)14139-8

gives rise to characteristic ion decompositions. In the case of PGE adducts of nucleotides, for example, positive ions from electrospray dissociate to give the protonated nucleotide base, which then loses phenol (PhOH) as one of the diagnostic fragmentations [1].



(1)

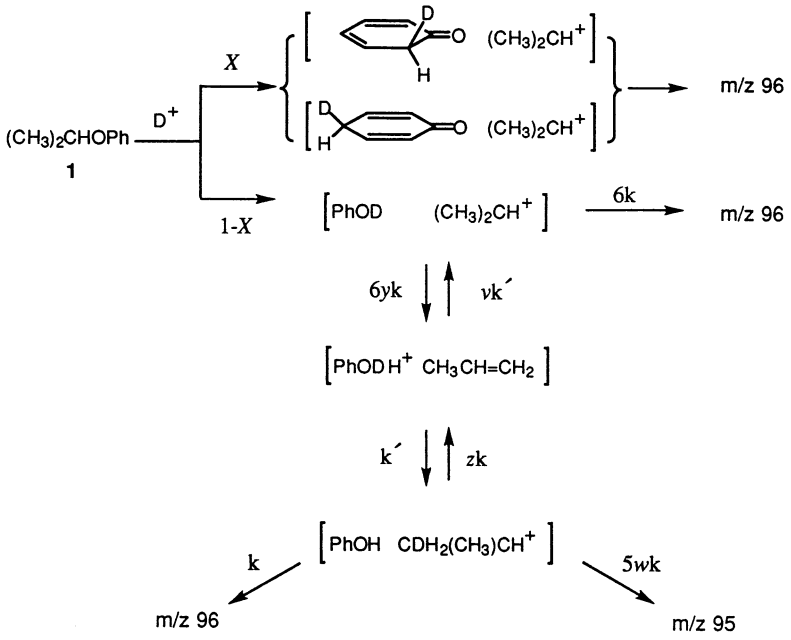
A straightforward mechanism for loss of phenol is not difficult to imagine. An *O*-protonated ion [2], as depicted on the left hand side of Eq. 1, undergoes R–O bond fission. Unless the resulting R^+ is acidic enough to transfer a proton to phenol, the simple cleavage products are observed. In cases where R^+ is sufficiently acidic (as in the chemical ionization mass spectrum of PGE itself) an ion-neutral complex forms, and the observed fragment ion is a protonated phenol, $C_6H_7O^+$ (*m*/*z* 95). This latter process contributes the dominant fragmentation in the chemical ionization (CI) mass spectra of alkyl phenyl ethers when R is a saturated hydrocarbon group.

Considered in greater detail the situation begins to appear more complicated. In PGE and its adducts the OPh group is connected to a methylene group. Simple cleavage would lead to formation of a primary carbocation, a very unstable species that is structurally labile. Therefore, structural rearrangement must surely accompany R–O bond fission. When R is a saturated hydrocarbon group, alkene constitutes the neutral fragment expelled when *m*/*z* 95 forms. As is well known [3–9], the isotopic label scrambles within saturated *n*-propyl sidechains, confirming the occurrence of the rearrangement.

As Harrison and Wang have recently reported, chemical ionization with deuterated reagent gases sometimes leads to R^+ that incorporate deuterium [3]. More significantly, as Benoit and Harrison first demonstrated over two decades ago [4], undeuterated $C_6H_7O^+$ ions form a substantial fraction of the ions that result from depositing a D^+ onto oxygen. These twin features—structural rearrangement and intramolecular hydron exchange—introduce significant complexities into the interpretation of the fragmentations of protonated phenoxy compounds.

Over the past several years controversy has arisen over the relative roles of *O* protonation versus ring protonation [2,5–9]. On the one hand, thermodynamics favor deposition of a hydron onto an sp^2 carbon in the benzene ring of a phenyl ether [10]. On the other hand, deposition onto oxygen is required in order to account for intramolecular hydron exchange. Scheme 1 illustrates the competition between acidification of the ring versus oxygen when D^+ adds to isopropyl phenyl ether (*i*PrOPh, **1**). The upper branch of the scheme (mole fraction *X*) depicts the ion-neutral complexes that arise from putting D^+ onto the ring: no observable exchange with hydrogen can occur. The lower branch (mole fraction $1 - X$) represents the ion-neutral complexes that result from putting D^+ onto oxygen: initially formed [phenol isopropyl cation] complexes interconvert with [*O*-protonated phenol/propene] complexes, exchanging the deuterium between oxygen and carbon. This mechanistic model accounts for fragment ion distribution in terms of *X* along with four ratios of rate constants, *w*, *v*, *y*, and *z*.

Measurements of the relative proportions of ring protonation and *O* protonation become complicated when the alkyl group rearranges in the course of forming an ion-neutral complex. The most extensive studies to date have dealt with *n*-propyl phenyl ether. Deuteration of various positions of the propyl group has demonstrated that no simple statistical model can account for the distribution of label in the fragment ions [9]. Fully dissecting the effects of hydron exchange and sidechain rearrangements presents such an obstacle that experimental measurements from metastable ion decompositions have been interpreted by assuming that either all of the decomposing ions result from deposition of a hydron onto oxygen [5,6], or else that all of the hydrogens in the propyl side chain randomize completely with the hydron on oxygen [7,8].



Scheme 1.

Testing the validity of these assumptions requires scrutiny of a case where sidechain rearrangement does not take place. Then the proportions of ring- versus *O* protonation can be determined, as well as relative rate constants for hydron exchange between carbon and oxygen. This article presents data for isopropyl phenyl ether, from which we can extract the mole fraction *X* and the relative rates of hydron transposition without making any of the above assumptions. Under the reaction conditions the isopropyl cation is stable and does not transpose hydrogens between its central carbon and the methyl groups, nor do any of the ring hydrogens undergo exchange [10].

This article analyses Scheme 1 using steady-state kinetics. The steady-state approximation facilitates solving the differential equations arising from unimolecular mechanistic models, such as Scheme 1. It gives an exact solution for branching ratios of reaction that have gone to completion and accurate ratios of rate constants for systems that obey first-order kinetics. As we have pointed out elsewhere [6], steady-state analysis of fragment ion distributions retains its validity even when a first-order kinetic regime is not strictly followed. Even though metastable ion decompositions may exhibit composite kinetics (the superposition of more than one parent ion population, each undergoing first-order decay with a different rate coefficient) some parent ions exhibit biexponential disappearance curves, with a fast component at short times and a slower component that resembles first-order decay at times longer than 2.5 μs [11]. The criterion for applicability of the steady-state approximation in the present study demands that the fragment ion distribution be the same at shorter times (e.g. in the first field-free region) as at the longer times at which the data are measured. [*i*PrOPh]D^+ meets this criterion (though the isomeric deuteronated *n*-propyl phenyl ether ions do not [10]). As a further check of the validity of the steady-state approximation, the ratio from [$(CD_3)_2$CHOPh]D^+ was not used in the data reduction, but instead predicted from the relative rate constants extracted from the results for $(CH_3)_2$CHOPh and $CH_3(CD_3)$CHOPh. We have adopted this approach as a means of testing the accuracy of mechanistic (as opposed to a phenomenological) models for multistep ion dissociations [12].

2. Experimental

$CH_3(CD_3)CHOPh$ was prepared by reduction of 2-phenoxypropionic acid (Aldrich Chemical Co.) with $LiAlD_4$, conversion of the resulting alcohol to its tosylate, and reduction of the tosylate with $LiAlD_4$. $(CD_3)_2CHOPh$ and $(CH_3)_2CHOPh$ were prepared as previously described [6]. All compounds were purified by two successive fractional distillations. Mass-analyzed ion kinetic energy (MIKE) spectra were recorded on a VG ZAB-2F double focusing (B–E) instrument. Chemical ionization was performed using H_2O or D_2O reagent gas [9]. H_3O^+ is usually assumed to protonate ethers at the collisional rate [13]. Relative ion abundances were found to vary with the amount of water in the ion source, so MIKE spectra were recorded at the highest accessible pressures, where the proportions *m*/*z* 95, 96, and 97 reached their limiting values. At the highest partial pressure of D_2O a comparison of the metastable ion decomposition of *m*/*z* 138 (from *i*PrOPh and D_3O^+) in the first field-free region (1st FFR) with the MIKE spectrum (2nd FFR) showed that both patterns exhibit the same *m*/*z* 95:*m*/*z* 96 ratio, confirming that the limiting value had been reached. Interference from ^{13}C–$M^{+\cdot}$ ions (which are isobaric with the MH^+ ions) in the H_2O chemical ionization spectra was ruled out by the absence of *m*/*z* 94 in the observed MIKE spectra. Relative peak intensities are based on averages of multiple measurements within independent trials performed on different days. Relative fragment ion abundances for chemical ionization spectra of $PhOCH(CD_3)CH_3$ were measured by fitting the spectra to Gaussian functions (all with the same peak width) [6]. Experimental ion abundance ratios were fit to the steady-state expressions derived from Scheme 1 by means of the nonlinear least-squares program in the SCIENTIST software package (MicroMath, Inc.).

3. Results

Table 1 summarizes the MIKE spectra for H^+ and D^+ CI of *i*PrOPh and two partially deuterated analogues. Metastable ion decomposition of $[i\text{PrOPh}]H^+$ shows only $C_6H_7O^+$ (*m*/*z* 95), so the table omits that entry. Similarly, $[(CD_3)_2CHOPh]D^+$ displays only $C_6H_5D_2O^+$ (*m*/*z* 97) [10], so that entry is also not included. We tabulate only the precursor ions for which we observe at least two peaks.

Table 1
Ion abundance ratios from metastable ion decompositions of conjugate acid ions of *i*PrOPh and its deuterated analogues. Calculated ratios are based on the parameters listed in Table 2

Precursor ion	Ion ratio	Observed	Calculated
$[(CH_3)_2CHOPh]D^+$	*m*/*z*96:*m*/*z*95	4.7	4.7
$[CH_3(CD_3)CHOPh]H^+$	*m*/*z*96:*m*/*z*95	0.71	0.70
$[CH_3(CD_3)CHOPh]H^+$	*m*/*z*97:*m*/*z*96	0.05	0.07
$[CH_3(CD_3)CHOPh]D^+$	*m*/*z*96:*m*/*z*97	2.2	2.2
$[CH_3(CD_3)CHOPh]D^+$	*m*/*z*95:*m*/*z*96	0.10	0.09
$[(CD_3)_2CHOPh]H^+$	*m*/*z*96:*m*/*z*97	4.7 [a]	4.7 [b]

[a] Not used in the data analysis.
[b] Predicted from analysis of the first five data points.

A glance at the experimental data summarized in Table 1 reveals that the first and last experimental entries—D^+ on undeuterated *i*PrOPh and H^+ on $(CD_3)_2CHOPh$—give the same ratios of unexchanged to hydron-exchanged fragments (the *m*/*z* 96:*m*/*z* 95 ratio in the former case; the *m*/*z* 96:*m*/*z* 97 ratio in the latter). The two parent ions have complementary labeling patterns: one D and six exchangeable H's in the former versus one H and six exchangeable D's in the latter. The equality of ratios might imply that hydrogen and deuterium both transfer with the same rate constant (i.e. that all isotope effects have a value $k_H/k_D = 1$).

We test the hypothesis that all isotope effects are unity by examining the proportions of ions from CI of $CH_3(CD_3)CHOPh$. Both $CI(H_2O)$ and $CI(D_2O)$ afford three peaks in the MIKE spectrum—*m*/*z* 95, *m*/*z* 96, and *m*/*z* 97—containing, respectively, zero, one, and two deuteria. The parent ions $[CH_3(CD_3)CHOPh]H^+$ and $[CH_3(CD_3)CHOPh]D^+$ are complementary: four H's and three D's in the former versus three H's and four D's in the latter. If the above hypothesis is correct, the MIKE spectra should be mirror images of one another. As Fig. 1 depicts, this is not the case. We analyze the data for $[i\text{PrOPh}]D^+$ and for the conjugate acid ions from d_3-isopropyl phenyl ether using the kinetic model exemplified by Scheme 1. The relevant steady-state kinetic expression for $[i\text{PrOPh}]D^+$ is

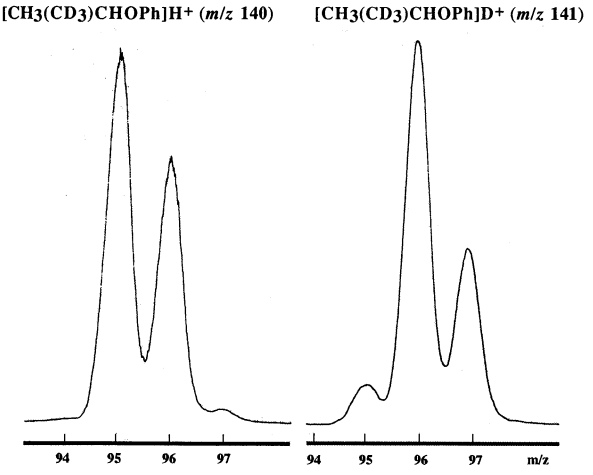


Fig. 1. MIKE spectra of conjugate acid ions from $CH_3(CD_3)CHOPh$ using H_2O and D_2O chemical ionization to produce the parent ions.

$$\frac{m/z\ 96}{m/z\ 95} = \frac{5wyX + 5w + 1 + 5\nu w + \nu + y + \nu wz}{5wy(1 - X)} \quad (2)$$

whereas the corresponding expressions for the four ion abundance ratios from d_3-isopropyl phenyl ether are given in the Appendix. Eq. 2 makes use of two primary kinetic isotope effects, $\nu = k'_H/k'_D$ and $w = k_H/k_D$. A third, independently treated isotope effect corresponds to the quotient of the two branching ratios, y/z. The 5 variables in Scheme 1 whose values can be extracted from fragment ion ratios consist of these three isotope effects (that all have values between 1.7 and 2), the mole fraction X, and the branching ratio y for exchange of the CI hydrogen with the sidechain. Table 2 lists the values of X and the ratios of rate constants ν, w, y, and z derived from the five equations in five unknowns.

Table 2
Parameters for Scheme 1 derived from the first five experimental ion abundance ratios in Table 1 via least-squares fitting

Symbol	Definition	Calculated
X	Mole fraction ring protonation	0.000
y	Hydron exchange branching ratio	0.748
z	y times k_D/k_H for hydron exchange	0.435
ν	k_H/k_D for O acidity	1.963
w	k_H/k_D for C acidity	1.968

Table 1 summarizes the agreement between the mechanistic model and the experimental data. The steady-state approximation gives a set of nonlinear equations, for which an iterative computer program gives calculated values within experimental uncertainty of the observed ion abundance ratios, although the best fit does not match the mean values exactly. One test of the model is the ratio it predicts for the sixth experimental data point, the m/z 96:m/z 97 ratio for $[(CD_3)_2CHOPh]H^+$ (that was not used in the data analysis). Eq. 3 expresses the expected ion ratio based on the relative rate constants represented in Scheme 1. Inserting the values from Table 2 into Eq. 3 turns out to give the experimentally observed value. If, alternatively, we introduce a secondary kinetic isotope effect as a sixth parameter and solve the six equations in six unknowns, the best fit matches the mean experimental ratios exactly and gives a value for the mole fraction of ring protonation of $X = 0.01$

$$\frac{m/z\ 96}{m/z\ 97} = \frac{5\nu + 5\nu^2 + 5\nu wzX + \nu w + wy + w + \nu w^2 z}{5\nu wz(1 - X)} \quad (3)$$

In summary, the data do not support the contention that all isotope effects have the value $k_H/k_D = 1$. Instead, they range from $y/z = 1.72$ to ν and $w \approx 2$. As stated before, MIKE spectra of the complementary ions $[CH_3(CD_3)CHOPh]H^+$ and $[CH_3(CD_3)CHOPh]D^+$ are not mirror images of one another. Steady-state analysis of five experimental ion abundance ratios predict the observed outcome, namely that the sixth measured ratio, m/z 96:m/z 97 from $[(CD_3)_2CHOPh]H^+$, should have the same value as does the m/z 96:m/z 95 ratio for $[(CH_3)_2CHOPh]D^+$. We ascribe no special importance to that equality, nor do we impute any significance to the result that two of the isotope effects derived from the data, ν and w, have virtually the same value.

4. Discussion

Protonated isopropyl phenyl ether decomposes to protonated phenol (phenol H^+) via loss of propene. Propene expulsion constitutes the only observed

metastable ion decomposition in the absence of collisional activation. Partially deuterated parent ions yield mixtures of deuterated and undeuterated phenol conjugate acid ions. Scheme 1 portrays a mechanistic interpretation that is not biased towards either of the simplifying assumptions that have been put forth to account for chemical ionization of alkyl phenyl ethers.

In terms of Scheme 1, these simplifying assumptions can be expressed as follows. One approach supposes that the branching ratio for hydron exchange has a value $y \gg 1$. In other words, ion-neutral complexes are assumed to interconvert much more rapidly than they expel propene. The alternative approach supposes that X can be neglected. In other words, no ring-protonated ions undergo metastable loss of propene. The experiments presented here provide enough data for an unbiased analysis that does not require either of these assumptions. Nevertheless, the outcome of the experimental data analysis yields a result that turns out to disagree with the first assumption (giving $y < 1$) but accords with the second (giving $X \leq 0.01$).

The [*i*PrOPh]D^+ ion gives the same proportion of phenol D^+ (m/z 96:m/z 95 = 4.6 and 4.9 in independent trials) as does the [$(CD_3)_2$CHOPh]H^+ ion (m/z 96:m/z 97 = 4.5 and 4.9 in independent trials). That is to say, hydron exchange occurs to the same extent in the two complementarily deuterated parent ions. This was not expected, nor does Scheme 1 necessitate it. The results from the latter ion were not used to fit the experimental data, but instead employed to provide a test of our model. As the final entry in Table 1 confirms, steady-state analysis of Scheme 1 predicts the observed outcome. The calculated values of the isotope effects ν and w (tabulated in Table 2) turn out to be nearly equal and slightly greater than the isotope effect $y/z = 1.72$.

The energetic dependence of hydron exchange has been previously examined for derivatives of *n*-propyl phenyl ether. In those studies, observed increases in hydron exchange have been explained in terms of reduced proportions of ring protonation [8]. For isopropyl phenyl ether, the published MIKE spectrum of [$(CD_3)_2$CHOPh]H^+ from methane CI [5] gives a fragment ion ratio (m/z 96:m/z 97 = 3.5) indicative of more extensive hydron scrambling than in the water CI spectra presented here. Since the mole fraction X cannot be less than zero we are forced to interpret an increase in hydron exchange in terms of changes in the relative rate constants ν, w, y, or z. Eq. 3 makes it clear that an increase in any of these will diminish the m/z 96:m/z 97 ratio. Given that methane CI imparts more energy to the resulting conjugate acid ions than does water CI, it seems unlikely that y is getting larger. One would anticipate that this branching ratio should stay the same or become smaller (in the direction of less ion-neutral complex formation) as internal energy increases. Similarly, the isotope effects ν and w would not be expected to increase with internal energy. By contrast, the branching ratio z might well be expected to increase with internal energy because that corresponds to a decrease in the primary isotope effect y/z. Moreover, Eq. 3 exhibits greater sensitivity to changes in z than any other parameter. If all the other variables in Eq. 3 are held constant, a 20% increase of z would account for the difference between water and methane CI.

Scheme 1 contains three primary isotope effects: k_H/k_D for proton transfer from carbon to oxygen (y/z), k_H/k_D for proton transfer from oxygen to carbon (ν), and k_H/k_D for proton transfer from carbon to phenol (w). The first and last of these have different values. We infer this result to mean that w does not reflect a proton transfer from carbon to oxygen, but rather from one carbon to another (i.e. from an isopropyl cation to the ring of phenol) that should yield the most stable fragment ion. While the conclusions from *i*PrOPh cannot necessarily be generalized to systems with substituted benzene rings or with larger sidechains, the experiments reported here suggest that the CI proton does not reside on the ring in the course of metastable decomposition of [*i*PrOPh]H^+ until formation of the final products (protonated phenol ions plus propene).

Acknowledgements

This work was supported by the CNRS and by NSF grant no. CHE 95-22604.

Appendix

Steady state expressions for ion abundance ratios from chemically ionized $CH_3(CD_3)CHOPh$.

$[CH_3(CD_3)CHOPh]H^+$

$$Q = \frac{6wy(2 + w)}{(1 + w)}$$

$$\frac{m/z\ 96}{m/z\ 97} = \frac{3w(4\nu z + 2\nu + 4\nu/w + 2 + 4/w) + QX + 12y(1 - X)}{QX + 12\nu z + 6\nu + 12\nu/w + 6 + 12/w}$$

$$\frac{m/z\ 96}{m/z\ 95} = \frac{3w(4\nu z + 2\nu + 4\nu/w + 2 + 4/w) + QX + 12y(1 - X)}{6wy(1 - X)}$$

$[CH_3(CD_3)CHOPh]D^+$

$$R = \frac{3z}{(4 + 2/w + 4y/\nu + 4/\nu + 2/\nu w)}$$

$$S = 3w + 3 + (4w + 2)\,R$$

$$\frac{m/z\ 96}{m/z\ 95} = \frac{(1 - X)(3 + 4Rw) + SX/(1 + w)}{3w(1 - X) + 3SwX/(1 + w)}$$

$$\frac{m/z\ 96}{m/z\ 97} = \frac{(1 - X)(3 + 4Rw) + SX/(1 + w)}{2R(1 - X)}$$

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