

Mass Spectrometric Study of Some Protonated and Lithiated 2,5-Disubstituted-1,3,4-Oxadiazoles

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The mass spectrometric behavior of lithiated derivatives of 2,5-disubstituted-1,3,4-oxadiazoles has confirmed the skeletal rearrangement presented earlier for protonated derivatives. In the case of $[M + H]^+$ ions the loss of isocyanic acid was observed and for $[M + Li]^+$ ions the loss of lithium isocyanate occurred. On the other hand, benzoyl ions $[RCO]^+$ were formed from $[M + H]^+$ ions, but not from $[M + Li]^+$ ions. Formation of benzoyl ions was in agreement with the differences between bond orders calculated for $[M + H]^+$ ions and neutral molecules. From $[M + Li]^+$ ions the $[RCNLi]^+$ fragment ions were formed, but the formation of $[RCNH]^+$ fragment ions from $[M + H]^+$ ions was not observed. This result can be explained on the basis of theoretically calculated stabilities of these fragment ions, since the calculated heats of formation of $[RCNLi]^+$ ions were found to be substantially lower than those of the respective $[RCNH]^+$ ions. (J Am Soc Mass Spectrom 2003, 14, 289–294) © 2003 American Society for Mass Spectrometry

Mass spectrometric decompositions of lithiated molecules are especially interesting, mainly from the point of view of the structural analysis of organic compounds and the interesting fragmentation pathways of $[M + Li]^+$ ions. A number of compounds have been ionized by lithiation and the mass spectrometric fragmentation pathways of generated $[M + Li]^+$ ions have been studied. Recently, mass spectrometric fragmentation of lithiated molecules has been reported for polysaccharides [1], nitrostyrenes [2], annoheptocins [3], nucleobases [4], fatty acids [5], valinomycin [6], lipids [7–9], iridoids [10], loganins [11], cerebrosides [12], ginsenosides [13], polyglycols [14] and ceramides [15].

Mass spectrometric fragmentation pathways of protonated 1,3,4-oxadiazoles ($[M + H]^+$ ions) have been recently studied by chemical ionization (CI) [16], electrospray ionization (ESI) and liquid secondary ion mass spectrometry (LSIMS) [17]. In this paper the mass spectrometric fragmentation pathways of protonated 1,3,4-oxadiazoles (1–6, Scheme 1) are analyzed in more detail and compared with the fragmentation pathways observed for lithiated derivatives.

The B/E linked scan mass spectra of metastable ions were recorded by using LSIMS as a method for ion generation. The isotope ^6Li was used in order to establish whether or not the fragment ions deriving from $[M + Li]^+$ ions contained lithium.

1,3,4-Oxadiazoles are known to show various types of biological activity [18–22] and are used in modern electronics [23, 24].

Experimental

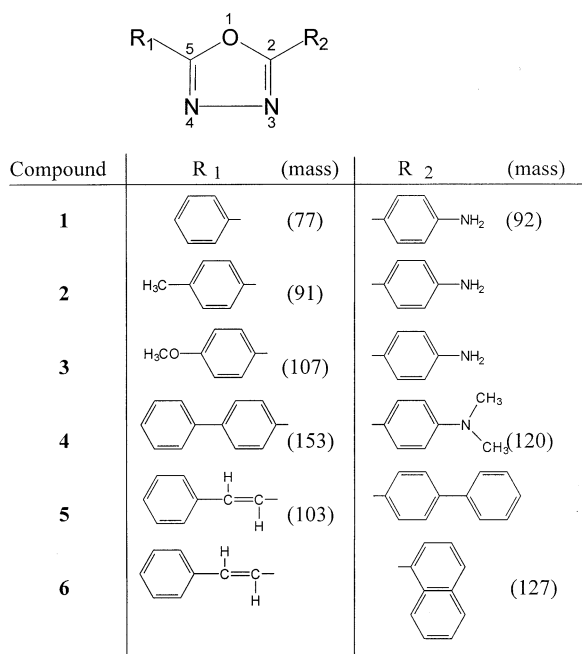
Compounds 1–6 were prepared according to the procedure described previously [25, 26].

The standard LSI mass spectra and B/E LSI mass spectra of metastable ions were obtained on an AMD 604 two sector mass spectrometer of the reverse B/E geometry, made by AMD Intectra (Harpstedt, Germany). A CsI gun supplied the primary ion beam (12 keV, Cs^+). The secondary ion beam was accelerated to 8 kV. The compounds were dissolved in NBA (3-nitrobenzyl alcohol, Aldrich). Lithium perchlorate was added in order to obtain the ion corresponding to the lithiated molecule of 1–6. The $^6\text{LiClO}_4$ was prepared from $^6\text{LiOH}$ (Aldrich, St. Louis, Missouri).

Semiempirical calculations were performed by using the Winmopac Version 2.0 package (Fujitsu Limited, Chiba, Japan). Geometry was carried out with the PM3 hamiltonian with precise key.

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Scheme 1. Compounds studied.

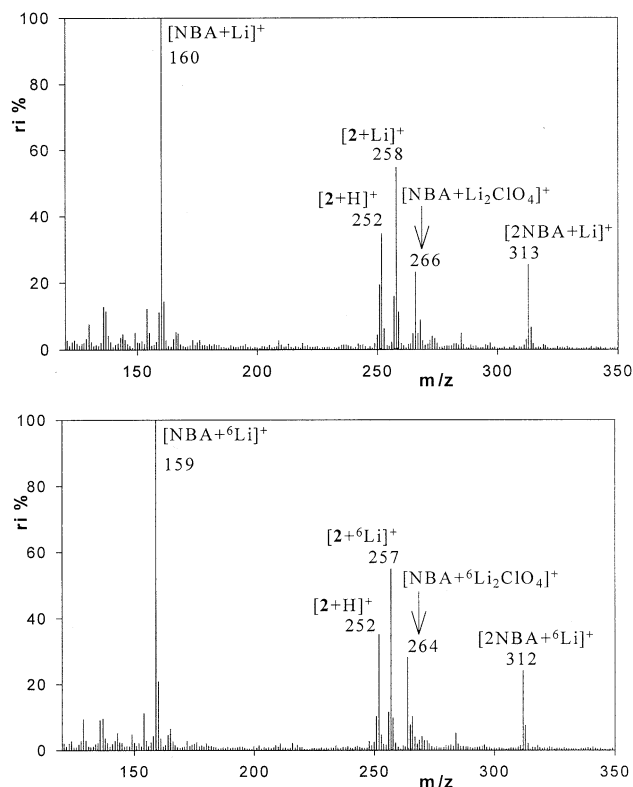
Results and Discussion

As follows from a large body of evidence [1–15] mass spectrometric decomposition of protonated and lithiated molecules show some similarities and some differences. We compared the mass spectrometric fragmentation patterns of protonated and lithiated 2,5-disubstituted-1,3,4-oxadiazoles. The standard LSI mass spectra of **2** with added Li⁺ or ⁶Li⁺ are shown in Figure 1 as representative examples. High signals of protonated and lithiated molecules were always present in the standard LSI mass spectra. The B/E mass spectra of [M + H]⁺ and [M + Li]⁺ ions were recorded.

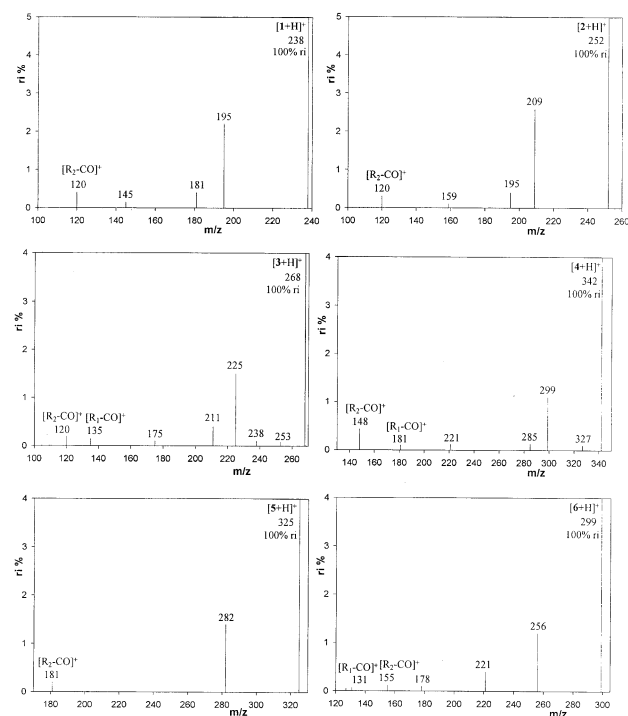
The B/E mass spectra of protonated **1–6** molecules ([M + H]⁺ ions) are shown in Figure 2. In the previous paper the fragmentation pathways of protonated molecules of 2,5-disubstituted-1,3,4-oxadiazoles were presented [17]. It was shown that these compounds lost the isocyanic acid molecule (HNCO, loss of mass 43) from the oxadiazole ring. During mass spectrometric decomposition of the protonated Compounds **1–6**, benzoyl ions ([RCO]⁺ ions) were also formed.

In the case of lithiated derivatives the loss of lithium isocyanate molecules (LiNCO) occurred. The respective fragment ions were clearly seen in the B/E mass spectra of [M + Li]⁺ and [M + ⁶Li]⁺ ions as shown in Figures 3 and 4. The respective product ions correspond to the loss of mass 49 for [M + Li]⁺ and 48 for [M + ⁶Li]⁺. However, formation of [RCO]⁺ ions was not observed. Instead of [RCO]⁺ ions, products ions rationalized as [RCNLi]⁺ ions were observed.

There is a logical correlation between the fragmentation pattern of [M + H]⁺ and [M + Li]⁺ ions: if the [R_nCO]⁺ ion is formed from the [M + H]⁺ ion, the [R_nCNLi]⁺ ion is formed from the [M + Li]⁺ ion as

Figure 1. Standard LSI mass spectra of Compound **2** obtained with added Li and ⁶Li cations.

shown in Figures 2–4. For example the [H₂N–C₆H₄–CO]⁺ ion ([R₂CO]⁺ ion, *m/z* 120) is formed from the [1 + H]⁺ ion, the [H₂N–C₆H₄–CNLi]⁺ ion

Figure 2. B/E mass spectra of [M + H]⁺ ions of Compounds **1–6**.

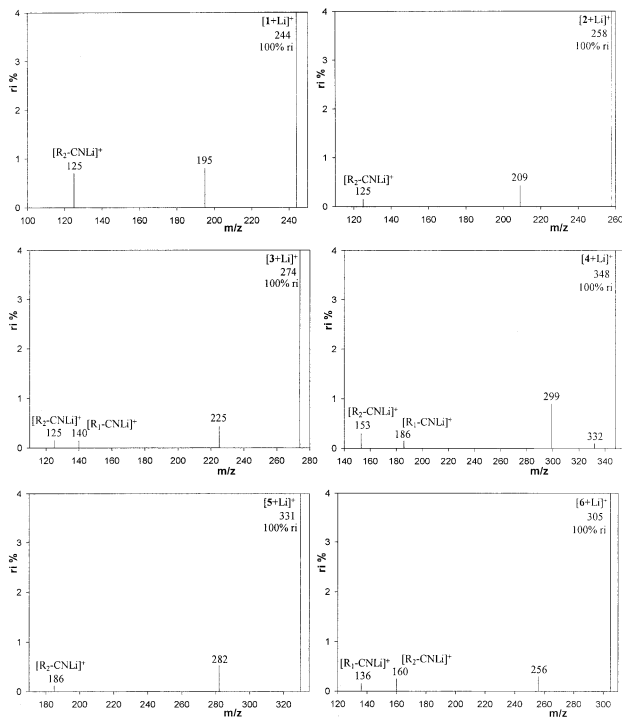


Figure 3. B/E mass spectra of $[M + Li]^+$ ions of Compounds 1–6.

($[R_2CNLi]^+$ ion, m/z 125 for Li and 124 for 6Li) is formed from the $[M + Li]^+$ ion.

Theoretical calculations were performed in order to explain these phenomena. First, the most likely site of protonation or lithiation should be identified. The sites

considered were the oxygen and two nitrogen atoms of the oxadiazole ring. The calculated heats of formation (ΔH_f°) of protonated 1–6 are shown in Table 1.

As Table 1 shows, the most stable protonated molecules are those with the proton attached to the N_3 atom because the heats of formation of the molecules protonated at N_4 atom are higher by about 5 kJ/mol (differences are not large but reasonable). In the case of 3, the probability of proton attachment to N_3 or N_4 is similar. Proton attachment to the O_1 atom is unlikely. The calculations have shown that in this case, in Compounds 1–4, the oxadiazole ring fragments, leading to a structure very unstable relative to those protonated at nitrogen. In the case of 5 the calculation was not successfully completed.

As follows from Figure 2 and Table 1, the formation of $[R_2CO]^+$ ions is favored over $[R_1CO]^+$ ions. The $[R_2CO]^{22}$ ions contain the carbonyl carbon atom connected to the protonated nitrogen atom (N_3 atom). In other words, the formation of the $[RCO]^+$ ion seems to be dependent on the protonation site.

In the case of $[M + Li]^+$ ions, the lithium cation appeared to be simultaneously connected to both nitrogen atoms of the oxadiazole ring by nearly equivalent bonds (Scheme 3) and this structure is favored over lithium attachment to the oxygen atom as shown in Table 2.

The formation of $[RCO]^+$ from protonated molecules can be rationalized on the basis of the differences between the bond orders of the oxadiazole ring calculated for $[M + H]^+$ ions and neutral molecules. The bond orders are shown in Scheme 2.

Formation of $[R_2CO]^+$ from $[M + H]^+$ ions required breaking the C_2-N_3 and O_1-C_5 bonds. In the case of $[M + H]^+$ ions the calculated bond orders of the C_2-N_3 and O_1-C_5 bonds were lower (the bonds were weaker) than in the neutral molecules (Scheme 2). On the other hand the bond orders of the O_1-C_2 bonds were higher in the $[M + H]^+$ ions (the bonds were stronger) than in the neutral molecules. Thus, the protonated molecules of 1–6 decomposed in such a way that the bonds of the lower order were cleaved, which is usually favored thermodynamically (requires less energy). The calculation of bond orders was also performed for $[M + H]^+$ ions with the proton situated at the N_4 atom and analogous results were obtained. The C_5-N_4 and O_1-C_2 bonds were weakened and O_1-C_5 bonds were strengthened, which led to the formation of $[R_1CO]^+$ ions. However, the formation of $[R_2CO]^+$ ions was favored over the $[R_1CO]^+$ ions. For example, in the case of 6 the $[R_2CO]^+$ ion ($[C_{10}H_7-CO]^+$, m/z 155) was more abundant than the $[R_1CO]^+$ ion ($[C_6H_4-C_2H_2-CO]^+$, m/z 131) as shown in Figure 2.

We recognize that bond energies should also be taken into consideration, however, it is difficult to determine which bonds are cleaved first and what are the structures of the neutral fragments eliminated on the formation of benzoyl ions. Therefore, the calculation of bond energies was not performed.

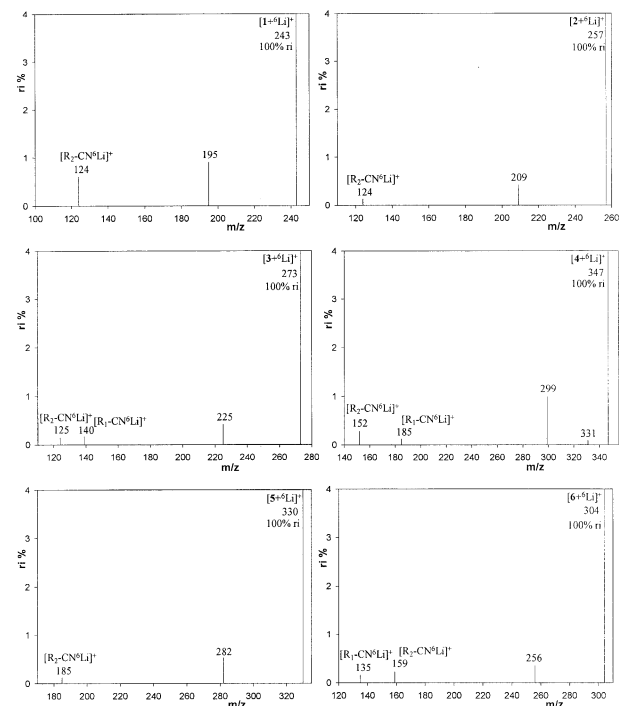


Figure 4. B/E mass spectra of $[M + ^6Li]^+$ ions of Compounds 1–6.

Table 1. Heats of formation (ΔH_f°) calculated for protonated Compounds 1–6

Compound	ΔH_f° for O ₁ protonated (kJ/mol)	ΔH_f° for N ₃ protonated (kJ/mol)	ΔH_f° for N ₄ protonated (kJ/mol)
1	950.7	904.0	911.5
2	905.8	860.5	866.6
3	781.5	736.4	737.0
4	1032.9	993.6	999.5
5	-	1071.7	1077.2
6	1309.6	1061.6	1064.8

We are aware that the differences in the calculated bond orders are not high but a correlation between the differences and fragmentation patterns of protonated 1–6 does not seem accidental.

The differences between bond orders of the oxadiazole ring calculated for $[M + Li]^+$ ions and neutral molecules were not in good agreement with the fragmentation pattern of $[M + Li]^+$ ions observed (Scheme 3).

The formation of $[R_2CNLi]^+$ ions required breaking the N₃–N₄ and O₁–C₂ bonds and the formation of $[R_1CNLi]^+$ ions required breaking the N₃–N₄ and O₁–C₅ bonds. Although the N₃–N₄ bonds were weakened by lithiation, the calculated bond orders of O₁–C_n were nearly the same as in neutral molecules (Scheme 3). However, it was found that the $[RCNLi]^+$ ions were substantially more stable than respective $[RCNH]^+$ ions which were not formed from $[M + H]^+$ ions. This result is presented in Table 3 where the calculated heats of formation of $[R_2CNLi]^+$ and $[R_2CNH]^+$ ions are compared.

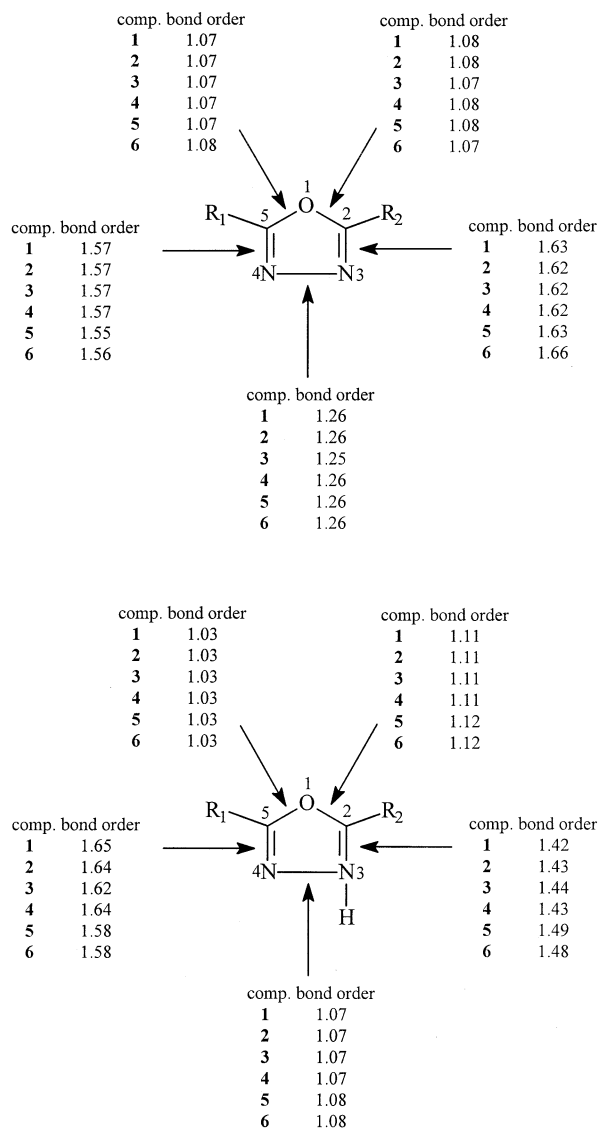
The differences in the bond orders calculated for $[M + H]^+$ and $[M + Li]^+$ ions are most likely related to the different structures of these ions, since the lithium is connected simultaneously to both nitrogen atoms (N₃ and N₄).

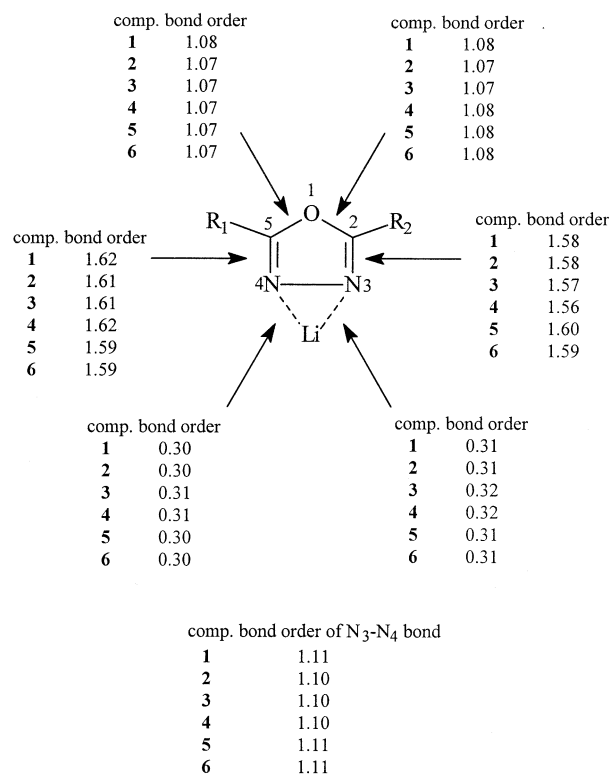
It is more difficult to explain why the formation of $[R_2CNLi]^+$ ions was favored over the $[R_1CNLi]^+$ ions. For example, in the case of 6 the $[R_2CNLi]^+$ ion ($[C_{10}H_7-CNLi]^+$, m/z 160) was more abundant than $[R_1CNLi]^+$ ($[C_6H_4-C_2H_2-CNLi]^+$, m/z 136) as shown in Figures 3 and 4. The calculated bond orders of N₃–Li bonds were always higher than in the case of N₄–Li bonds, but the differences were only 0.01 (Scheme 3). However, it seems to be reasonable that lithium was

Table 2. Heats of formation (ΔH_f°) calculated for lithiated Compounds 1–6

Compound	ΔH_f° for O ₁ lithiated (kJ/mol)	ΔH_f° for N ₃ –N ₄ lithiated (kJ/mol)
1	895.6	787.9
2	853.1	745.1
3	733.5	628.4
4	985.0	887.2
5	1067.8	955.2
6	1041.1	944.1

more firmly bound to the N₃ atom than to N₄, as deduced for $[M + H]^+$ ions (Table 1). This hypothesis can be confirmed by studies of the elimination of lithium isocyanate from an isotopic labeled compound, for example containing ¹³C₂ atom. For this compound, if the loss of LiN¹³CO (loss of mass 50) appears to be favored over loss of LiNCO (loss of mass 49), the

**Scheme 2.** The bond orders of oxadiazole ring calculated for neutral (top) and protonated (bottom) Compounds 1–6.



Scheme 3. The bond orders of oxadiazole ring calculated for lithiated Compounds 1–6.

hypothesis will be confirmed. The preparation of this compound is in progress.

Conclusion

The mass spectrometric decomposition of lithiated and protonated 1,3,4-oxadiazoles revealed both similarities and differences. The decompositions consisting of skeletal rearrangement (loss of HNC₂O for [M + H]⁺ and LiNCO for [M + Li]⁺ ion) were observed in both cases. On the other hand, in the case of [M + Li]⁺ ions, the [RCNLi]⁺ fragment ions were formed, but [RCNH]⁺ fragment ions were not formed from [M + H]⁺ ions. This phenomenon can be explained on the basis of the stabilities of [RCNLi]⁺ and [RCNH]⁺ ions, the former being more stable than the latter. Further, in the case of [M + H]⁺ ions, the [RCO]⁺ ions were formed and this seems to be related to the variations in the bond orders as a consequence of the protonation site.

Table 3. Heats of formation (ΔH_f°) calculated for [R₂CNLi]⁺ and [R₂CNH]⁺ ions

Compound	ΔH_f° for [R ₂ CNLi] ⁺ (kJ/mol)	ΔH_f° for [R ₂ CNH] ⁺ (kJ/mol)
1-3	745.1	917.4
4	740.8	911.4
5	857.3	1040.6
6	836.3	1118.6

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