

# ORGANIC SEMINAR

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### “Gas-phase fragmentation reaction mechanisms of protonated N-nitrosamines”



The untargeted detection of novel N-nitrosamines is highly challenging. N-nitrosamines are classified as probable carcinogens, and the presence of N-nitrosamine impurities has caused the recall of several drugs. Methods that rely on  $\cdot\text{NO}$  elimination (tandem mass spectrometry, apparent total nitrosamine content analysis, etc.) are prone to false positive and negative results because not all N-nitrosamines release  $\cdot\text{NO}$  while many other compounds do (e.g., nitro-, C-, and S-nitroso compounds).

We have used high-resolution tandem mass spectrometry coupled with collision-activated dissociation to examine the gas-phase fragmentation patterns of 82 protonated nitroso model compounds, including 50 N-nitrosamines and 32 O-, S- or C-nitroso compounds. Elimination of a nitrosyl ( $\cdot\text{NO}$ ) radical was identified as being generally diagnostic for the presence of a nitroso group. However, this reaction only occurred for 50% of the N-nitrosamine model compounds. Some classes of protonated N-nitrosamines (e.g., aliphatic cyclic N-nitrosamines, N,N-dialkyl-N-nitrosamines) eliminated other structurally diagnostic neutral molecules (e.g., nitrosyl hydride or hydroxydiazene) that enabled their identification specifically as N-nitrosamines. This applies to 38% of the N-nitrosamines. However, 98% of the N-nitrosamine model compounds could be classified generally as nitroso compounds.

DFT and coupled-cluster quantum chemical calculations were used to delineate fragmentation mechanisms for the observed nitroso compound-specific reactions. These fragmentation reactions can, in most cases, be confidently used to determine whether an unknown compound is a nitroso compound. If the specific reactions diagnostic for N-nitrosamines (observed for 38% of N-nitrosamine model compounds) are detected, then an N-nitrosamine has been identified, thus improving the reliability of untargeted MS-based nitrosamine detection methods. In some cases, diagnostic fragmentation reactions coupled with elemental composition data can be used to differentiate N-nitrosamines from O-, S-, and C-nitroso compounds.