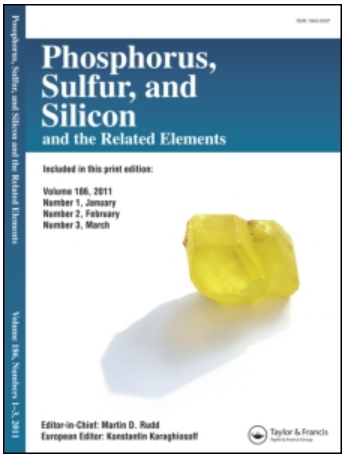

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MASS SPECTROMETRIC STUDY OF LINEAR AND CYCLIC PHOSPHONOACETALS

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MASS SPECTROMETRIC STUDY OF LINEAR AND CYCLIC PHOSPHONOACETALS†

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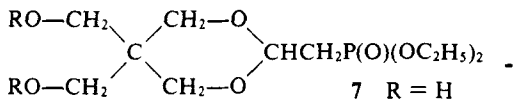
Electron impact mass spectra of a homologous series of linear phosphonoacetals and of 2-ethylphosphonoester substituted 1,3-dioxolan and 1,3-dioxan systems are discussed and compared. Results indicate direct involvement of the phosphoryl group on the formation of intermediates from the acetalic linkage. In monocyclic derivatives the main fragmentation follows expulsion of the phosphorus substituent. In bicyclic derivatives of hexitols another degradation pattern is found beside the expected "h-rupture".

INTRODUCTION

Since the initial isolation of 2-aminoethylphosphonic acid from ciliated protozoa,[1] followed by its discovery in human brain,[2] phosphonated derivatives were subjected to many chemical and biological investigations. The isolation of the natural antibiotic phosphonomycin,[3] the elucidation of its structure[4] and its antibilharziosis action,[5] are directly linked to these efforts. Of special interest was the study of sugar acetals having a phosphonate substituent on the monosaccharide ring.[6] We studied phosphonoacetalated sugar alcohols,[7,8] wherein the P—C bond is linked directly to the acetalic moiety.

Mass spectrometry of acetals has been extensively studied.[9] Since the acetal functions strongly control the fragmentation occurring upon electron impact, providing easily interpretable spectra, they have been used in great measure in structure elucidation investigations.[10] The electron impact mass spectrometric behavior of organophosphorus compounds has also been reviewed.[11] However, little information is given in the literature on the spectra of phosphonated acetals or ketals.[12] The homologous linear phosphonoacetals studied are $(EtO)_2P(O)(CH_2)_nCH(OEt)_2$ with $n = 0.1$ or 2, namely: diethyl diethoxymethylphosphonate (**1**), diethyl 2,2-diethoxyethylphosphonate (**2**) and diethyl 3,3-diethoxypropylphosphonate (**3**). Their preparation, physical properties and acid catalyzed hydrolysis have been presented in our previous reports.[13] The cyclic phosphonoacetals: 2-diethylphosphonomethyl-1,3-dioxolan (**4**), 2-diethylphosphonomethyl-1,3-dioxan (**5**) and bis-*O*-(diethylphosphonoethyl)pentaerythritol (**6**) have been reported as well.[14] We describe and characterize here two new members, the *O,O*-diethylphosphonomethylpentaerythritol (**7**) and its dibenzoyl derivative (**8**). A full description of the preparation of the 1,3 : 4,6-Di-*O*-(2-diethoxyphosphinylethylidene) acetals of dulcitol (**9**) and mannitol (**10**) whose mass spectra are compared in this study, was given elsewhere.[7,8]



7 R = H
8 R = C(O)Ph

† Phosphonated Acetals. Part VI.

EXPERIMENTAL

Mass spectra were taken on a Varian MAT-731 mass spectrometer using a direct insertion probe (±0.3°C temperature stabilization). The source temperature was 250–280°C, emission current 0.8 mA and electron energy 70 eV. Methods of preparation, purification and spectral analysis were previously described.[7,8,13,14]

O,O-[1-(diethylphosphono)methyl]-pentaerythritol (**7**)

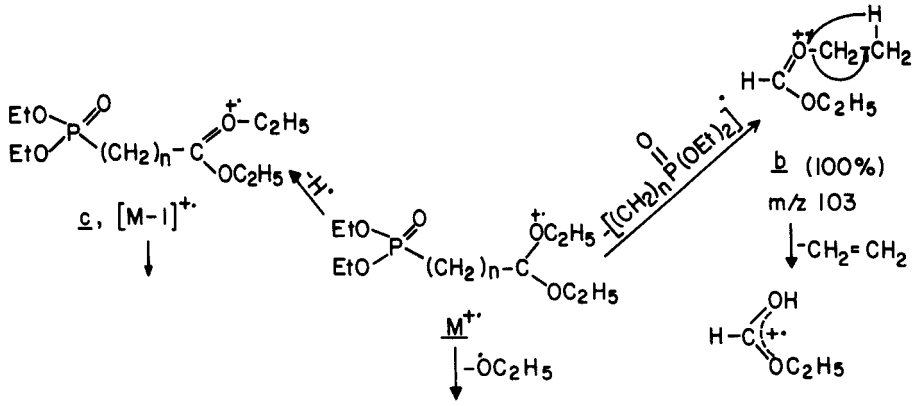
To a suspension of 68 gr pentaerythritol in 100 ml of water, 5 ml of concentrated HCl, and 128 gr of diethyl 2,2-diethoxyethylphosphonate (**2**) were added and the mixture stirred overnight at room temperature. After neutralization and evaporation of solvent, the residue was washed by ethanol, filtered and concentrated to a syrupy product 109.2 gr (73%). n_D^{25} 1.4665. Found: P, 10.6; Calc.: 10.4%. δ_H (270 MHz) 1.32 (6H, t, J 7.04 Hz, $2CH_3$), 2.20 (2H, dd, J_{HH} 5.28, J_{PH} 18.78, P—CH_2), 3.55, 4.01 (4H, AB, J 12.32, ring CH_2), 3.41, 3.96 (4H, s, $2CH_2O$ ring substituent), 4.06 (2H, s, 2OH), 4.09 (4H, quintet, J_{HH} 7.04, J_{PH} 7.92, CH_2OP), 4.80 (1H, sextet, J_{HH} 5.28, acetalic proton). δ_C 16.23, 16.49 (CH_3), 29.48, 35.78 (PCH_2), 39.06 (C quart.), 61.97, 62.23 ($POCH_2$), 61.62, 63.35 (CCH_2OH), 69.87 eq. 70.09, 70.65 aq. (CH_2 ring), 97.92 eq. 98.48 aq. (C acetalic). δ_P—26.7; m/z 298 ($M^{\ddagger}$, 3.9%), 266 [$(M—CH_2OH)^{\ddagger}$, 12.6], 196 (24.4), 180 (100), 152 (3.5), 125 (100), 147 {$[M—CH_2P(O)(OEt)_2]^{\ddagger}$, 3.2}, 297 [$(M—1)^{\ddagger}$, 0.8].

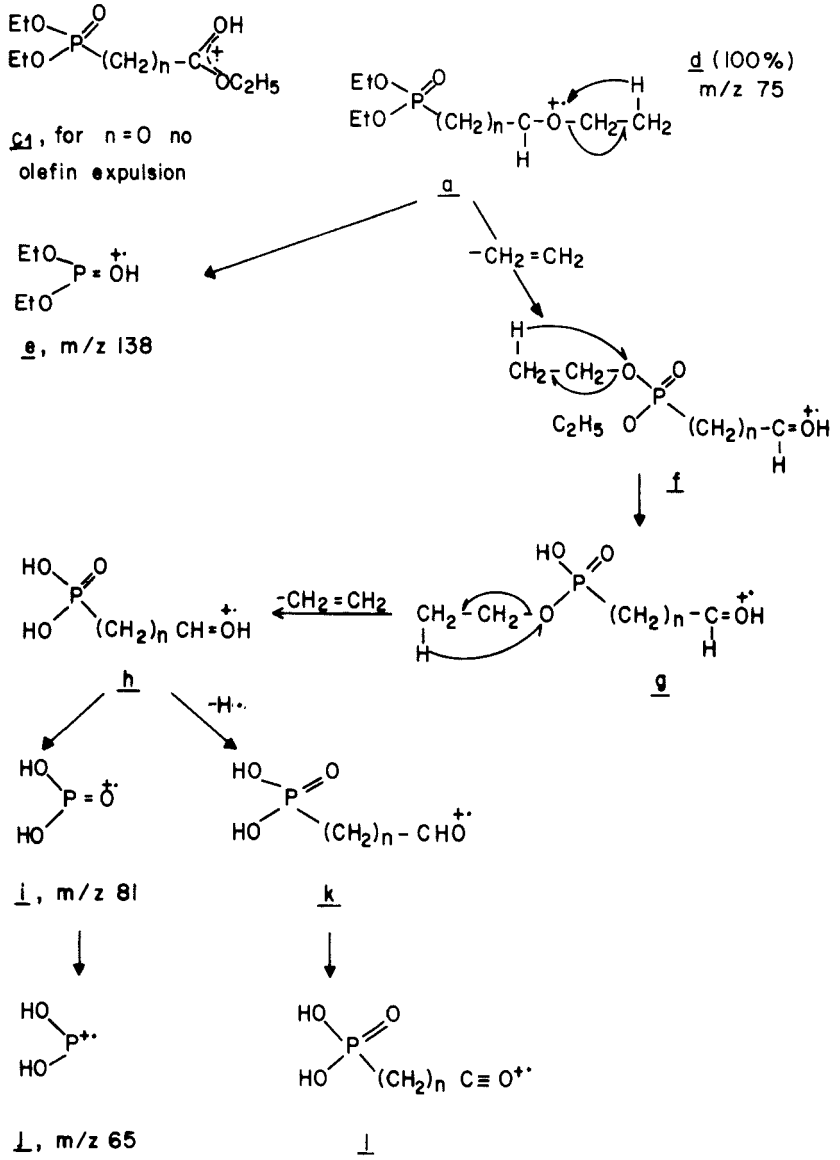
O-Dibenzoyl-O,O-diethylphosphonomethylpentaerythritol (**8**)

696.6 mg of **7** in 10 ml anhydrous pyridine were treated with 0.6 ml of benzoylchloride and left for 24 hr at room temperature. The reaction mixture was slowly mixed with 100 ml of water and left for one hour at 4°C. The product crystallized as white needles, 540 mg (45%), m.p. 91–2°C. Found: P, 5.8; Calc.: 6.1%. δ_H (270 MHz) 1.32 (6H, t, J 7.04, $2CH_3$), 2.25 (2H, dd, J_{HH} 5.28, J_{PH} 18.49, P—CH_2), 3.89, 4.18 (4H, AB, J 11.74, CH_2 ring), 4.11 (4H, quintet, J_{HH} 7.04, J_{PH} 7.92, CH_2OP), 4.23, 4.73 (4H, s, subst CH_2), 4.95 (1H, quartet, J_{HH} 5.28, J_{PH} 5.87, acetalic proton), 7.43 (dt), 7.56 (oct.), 8.00 (dt) protons of phenyl ring. δ_C 16.23, 16.53 (CH_3), 29.52, 35.78 (PCH_2), 37.5 (quart. C), 61.48, 62.15 ($POCH_2$), 63.35, 64.00 (subst. CH_2), 69.31 (ring CH_2), 98.57 (acetalic C); m/z 506 ($M^{\ddagger}$, 10.7%), 505 [$(M—1)^{\ddagger}$, 8.4], 401 [$(M—PhCO)^{\ddagger}$, 25.3], 384 [$M—PhCO_2H)^{\ddagger}$, 2.9], 355 {$[M—CH_2P(O)(OEt)_2]^{\ddagger}$, 100}, 249 (26.2).

RESULTS AND DISCUSSION

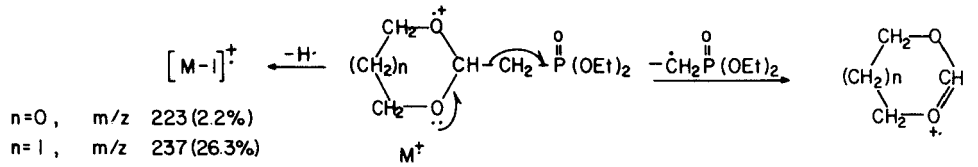
Significant fragments formed from compounds **1–3** are given in *Table I*. The molecular ions are in very low abundance. Generally, the ethyl phosphorus esters produce a fairly abundant (ca. 20% relative intensity) molecular ion.[11] Our results in this study resemble the behavior of alkyl phosphonates, where no detectable molecular ion was found with EIMS.[15] Scheme 1 summarizes the fragmentation patterns observed. This degradation is consistent with the principle[16] that expulsion of a large free radical fragment, in an α-cleavage, is favored to the expulsion of a smaller one. The same behavior is observed with the 1,3-dioxolan (**4**) and 1,3-dioxan (**5**) systems





SCHEME 1

with expulsion of the 2-phosphonomethyl radical and the formation of the stable oxonium ions, m/z 73 and 87, respectively (Scheme 2):



SCHEME 2

TABLE I

Mass numbers (and relative abundance) of the main ions arising from acetals **1–3**

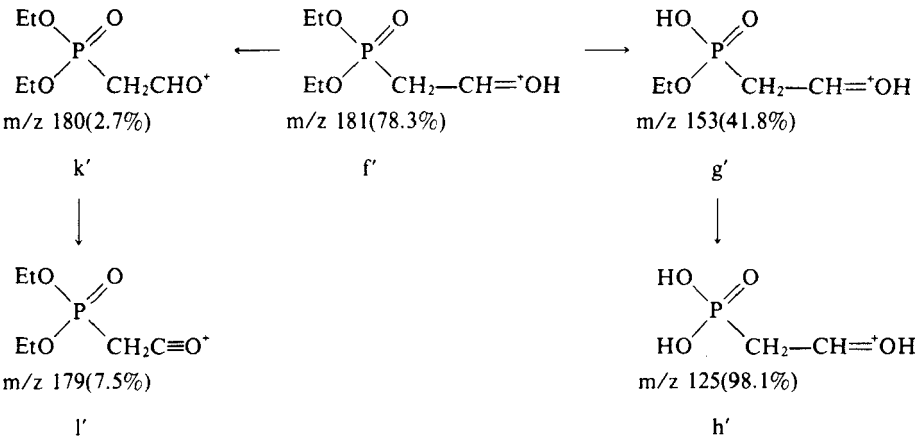
Compound	m/z (%) M^+	*a*	*b*	*c*	c_1	*d*	*f*	f_1	f_2	*g*	*h*	*k*	*l*
1	240 (0.08)	195 (12)	103 (100)	239 (0.14)		75 (100)	167 (29)	166 (2.5)		139 (31.3)	111 (73.6)	110 (11)	109 (25.5)
2	254 (0.14)	209 (64.9)	103 (82.8)	253 (0.55)	225 (7.5)	75 (44.3)	181 (78.3)	180 (2.7)	179 (7.5)	153 (41.8)	125 (98.1)	124 (4.5)	123 (26.2)
3	268 (0.06)	223 (46.2)	103 (100)	267 (0.12)	239 (3.2)	75 (37.1)	195 (5.8)	194 (2.5)	193 (8.8)	165[a] (6.7)	139 (10)		

[a] From f_2, but also from *f* and f_1 with less abundance.

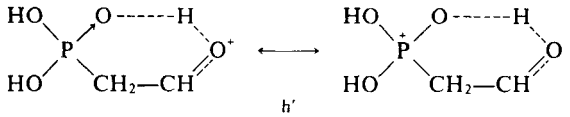
With unsubstituted acetals[9] the elimination of the ethoxyl group is preferred to the alkyl. The existence of the phosphorus substitution causes $(M—OC_2H_5)^+$ to be in low abundance compared to $[M—CH_2P(O)(OC_2H_5)_2]^+$ (Table I).

The fragmentation route of $f \rightarrow g \rightarrow h$ (Scheme 1), seems to be common to other phosphonate derivatives as well.[15] The driving force behind it are the extra binding facilities of the phosphorus by its *d* orbitals, preserving its tetragonal structure. As is so often the case, we see in the first member of a homologous series (acetal **1**) a non-representative behavior, atypical of the others, in that it does not undergo olefin expulsions from *M*-1 fragments (Table I, c_1).

The major peaks in the EIMS of **2** are common to all diethyl ethylphosphonates. These are the peaks derived from phosphonoacetaldehyde:



Fragment *h'* is highly abundant in all the ethyl phosphonated acetals. It is analogous to m/z 111, a major peak in the EIMS of dialkyl ethylphosphonates.[15] The very high abundance of this ion-radical suggests that it is of a remarkably high stability, probably due to intramolecular hydrogen bonding to the phosphoryl group:



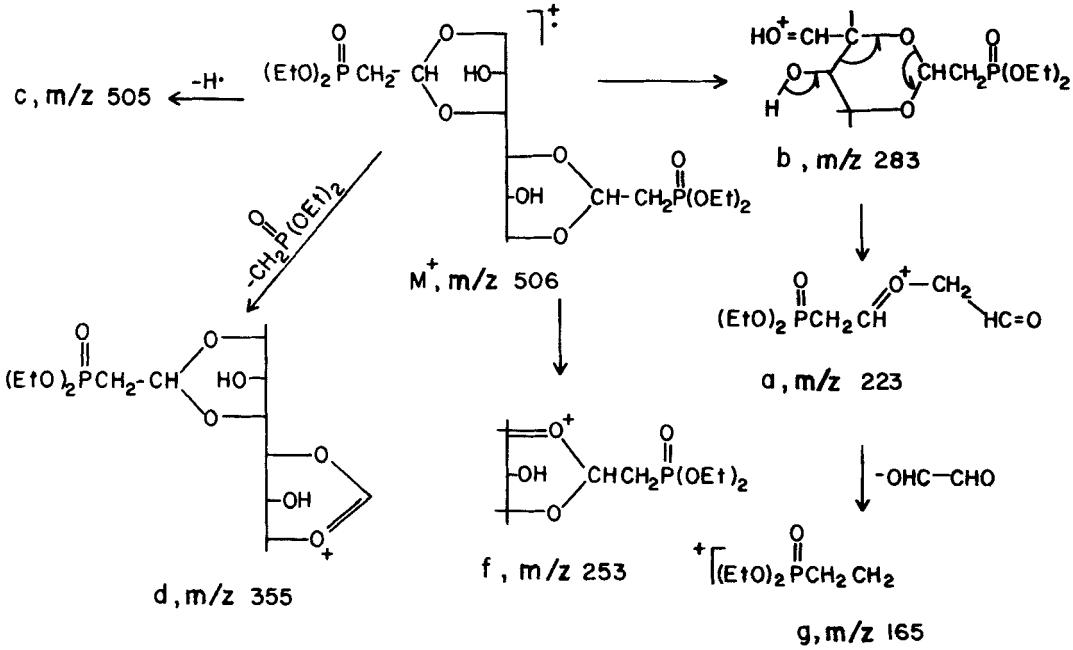
Either one of the two structures can preserve. The right hand one, however, seems more likely because it shows the high polarity of the P=O bond and because it would have three tautomeric forms and thus more stability. The existence of this six membered structure enables the involvement of the phosphorus substituent in processes taking place at the acetal linkage. The equivalent ion in acetal **3**, with an additional CH_2 group in the phosphonate chain, m/z 139 is only 10% (Table I). Therefore we may expect a very low effect of this substitution for the propylphosphonates. This observation resembles results obtained with ion products in solutions with the same compound.[13,14]

The typical phosphonoacetaldehyde fragmentation shown for acetal **2** is observed in all the cyclic ethylphosphonoacetals. The peak abundancies for the 1,3-dioxan system (**5**) are higher as compared to the 1,3-dioxolan one (**4**):

m/z	125	←	153	←	181	→	180	→	179
4 (%)	100		14		3.4		5		29.6
5 (%)	100		48.6		96.2		7.8		39.3

This prevalence of the 1,3-dioxan ring is observed by the higher abundance of the molecular ion of the spiro derivative **6**. Jeremic *et al.*[17] suggested recently that hydrogen shift from the 5-alkyl group is exclusively responsible to the oxonium ion formation in 1,3-dioxanes. Previous[18] works indicated position 5 as an origin to hydrogen transferred to the acetalic oxygen. Since compounds **6**, **7**, and **8** have disubstituted 5 positions, and yet m/z 181 is a prominent peak in their spectra, it seems that the hydrogen transfer for our compounds is from the alkyl substituent.

Indication of phosphoryl implication in the fracture of cyclic phosphonoacetals is found for the sugar alcohol derivatives. The fragmentation pattern deviates from the rules determined by Kochetkov and Chizhov[19] for the isopropylidene acetals of alditols. The main fragmentation goes through the ion radical *b* to *a*, which is also the base peak in the spectrum (Figure 1, Scheme 3). Although $b + a = M^+$, a meta-



SCHEME 3

stable transition screening showed that the origin of *a* is not directly from M^+ but from *b*. The energetically favorable process observed[20] in similar symmetrical acetals, lead to fragment *f* as the base peak of the spectrum. Considering this result as well as the predominance of the 1,3-dioxan system shown in the previous paragraph, it was unexpected to find the abundance of peak *f* for 1,3:4,6-Di-*O*-(2-diethylphosphinylethylidene)—galactitol (**9**) and 1,3:4,6-Di-*O*-(2-diethylphosphinylethylidene)—mannitol (**10**) at a level of about 4.5% (Table II).

We suggest that the driving force generating ion *b* (Scheme 3) is the presence of the phosphonyl group in the molecule. In a sample of acetal **9** in which the free OH groups were deuterated the following results are obtained: m/z (%) 284 (73.7), 285 (13.6), 224 (61.1), 225 (10.8), 182 (100), 183 (23.9); the equivalent ions for the undeuterated compound resulted in the following abundances: m/z (%) 283 (48.0), 284 (5.6), 223 (100), 224 (10.8), 181 (100), 182 (23.4). Thus, it follows that the charge deposition on the phosphoryl group is caused by a proton transfer from the free hydroxyl groups. This causes the unusual splitting of the molecule at the site of the transferring group (Scheme 3).

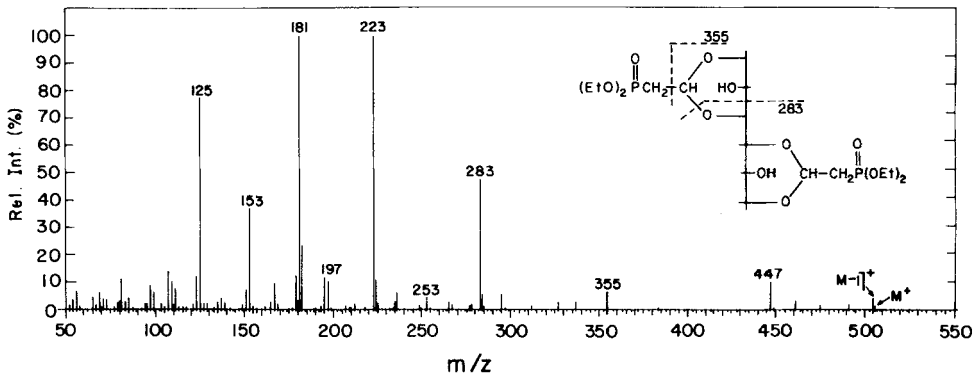


FIGURE 1

The formation of ion *a* from *b* is by the regular "h-rupture" mechanism which was suggested by Chizhov *et al.*[20] for 5-hydroxy-2-phenyl—1,3-dioxan derivatives. Scheme 3 shows the alternative possibility of receiving oxonium ion by protonation of an acetalic oxygen atom. It explains the formation of *a* (m/z 223) from *b* by the "h-rupture" mechanism and it explains the route *a* → *g* through expulsion of a stabile neutral glyoxal molecule by the following mechanism:

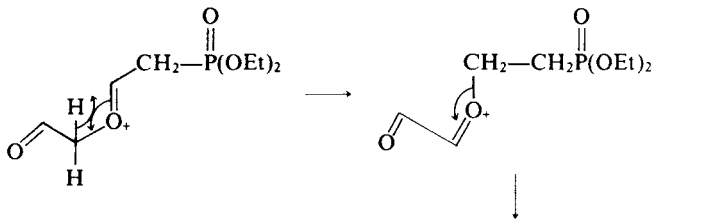


Table II compares between main peaks for acetals **9** and **10**. A similar pattern is observed, the only difference being in the relative abundancies.

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TABLE II

Comparison (relative abundance) of the main fragmentation ions between acetals **9** and **10**

ion	*a*	*b*	*c*	*d*	*e*	*f*	*g*	M^+
m/z	223	283	505	355	447	253	165	506
9	100	48.0	4.2	6.5	10.6	4.6	4.3	1.0
10	100	22.2	2.2	3.1	5.3	4.4	2.5	1<

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