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Quantitation of isomeric ethyl pyridine mixtures by multivariate calibration applied to ion-molecule reaction/collision-induced dissociation triple-stage mass spectra

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Abstract

In reactions of the distonic ion $^{+}CH_2–O–CH_2^{\bullet}$ with the three isomeric ethyl pyridines, ionized methylene transfer occurs readily yielding distonic *N*-methylene-ethylpyridinium ions. On-line mass selection and 10 eV collision-induced dissociation (CID) of the $CH_2^{+\bullet}$ transfer products yields characteristic fragment ions, which are formed via processes greatly influenced by the *ortho*, *meta* or *para* location of the ethyl substituent in the pyridine ring. Quantitation of mixtures of isomeric 2-, 3-, and 4-ethyl pyridines of varying compositions was then performed by multivariate calibration in the form of the partial least square (PLS) model applied to both single-stage (MS) 70 eV electron ionization (EI) and pentaquadrupole triple-stage sequential ion-molecule reaction/CID product ion mass spectra. The results exemplify the superior ability of combined chemometric analysis and sequential mass spectrometric techniques, which benefits from both characteristic ion chemical reactivity and dissociation behavior, for rapid and accurate quantitation of complex isomeric mixtures.

Keywords: Ion-molecule reactions; Sequential analysis; Multivariate calibration; Pentaquadrupole mass spectrometry; Isomer distinction

1. Introduction

Ion-molecule reactions [1] are widely applied for structural elucidation of ions and neutral molecules [2], to mechanistic studies of reactions of fundamental and practical importance involving key ionic intermediates [3], and for gas-phase methods of isomer distinction [4]. In the gas phase, collision-induced dissociation (CID) of ionized molecules and their ionic fragments is often greatly influenced by structural variations, and CID has been applied extensively for structural elucidation. These studies are greatly refined when ion mass-selection and ion-molecule reactions under controlled conditions are performed via multiple-stage mass spectrometry [5]. The gas-phase chemistry of

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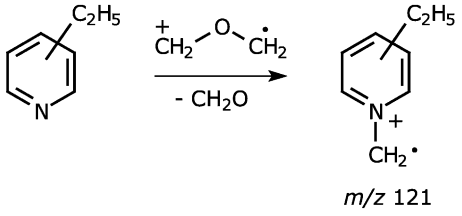
the unconventional ambident distonic ions [6] has been studied extensively [7], and their reactions [7] have found use in structural analysis and isomer distinction [8]. By performing sequential mass spectrometric experiments in a pentaquadrupole mass spectrometer, we have demonstrated [9] that the distonic ion $^{+}CH_2–O–CH_2^{\bullet}$ reacts readily with the three isomeric ethyl pyridines by ionized methylene ($CH_2^{+\bullet}$) transfer (Scheme 1), and that CID of each isomeric distonic *N*-methylene-ethyl-pyridinium ions so formed display characteristic, structurally diagnostic dissociation behavior.

The *N*-methylene-ethylpyridinium ion of *m*/*z* 121 from 2-ethyl pyridine yields two characteristic ionic fragments: that of *m*/*z* 120 by the loss of a hydrogen atom—an interesting *ortho* effect [10]—and that of *m*/*z* 93 by ethene loss (Scheme 2).

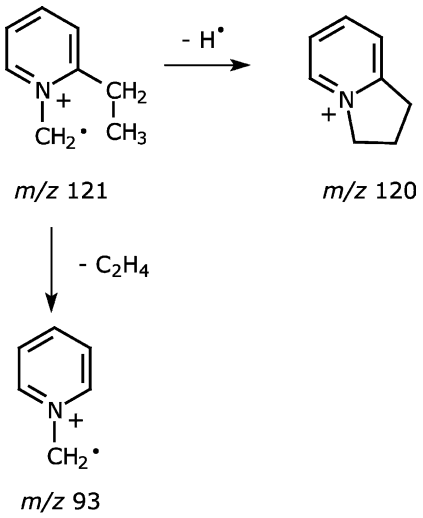
The *N*-methylene-ethylpyridinium product ion of *m*/*z* 121 from 4-ethyl pyridine yields almost exclusively a single fragment ion of *m*/*z* 106 by the loss of a methyl radical—an interesting *para* effect (Scheme 3).

The *para* and *ortho* effects observed for the other isomers cannot operate for the *meta*-substituted *N*-methylene-ethylpyridinium ion of *m*/*z* 121 from 3-ethyl pyridine; hence, neither hydrogen atom nor methyl radical loss is favored. The *meta* isomer shows the greatest stability toward dissociation and yields upon 10 eV CID a series of minor fragment ions of *m*/*z* 120, 106, 93, 92 and 79.

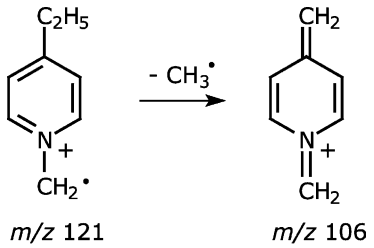
The application of ion-molecule reactions with $^{+}CH_2–O–CH_2^{\bullet}$ followed by on-line CID of the *N*-methylene-ethylpyridinium ion of *m*/*z* 121 is, therefore, likely to allow accurate quantitation of isomeric ethyl pyridine mixtures, particularly if the data is treated by chemometric methods [11]. In this study, we use the isomeric ethyl pyridines as a



Scheme 1.



Scheme 2.



Scheme 3.

'proof-of-principle' case to investigate whether isomeric mixture quantitation with multivariate calibration applied to sequential analysis (ion-molecule reaction/CID data) is feasible. The accuracy of the sequential mass spectra analysis procedure is then compared with that using simple 70 eV electron ionization (EI) mass spectra data. Multivariate calibration [12] was selected since, unlike univariate methods, it has the advantage of enabling quantitation of complex mixtures for which not every component in the mixture displays a unique selective fragment.

2. Partial least squares (PLS)

Chemometric procedures for classification, multivariate calibration and mixture resolution have

been applied to different types of mass spectra data, such as inductively coupled mass spectrometry (ICP/MS) [13], gas chromatography/mass spectrometry (GC/MS) [14], membrane introduction mass spectrometry (MIMS) [15], direct sampling mass spectrometry (DSMS) [16], pyrolysis mass spectrometry (Py/MS) [17], and mass spectrometry/mass spectrometry (MS/MS) data [18].

PLS is currently one of the most popular multivariate calibration methods [19] and is incorporated into the data analysis software of many commercial instruments. PLS can handle large amounts of highly collinear data typically produced by modern analytical instruments, and allow quantitation in cases where univariate calibration is not applicable. However, widespread use of the full set of analytical tools will occur only if the analyst becomes familiar with the general goals and advantages of multivariate methods.

PLS is a multivariate regression method, and can be used to relate one response variable, **y**, or more response variables, **Y**, to a set of explanatory variables, **X**. In chemistry, the response is typically a chemical property, such as compound concentration, and the explanatory variables are indirectly related measurements, such as mass spectra.

The method includes the dependent variable in the data compression and decomposition operations, i.e. both **y** and **X** data are actively used in the data analysis. This action serves to minimize the potential effects of **X** variables, which have large variances but which are irrelevant to the calibration model. The simultaneous use of **X** and **y** information makes the method more complex than other regression methods as both loadings and weights vectors are required to provide orthogonality of the component.

The dependent and independent variables are mean centered to give data matrix $\mathbf{X}_0$ and vector $\mathbf{y}_0$. Then for each factor, $k=1, \ldots, K$, to be included in the regression model, the following steps are performed:

a) The loading weight vector $\mathbf{w}_k$ is calculated by maximizing the covariance between the linear combination of $\mathbf{X}_{k-1}$ and $\mathbf{y}_{k-1}$ given that $|\mathbf{W}_k| = 1$.
b) The factor scores, **t**, are estimated by projecting $\mathbf{X}_{k-1}$ on $\mathbf{w}_k$.
c) The loading vector $\mathbf{p}_k$ is determined by regressing $\mathbf{X}_{k-1}$ on $\mathbf{t}_k$ and similarly $\mathbf{q}_k$ by regressing $\mathbf{y}_{k-1}$ on $\mathbf{t}_k$.
d) From $(\mathbf{X}_{k-1} - \mathbf{t}_k\mathbf{p}_k^{\mathrm{T}})$ and $(\mathbf{y}_{k-1} - \mathbf{t}_k\mathbf{p}_k^{\mathrm{T}})$ new matrices $\mathbf{X}_k$ and $\mathbf{y}_k$ are formed.

The optimum number of components to include in the model can be found by using validation statistics and/or observing the plotted model components. The PLS model can be written in the form of a generalized regression equation:

$$\mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{e} \quad (1)$$

where **e** is the prediction error. The regression coefficients, **b**, can be calculated by

$$\mathbf{b} = \mathbf{W}(\mathbf{P}^{\mathrm{T}}\mathbf{W})^{-1}\mathbf{q} \quad (2)$$

where **W** is the matrix of loading weights, each column is a weight vector, and **P** the matrix of loadings. The PLS model is calculated using a set of training samples. After that, the developed model can be used for making response predictions for new samples of unknown composition.

3. Experimental section

The experiments were performed using an Extrel (Pittsburgh, PA) pentaquadrupole mass spectrometer which is described in detail elsewhere [21]. The mass spectrometer consists of an on-line arrangement of three mass analyzing (Q1, Q3, Q5) and two reaction or dissociation rf-only quadrupoles (q2, q4).

Two different experiments were performed using 33 mixtures of isomeric pyridines that were prepared in an ampoule having a total volume of 100 μl. The compositions of the samples are given in molar fractions and shown in Table 1. The volume and density were used to find the relative mass for each compound in the mixture.

The ampoules were coupled to the instrument and direct atmospheric sampling under the vacuum of the mass spectrometer injected the vapor sample for analysis. In the first set of experiments, the vapor samples in equilibrium with the liquid

Table 1
Molar fractions of the isomeric ethyl pyridine mixture samples

	2-Ethyl pyridine	3-Ethyl pyridine	4-Ethyl pyridine
Training samples			
1	0	1.000	0
2	0.249	0.751	0
3	0.499	0.501	0
4	0.749	0.251	0
5	1.000	0	0
6	0.125	0.750	0.125
7	0.749	0.125	0.126
8	0	0.750	0.250
9	0.249	0.500	0.251
10	0.499	0.250	0.251
11	0.749	0	0.251
12	0	0.500	0.500
13	0.249	0.250	0.501
14	0.499	0	0.501
15	0	0.250	0.750
16	0.124	0.125	0.751
17	0.249	0	0.751
18	0	0	1.000
Test samples			
1	0.249	0.626	0.125
2	0.374	0.501	0.125
3	0.499	0.376	0.125
4	0.624	0.251	0.125
5	0.125	0.625	0.250
6	0.374	0.375	0.251
7	0.624	0.125	0.251
8	0.125	0.500	0.375
9	0.249	0.375	0.376
10	0.374	0.250	0.376
11	0.499	0.125	0.376
12	0.125	0.375	0.500
13	0.374	0.125	0.501
14	0.124	0.250	0.626
15	0.249	0.125	0.626

phase were introduced into the ion-source and their simple 70 eV EI mass spectra were acquired. All quadrupoles were set to operate at the rf-only full ion transmission mode, except Q5, which was set to scan over the selected m/z range of 20–120 at mass increase of 0.1. In the second set of experiments, the samples were measured by sequential analysis, in which ion-molecule reaction/CID product ion mass spectra were obtained. The vapor sample was added to q2, and then ion-molecule reactions with the distonic $^{+}CH_2–O–CH_2^{\bullet}$ ion of m/z 44 (generated in the ion-source by 70 eV EI of ethylene oxide [22] and mass selected by Q1) were performed at near 1 eV collision-energy. The product ions of m/z 121 were then mass-selected by Q3 and dissociated by 10 eV collisions with argon in q4 while scanned by Q5 to acquire the mass spectrum, with a range of m/z 40–130 at intervals of 0.1. Due to small changes in the internal pressure that result in changes in the spectra, each sample is represented by a spectrum, which is the mean of five successively recorded spectra.

A total of 33 samples were analyzed, in both experiments, of which 18 were used to build the PLS calibration model and the remaining 15 were used to test the model. PLS [23] was applied on a PC running MATLAB Version 5.3 [24].

The predictive ability of the model is calculated in terms of the percentage standard error of prediction, %SEP, given as:

$$\%\mathrm{SEP} = \frac{100}{\bar{y}} \sqrt{\frac{\sum_{n=1}^{N}(y_n - \bar{y}_n)^2}{N}} \quad (3)$$

where y_n and $\hat{y}_n$ are respectively the true and predicted concentrations for test sample, n, the number of test samples used is N and $\bar{y}$ is the mean test sample concentration.

4. Results and discussion

When multivariate calibration is used to quantitate samples, the preprocessing of the data and the variable selection steps can be very important [20]. For mass spectrometry data, preprocessing is of fundamental importance and must be used to remove noise.

The mass spectra were, therefore, preprocessed using the log transformation to transform heteroscedastic noise into homoscedastic noise [25]. Heteroscedastic noise, in mass spectra, is proportional to signal intensity and, therefore, influences more pronouncedly the more intense peaks whereas homoscedastic noise has a uniform level across the spectrum. As most calibration models give equal weight to the residuals at each variable, it is preferable to transform the noise to be

approximately uniform across the spectral range. This transformation is implemented by using a log transform of the data. Because the minimum value in the baseline is zero, a value of 1 was added to all the variables before the application of the log transform as described by equation Eq. (4).

$$\mathbf{X} = \log(\mathbf{X} + 1) \quad (4)$$

where **X** is the mass spectra matrix.

In contrast, the variable selection may not affect so pronouncedly the results. Selection of specific mass spectra peaks does not improve quantitation hence the whole set of mass spectra peaks was used in the multivariate calibration.

After log transform preprocessing, mass spectra were normalized by the maximum peak and mean centered and used to build the PLS calibration model. A separate PLS model was built for each of the three isomers and the number of model components was selected using leave-one-out cross-validation with a preference for a low number of model components.

4.1. First set of experiments: 70 eV EI MS

Fig. 1 displays the simple 70 eV EI mass spectra collected for the pure isomeric ethyl pyridines. The dissociation induced by 70 eV EI produces the molecular ion of m/z 107 and a set of fragment ions of variable abundances [26].

The number of components found by cross-validation in PLS calculations for the mass spectra of the three isomeric 2-, 3-, and 4-ethyl pyridines were 5, 5 and 6 components, respectively. These relatively high numbers of components is due to the complexity of the EI mass spectra. After building the models, predictions were made for the 15 test samples and the %SEP for each isomer was calculated (Table 2). A model was also built without any preprocessing (Table 2). From this comparison it is possible to verify the importance of log transformation to improve quantitation.

When using simple 70 eV EI mass spectra data, however, poor %SEP is obtained for all three

Table 2
%SEP for quantitation of 70 eV EI mass spectra

	%SEP		
	2-Ethyl pyridine	3-Ethyl pyridine	4-Ethyl pyridine
No preprocessing	22.1	27.4	32.5
Log transform	18.0	16.5	28.9

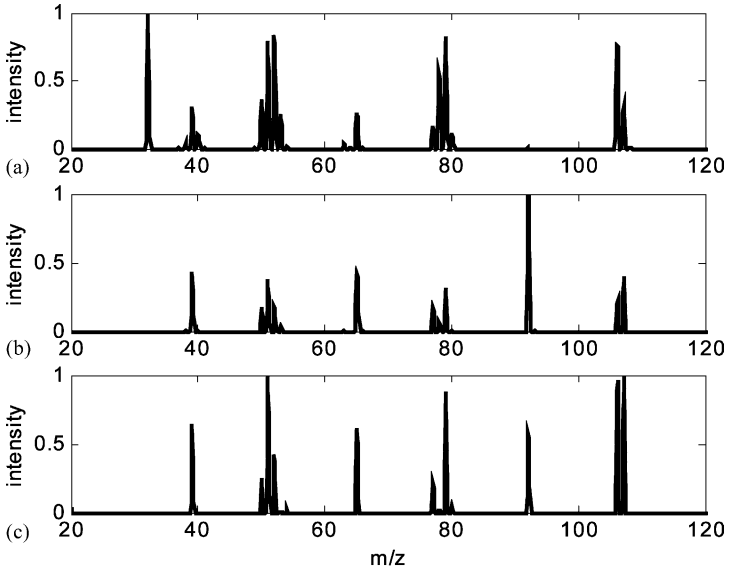


Fig. 1. Seventy eV EI mass spectra of (a) 2-ethyl, (b) 3-ethyl and (c) 4-ethyl pyridine.

isomeric pyridines, which leads to imprecise quantitation of mixtures of the three isomeric ethyl pyridines, even when optimal preprocessing and multivariate calibration methods are applied.

4.2. Second set of experiments: ion-molecule reaction plus CID

Fig. 2 displays the triple-stage sequential product ion mass spectra for each of the three pure isomeric ethyl pyridines. As already discussed, the *N*-methylene free-radical sites of the respective *ortho* and *para* isomeric *N*-methylene-ethylpyridinium ions promote interesting *ortho* and *para* effects (Schemes 2 and 3) that greatly diversify their dissociation patterns, thus allowing straightforward distinction of the *ortho* and *meta* isomers. The ionized methylene-transfer product ion of *m*/*z* 121 from 2-ethyl pyridine (Fig. 2a) yields two characteristic fragment ions of *m*/*z* 93 and 120, whereas the ionized methylene-transfer product ion of *m*/*z* 121 from 4-ethyl pyridine (Fig. 2c) almost exclusively yields a fragment ion of *m*/*z* 106.

The product ion of *m*/*z* 121 from 3-ethyl pyridine (Fig. 2b) also dissociates distinctively, but no particularly abundant fragment ion is formed. It yields fragment ions of *m*/*z* 120, 106, 93, 92 and 79 of relatively low abundance, which interfere with those of the *ortho* and *para* isomers. This interference makes quantitation of mixtures containing the three isomers difficult and simple univariate calibration is not applicable. The use of multivariate calibration to the sequential product ion mass spectrum of a mixture of the three isomers, as exemplified by Fig. 3, may, however, result in accurate quantitation since not only the abundance of selected ions but the full relationship between combinations of the various fragment ions in the mass spectra will be considered.

Before building the PLS calibration model, the triple-stage mass spectra were preprocessed as before. The number of components used in PLS model in the second set of ion-molecule reaction plus CID experiments for the 2-, 3-, and 4-ethyl pyridine isomers were 4, 3 and 4, respectively. After the models were developed, predictions were performed again for the 15 test samples and the %SEP for each isomer was calculated (Table 3). A model was also built from the mass spectra with no data preprocessing (Table 3).

Clearly, mixture quantitation using data preprocessing is superior to that using no preprocessing, and the sequential product ion mass spectra

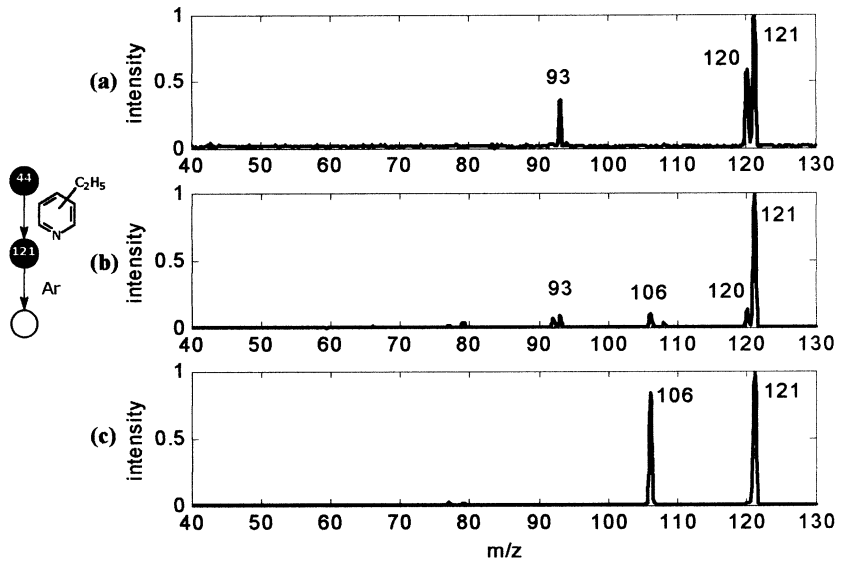


Fig. 2. Triple-stage sequential CID (10 eV with argon) product ion mass spectra of the *m*/*z* 121 ions formed by ion-molecule reactions of the distonic ion $^{+}CH_2–O–CH_2^{\bullet}$ with (a) 2-ethyl, (b) 3-ethyl and (c) 4-ethyl pyridine.

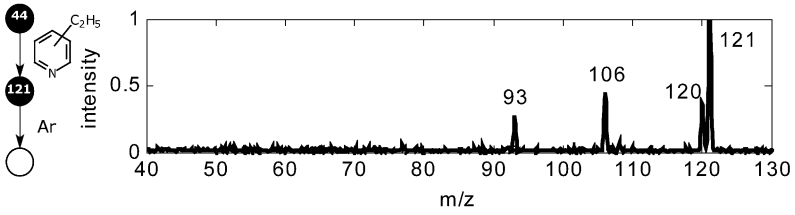


Fig. 3. Triple-stage sequential CID product ion mass spectra of *m/z* 121 ions formed by ion-molecule reactions of $^{+}CH_2–O–CH_2^{\bullet}$ with a 0.624:0.251:0.125 molar mixture of 2-ethyl, 3-ethyl and 4-ethyl pyridine.

Table 3
%SEP for quantitation of sequential product ion mass spectra

	%SEP		
	2-Ethyl pyridine	3-Ethyl pyridine	4-Ethyl pyridine
No preprocessing	20.8	18.0	21.1
Log transform	7.6	13.8	12.5

data analysis is much superior than that using simple 70 eV EI mass spectra data. However, the preprocessing by log transform is not yet the best solution for the heteroscedastic noise, because in log transformation the higher the concentration the lower the linearity of the mass spectral intensities. We are currently applying weighted regression methods [27] to test whether improved quantitation will be achieved.

5. Conclusion

The accuracy for quantitation of mixtures of the three isomeric ethyl pyridines using the PLS multivariate calibration model applied to a combination of ion-molecule reactions and CID is significantly higher than that obtained when applying PLS multivariate calibration to simple 70 eV EI mass spectra data. The results exemplify the superior ability of combined chemometric and sequential analysis techniques that benefits from both characteristic chemical reactivity and dissociation behavior of product ions for accurate and rapid quantitation of isomeric mixtures. We are currently investigating the application of this robust analytical tool to accurately quantitate other isomeric mixtures of increasing complexity.

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