Electron Ionization Mass Spectra of Alkylated Sulfabenzamides

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Abstract

Mono-, di- and trialkyl derivatives of "sulfabenzamide" (N-4-aminophenylsulfonyl-benzamide) are prepared and their EI mass spectra are examined. It is found that the fragmentation of N-alkylsulfabenzamides (Alkyl = CH_3 to n-C_5H_{11}) proceeds via a very specific rearrangement process involving migration of carbonyl O-atom to sulfur. The proposed mechanism involves an intermediate formation of distonic molecular ions, and the driving force for this process is the formation of stable N-alkylcyanobenzene cations [R-N^+≡CC_6H_5]. The findings are confirmed by exact mass measurement, MS/MS experiments and deuterium labeling.

Introduction

Two main kinds of activities of the NIST Mass Spectrometry Data Center (MSD), among the others, include measurement of electron ionization (EI) mass spectra and gas chromatographic indices for compounds (a) with low quality EI spectra present in the 2008 edition of the NIST/NIH/EPA mass spectral library[1,2], and (b) with poor gas chromatography properties and liable chemicals under GC-MS conditions. Among them metabolites, drugs and environmentally important compounds are in the priority list of NIST MSD. In this study the derivatization of a antimicrobial sulfonamide drug - sulfabenzamide is conducted to explore the best derivatives for its analysis by GC-MS.

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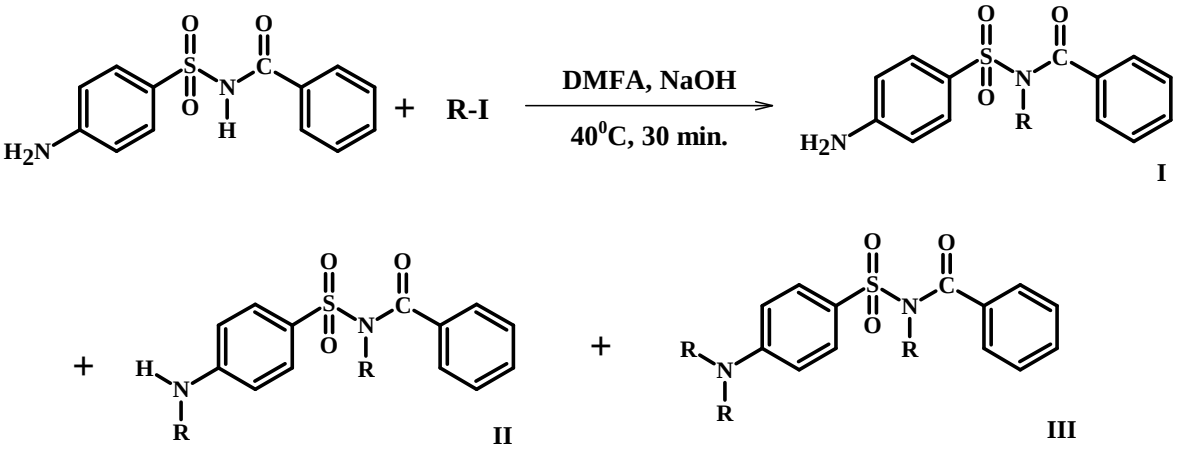
Common derivatization reactions[3], such as trialkylsilylation and perfluoroacylation, appear to be unsuitable for the GC-MS analysis as sulfabenzamide is liable under the reaction conditions and mainly derivatives of degradation products are formed . Alkylation with alkyl iodides and N,N-dimethylformamide dialkyl acetals are more successful and afford the derivatives (I-III) and (IV) respectively.

Experimental

*Chemicals****. "Sulfabenzamide", methyl, trideuteromethyl, ethyl, pentadeuteroethyl, n-propyl, n-butyl, n-pentyl iodides, N,N-dimethylformamide dimethyl and diethyl acetals are commercially available (Sigma-Aldrich, St. Louis, MO, USA) .

Synthesis of derivatives. Alkylation of "sulfabenzamide" is accomplished by heating (40 ^{o}C, 30 min.) with alkyl iodides in DMFA in the presence of NaOH. As a result, mono-, di- and tri-alkyl derivatives (I-III) are obtained (Scheme 1):

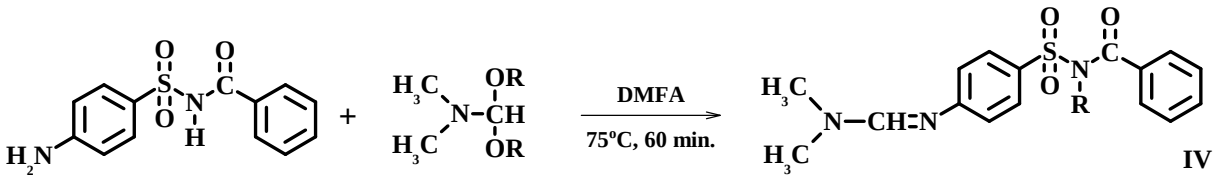
Scheme 1



(I) - (III): R = CH_3, CD_3, C_2H_5, C_2D_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}

The mixed derivatives (IV) are obtained by alkylation of "sulfabenzamide" with N,N-dimethylformamide dialkyl acetales (DMFA, 75°C, 60 min) (Scheme 2):

Scheme 2



(IV): $R = CH_3, C_2H_5$

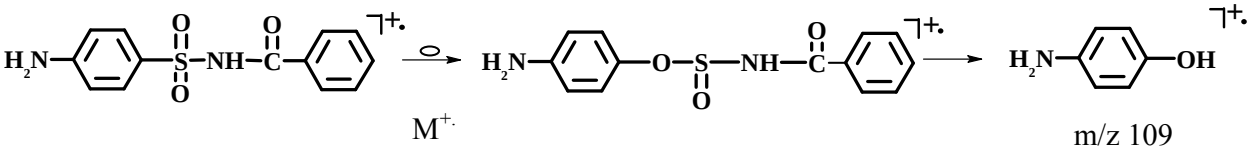
*Instrumentation****.** The EI mass spectra are recorded on gas chromatography/mass spectrometry systems with quadrupole (Agilent 6890/5973: Agilent Technologies, Santa Clara, CA, USA; ionization energy 70 eV; ion source temperature 230°C) and magnetic sector analyzers (Finnigan MAT 95XL: ThermoScientific, Bremen, Germany; ionization energy 70 eV, temperature of ionization chamber 220°C). A fused quartz capillary column (30 m x 0.25 mm i.d.) with non-polar stationary liquid phases (polydimethylsiloxane, containing 5% of phenyl groups); injection temperature was 250 to 270° C; temperature of the oven increased from 60°C to 200-270°C at a rate of 5°/min) for the sample separation. Exact mass determinations and linked-scan experiments (CID, helium as a collision gas) are performed on a GCmate II magnetic sector mass spectrometer (JEOL, Tokyo, Japan).

**Certain commercial materials are identified in this paper in order to specify the experimental procedure adequately. Such identification is not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to imply that the identified materials are necessarily the best available for the purpose.

Results and Discussion

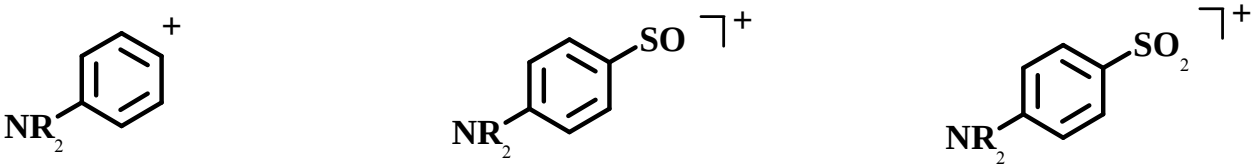
EI mass spectrum of the initial "sulfabenzamide" can be easily interpreted on the basis of known fragmentation rules. In fact, it reveals rather small peaks for $M^{+\cdot}$ and $[M\text{-}SO_2]^{+\cdot}$ ions and expected intensive peak for benzoyl cation at m/z 105. However the base peak in the spectrum at m/z 109 is a product of an expected rearrangement process[4] of the $M^{+\cdot}$ followed by hydrogen migration (Scheme 3). Analogs of this radical cation are not present in the spectra of alkyl derivatives.

Scheme 3



Other peaks in the high region of the spectrum correspond to ions due to simple bond cleavages (Scheme 4). The same set of ions is present in the spectra of alkyl derivatives (I)-(IV).

Scheme 4



Mass spectra of mono-, di- and trimethylsulfabenzamides (1-III, R=CH_3) are depicted in Figure 1a-c. The base peaks having m/z 118 cannot be explained on the basis of any simple bond cleavage or known fragmentation pathways for similar compounds. The same mass value (m/z 118) in all three spectra may point to the benzamide moiety as a resource for the formation of the corresponding ion (***a***). The m/z value of this peak in the spectra of tri-, hexa- and nonadeutero analogs (Figure 1d) is shifted by 3 Da from 118 to 121. All the above indicate the presence in the ion of methyl (trideuteromethyl) group attached to the amide N-atom and absence of carbonyl oxygen atom. As a result the only possible element composition C_8H_8N can be suggested for this ion. It is corroborated by exact mass measurements of the ion: experimental value - 118.0656, and calculated value - 118.0657 (error: ± 0.8 ppm).

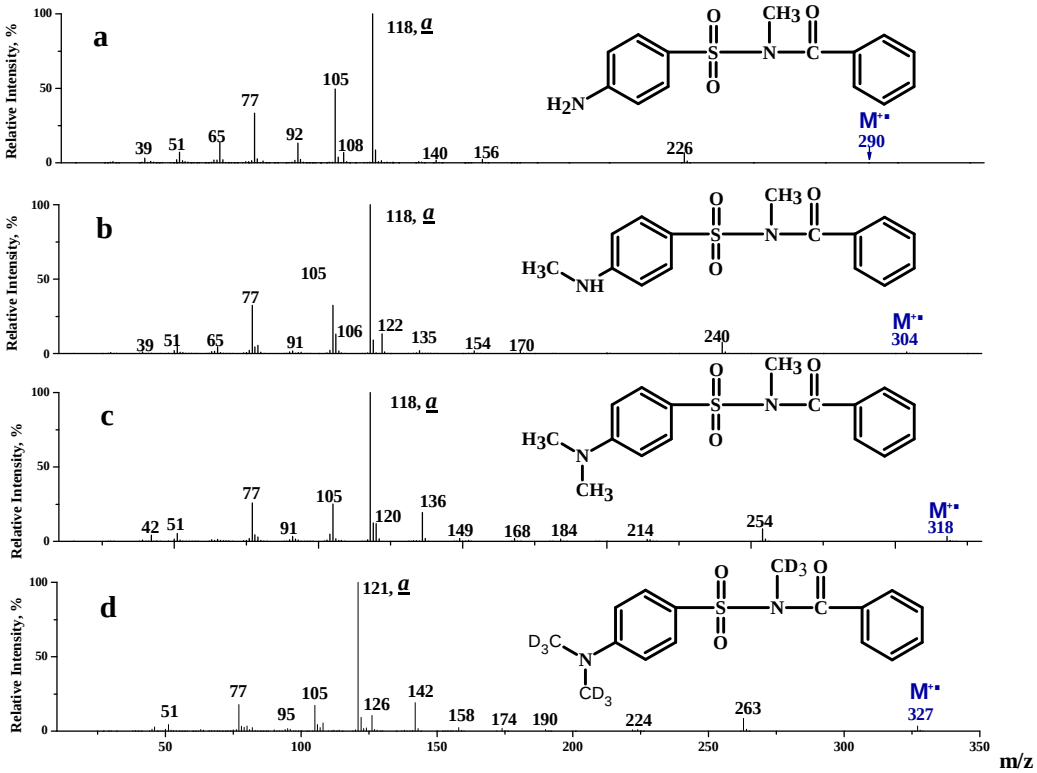


Figure 1. EI mass spectra of N-methyl-N-(4-aminophenylsulfonyl)- (a), N-methyl-N-(4-methylaminophenylsulfonyl)- (b), N-methyl-N-(4-dimethylaminophenylsulfonyl)- (c) and N-trideuteromethyl-N-(4-di(trideuteromethyl)aminophenylsulfonyl)-benzamides (d)

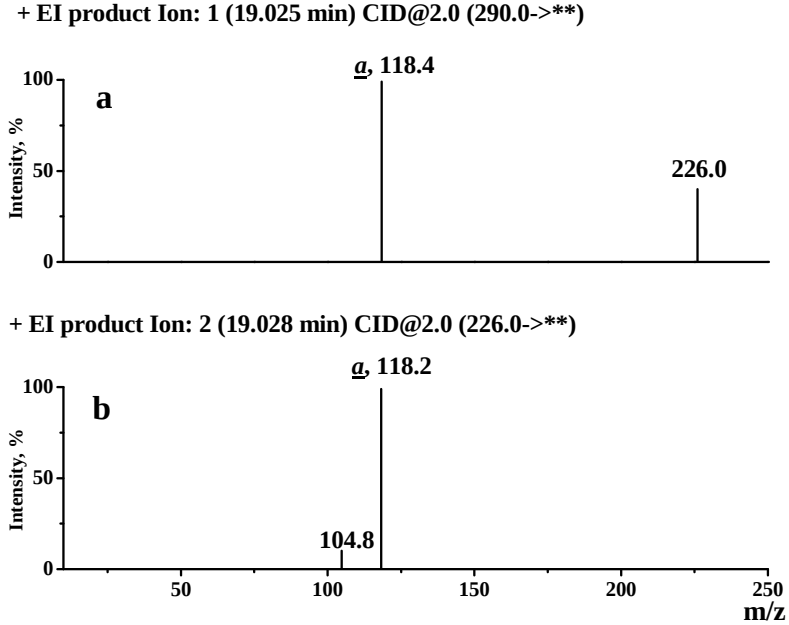
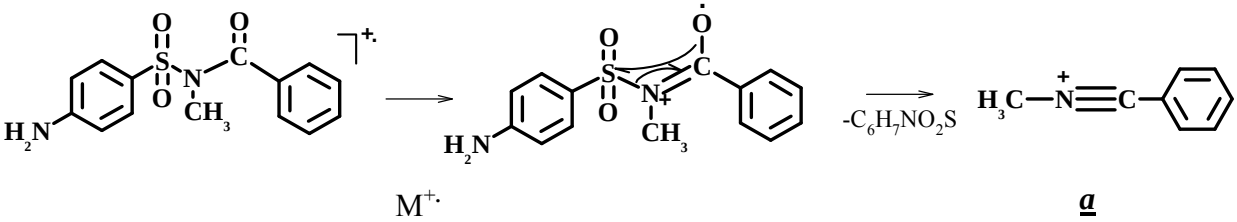


Figure 2. Product ion spectra recorded for a) molecular ion (m/z 290) and b) ion $[M\text{-}SO_2]^{+\cdot}$ (m/z 226) derived from N-methyl-N-(4-aminophenylsulfonyl)benzamide (I, R=CH_3)

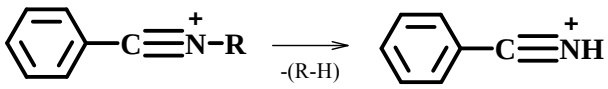
Collision induced dissociation experiments indicate that the ion (***a***) can be derived from both molecular and $[M\text{-}SO_2]^+$ ions (Figure 2). The mechanism of formation of the ion (***a***) from $M^{+\cdot}$ is most likely involves a skeletal rearrangement accompanied with a migration of carbonyl oxygen atom to sulfur followed by S-N bond cleavage. The driving force for the rearrangement process is likely the formation of a stable immonium cation via a distonic molecular ion: (Scheme 5):

Scheme 5



The same ions (***a***) are easily formed from derivatization products (IV; Figure 3)) and compounds with higher N-alkyl groups (I-III, R = C_2H_5, C_3H_7, C_4H_9, C_5H_{11}; Figure 4) and appear as base peaks in the spectra. As anticipated ions (***a***) in these cases (R ≥C_2H_5), eliminate olefin molecules (R-H) giving rise to an ion with m/z 104 (Scheme 6):

Scheme 6



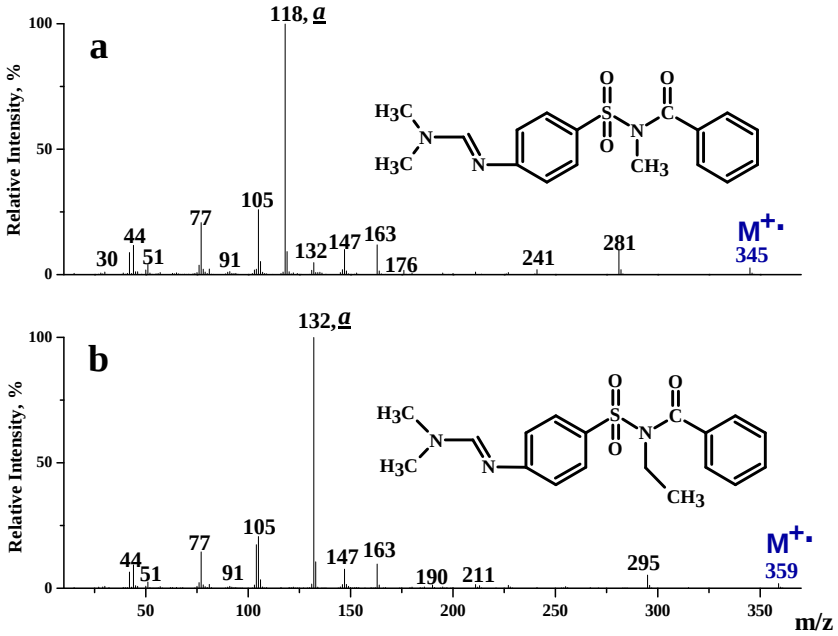


Figure 4. EI mass spectra of N-methyl- (a) and N-ethyl-(4-dimethylaminomethyleneaminophenylsulfonyl)benzamides (b)

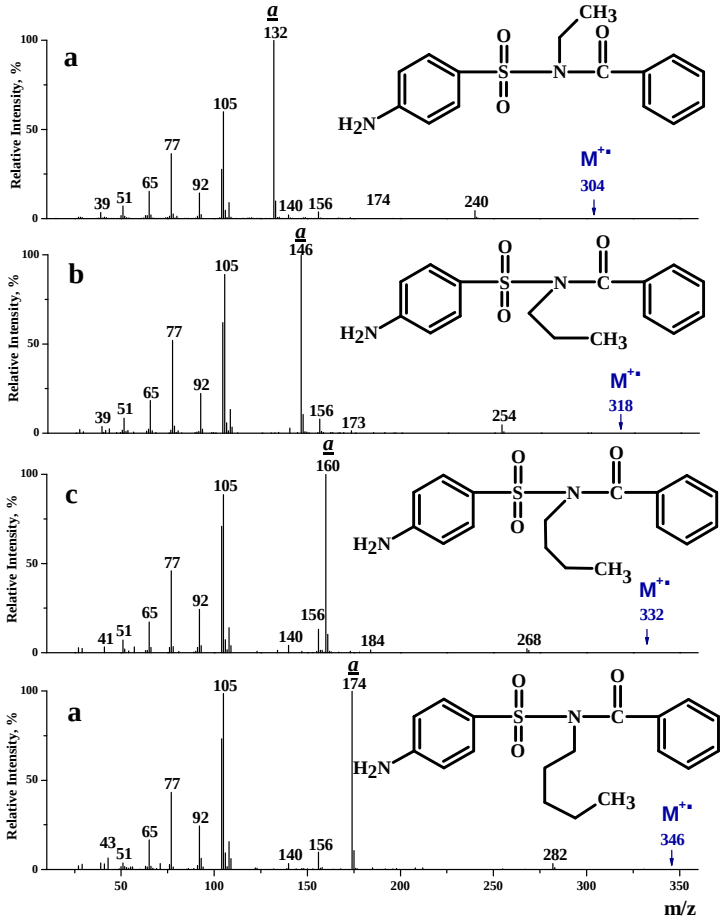


Figure 5. EI mass spectra of N-ethyl- (*a*), N-propyl- (*b*), N-butyl- (*c*) and N-pentyl-N- (4-amino phenylsulfonyl)- benzamides (*d*).

Along with the base peaks of ions (***a***) a competing reaction leading to benzoyl cation (m/z 105) due to benzamide moiety becomes significant in the spectra of compounds with an alkyl group greater than CH_3 at the amide N-atom (Figures 4b, 5a-d); the ions characterizing the arylsufonyl part of the molecule are present as well: $[NH_2C_6H_4]^+$ (m/z 92), $[NH_2C_6H_4SO]^+$ (m/z 140), $[NH_2C_6H_4SO_2]^+$ (m/z 156) and $[NH_2C_6H_4O]^+$ (m/z 108). The latter ion is a product of a rearrangement process similar to that given in Scheme 3. However it proceeds without a hydrogen migration since the amide hydrogen atom is substituted by an alkyl group.

It should be emphasized that a migration of carbonyl oxygen atom under electron ionization conditions have not been reported earlier[5,6].

Conclusion

The possibility of obtaining derivatives for sulfabenzamide by blocking amine and amide N-atoms is studied. A skeletal rearrangement of alkylated sulfabenzamides under EI conditions is discovered; this process leads to the formation of N-alkyl-phenylcyanate cations and involves a migration of carbonyl O-atom. The mechanism of the reaction is suggested via an intermediate formation of distonic molecular ions.

References

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