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Selected ion flow tube, SIFT, studies of the reactions of H_3O^+, NO^+ and O_2^+ with some biologically active isobaric compounds in preparation for SIFT-MS analyses

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ABSTRACT

A study of the reactions of H_3O^+, NO^+ and O_2^+ ions with two groups of four isobaric, biologically active compounds with molecular weights, MW, of 86u and 88u has been carried out using the selected ion flow tube, SIFT, technique in preparation for the analyses of these compounds in the headspace of bacterial and cell cultures using SIFT-MS. These compounds are: MW 86u: 2,3 butanedione (diacetyl), $C_4H_6O_2$; allyl ethyl ether, $C_5H_{10}O$, cyclopropane carboxylic acid, $C_4H_6O_2$: γ-butyrolactone, $C_4H_6O_2$. MW 88u: 3-hydroxybutanone (acetoin), $C_4H_8O_2$; n-butyric acid, $C_4H_8O_2$; ethyl acetate, $C_4H_8O_2$; pyruvic acid, $C_3H_4O_3$. All 24 reactions proceed at the gas kinetic rate, the dominant primary product ions of the H_3O^+ reactions being the protonated reactant molecules, MH^+ with a common mass-to-charge ratio, m/z, in each group of isobaric compounds; those of the NO^+ reactions being the adduct ions, NO^+M, also with a common m/z value; for the O_2^+ ion reactions, fragmentation ions of the nascent parent ion M^+ are produced. SIFT-MS analysis of each compound individually is straightforward, but when more than one isobaric compound is present, SIFT-MS analyses become more challenging. However, hydration of some, but not all, of the primary MH^+ and NO^+M primary ions occurs, variously generating $MH^+(H_2O)_{1,2}$ and NO^+MH_2O ions, and the occurrence/non-occurrence of these hydrates can assist in distinguishing between some of the isobaric compounds. From the kinetic data obtained in this study, the required SIFT-MS kinetics library entries for each compound can be constructed that allow their quantification. As an example, SIFT-MS spectra are presented relating to the analysis of the headspace of incubated yoghurt, which show the presence of several volatile organic compounds, including acetoin and diacetyl.

1. Introduction

Since its inception, selected ion flow tube mass spectrometry, SIFT-MS, [1–3] has been applied to the analysis of many gas phase media, notably humid exhaled breath and urine headspace, aimed at clinical diagnosis and therapeutic monitoring [4], bacterial cultures in medicine [5] and food and foods flavours [6,7]. In essence, this often requires the detection and quantification of a wide range of volatile organic compounds, VOCs, present in humid air at concentrations down to parts-per-billion by volume, ppbv. A major objective in the development of SIFT-MS has been to facilitate real time analyses of VOCs present in exhaled breath and those emitted from aqueous solutions and moist samples such as food products, obviating sample collection and manipulation with subsequent analysis, procedures that can compromise the samples. The growing literature on SIFT-MS studies demonstrates its unique utility, especially for breath analysis, as summarised in our recent reviews [2,8,9].

An essential requirement for SIFT-MS is an extensive kinetics library of rate coefficients and product ions for the gas phase reactions of the available precursor ions H_3O^+, NO^+ and O_2^+ with a wide variety of VOCs that are present in naturally occurring media, because it is on these reactions that the analytical technique depends, especially accurate quantification [10]. We and others (see [11,12] and references therein) have given a great deal of time and effort to building and continuously extending the SIFT-MS kinetics library, by supplementing it as gas analysis is extended to encompass different areas of research and the monitoring of, for example, food freshness via VOC emissions when an increasing number of compounds are detected that need to be quantified [13]. In general, the media of interest are humid, in the case of exhaled breath it is saturated with water vapour at about 6% absolute humidity. Because of the presence of water vapour in the samples to be analysed, the H_3O^+, NO^+ and O_2^+ precursor ions used for the analysis are partially converted to their hydrates $H_3O^+(H_2O)_{1,2,3}$, $NO^+(H_2O)_{1,2}$ and $O_2^+(H_2O)_{1,2}$, by sequences of three-body reactions

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[14,15] and if these hydrates are not accounted for then erroneous analyses will result. Equally important is that the reactions of these hydrated ions with the trace compounds, M, can produce hydrated ions like $MH^+(H_2O)_{1,2,3}$ and NO^+MH_2O and these must be recognised and included in the total of characteristic product ions for accurate analyses [10,14]. Furthermore, the primary products of the analytical reactions, especially MH^+ ions, can undergo direct three-body association with H_2O molecules again producing $MH^+(H_2O)_{1,2,3}$ ions. Therefore, when studying these ion/molecule reactions with a view to establishing SIFT-MS library entries, it is essential in the presence of water molecules (humid samples) to record all the products of the reactions, obviously including the primary products of the precursor ion reactions with M and also the hydrated product ions that form from them.

In our laboratories at Keele and Prague, not least prompted by our collaborations with local clinicians and groups in other universities and research institutes, we have initiated studies of the VOC emissions from cell cultures [16], bacterial cultures and processed cultures such as yoghurt, fermented meat [7], alcoholic beverages [17], and compounds involved in other biochemistries both *in vitro* and *in vivo*. In these endeavours, we are constantly recognising VOCs that we need to analyse for which SIFT-MS library entries are not yet available. Thus, we have seen that, for us, there are new compounds being observed for which kinetics library entries are required if they are to be analysed by SIFT-MS. We are also seeing that some of these biochemically related compounds have the same nominal molecular weight, MW, (isobaric compounds) and then the challenge is to identify them via the characteristic product ions that are likely to form using the available precursor ions in SIFT-MS. The essential points to recognise are that there is no pre-separation of trace compounds prior to analysis in SIFT-MS (as there is in GC–MS) and that the resolution of the analytical mass spectrometers on current SIFT-MS instruments is not sufficiently high to obtain fractional mass-to-charge ratios, *m*/*z*. Thus, to progress this analytical method, it is necessary to carry out a detailed study of the product ions of the reactions of such isobaric compounds with the SIFT-MS precursor ions in order to explore this potentially confounding ion chemistry and to see if differing characteristic product ions are formed with the three precursor ion species that might allow the separate identification of these isobaric compounds.

1.1. Compounds of interest

The compounds of interest in this study together with their molecular weights, MW, and their molecular formulae are the following: (see Table 1)

MW 88u: 3-hydroxybutanone (acetoin), $C_4H_8O_2$; n-butyric acid, $C_4H_8O_2$; ethyl acetate, $C_4H_8O_2$; pyruvic acid, $C_3H_4O_3$

MW 86u: 2,3 butanedione (diacetyl), $C_4H_6O_2$; allyl ethyl ether, $C_5H_{10}O$, cyclopropane carboxylic acid, $C_4H_6O_2$: γ-butyrolactone, $C_4H_6O_2$

Note that three of the four isobaric compounds in each of the two groups have the same molecular formula. The structural formula of each compound is given below in Tables 2 and 3. The selected ion flow tube, SIFT, technique was used previously to provide the basic kinetic data for the reactions of five of these eight compounds in support of the earliest SIFT-MS work [18–21], but in those early measurements the hydrated ions referred to above were not reported; this is now considered essential for accurate SIFT-MS analyses of humid samples and we pay some attention to this in this study. In general, the primary product ions of the reactions seen in the present studies conform to the results obtained previously, as will be remarked upon later when discussing the results. The new compounds not studied previously are acetoin, pyruvic acid and cyclopropane carboxylic acid.

Acetoin is a used as an external energy store by a number of fermenting bacteria [22]. Along with diacetyl [23], it is one of the compounds giving butter its characteristic flavour. Acetoin is present in many fruits and vegetables and is used as food flavouring. Both compounds are quite volatile, the vapour having a pleasant odour and should readily be detected using SIFT-MS. They are added to margarine to give it a buttery flavour. Their molecular structures are sufficiently different (see Tables 2 and 3) suggesting that their chemistry may be sufficiently different to provide a means to distinguish between them by SIFT-MS. The structural isomeric compounds acetoin, ethyl acetate and butyric acid are also emitted from natural products including ripe fruit [24]. When these compounds coexist it will be a challenge to distinguish between them; to explore this is an objective of the study described here.

Pyruvic acid (in solution, its anion usually referred to as pyruvate) is the simplest volatile alpha-keto acid and there are three active centres (see Table 2). For this alone its ion chemistry is worthy of study. Pyruvate is an important chemical compound in biochemistry. It is the output of the metabolism of glucose, viz. glycolysis, which provides energy for an organism; the detailed chemistry is described by the Krebs cycle [25]. γ-Butyrolactone (or GBL) is often used as an aroma compound. In humans it acts as a prodrug for γ-hydroxybutyrate, GHB, a naturally occurring substance found in the central nervous system and in almost all animals in small amounts, and is a component of some wines, beef, and small citrus fruits. GBL is also categorized as an illegal drug in many countries and it is used as a recreational intoxicant. Both pyruvic acid and GBL are volatile and might be detectable in the gas phase above natural products using SIFT-MS. Hence, the reason for studying the ion chemistry of these and the other six compounds listed above and given in Tables 2 and 3.

2. Experimental

Selected ion flow tube mass spectrometry, SIFT-MS, has been developed principally for the rapid, real time analysis of trace gases in air and exhaled breath [1,16]. The need for kinetic data on the reactions of the available precursor ions, H_3O^+, NO^+ and O_2^+, with any compound to be analysed is explained in detail in our previous review papers [2,3] and the method of quantification of trace compounds in humid air, including the involvement of water vapour in the ion chemistry, is treated in detail in two recent papers [10,26]. The currently used, most highly developed SIFT-MS instrument is the *Profile 3* [26,27]. This analytical instrument can equally well be used as a SIFT instrument for the study of ion/molecule reactions under the very conditions that pertain to SIFT-MS, and it is the *Profile 3* instrument (Instrument Science Limited, Crewe, UK) that was used for the present study. The precursor ions are formed in a microwave discharge source and the H_3O^+, NO^+ and O_2^+ ions can be individually selected and injected into flowing helium carrier gas where they are convected along the flow tube as a thermalised swarm. These three ion species can also be injected together into the helium carrier gas by drastically lowering the resolution of the upstream mass filter, as is needed to determine the rate coefficients for the ion/molecule reactions (see below).

In order to identify the products of the reaction of each precursor ion with those neutral compounds (purchased from Sigma–Aldrich) included in this study, it is only necessary to inject the precursor ions and then to offer up the vapour of the solid or liquid present in the small compound container to the sampling port of the instrument, ensuring only that the flow rate of the sample of laboratory air/compound vapour is low enough that the fractional loss of precursor ions does not exceed a few percent (as required for any SIFT-MS analysis [10]). Then the downstream analytical mass spectrometer is operated in the full scan (FS) mode over a range of mass-to-charge-ratio, *m*/*z*, to encompass all precursor and product

ions and their hydrates and for a sufficient number of full scans to ensure appreciable count rates of all ions in the spectrum. In practice, 3 scans of 20 s duration is all that was required to accumulate data that allowed accurate product branching ratios to be obtained from the signal intensities of each ion on the spectrum. By targeting the known product ions using the multi-ion monitoring (MIM) mode of the SIFT-MS instrument, more accurate product ion distributions are obtained if required [3]. In the current instrument, the product ion intensities are corrected for mass discrimination and differential diffusion effects [26], which if ignored can seriously distort product ion ratios, especially when their m/z values are widely different.

Additional to these compound vapour analyses, and cognisant that most of the compounds included in this study would be encountered in the liquid phase, we chose to dissolve these compounds in water to explore their stability in the dissolved state, by analysing the headspace of the air/water vapour/compound vapour that developed above 50 ml of the solution contained in a glass bottle of volume about 200 ml sealed with a septum at about 20 °C. The headspace was sampled by puncturing the septa with a hypodermic needle coupled directly to the input port of the instrument. The molar concentrations of the solutions were chosen empirically such that sufficient concentrations of the VOCs were established above the solution; these concentrations are given in Tables 2 and 3. These vary, principally due to the differing Henry's Law (partition) coefficients of these compounds in aqueous solution. This solution approach was further prompted because acetoin existed as a mixture of its monomer and dimer, both of which are partially volatile and so the evolving vapour consists of a mixture of monomer and dimer molecules; more is said about this when discussing the reactions of acetoin. Concerning the pyruvic acid measurements, we found it beneficial to acidify the aqueous solution with hydrochloric acid in order to enhance the partition of this weaker fatty acid into the vapour phase, but this approach had interesting consequences, as described and discussed later. An added benefit of these solution studies was that the headspace sample was more humid than that of the lab air/compound vapour sample and so the hydrates of the product ions were more clearly defined on the SIFT spectra ensuring their positive detection. From these data the three-body rate coefficients for the formation of the monohydrates of the primary product ions were determined, as described later. Finally, a note of caution; if either the supplied compounds contain volatile impurities or if partial hydrolysis occurs in solution to generate new volatile compounds, then these may be seen at relatively high levels in the headspace of the solutions should they be more readily be partitioned into the vapour phase than is the major compound of interest.

To determine the rate coefficients for the reactions of the precursor ions with each compound, the vapour above its liquid/solid was introduced into the helium at sufficiently high flow rates to reduce the precursor ion count rates at the downstream mass spectrometer by about an order-of-magnitude or more [28]. Then plots of the decay rates of the three precursor ions were constructed, and assuming that the rate coefficient of the exothermic proton transfer reactions of H_3O^+ ions with all the eight compounds are collisional, then the rate coefficients for the NO^+ and O_2^+ ions can be obtained from the relative decay rates of these ions. This procedure has been justified and explained in detail in previous publications [18–20]. In this way, the rate coefficients for the reactions of H_3O^+, NO^+ and O_2^+ have been determined with many types of compounds and thus a large kinetics library has been built up in support of SIFT-MS analyses (see [2,3] and the references therein).

3. Results and discussion

The collected data obtained in this study are given in four tables. Table 1 gives the two-body (binary) rate coefficients and the effective two-body rate coefficients for the primary reactions of the H_3O^+, NO^+ and O_2^+ ions with the 8 compounds, M, involved in this study. Tables 2 and 3 present the data on the primary product ion distributions for the primary ion/molecule reactions, also indicating which of these primary products form hydrates, and Table 4 gives the derived three-body (ternary) rate coefficients for the association reactions of the protonated compounds, MH^+, with H_2O molecules.

3.1. Binary rate coefficients

The proton affinities of all eight compounds generously exceed that of the water molecule and so proton transfer between H_3O^+ and all eight compounds, M, is exothermic. So, as noted previously, it can be assumed that the rate coefficients, k, for these exothermic proton transfer reactions proceed at the collisional rate described by the collisional rate coefficient k_c [29]. The latter can be calculated according to the formulation given previously [30] if both the permanent dipole moment and the electric polarisability of the reactant molecule are known or if these parameters can be estimated as was needed for both acetoin and pyruvic acid. Using these physical parameters, the k_c values for the NO^+ and O_2^+ reactions can also be calculated; these k_c values are given in parentheses in Table 1 for the total of 24 reactions. Also given are the experimentally derived k values for the NO^+ and O_2^+ by the approach outlined in the previous section, where it can be seen that all these k values are very close to their respective k_c values. Thus, there are no inefficient reactions in this group of 24, which means that they can all be useful, in principle, for SIFT-MS analysis of these 8 compounds. These k values are used to construct the kinetics library entries for these compounds, as indicated later in this paper. The k values obtained in this study are in excellent agreement with those determined in previous SIFT studies for n-butyric acid, ethyl acetate [19], diacetyl [18], allyl ethyl ether [20] and γ-butyrolactone [21], as are the observed products of these reactions.

Table 1
The collisional rate coefficients, k_c, given in square brackets, for the reactions of H_3O^+, NO^+ and O_2^+ with four isobaric compounds of molecular mass (m) 88u, and four of molecular mass 86u, as calculated using their polarisabilities, α, and their permanent dipole moments, μ, [39] in the formulation given by Su and Chesnavich [30] together with experimentally derived rate coefficients, k, for the NO^+ and O_2^+reactions; see the text and [18] for further explanation.

Compound	m (u)	α (10^{-24} cm^3)	μ (D)	[k_c] (H_3O^+)	k [k_c] (NO^+)	k [k_c] (O_2^+)
3-Hydroxybutanone	88	8.8*	2.6	[3.7]	3.0 [3.1]	3.4 [3.0]
n-Butyric acid		10	1.8	[3.0]	2.4 [2.5]	2.6 [2.4]
Ethyl acetate		9.7	1.8	[2.9]	2.3 [2.4]	2.5 [2.4]
Pyruvic acid		6.6[a]	2.3	[3.2]	2.1 [2.7]	2.8 [2.6]
2,3-Butanedione	86	8.2	0	[1.7]	1.4 [1.4]	1.5 [1.4]
Allyl ethyl ether		10.7	1.2	[2.5]	2.2 [2.1]	2.1 [2.0]
Cyclopropane carboxylic acid		10	1.8	[3.0]	2.1 [2.5]	2.4 [2.4]
γ-Butyrolactone		8.5	3	[4.1]	3.5 [3.4]	3.9 [3.3]

Table 2
The percentages, %, of the primary product ions (in bold) of the reactions of H_3O^+, NO^+ and O_2^+ with the four isobaric molecules indicated that have a common molecular weight, MW, of 88u. Also included in parentheses are the observed hydrates of the primary ions when they occur, that must be accounted for in SIFT-MS analyses of these compounds. These experimental data were obtained for the analyses of these compounds in the headspace of aqueous solutions; see the text. The ionisation energies of each compound in electron volts [31] are also given in italics.

Compound	Physical state	H_3O^+		*m/z*	NO^+		*m/z*	O_2^+		*m/z*
3-hydroxybutanone (acetoin) $C_4H_8O_2$ *9.4**	Solid	$C_4H_9O_2^+$	100%	**89** (107, 125)	$C_4H_8O_2NO^+$	80%	**118**	$C_2H_5O^+$	85%	**45** (63, 81)
3-hydroxybutanone (acetoin) $C_4H_8O_2$ *9.4** 										
	MP 15 °C solution 0.2M				$C_2H_5O^+$ $C_4H_8O_2^+$ $C_4H_7O_2^+$	10% ≤5% ≤5%	**45** (63, 81) **88** **87** (105)	$C_2H_3O^+$	15%	**43**
n-butyric acid $C_4H_8O_2$ *10.2*	Liquid	$C_4H_9O_2^+$	95%	**89** (107, 125)	$C_4H_8O_2NO^+$	80%	**118** (136)	$C_2H_4O_2^+$	85%	**60** (78, 96)
n-butyric acid $C_4H_8O_2$ *10.2* 										
	BP 163 °C solution 0.02 M	$C_4H_7O^+$	5%	**71**	$C_4H_7O^+$	20%	**71**	$C_3H_5O_2^+$ $C_4H_8O_2^+$ $C_2H_3O^+$	5% 5% ≤5%	**73** **88** (106) **43**
Ethyl acetate $C_4H_8O_2$ *10.0*	Liquid	$C_4H_9O_2^+$	100%	**89** (107)	$C_4H_8O_2NO^+$	100%	**118**	$C_2H_5O_2^+$	40%	**61** (79, 97)
Ethyl acetate $C_4H_8O_2$ *10.0* 										
	BP 79 °C solution 0.1 M							$C_2H_5O^+$ $C_4H_8O_2^+$ $C_2H_3O^+$	20% 20% 20%	**45** (63, 81) **88** (106) **43**
Pyruvic acid $C_3H_4O_3$ *9.9–10.4*	Liquid	$C_3H_5O_3^+$	80%	**89** (107,125,143)	$C_3H_4O_3NO^+$	100%	**118** (136)	$C_2H_3O^+$	100%	**43**
Pyruvic acid $C_3H_4O_3$ *9.9-10.4* 										
	BP 165 °C solution 2M	$C_2H_3O^+$	20%	**43**						

[a]Calculated ionisation energy [40].

3.2. Product ion distributions for the H_3O^+, NO^+ and O_2^+ reactions

Insignificant differences are seen in the primary product ion distributions for all 24 reactions using the direct vapour on the one hand and the aqueous solution headspace on the other hand. Thus, in Tables 2 and 3 we list only the data obtained for the liquid headspace vapour analyses. Inspection of the data in these tables reveals that within each group of four isobaric compounds there is a high degree of commonality for the *m/z* values of the product ions (given in bold) for the H_3O^+ and NO^+ reactions, whilst there are clear differences in the products of the O_2^+ reactions. Thus, the O_2^+ reactions might be a route to the separate identification and analysis of the individual isobaric compounds when two or more are present in a sample, but this requires much further consideration. For some of these reactions there are minor product ions observed at the percentage level, but we omit these and place a lower limit of 5% of the reported primary product ions, as can be seen in the tables. Also indicated in parentheses in the tables are the *m/z* values of the observed hydrates of the primary product ions that should be included in the kinetics library entries to obtain accurate analyses of each compound. Included in the tables are the ionisation energies, IE, of the compounds, mostly known from experiments, but with two values derived theoretically as indicated. The IE for most compounds exceed that for the NO molecule, so charge exchange between ground state NO^+ and these molecules is endothermic and cannot occur. For two of the compounds their IE is close to that of NO and these reactions are discussed below.

3.3. Isobaric compounds with MW 88u

The reaction of H_3O^+ with all four compounds, M, proceed rapidly and the dominant primary product ion in all cases is the protonated parent molecule, MH^+ (see Table 2). These primary product MH^+ ions form hydrates, as is indicated in parentheses after each MH^+ ion species, and the association reactions by which they form are discussed later in a separate section. In only the pyruvic acid reaction is a second significant primary product ion observed:

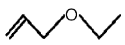
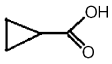
$$H_3O^+ + C_3H_4O_3 \rightarrow C_3H_5O_3{}^+ + H_2O(80\%) \quad (1a)$$

$$\rightarrow C_2H_3O^+ + CH_2O_2 + H_2O(20\%) \quad (1b)$$

The neutral product in reaction channel (1b) is most probably a formic acid molecule, HCOOH. Noted in Table 2 is that a relatively high molar strength of pyruvic acid solution was required to generate a measurable headspace concentration. However, to enhance the headspace concentration the solution was acidified with the stronger hydrochloric acid. However, this acidification resulted in the production of methanol, which was readily measured in the headspace. After two days held at 37 °C the pyruvic acid in the acidified solution (headspace) had been largely removed and apparently totally converted to methanol. We cannot describe the complex solution phase chemistry that occurs, but occur it most surely does!

The other new data are for 3-hydroxybutanone, acetoin, which results in just one product ion. However, as stated earlier, the sample of acetoin consists of a mixture of its monomer (low melt-

Table 3
The percentages, %, of the primary product ions (in bold) of the reactions of H_3O^+, NO^+ and O_2^+ with the four isobaric molecules indicated that have a common molecular weight, MW, of 86u. Also included in parentheses are the observed hydrates of the primary ions when they occur, that must be accounted for in SIFT-MS analyses of these compounds. These experimental data were obtained for the analyses of these compounds in the headspace of aqueous solutions; see the text. The ionisation energies of each compound in electron volts are also given in italics [31].

Compound	Physical state	H_3O^+		*m/z*	NO^+		*m/z*	O_2^+		*m/z*
2,3-butanedione (diacetyle) $C_4H_6O_2$ *9.3*	Liquid BP 88 °C solution 0.05M	$C_4H_7O_2^+$	100%	**87** (105, 123)	$C_4H_6O_2^+$	75%	**86**	$C_2H_3O^+$	65%	**43**
2,3-butanedione (diacetyle) $C_4H_6O_2$ *9.3* 										
					$C_4H_6O_2NO^+$	25%	**116**	$C_4H_6O_2^+$	35%	**86**
Allyl ethyl ether $C_5H_{10}O$ *9.6**	Liquid BP 66 °C solution 0.01M	$C_5H_{11}O^+$	75%	**87** (105)	$C_5H_9O^+$	95%	**85**	$C_3H_6O^+$	70%	**58** (76, 94)
Allyl ethyl ether $C_5H_{10}O$ *9.6** 										
		$C_3H_7O^+$	15%	**59** (77, 95)				$C_5H_{10}O^+$	15%	**86**
		$C_2H_5O^+$	10%	**45** (63, 81)				$C_3H_5O^+$	10%	**57** (75)
								$C_3H_5^+$	≤5%	**41**
Cyclopropane carboxylic acid $C_4H_6O_2$ *10.6*	Liquid BP 183 °C solution 0.5 M	$C_4H_7O_2^+$	90%	**87** (105, 123)	$C_4H_6O_2NO^+$	60%	**116** (134)	$C_4H_6O_2^+$	35%	86 (104)
Cyclopropane-carboxylic acid $C_4H_6O_2$ *10.6* 										
		$C_4H_5O^+$	10%	**69**	$C_4H_5O^+$	40%	**69**	$C_4H_5O_2^+$	20%	**85** (103)
								$C_4H_5O^+$	20%	**69** (87)
								$C_2H_2O_2^+$	15%	**58** (76)
								$C_3H_6^+$	10%	**42**
γ-butyrolactone $C_4H_6O_2$ *10.3*	Liquid BP 206 °C solution 0.5 M	$C_4H_7O_2^+$	100%	**87** (105, 123)	$C_4H_6O_2NO^+$	100%	**116**	$C_2H_2O^+$ or $C_3H_3^+$	80%	**42** (60)
γ-butyrolactone $C_4H_6O_2$ *10.3* 										
								$C_4H_6O_2^+$		
									20%	**86**

[a] Calculated ionization energy from [41]

ing point, coloured yellow) and its dimer (higher melting point, white crystals) and a wide *m/z* scan using both H_3O^+ and NO^+ precursor ions clearly revealed the presence of the dimer in the headspace vapour, but at a much lower concentration than that of the monomer. On vacuum pumping above the composite material the volatile monomer was gradually removed by evaporation leaving only the white crystalline acetoin dimer. When the latter was dissolved in water the headspace vapour contained only monomer acetoin molecules indicating that this dimer had dissociated in aqueous solution. Hence, the data given in Table 2 were obtained for this solution headspace. The results for the n-butyric acid and ethyl acetate are in good agreement with previous SIFT data obtained several years ago [19].

In all the NO^+ reactions the major primary product ion, or the only product ion, is the adduct NO^+M, which form very efficiently at the gas kinetic rate (see Table 1) mediated by the He carrier gas atoms and the major air molecules. The acetoin reaction is the most complex:

$$NO^+ + C_4H_8O_2 + (He,\ N_2, O_2) \rightarrow NO^+C_4H_8O_2 + (He,\ N_2, O_2)(80\%) \quad (2a)$$

$$\rightarrow C_2H_5O^+ + CH_3CONO(10\%) \quad (2b)$$

$$\rightarrow C_4H_8O_2{}^+ + NO(< 5\%) \quad (2c)$$

$$\rightarrow C_4H_7O_2{}^+ + HNO(< 5\%) \quad (2d)$$

Reaction channel (2b) involves the abstraction of the CH_3CO group from the acetoin molecule (see the structure of acetoin in Table 2). The minor channels proceed via slightly endothermic charge transfer (2c), which is possible because of the proximity of the ionisation energies of the acetoin molecule (9.4 eV [31]) and the recombination energy of NO^+ (9.26 eV [31]), and the well-known process of hydride ion (H^-) transfer (2d). The minor channel observed in the NO^+/butyric acid reaction proceeds via hydroxyl ion

Table 4
Kinetic data for the formation of hydrates of the protonated compounds indicated, as formed by ligand switching and three-body association. See the text.

Compound	No. of functional groups	A_{eff}[a]	k_3 (10^{-27} cm^6 s^{-1})[b]
3-Hydroxybutanone	1	1.8 ± 0.1	0.8 ± 0.3
n-Butyric acid	2	10.1 ± 4.4	5.8 ± 2.6
Ethyl acetate	1	5.8 ± 0.8	3.3 ± 0.6
Pyruvic acid	3	13.5 ± 0.8	7.8 ± 0.6
2,3-Butanedione	2	7.2 ± 0.1	4.1 ± 0.1
Allyl ethyl ether	1	6.2 ± 0.1	3.5 ± 0.1
Cyclopropane carboxylic acid	2	8.5 ± 0.3	4.9 ± 0.3
γ-Butyrolactone	2	4.9 ± 0.3	2.7 ± 0.3

[a] Association efficiency calculated from the experimental data. The uncertainties correspond to the differences between the results from the experiment using the vapours form the neat compounds and those obtained using the headspace of aqueous solutions.

[b] Three-body association rate coefficients estimated from A_{eff} using the theoretical maximum contribution of ligand switching reactions [35] and an assumed value of $k_{H_3O^+}$; see the text.

(OH^-) transfer. These last two reaction processes commonly occur in many NO^+ reactions with organic compounds containing an –OH group [3,19].

The O_2^+ reactions mostly proceed via dissociative charge transfer producing fragment ions, although the parent cation represents 20% of the total product ions in the ethyl acetate reaction. The pyruvic acid reaction apparently results in a single product ion:

$$O_2^+ + C_3H_4O_3 \rightarrow CH_3CO^+ + HCOOH(100\%) \quad (3)$$

Here, the centre C–C bond is cleaved producing the observed ion at m/z 43 and a formic acid molecule. The single product ion is surely CH_3CO^+, as indicated, and we know from numerous SIFT studies that this ion does not hydrate under SIFT and SIFT-MS conditions and none is seen to be formed as a secondary product. More will be said about hydration later in a separate section. It should also be reported here that in our much earlier paper [19] we reported that a product ion at an m/z value of 31 was seen in the O_2^+/ethyl acetate reaction, yet we do not see this in the present study. Therefore, we accept that the previous report of this product ion, identified as CH_3O^+, is in error, and this is further evidenced by the fact that an ion at m/z 31 is not seen in the NIST library electron ionisation spectrum [32]. No further comment is necessary on these O_2^+ reactions.

3.4. Isobaric compounds with MW 86u

As for the previous four compounds, the reaction of H_3O^+ of these four compounds, M, proceed rapidly and again the dominant primary product ion in all cases is the protonated parent molecule, MH^+ (see Table 3) that invariably form hydrates, as is indicated. The most complex of these reactions is that of allyl ethyl ether which, unusually for exothermic proton transfer, results in three product ions:

$$H_3O^+ + C_5H_{10}O \rightarrow C_5H_{11}O^+ + H_2O(75\%) \quad (4a)$$

$$\rightarrow C_3H_7O^+ + C_2H_4 + H_2O(15\%) \quad (4b)$$

$$\rightarrow C_2H_5O^+ + C_3H_6 + H_2O(10\%) \quad (4c)$$

Note the release of the hydrocarbon molecules and the production of the RO^+ ions that readily hydrate (see Table 3). The protonated cyclopropane carboxylic acid partially releases an H_2O molecule leaving an $RC{=}O^+$ ion which rarely hydrate. The two ketones remain intact after protonation, as is usually the case.

The NO^+ reactions with these four MW 86u isobaric compounds are more varied than the NO^+ reactions with the MW 88u compounds. In the γ-butyrolactone reaction the single product ion is the NO^+M adduct formed by association in the corresponding way to reaction (2a). The single product ion in the allyl ethyl ether reaction is the result of hydride ion abstraction, a process commonly seen in the reactions of NO^+ with alkenes [33]. In both the 2,3-butanedione and the cyclopropane carboxylic acid reactions, adduct ion formation is the major channel, but in the former reaction charge transfer competes with adduct formation:

$$NO^+ + C_4H_6O_2 + (He, N_2, O_2)$$

$$\rightarrow NO^+C_4H_6O_2 + (He + N_2 + O_2)(75\%) \quad (5a)$$

$$\rightarrow C_4H_6O_2^+ + NO(25\%) \quad (5b)$$

Charge transfer is energetically allowed because the IE of 2,3-butnedione at 9.3 eV [31] is only slightly greater than the recombination energy of NO^+. In the cyclopropane carboxylic acid reaction, hydroxide ion transfer produces $C_4H_5O^+$ ions and nitrous acid, HNO_2 molecules. Note that the product ion $RC{=}O^+$ does not hydrate, as predicted.

In all four O_2^+ reactions the parent cations are significant products and multiple fragmentation products are evident in most (see Table 3). An interesting point is that a product ion at m/z 42 is seen in both the cyclopropane carboxylic acid and the γ-butyrolactone reactions. In the former reactions this ion must be $C_3H_6^+$, but in the latter reaction it could be either $C_3H_6^+$ or $C_2H_2O^+$, but note that this product ion hydrates (Table 3) and so we favour the production of a $C_2H_2O^+$ ion and a C_2H_4O neutral molecule. The results for the product distributions for the 2,3-butanedione and γ-butyrolactone reactions are in good agreement with previous SIFT data obtained several years ago [18,21].

3.5. Hydration of the primary product ions MH^+ and NO^+M

At several points in the presentation and discussion of the data obtained in this study we have referred to the hydration of the primary product ions and how this is dependent on the structure of the ion. Now we focus only on the protonated parent compounds, MH^+, formed in the H_3O^+ reactions and consider the efficiency of the first step of hydration via the three-body association reaction:

$$MH^+ + H_2O + (He, N_2, O_2) \rightarrow MH^+H_2O + (He, N_2, O_2) \quad (6)$$

H_3O^+ and its hydrates $H_3O^+(H_2O)_{1,2,3}$ are always the dominant ions on the SIFT spectra and the distribution of these ions provides a measurement of the humidity of the sample being analysed [34]. In the present measurements using the laboratory air/compound vapour mixture the water vapour content was typically 1.5% whereas when analysing the aqueous solutions in the sealed bottles the water vapour content was typically 3%. The initial hydration reaction is:

$$H_3O^+ + H_2O + (He, N_2, O_2) \rightarrow H_3O^+H_2O + (He, N_2, O_2) \quad (7)$$

The three-body rate coefficient for reaction (7) has been previously determined to be $K_{H_3O^+} = 6 \times 10^{-28}\,cm^6\,s^{-1}$ [34]. By a sequence of similar reactions the $H_3O^+(H_2O)_{2,3}$ hydrates are formed. In addition to reaction (6), the $MH^+(H_2O)$ ions can be formed via ligand switching reactions involving the $H_3O^+(H_2O)_{1,2,3}$ cluster ions [35]:

$$H_3O^+(H_2O)_{1,2,3} + M \rightarrow MH^+(H_2O)_{1,2,3} + H_2O \quad (8)$$

So these hydrated protonated molecules $MH^+(H_2O)_{1,2,3}$ can be produced by two routes. Since reactions (6)–(8) occur in parallel, then measurements of the count rates of each of the ions involved in the ion chemistry contain the information required to calculate the three-body rate coefficients, k_{MH+}, of the hydration reaction (6). Essentially, this involves comparison of the efficiencies of reactions (6) and (7) expressed by a dimensionless association efficiency coefficient, A_{eff}, [14] describing how efficiently the product ions form hydrates with respect to H_3O^+. The value of A_{eff} is obtained experimentally from the ratio of the count rates of MH^+ to the total count rate $MH^+(H_2O)_{1,2,3}$ taken relatively to a corresponding ratio for H_3O^+ and its hydrates. Details of this calculation, including all equations and numerical examples, are given in a recent paper on ion chemistry of esters released by plants [36]. The value of A_{eff} should be invariant with the sample humidity for a given compound concentration (or its flow rate into the helium carrier gas) and this has been validated in the present experiments by calculating its value at two different humidities, as realized using the direct vapour measurements and the aqueous solutions of the compounds, as referred to in Section 2. The contribution of the switching reactions (8) to A_{eff} can be calculated theoretically, assuming collisional rate coefficients for reaction (8), and it has a typical value of $S_{eff} = 0.4$ [14,36]. The k_{MH+} values are then obtained as $(A_{eff} - S_{eff})k_{H_3O}$ and the

results for the 8 compounds included in this study are given in Table 4.

Note that the hydration rates of these protonated compounds are more efficient than the hydration rate of H_3O^+ ions, so production of MH^+ hydrates is inevitable in SIFT-MS. If these hydrates are not accounted for in SIFT-MS analyses, erroneously low quantification of these compounds will result. Note in Tables 2 and 3 that dihydrates of the MH^+ ions are usually formed and that the trihydrate of protonated pyruvic acid is seen; all these hydrates must be included in the analyses. The data in Table 4 reveals that the protonated compounds with the most active sites tend to hydrate most efficiently. Thus, protonated pyruvic acid most efficiently adds a water molecule, presumably because there are three active sites in this molecule, and the hydration of the two protonated fatty acids that have two active sites is also relatively efficient. Hydration of the protonated ester, ether and ketones is relatively less efficient. Whilst this is not the basis of a hard-and-fast rule, observation of hydration rates of a particular protonated molecule can give a clue to the nature of the molecule.

Concerning hydration of the adduct product ions of the NO^+ reactions, NO^+M. A glance at Table 2 shows that the two acid molecule adducts do form hydrates NO^+MH_2O, whereas the NO^+ adduct of the hydroxyketone and the ester do not form hydrates under the conditions of SIFT-MS. Similarly, it can be seen in Table 3 that, again, the acid molecule adducts form hydrates whereas the two ketones and the ether adducts do not. This has its parallel in the MH^+ hydration, as can be seen in Table 4. Such features can assist analyses of isobaric compounds, and this has been carried out to great effect in distinguishing acetic acid from the isobaric methyl formate [37], which has allowed the definite detection and quantification of acetic acid in exhaled human breath [38].

3.6. Kinetics library entries for the MW 86u and MW 88u compounds

From the kinetics data given in Table 1 (rate coefficients) and the m/z values for primary product ions and their hydrates (Tables 2 and 3), SIFT-MS kinetics library entries can be constructed for these eight compounds, as appropriate to the *Profile 3* instrument. The kinetic library entries for acetoin and for diacetyl are given in Table 5. These entries define the coefficients specific for each compound that should be used in the equations given in [10] for the absolute quantification of the concentrations of trace compounds present in humid air. Each row in the precursors section gives the m/z of each precursor ion followed by the rate coefficient for its reaction with the given compound and terminated by a coefficient by which the ion count rate should be multiplied (normally 1.0, meaning that the total ion count obtained at that m/z value should be included). Rows in the products section again give the m/z values for each product ion followed by a similar multiplication coefficient. In this case the calculation simply involves the sum of the count rates of all product ions of the reactions together with their hydrates.

Note that in the case of these MW 86u and MW 88u compounds it is not possible to construct reliable kinetics library entries that would automatically and separately quantify their concentrations when two or more of them are simultaneously present in a sample. This is because the degree of overlap at the dominant product ions (m/z 87, m/z 89, m/z 116 and m/z 118) is too great. Thus, for example, the entry acetoin (H_3O^+) from Table 5 will provide calculation of the total concentration of acetoin, all isomers of butyric and pyruvic acids and ethyl acetate, in principle giving an upper limit to the concentration of any of the individual compounds. However, careful examination of the SIFT-MS mass spectra obtained using all three precursor ions, with reference to the branching ratio data given in this paper and considering the relative count rates of the hydrated ions, can help the researchers to narrow down the list of the isobaric compounds that are present. It is strongly recommended that if only selected characteristic product ions are used to determine the concentration of a particular compound rather than all the characteristic ions and their hydrates, then the branching ratio for the primary product ions and any hydrates formed in the reaction of the chosen precursor ion with the particular compound should be experimentally determined under identical conditions of sample humidity to those used in the actual analysis.

Table 5
SIFT-MS kinetics library entries in the format required by the SIFT-MS software for on-line calculations of the concentrations of acetoin and diacetyl using both H_3O^+ and NO^+ precursor ions.

Acetoin (H_3O^+)	Diacetyl (H_3O^+)
4 Precursors	4 Precursors
19 3.7e−91.0	19 1.7e−9 1.0
37 3.0e−91.0	37 1.3e−9 1.0
55 2.4e−91.0	55 1.0e−9 1.0
73 1.5e−91.0	73 0.6e−9 1.0
3 Products	3 Products
89 1.0	87 1.0
107 1.0	105 1.0
125 1.0	123 1.0
Acetoin (NO^+)	Diacetyl (NO^+)
3 Precursors	3 Precursors
30 3.0e−91.0	30 1.4e−91.0
48 2.6e−91.0	48 1.1e−91.0
66 2.2e−91.0	66 0.8e−91.0
4 Products	2 Products
45 1.0	861.0
63 1.0	1161.0
81 1.0	
118 1.0	

4. A case study of VOCs present in the headspace of incubated yoghurt

This reaction kinetics study follows our well-established procedure by which the SIFT-MS the kinetics library is extended to encompass new compounds. The compounds included in the present study reflect the extension of our research work into the analysis of VOCs emitted from cell and bacterial cultures *in vitro,* and also the probing by breath analysis of lung cancer [38] and respiratory infection [5]. To demonstrate the utility of SIFT-MS and some of the new kinetic library entries given above, we show in Fig. 1 the SIFT-MS spectra obtained for the analysis of the headspace of supermarket probiotic yoghurt contained in a glass bottle that has been held at 37 °C for 2 weeks. Fig. 1a is the spectrum obtained using H_3O^+ precursor ions and Fig. 1b is that obtained using NO^+ ions; each spectrum is a composite of only 3 spectral scans of 20 s duration. The richness of these spectra is clear, some 8 compounds being immediately identified by their characteristic product ion m/z values. The headspace concentrations given in the figures have been obtained using existing library entries and the new entries for acetoin (3-hydroxybutanons) and diacetyl (2,3-butanedione), both compounds (known to be present in the headspace of fermented milk from previous GC–MS studies [22,23]) being seen on both the H_3O^+ and NO^+ spectra. These spectra are included as examples of how the VOC emissions from these bacterial cultures can simply and rapidly be investigated. The concentrations of the compounds in the headspace relate only to this particular yoghurt and its treatment. Note that the ammonia concentration is relatively low in the headspace, but this will be sensitively dependent of the pH of the yoghurt medium.

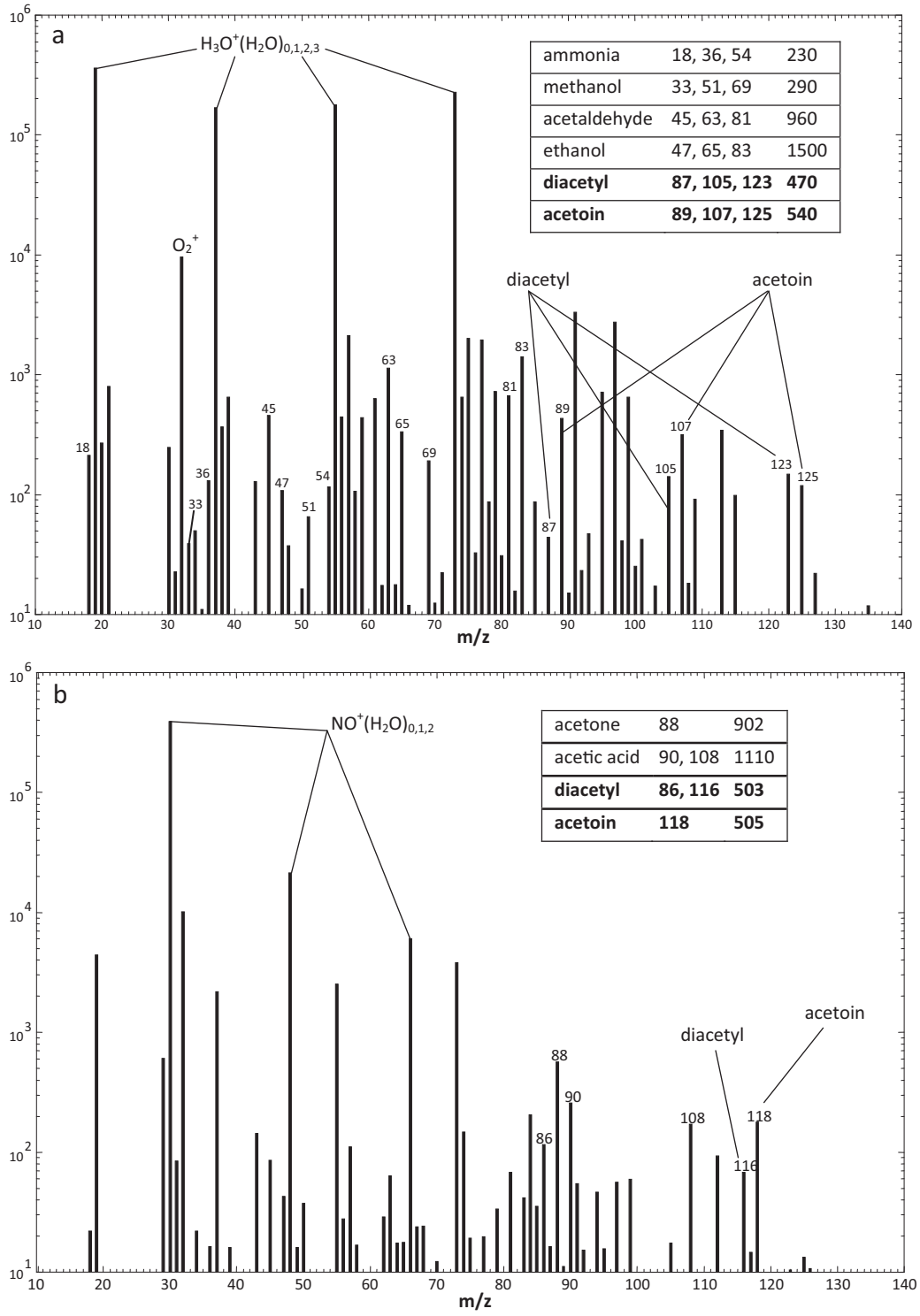


Fig. 1. Full scan (FS) SIFT-MS spectra (ion counts per second, c/s, against mass-charge-ratio, m/z) obtained using (a) H_3O^+ and (b) NO^+ precursor ions for the analysis of the headspace above a commercially available probiotic yoghurt sample following incubation at 37 °C for 2 weeks. Some of the readily identifiable compounds are indicated in the tables along with the m/z values of their characteristic product ions and their partial pressures in the headspace in parts-per-billion, ppb. Two of the compounds studied in detail in this paper, acetoin and diacetyl, are highlighted. Further explanation is given in the text.

5. Summary and concluding remarks

The choice of the isobaric compounds included in this study was predicated on those that are often met in biological media and fluids. The compounds present in each of the MW 86u and MW 88u groups can now readily be analysed by SIFT-MS when in isolation; then spectral m/z overlaps are not a problem. But when two or more isobaric compounds are present in a sample, overlaps will inevitably occur, since when using H_3O^+ precursor ions the major primary ion formed is MH^+, obviously having a common m/z value, and when using NO^+ precursor ions the common primary product is the NO^+M adduct ion. However, all is not lost, because compound types can be distinguished by their degree of hydration, for example, protonated carboxylic acids are efficiently hydrated forming

their monohydrate and a dihydrate by the water vapour molecules that are inevitably present in real media, whereas protonated esters and ethers are more slowly hydrated producing only a monohydrate under SIFT-MS conditions. Perhaps the use of NO^+ precursor ions holds more promise to distinguish between these isobaric compounds. For some specific compound types, the NO^+M common primary product ion of these reactions readily hydrate to form NO^+MH_2O ions, a process that is efficient when M is a carboxylic acid but does not occur when M is an ester, ether and a ketone. These tendencies are apparent in the data in Tables 2, 3 and 4, but it should be stressed that we do not have sufficient data to consider these trends to necessarily encompass all compounds. Hydration also occurs for some of the products of the O_2^+ reactions with M, but these are not so readily utilized for analysis because multiple productions usually result from these reactions. Nevertheless, the analytical spectra obtained using O_2^+ precursor ions can sometimes be useful as supplementary data to support compound identification.

Automated analyses of SIFT-MS data containing mixtures of isobaric compounds are clearly desirable. However, at the current state-of-the-art there is no substitute for careful examination of the full scan analytical mass spectra in the initial phases of any study using SIFT-MS. On the basis of such examinations, noting the important directions given in the last paragraph of Section 3.6, perhaps one or two characteristic product ions can be chosen from several (including hydrates) for inclusion in the kinetics database, in order to facilitate very efficient, high throughput quantification of the chosen compounds using the multiple ion monitoring mode of operation of SIFT-MS.

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