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The formation of resonance-stabilized sulfur-based radical cations and their gas-phase reactivity

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Dedicated to the 65th anniversary of Prof. Veronica M. Bierbaum in appreciation of her scientific and service contributions to the gas-phase ions community and mass spectrometry as a whole.

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ABSTRACT

Gas-phase reactivity of several sulfur-based radical cations with various volatile neutrals was studied in a modified quadrupole ion trap mass spectrometer. The radical cations were formed by two methods. The first method (introduced by Siu and co-workers) involved electron transfer from the sulfur-containing ligand of interest (all with a C═S double bond) to Cu^{2+} ion in a ternary complex upon collision-induced dissociation. The second method utilized aromatic/heterocyclic thiol compounds which upon oxidation formed disulfides. Collision-induced dissociation of protonated disulfides lead to homolytic cleavage of S—S bond (often among other products). The radical cations produced by these two methods displayed very similar reactivity toward the five neutrals used in this study. This was explained by the resonance stabilization of these species within the N—C—S motif leading to similar structures. Density functional theory calculations showed that in all of these systems independent of the method of production most of the spin density resided on the sulfur atom and the C—S bond held a partially double character.

1. Introduction

Gas-phase chemistry of radical ions has attracted considerable interest of the mass spectrometry community for decades. From the discovery of electron impact (EI) [1] ionization which produces odd-electron molecular ions to the modern peptide/protein fragmentation techniques like electron capture dissociation (ECD) [2] and electron transfer dissociation (ETD) [3] – chemistry of radical ions keeps offering complementary information and sometimes advantages over the even-electron processes.

Recent advances have been especially noticeable in the analysis of biological molecules. However, exciting findings have been reported in many other areas of gas-phase free radical chemistry, including contributions of Bierbaum's group to understanding of interstellar processes [4–7], as well as works of Kenttämaa and co-workers on chemistry of various phenyl radicals [8–11].

Among the plethora of radical ions, sulfur-based radicals play an especially important role. In the protein systems, radicals often reside on the side chains of methionine and cysteine, and disulfide bridges participate in radical chemistry as well [12]. Cysteine thiyl ($RS^{\bullet}$) radical oxidation can lead to sulfinyl ($RSO^{\bullet}$) [13] and sulfonyl ($RSO_2^{\bullet}$) radicals [14]. The general stability of sulfur-based radicals has led to multiple studies of their properties in small organic systems [15–17].

One of the most straightforward ways to generate radical cations in the gas phase was developed by Siu and coworkers [18,19] and has been applied extensively to the creation of radical cations of amino acids [20] and peptides [21,22], including methionine- and disulfide-based radicals [23,24]. In this method, an analyte molecule is complexed with a RedOx-active metal ion and an auxiliary ligand, subsequent CID of the ternary complex often results in the electron transfer from the analyte M (see Eq. (1) for example).

$$[Cu^{II}(terpy)(M)]^{2+} \rightarrow [Cu^{I}(terpy)]^{+} + M^{\bullet+} \quad (1)$$

This technique has also been applied toward the creation of gas-phase radical cations from nucleic acids [25] and amino acids. Numerous multidentate ligands have been evaluated for suitability in such experiments [26–28], including triamines, terpyridines,

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crown ethers, and their derivatives. Most experiments have used divalent copper as the metal in these ternary complexes, but other metal ions have also been tried [26,29].

In this work, we employ Siu's method to create radical cations from six organic compounds containing C=S bonds: thioacetanilide, thioacetamide, thiourea, 2-thiouracil, 2-thiocytosine, and 6-thioguanine (compounds **1**–**6** in Scheme 1).

One of the radical cations formed in our study is from the analyte 2-thiouracil, which in addition to being a known anticancer and antithyroid agent, is also a naturally occurring component of transfer RNA [30,31]. Evidence exists that DNA damage by UV radiation, which is believed to involve free radicals, is significantly increased in the presence of 2-thiouracil [32]. Many works have investigated the damage that free radicals can cause to nucleic acids [33–36], including strand breakage, alteration of bases, formation of adducts, and ultimately mutation of the sequence of bases or apoptosis of the affected cell [37]. Several studies have sought to investigate the properties of 2-thiouracil in its neutral, ionic, and radical forms [31,38–42], most of a theoretical nature. Thus, our studies on generation and intrinsic reactivity of 2-thiouracil can contribute to the limited experimental body of knowledge.

Another technique that has been utilized to create gas-phase sulfur-based radicals from cysteine derivatives/peptides and some other thiol-containing molecules involves thiol nitrosylation followed by homolytic cleavage of the labile S—NO bond [43–47]. Not all thiols, however, undergo easy nitrosylation. In our previous study we found that, for instance, some aromatic thiols, like 2-mercaptopyridine, fall into that category. While trying to nitrosylate 2-mercaptopyridine, we found that it only oxidized into the corresponding disulfide (Eq. (2)) [48]. Similar results were obtained by us previously during nitrosylation of peptides containing two cysteine residues [49].

$$2RSH \rightarrow RSSR + 2H^+ + 2e^- \quad (2)$$

Homolytic cleavage of disulfides can be achieved by electron capture dissociation, where radical fragmentation at disulfide linkages is one of the dominating processes [50]. Another way of radical splitting of disulfides was reported by Xia et al., who used oxidative cleavage by hydroxyl radicals (formed in a low-temperature plasma source) to produce sulfinyl radical ions. [51,52] (Eq. (3)):

$$RSSR' + {}^{\bullet}OH \rightarrow RSO^{\bullet} + R'SH \quad (3)$$

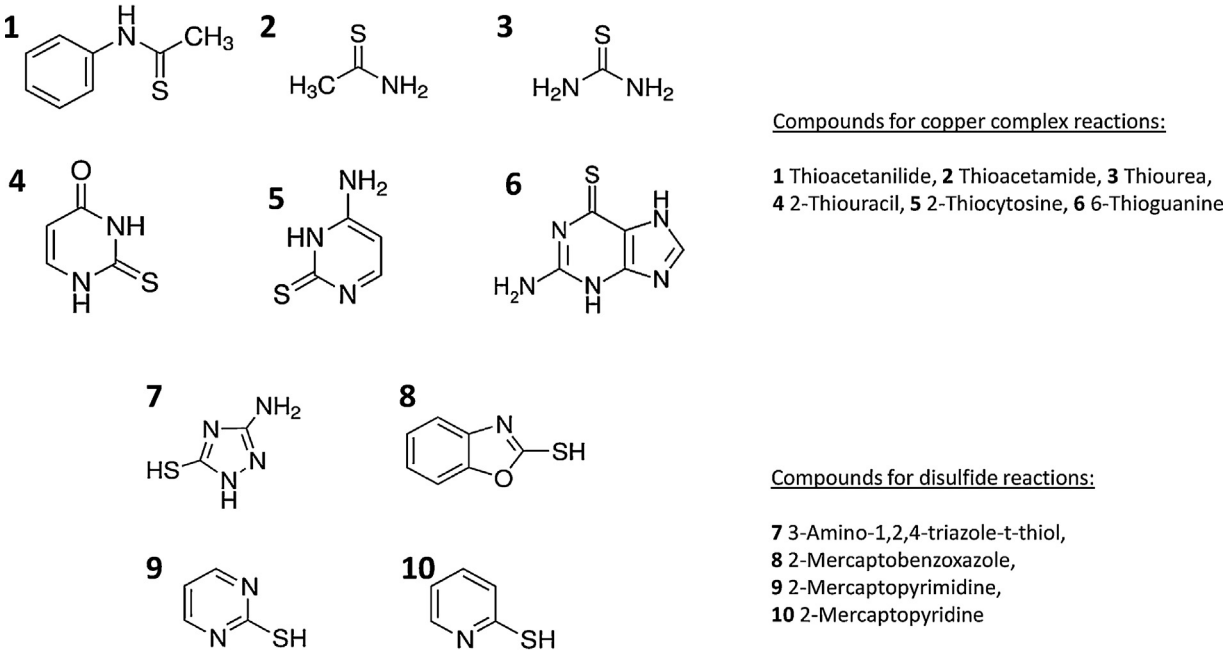
CID of S—S bonds in peptides does not succeed in generating sulfur-based radicals because other lower-energy fragmentation channels are available. There are, however, several studies that have reported the effects of using CID to cleave the disulfide bonds in positively [53,54] and negatively charged peptides [55,56]. The use of metals and metal complexes to serve as disulfide cleavage agents during CID fragmentation has also been investigated [57–60]. In none of these experiments did the CID cleavage products include sulfur-based radical ions.

It would be advantageous to identify the types of compounds that could produce sulfur-based radicals via homolytic cleavage of the S—S bond upon CID of the protonated disulfide formed via ESI (Eq. (4)):

$$R(H)SSR^+ \rightarrow R(H)S^{\bullet+} + RS^{\bullet} \quad (4)$$

Thus, we explore a set of aromatic heterocyclic disulfides in which the cleavage of the S—S bond is likely to be one of the lower-energy fragmentation pathway. These disulfides were created through the oxidative dimerization of four different thiols: 3-amino-1,2,4-triazole-t-thiol, 2-mercaptobenzoxazole, 2-mercaptoppyrimidine, 2-mercaptopyridine, and 2-mercaptothiazoline (compounds **7–11** in Scheme 1) via Eq. (2).

In addition to the evaluation of the two methods (Eqs. (1) and (4)) for the production of sulfur-based radical cations, we explore their gas-phase reactivity toward several volatile neutrals: allyl bromide, allyl iodide, dimethyl disulfide, tert-butyl isocyanide, and 1-propanethiol. These neutrals have often been used as reactive species to characterize sulfur-based radicals in the gas phase [61,62].



Scheme 1. Neutral structures of compounds used to form radical cations through both copper-complex reactions and disulfide reactions.