



Use of ion clustering equilibrium for isomer identification in electron capture mass spectrometry
by Lisa A Krieger

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Chemistry

Montana State University

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Abstract:

This work explores the possibility of isomer distinction by taking advantage of unique solvation equilibrium constants for the clustering of ions with neutral solvating molecules. Each isomer would exhibit a unique ratio of MS^-/M^- from a mass spectrum of the compound and the solvating molecule which could theoretically be predicted if the equilibrium constant and the solvating molecule concentration are known. This is assuming that equilibrium exists in the source, which is shown to be true for the atmospheric pressure ionization source.

A number of substituted nitrobenzenes were tested with dimethylsulfoxide (DMSO) as the neutral solvating molecule. These experiments showed that the method has promise, but is not as straightforward as the theory predicts. An attempt was made to mathematically describe the observed deviations from expectation. This resulted in an expression that closely described the system, but could not calculate the reference value of K_f .

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3/6/87
Date

Eric Drimmer
Chairperson, Graduate Committee

Approved for the Major Department

3/6/87
Date

E. Abbott
Head, Major Department

Approved for the College of Graduate Studies

March 9, 1987
Date

Henry L. Parsons
Graduate Dean

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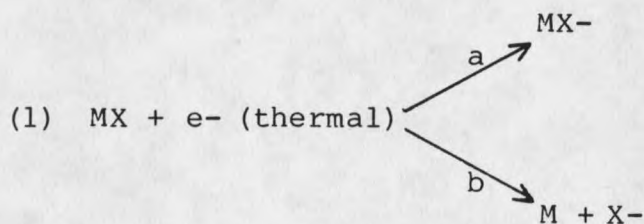
ABSTRACT

This work explores the possibility of isomer distinction by taking advantage of unique solvation equilibrium constants for the clustering of ions with neutral solvating molecules. Each isomer would exhibit a unique ratio of MS^-/M^- from a mass spectrum of the compound and the solvating molecule which could theoretically be predicted if the equilibrium constant and the solvating molecule concentration are known. This is assuming that equilibrium exists in the source, which is shown to be true for the atmospheric pressure ionization source.

A number of substituted nitrobenzenes were tested with dimethylsulfoxide (DMSO) as the neutral solvating molecule. These experiments showed that the method has promise, but is not as straightforward as the theory predicts. An attempt was made to mathematically describe the observed deviations from expectation. This resulted in an expression that closely described the system, but could not calculate the reference value of K_f .

INTRODUCTION

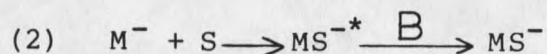
One of the most sensitive detection techniques for trace analysis is electron-capture mass spectrometry (ECMS). There are two routes the electron-capture process can take. One is resonance electron capture, where a thermalized electron is captured by a molecule to form the molecular anion, as shown by route 1a below. The other is dissociative electron capture, as shown by route 1b, which involves the dissociation of the molecular anion as it captures the electron.



ECMS is a sensitive technique compared to other ionization reactions because electron-capture is one of the fastest ionic reactions, having a rate constant, k_{ec} , up to $4 \times 10^{-7} \text{ cm}^3/\text{sec}$. Ion-molecule reactions are no faster than $k_{\text{i/m}} = 1 \times 10^{-9} \text{ cm}^3/\text{sec}$, which is two orders of magnitude slower than electron capture. The speed of reaction is one reason for ECMS sensitivity. The other reason is that in the resonance EC process the analyte forms the molecular ion, M^- , with little or no fragmentation. Thus, identification and quantitation can be monitored from the same signal. With only M^- being formed, trace

amounts are detectable since the total available signal is concentrated on one ion, M^- . The one problem with ECMS is that although it provides sensitive signals for trace analysis, it often does not indicate which isomer is present. Since isomers differ only in the physical orientation of the atoms in the molecule, the masses of two or more isomers are identical, thus it is impossible to distinguish between them with electron-capture mass spectrometry if the signal is M^- .

Kebarle and co-workers have been studying the solvation of molecular anions by neutral molecules such as dimethylsulfoxide, acetonitrile, and methanol.¹ The molecular ion, M^- , is solvated by the neutral solvator, S , to form a cluster ion, MS^- . This reaction requires a buffer gas, B , to collisionally stabilize the cluster ion so it does not immediately fall apart. The reverse of reaction 2 also occurs.



The equilibrium expression for the solvation of M^- by S is:

$$(3) \quad K_f = \frac{[MS^-]}{[M^-][S]}$$

and then:

$$(4) \quad K_f[S] = \frac{[MS^-]}{[M^-]} .$$

According to Kebarle,¹ the K_f values vary between isomers for substituted nitrobenzenes (NB). Table 1 shows some of these compounds and their respective K_f values for the solvating compounds, methanol, acetonitrile and dimethylsulfoxide.

Table 1. K_f^K Values for Compounds at 70°C

Compound	K_f		
	CH ₃ OH	CH ₃ CN	DMSO
o-FNB	5.1 x 10 ³		
m-FNB	3.6 x 10 ³	6.5 x 10 ³	9.8 x 10 ⁴
p-FNB	7.0 x 10 ³	1.0 x 10 ⁴	1.6 x 10 ⁵
o-diNB	1.3 x 10 ²	1.2 x 10 ³	8.9 x 10 ³
m-diNB	2.5 x 10 ²	5.2 x 10 ²	5.3 x 10 ³
p-diNB	3.0 x 10 ¹	1.0 x 10 ²	6.6 x 10 ²

Since K_f is dependent upon isomeric differences of a given compound, the value $[MS^-]/[M^-]$ should change with the isomer in accordance with equation 4. This solvation equilibrium could then be applied to analytical mass spectrometry assuming five conditions:

1. The equilibrium constants of the isomers must not be equal, ie. $K_{ortho} \neq K_{meta} \neq K_{para}$
2. S, the solvating molecule, must not capture electrons.
3. S must be a good solvator of negative ions so that MS^- as well as M^- is observable.
4. The system must be in equilibrium so that $K_f[S] = [MS^-]/[M^-] = \text{CONSTANT}$.
5. The mass spectrometer must accurately measure $[MS^-]/[M^-]$.

Condition #1 has been shown to be true for substituted nitrobenzenes as described previously. Conditions #2 and #3 are met by choosing an appropriate solvent, molecule such as dimethylsulfoxide (DMSO), that has a sufficiently large K_f value with the analyte of interest to give observable signals for both M^- and MS^- . It also must not give a significant background spectrum. Condition #4 states that the system must be in equilibrium. Whether or not this is true will depend on what type of ionization system is chosen to work with. Two possible choices are negative chemical ionization (NCI) and atmospheric pressure ionization (API). By analyzing the chemical dynamics of the reactions in both systems, one of these turns out to be the more likely system in which the solvating equilibrium will take place.

Condition #5 requires that the mass spectrometer accurately measures the ratio, R , of $[MS^-]/[M^-]$ in the source. This condition may be difficult to meet, as the transport of ions through the aperture into the mass analyzing region may be accompanied by collisions which could dissociate MS^- .² In the APIMS extreme pressure and temperature gradients exist in the region of the aperture which may also alter the observed R from the actual value of R that is in the source.

STATEMENT OF THE PROBLEM

As shown in the introduction, the identification of isomers may be possible using a neutral solvating molecule. Each isomer should have a characteristic ratio of $[MS^-]/[M^-]$, stemming from a different K_f value.

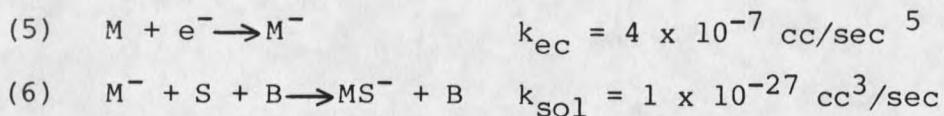
The purpose of this research is to explore the method described in the introduction to see if the solvation equilibria method works and the theory holds under conditions of analysis by GC/ECMS. The equilibrium between two ions will be examined and compared to expected values to determine if equilibrium is achieved. If there are any deviations from the theory, an attempt will be made to explain them.

CHEMICAL DYNAMICS

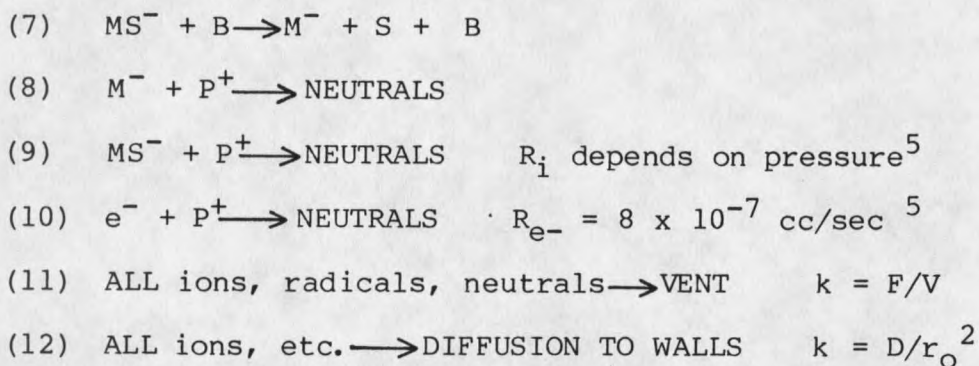
The fourth condition necessary for distinguishing isomers by solvation equilibria, that of requiring equilibrium, can be theoretically examined by predicting the chemical dynamics in the ion source. The equations obtained from these predictions should reduce to $K_f[S] = [MS^-]/[M^-]$, if equilibrium is achieved in the source.

The ion and electron reactions in NCI and API are similar as shown in reactions 5 - 12 below. The identities of some species such as B and P^+ may differ between API and NCI, but the reactions as written occur for both methods. A more detailed description of how the NCI ionization source works is given by Harrison.³ The API source is described by McKeown and Siegel.⁴ The following reactions describe what is happening within either source. P^+ means any positive ion, the rate constant, F/V , is the volumetric flow rate through the source divided by the volume of the source, and the diffusion constant, D/r_0^2 , is a value that is dependent on the geometry of the source. This rate constant will be given a numerical value later. All of the rate constants have been chosen to present the most favorable case.

Formation Reactions



Loss Reactions



From the above equations, an expression can be written for the production of MS^- with time:

$$(13) \quad \frac{d[MS^-]}{dt} = k_{sol} [M^-][S][B] - k_{-sol}[MS^-][B] \\ - R_i [MS^-][P^+] - [F/V][MS^-] - [D/r_0^2][MS^-]$$

The steady state approximation, $d[MS^-]/dt = 0$, may be applied to this flow-through reactor in which mixing by diffusion is much more rapid than ventilation through the cell. Setting equation 13 equal to zero and rearranging, results in equation 14:

$$(14) \quad \frac{[MS^-]}{[M^-]} = \frac{k_{sol}[S][B]}{k_{-sol}[B] + R_i[P^+] + F/V + D/r_o^2}$$

Condition four states:

$$(15) \quad \frac{[MS^-]}{[M^-]} = K_f[S]$$

Equation 14 can reduce to equation 15 only if the last three terms in the denominator, $R[P^+] + F/V + D/r_o^2$, are negligible with respect to the first term, $k_{-sol}[B]$.

Using the following typical NCI values for the parameters in the denominator of equation 14:

$$k_{sol} = 1 \times 10^{-27} \text{ cc/sec}$$

$$[S] = 2 \times 10^{15} \text{ cc}^{-1} \text{ (at 0.1 Torr)}$$

$$[B] = 2 \times 10^{16} \text{ cc}^{-1} \text{ (at 1 Torr)}$$

$$R_i = 6.4 \times 10^{-8} \text{ cc/sec}^6$$

$$[P^+] = 3 \times 10^{10} \text{ cc}^{-1}$$

$$F/V = 100 \text{ sec}^{-1} \text{ (100cc/sec/cc)}$$

$$D = 100 \text{ cm}^2/\text{sec} \text{ (at 1 Torr)}^5$$

$$r_o^2 = 0.02 \text{ cm}^2^5$$

$$k_{-sol} = 1.7 \times 10^{-12} \text{ cc/sec}$$

(The value for k_{-sol} was calculated from Eq. 14 using the above values and assuming an observable ratio of 1.)

From the values given:

$$k_{-sol}[B] = 3.4 \times 10^4$$

$$R[P^+] + F/V + D/r_o^2 = 7.0 \times 10^3.$$

The sum of the last three terms of the denominator, which are due to recombination, ventilation, and diffusion respectively, is about 20 percent of the first term, so negligibility is not proved.

Using the maximum value for [S] under NCI conditions (1.3×10^{-4} atm.), and assuming a reasonable K_f value (500 atm.^{-1}), the maximum theoretical ratio is obtained from equation 15:

$$[\text{MS}^-]/[\text{M}^-] = K_f[\text{S}] = (500 \text{ atm.}^{-1})(1.3 \times 10^{-4} \text{ atm.}) = 0.065$$

This maximum signal for MS^- is less than 1 percent that of M^- , which would make MS^- difficult to observe. Since [S] cannot be further increased to favor formation of MS^- , NCI is not a favorable ionization technique for this type of isomer distinction.

The following values for API can be applied in the same manner. k_{sol} has been calculated the same way as before.

$$k_{\text{sol}} = 7 \times 10^{-11} \text{ cc/sec}$$

$$k_{\text{sol}} = 1 \times 10^{-27} \text{ cc}^2/\text{sec}$$

$$[\text{B}] = 1 \times 10^{19} \text{ cc}^{-1}$$

$$[\text{S}] = 7 \times 10^{16} \text{ cc}^{-1}$$

$$R_i = 1 \times 10^{-6} \text{ cc/sec} \quad 5$$

$$[\text{P}^+] = 10^8 \text{ cc}^{-1}$$

$$F/\bar{V} = 1 \text{ sec}^{-1} (1 \text{ cc/sec}/1 \text{ cc})$$

$$D = 0.25 \text{ cm}^2/\text{sec} \quad 7$$

$$r_o^2 = 0.04 \text{ cm}^2 \quad 7$$

From the API values:

$$k_{\text{sol}}[\text{B}] = 7 \times 10^8$$

$$R_i[\text{P}^+] + F/V + D/r_o^2 = 107.25$$

The last three terms in the denominator are definitely negligible with respect to the first term. This enables the complete expression for R to reduce to equation 15, $[\text{MS}^-]/[\text{M}^-] = K_f[\text{S}]$, which suggests that the solvation equilibria method of isomer distinction in the API is theoretically possible.

The reason API is predicted to surpass NCI for this type of analysis lies in the fact that the solvation reaction is third order. The rate of a third order reaction is calculated by:

$$(16) \text{ Rate} = k_{\text{sol}}[\text{M}^-][\text{S}][\text{B}].$$

Since the buffer gas concentration is close to three orders of magnitude higher in API than NCI, the rate of reaction is much faster in API. This rate is $7 \times 10^8[\text{M}^-]$ compared to the NCI rate of $4 \times 10^4[\text{M}^-]$. Also, the concentration of the solvating molecule can be made higher in API, further increasing the rate of the solvating reaction.

Using an easily achieved value of $[\text{S}]$, 5×10^{-3} atm., and a K_f of 500, the calculated R would be 2.5. This would provide an easily observable ratio of signals. Thus, according to theory under reasonable operating conditions, the API source should work for this method of isomer distinction.

EXPERIMENTAL

The instrument used in this research was a specialized, home-built mass spectrometer. The source was an atmospheric pressure ionization source that could also be used as an ECD or a corona discharge source. A detailed description of the source will be given later. To introduce samples into the source, a gas chromatograph was used with nitrogen as the carrier gas. The nitrogen was passed through oxygen and water-removing traps prior to entering the column.

The gas chromatograph was a Gow-Mac model 750 that was modified to accommodate a Hewlett Packard 530 micrometer, 10 meter macrobore column (number 19095Z-121). The macrobore column was installed to reduce the amount of column bleed introduced into the source. The column was threaded through a stainless steel, heated, transfer line and fed directly into the source. The net result was that the column ended approximately flush with the entrance into the source.

Two methods were used to introduce the solvent molecules into the source. The first one was via a diluter, which was a large, airtight volume, with make-up gas flowing through it and into the source to mix with the GC effluent. The dilution volume has a septum port which allows the injection of a known quantity of solvating compound into the diluter. This is then diluted by the make-up gas and some is carried into the source. Knowing the

flow rate through the diluter, the total flow rate through the source, the volume of the diluter, the pressure inside the diluter (which in most cases is atmospheric), the amount of solvating molecule injected, and the time from the initial injection, the concentration of the solvating molecules in the source can be calculated. The amount flowing out of the diluter at any time can be calculated from: $C = C_0 e^{-(F/V)t}$, where F is the volumetric flow rate through the diluter, V is the volume of the diluter and t is the time elapsed since injection of the solvating molecule. Once C is found, the amount of solvating molecule in the source is: $C_s = C(F_d/F_t)$, where F_d is the flow rate through the diluter and F_t is the total flow rate of both the column and the make-up gas through the source.

A disadvantage of this system is that the concentration of S , the solvating compound, is always changing due to the constant flow of make-up gas into and out of the diluter. Also, it takes days to completely clean the diluter of one solvator in preparation for a different one. Another problem is that the choice of solvating compounds is limited because they have to have sufficient vapor pressure to evaporate into the diluter. Another system was devised to alleviate these drawbacks of the diluter.

The second system tested was called a "bubbler". The first of these constructed was a simple cylindrical tube, one inch in diameter, with a one-quarter inch glass tube that was drawn to a fine opening inside the larger cylinder. This was the make-up

