Unexpected Gas-Phase Nitrogen-Oxygen Smiles Rearrangement: Collision-induced Dissociation of Deprotonated 2-(N-Methylanilino)ethanol and Morpholinylbenzoic Acid Derivatives

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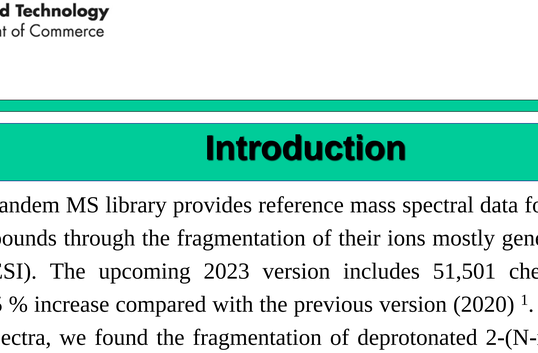
Introduction

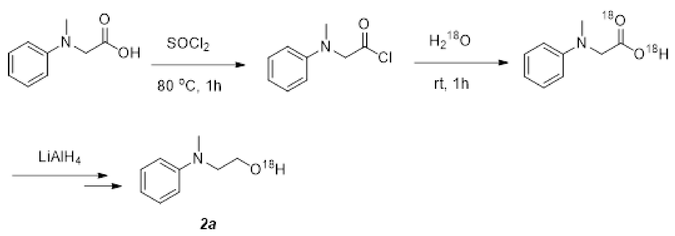
The NIST tandem MS library provides reference mass spectral data for the identification of various compounds through the fragmentation of their ions mostly generated by electrospray ionization (ESI). The upcoming 2023 version includes 51,501 chemical compounds, a significant 65 % increase compared with the previous version (2020) [1]. During the process of evaluating spectra, we found the fragmentation of deprotonated 2-(N-methylanilino)ethanol generated some unexpected fragment ions under CID. A nitrogen-oxygen Smiles rearrangement mechanism was proposed, which involves a five-membered ring rearrangement, followed by loss of a neutral ethylidene(methyl)amine molecule to form a phenoxide ion ($C_6H_5O^-$, m/z 93.0343). The Smiles rearrangement can be extended to various morpholine substituted benzoic acids and other compounds.

Materials and Methods

2-(N-Methylanilino)ethanol and morpholinyl benzoic acid solutions were prepared at a concentration of about 0.1 g/L by dissolving them into water/acetonitrile/ammonium hydroxide (50:50:0.1, v:v:v) and water / acetonitrile /formic acid (50:50:0.1, v:v:v), respectively. All samples were analyzed on an Orbitrap mass spectrometer via a nano electrospray source with direct infusion. HCD and FT-IT (ion trap) spectra were measured in the negative mode. The raw data were processed by NIST developed software and visualized through NIST MS Search 2.4.



Scheme 1. *Structures of 2-anilinoethanol, 4-(4-morpholinyl)benzoic acid and their derivatives*



Scheme 2. *Synthesis of 2-(N-methylanilino)ethanol-^{18}O*

Results

1. *Comparison of mass spectra of deprotonated 2-anilinoethanol 1 with 2-(N-methylanilino)ethanol 2*

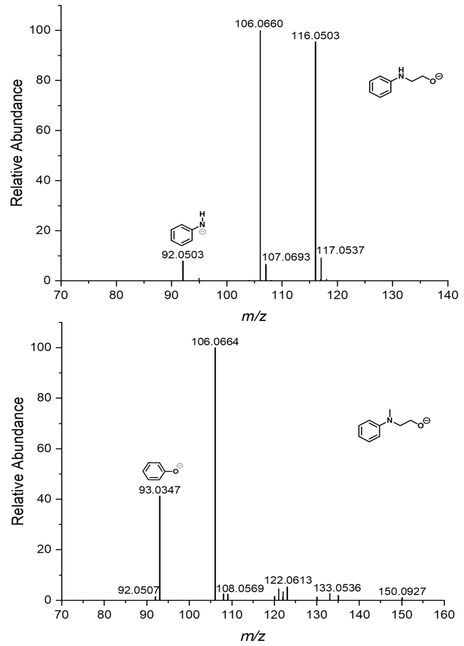


Figure 1. *a) Tandem mass spectrum of deprotonated 2-anilinoethanol 1 (ion trap, precursor m/z 136, top), b) Tandem mass spectrum of deprotonated 2-(N-methylanilino)ethanol 2 (ion trap, precursor m/z 150, bottom)*

2. *Tandem mass spectrum of deprotonated 2-(N-methylanilino)ethanol-^{18}O 2a*

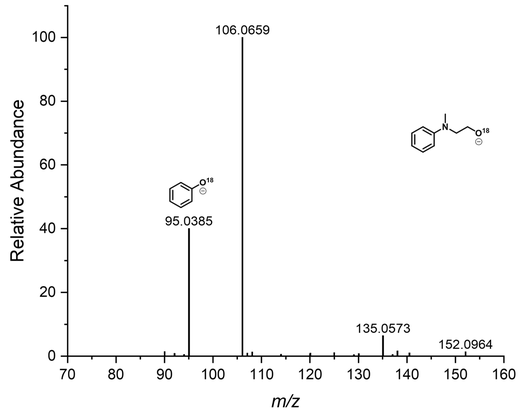
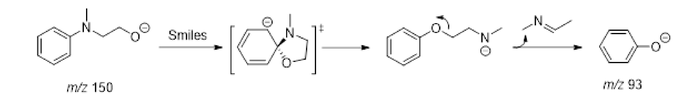


Figure 2. *Tandem mass spectrum of deprotonated 2-(N-methylanilino)ethanol-^{18}O 2a (ion trap, precursor m/z 152)*



Scheme 3. *Proposed nitrogen-oxygen Smiles rearrangement mechanism for the formation of the phenoxide ion at m/z 93.*

3. *Tandem mass spectrum of deprotonated 4-(4-morpholinyl)benzoic acid*

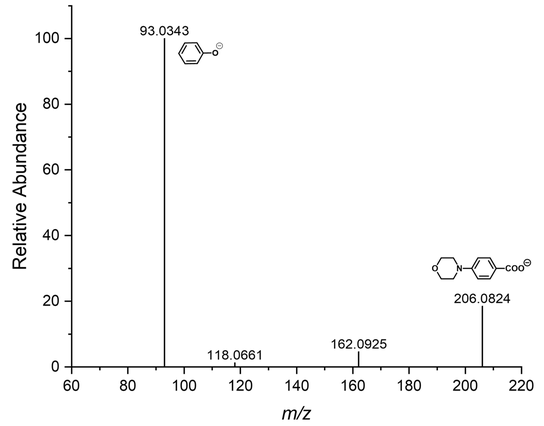
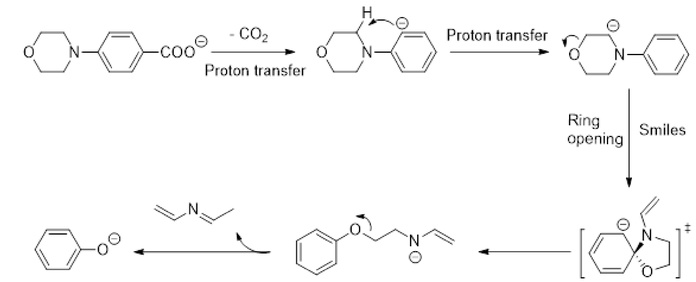


Figure 3. *Tandem mass spectrum of deprotonated 4-(4-morpholinyl)benzoic acid (HCD, NCE at 27, precursor m/z 206).*

4. *Proposed mechanism*



Scheme 4. *Proposed mechanism to rationalize the formation of the phenoxide ion and other product ions from deprotonated 4-(4-morpholinyl)benzoic acid.*

Summary

Novel Smiles-type mechanism was proposed for fragmentation of deprotonated 2-(N-methylanilino)ethanol and morpholinylbenzoic acid derivatives.

*Certain commercial instruments are identified in this document. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the products identified are necessarily the best available for the purpose.

Reference: [1] NIST MS/MS library (http://chemdata.nist.gov)