



Gas-phase Smiles rearrangement in structural analysis of a pseudo-oxidative impurity generated in the pharmaceutical synthesis of S-(thiobenzoyl)thioglycolic acid

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ABSTRACT

Several mass spectrometry (MS) techniques including accurate MS and MS/MS, as well as hydrogen/deuterium (H/D) exchange, were utilized to characterize a pseudo-oxidative reaction by-product (impurity **I**) in the pharmaceutical synthesis of S-(thiobenzoyl)thioglycolic acid. The negative ion MS/MS data provided complementary structural information to the positive ion MS/MS data. An understanding of the gas-phase Smiles rearrangement upon collision-induced dissociation (CID) in the negative ion MS/MS mode played an important role in structural elucidation of impurity **I**. The theoretical calculations by density functional theory (DFT) at the B3LYP/6-311G(d,p) level provided insights into the thermochemistry of the Smiles rearrangement reaction. This pseudo-oxidative impurity is proposed to be generated via the base-catalyzed hydrolysis in solution.

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1. Introduction

The Smiles rearrangement is the classical example of an aromatic *ipso* nucleophilic substitution reaction that occurs in the condensed phase [1]. It occurs through a base-catalyzed rearrangement mechanism via the formation of a Meisenheimer complex [2–4]. The Smiles rearrangement has been widely employed in the organic synthesis of olefins [5], aminobenzofuran [6], and heterocyclic compounds including pyridine derivatives [7–10], where S–N or O–N replacements most commonly occur via the transition state of a five-membered ring. Recently, Zard and co-workers reported an unusual radical Smiles rearrangement which proceeds by the C–N radical replacement through a four-membered ring [11]. In solution, the nucleophilic reaction that causes the Smiles rearrangement normally requires an activating electron-withdrawing group (e.g. Z = nitro, sulphonyl, or halogen) in either the *ortho* or *para* positions of the phenyl ring with a good leaving group X and a strong nucleophile Y (illustrated by Scheme 1) [12].

In the gas-phase, however, the Smiles rearrangement can also occur upon collisional activation even without the requirement of an additional electron withdrawing substituent on the phenyl ring [13]. For example, in the negative ion mode mass spectrometry (MS), deprotonated 2-(4,6-dimethoxypyrimidin-2-

ylsulfanyl)-N-phenylbenzamide and phenoxy-N-phenylacetamide derivatives undergo the gas-phase S–N type and S–O type Smiles rearrangements upon collision-induced dissociation (CID) [14,15]. In addition, in the positive ion mode MS, protonated 2-pyrimidinyl-N-arylbenzyl amine derivatives were also observed to proceed via the gas-phase O–N type Smiles rearrangement [16]. Furthermore, protonated 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine [17] and the *p*-aminophenylsulfonyl cation [18] undergo the Smiles rearrangements to give rise to the product ions resulting from the gas-phase sulfonyl–sulfinate conversion. Similar to that in the solution phase, the gas-phase Smiles rearrangement has been shown to favorably undergo *ipso* nucleophilic substitution reactions based on the isotope-labeling experiment [13] and theoretical calculations [19].

S-(thiobenzoyl)thioglycolic acid is a useful thiobenzoylating agent [20] and has been utilized in synthesis of biological diorganotin dithioate derivatives [21]. It serves as an important reversible addition–fragmentation chain transfer polymerization agent [22,23]. S-(thiobenzoyl)thioglycolic acid is also an important starting material in the synthetic route for elesclomol, a small-molecule oxidative stress inducer being investigated for the treatment of metastatic melanoma and other cancers [24]. Herein we present the application of the gas-phase Smiles rearrangement in the structural analysis of a pseudo-oxidative impurity generated in the pharmaceutical synthesis of S-(thiobenzoyl)thioglycolic acid (Scheme 2) [25].

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Scheme 1. Classical example of the Smiles rearrangement in the condensed phase.

2. Experimental

2.1. Chemicals

Authentic samples of S-(thiobenzoyl)thioglycolic acid and (benzoylthio)acetic acid were obtained from Synta Pharmaceuticals Corporation (Lexington, Massachusetts, USA).

2.2. LC-UV DAD analysis

Samples were separated on an Agilent 1100 HPLC system (Agilent Technologies, Willington, DE, USA). Reversed-phase chromatographic separation was achieved using an Agilent Zorbax SB-C18 column (150 mm × 4.6 mm, 5 μm particle size) with mobile phase A of 0.1% formic acid (FA) in water and mobile phase B of 0.1% FA in acetonitrile. The column temperature was kept at 35 °C. The mobile phase composition was kept at 15% B for 10 min then was linearly ramped to 70% B over 20 min with a flow rate of 1.5 ml/min. The UV detection was performed using an Agilent 1100 diode-array detector (DAD) in the wavelength range of 190–400 nm with the interval and peak width of 1 nm and 0.1 min, respectively. For the hydrogen/deuterium (H/D) exchange experiments, D₂O was substituted for H₂O in mobile phase A [26].

2.3. Accurate mass, MS/MS and MS/MS/MS analysis

The exact mass measurements and MS/MS experiments were performed on a Q-TOF Premier quadrupole orthogonal acceleration time-of-flight mass spectrometer with LockSpray™ controlled by MassLynx 4.1 software (Waters Corporation, Manchester, UK). The electrospray ionization (ESI) source was operated in the positive ion mode (with a spray voltage of –3.5 kV) or the negative ion mode (with a spray voltage of +2.5 kV), source and desolvation gas temperatures of 120 and 300 °C, an argon collision gas flow rate of 0.45 ml/min in the T-Wave™ guide Mark II collision cell, a collision energy of 20 eV for the CID experiments, a desolva-

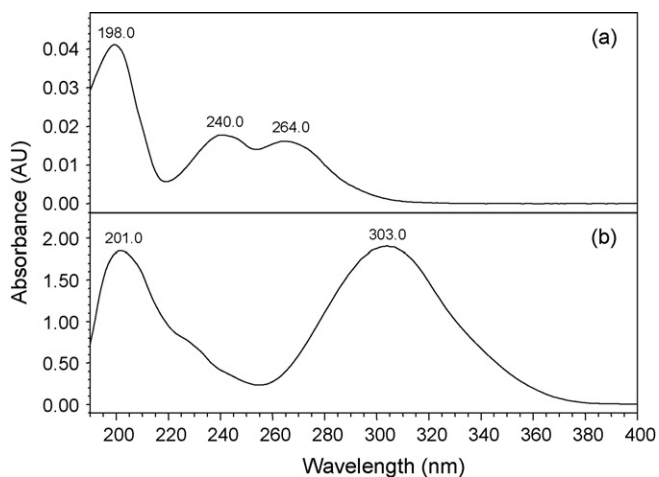
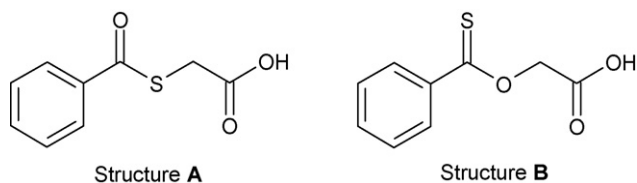


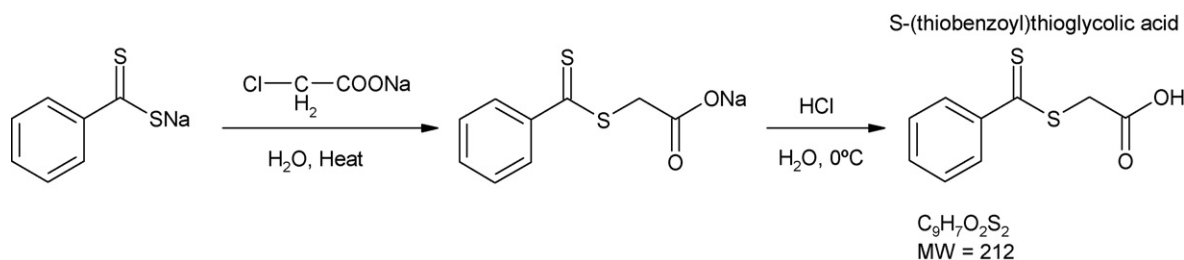
Fig. 1. LC-UV DAD spectra of (a) impurity I and (b) S-(thiobenzoyl)thioglycolic acid.



Scheme 3. Two possible structures A and B proposed for impurity I.

tion gas flow rate of 600 l/min, and a sample cone voltage of 30 V. The Lockspray™ was operated under identical conditions except with a flow rate of 3 μl/min for infusion of leucine-enkephalin (Leu-Enk). The Q-TOF was calibrated with sodium formate solution at a concentration of 0.01 mg/ml. All masses were corrected by the internal reference ions of *m/z* 556.2771 (protonated Leu-Enk) and 554.2615 (deprotonated Leu-Enk) that were introduced by the Lockspray™ in the positive and negative ion modes, respectively.

The MS/MS/MS experiment was performed on a linear ion trap LTQ mass spectrometer controlled by Xcalibur 1.4 software (Thermo Electron, San Jose, CA, USA). The ESI source was operated



Scheme 2. Chemical reaction for the synthesis of S-(thiobenzoyl)thioglycolic acid.

Table 1

Exact mass measurements of the protonated and deprotonated molecule of impurity I in S-(thiobenzoyl)thioglycolic acid.

Ionization mode	Precursor ion	Elemental composition	Theoretical mass	Experimental mass	Delta (ppm)
Positive ^a	[M+H] ⁺ Protonated	C ₉ H ₉ O ₃ S	197.0272	197.0278	3.0
Negative ^b	[M-H] ⁻ Deprotonated	C ₉ H ₇ O ₃ S	195.0116	195.0109	-3.6

^a Using protonated Leu-Enk of *m/z* 556.2771 as the lock mass.

^b Using deprotonated Leu-Enk of *m/z* 554.2615 as the lock mass.

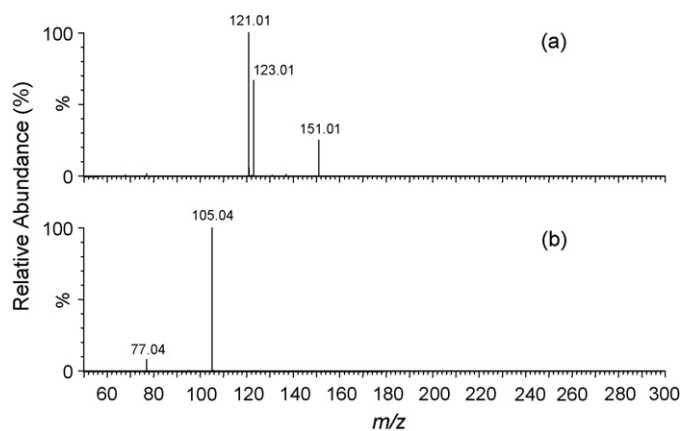


Fig. 2. MS/MS spectra of (a) $[M-H]^-$ of m/z 195 in the negative ion mode and (b) $([M+H]^+$ of m/z 197 in the positive ion mode.

in the positive ion mode under the following conditions: spray voltage, -4.0 kV; heated capillary temperature, 300°C ; capillary voltage, 30 V; tube lens offset voltage, 30 V; sheath gas (nitrogen) flow rate, 30 arbitrary units. In the full-scan MS/MS/MS mode, the precursor ion of interest was isolated by applying multiple frequency waveforms to remove undesired ions through broadband excitation. The isolated ions were then subjected to a supplementary AC potential for resonant excitation to cause collision-induced dissociation (CID). The Mathieu q_z values chosen for resonance excitation and ejection were 0.25 and 0.88 , respectively. The activation time used was 30 ms with helium as the collision gas. The nor-

malized activation energy was set to 25% of 0 – 5 V peak-to-peak potential.

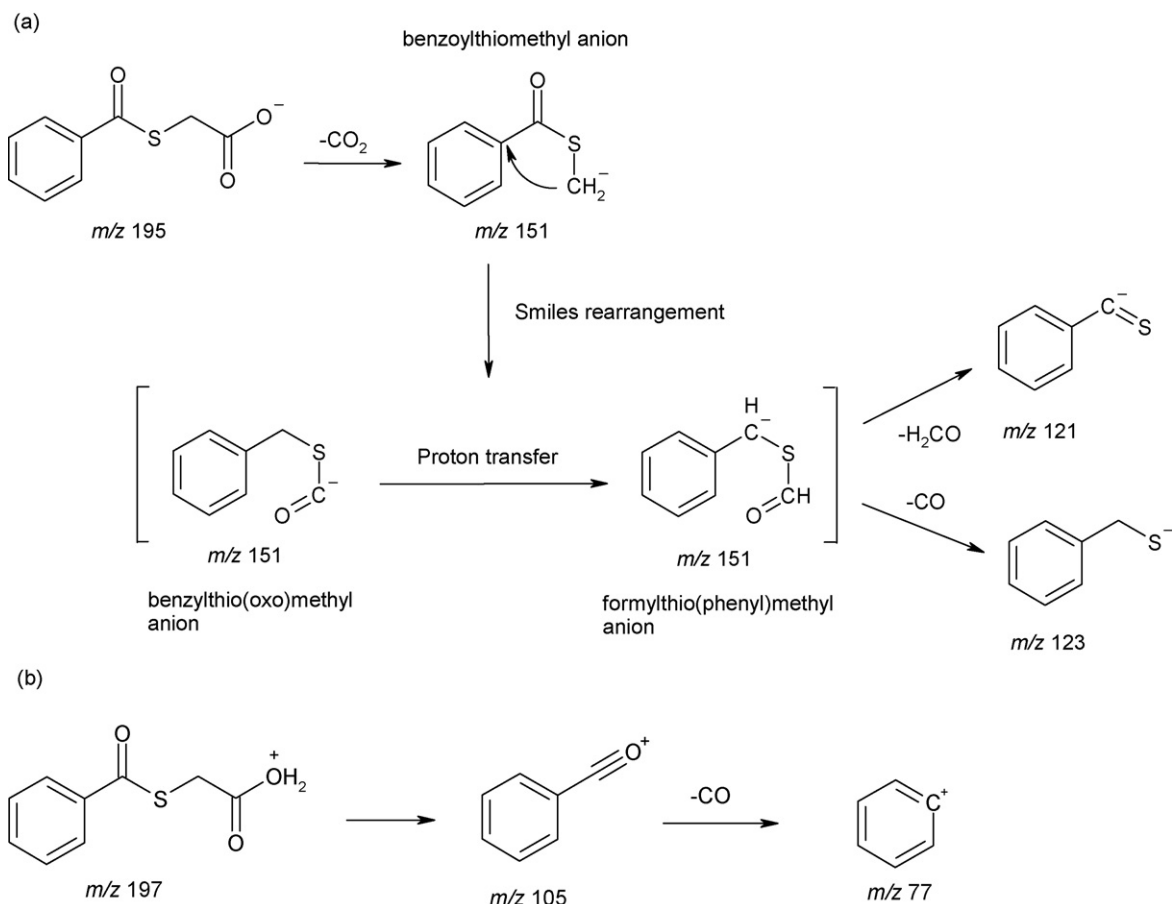
2.4. Theoretical calculations

Theoretical calculations were performed using density functional theory (DFT) and Becke's three-parameter hybrid functional with the Lee, Yang and Parr correlation (B3LYP) [27]. All geometry optimizations including a frequency calculation were calculated at the B3LYP/6-311G(d,p) level of theory, to verify that a local energy minimum have been located. The transition state of the Smiles rearrangement was calculated using the Synchronous Transit-Guided Quasi-Newton (STQN) method with the optimized reactant and product structures, and an initial transition state structure, supplied as the input [28]. UV-vis spectra were predicted using time-dependent DFT (TDDFT) [29–31], also using the B3LYP/6-311G(d,p) level of theory. A total of 64 states were predicted, including singlet and triplet excitations, and a Gaussian smearing function of 0.333 eV (half-width at half-height) was applied to produce the theoretical spectra. The Gaussian 03 program (revision D.02) [32] running on a Microsoft Windows Intel Xeon workstation and a LINUX-based IBM e1350 Blade Center cluster was used for all calculations.

3. Results and discussion

3.1. LC-UV DAD spectra of impurity I in *S*-(thiobenzoyl)thioglycolic acid

LC-UV DAD analysis of *S*-(thiobenzoyl)thioglycolic acid identified an impurity (labeled as I) at about 0.1% level (by the



Scheme 4. Fragmentation pathways of (a) $[M-H]^-$ of m/z 195 in the negative ion mode and (b) $([M+H]^+$ of m/z 197 in the positive ion mode.

response in peak area at 220 nm) eluting at a relative retention time (RRT) 0.82. Fig. 1 compares the UV DAD spectra of impurity **I** (Fig. 1(a)) and S-(thiobenzoyl)thioglycolic acid (Fig. 1(b)). S-(thiobenzoyl)thioglycolic acid shows a strong UV absorbance maximum at 303 nm which results from the conjugation of thione (C=S) with the phenyl ring. However, impurity **I** gave a different UV absorbance profile displaying two UV absorbance maxima at 240 and 264 nm, respectively. The hypsochromic shift of the UV absorbance for impurity **I** indicates a perturbation or disturbance of the conjugated system in S-(thiobenzoyl)thioglycolic acid.

3.2. Accurate mass measurements of the oxidative impurity

LC-MS analysis showed that impurity **I** has molecular weight (MW) 196, which is 16 Da mass units less than that of S-(thiobenzoyl)thioglycolic acid (C₉H₇O₂S₂, MW 212). As tabulated in Table 1, the accurate mass measurements of the protonated molecule (in the positive ion mode) and the deprotonated molecule (in the negative ion mode) are *m/z* 197.0278 and 195.0109, respectively. Together with the criteria of the isotope fitting, the accurate mass measurements strongly suggested that the neutral molecule of impurity **I** would have the molecular formula C₉H₈O₃S, given the accuracy of the mass measurements to within 3.6 ppm in both ionization modes. This confirms that 16 Da difference is due to the S–O replacement from S-(thiobenzoyl)thioglycolic acid. In the H/D exchange experiments, [M–H][−] of *m/z* 195 and [M+H]⁺ of *m/z* 197 became *m/z* 195 and 199, respectively. This suggests that impurity **I** has one exchangeable proton. Based on the structure of S-(thiobenzoyl)thioglycolic acid, two possible structures **A** and **B** (Scheme 3) were initially proposed and subjected to further investigation by MS/MS analysis and UV spectroscopy.

3.3. Structural characterization of the pseudo-oxidative impurity by tandem mass spectrometry and UV spectroscopy

In the negative ion MS/MS mode of [M–H][−], the major loss of 44 Da (CO₂) and further losses of 28 Da (CO) and 30 Da (HCHO) (Fig. 2(a)) were observed and confirmed by the accurate mass measurements (to within 5.6 ppm). Between the two possible structures in Scheme 3, structure **B** is easy to fit the rationale of the further loss of CO in the negative MS/MS spectrum. However, structure **B** did not easily fit the MS/MS of [M+H]⁺ obtained in the positive ion mode, e.g. predominantly forming the product ion of *m/z* 105 (Fig. 2(b)), which is typically the benzylideneoxonium ion resulting from structure **A**.

By re-examination of the MS/MS spectrum in the negative ion mode (Fig. 2(a)), it was postulated that the benzoylthiomethyl anion (the fragment ion of *m/z* 151) should undergo the Smiles rearrangement followed by the rapid proton transfer to give rise to formylthio(phenyl)methyl anion. The formylthio(phenyl)methyl anion undergoes further fragmentation to yield the ions of *m/z* 123 and *m/z* 121 via the losses of CO and HCHO, respectively (illustrated in Scheme 4(a)). The proposed fragmentation pathways in the negative ion MS/MS mode was supported by the MS/MS experiment of *m/z* 151 (the product ion from MS/MS of *m/z* 195) to give rise to the sub-product ions of *m/z* 123 and *m/z* 121 in the linear ion trap mass spectrometer (data not shown). Furthermore, in the positive ion MS/MS spectrum, the benzylideneoxonium ion of *m/z* 105 undergoes the loss of CO, leading to the formation of the ion of *m/z* 77 (Scheme 4(b)). Therefore, structure **A** rather than **B** best fits the observed MS/MS data.

The UV spectra of structures **A** and **B** can provide additional structural confirmation. As previously noted, empirical consideration of the structures suggests that structure **A** is most consistent

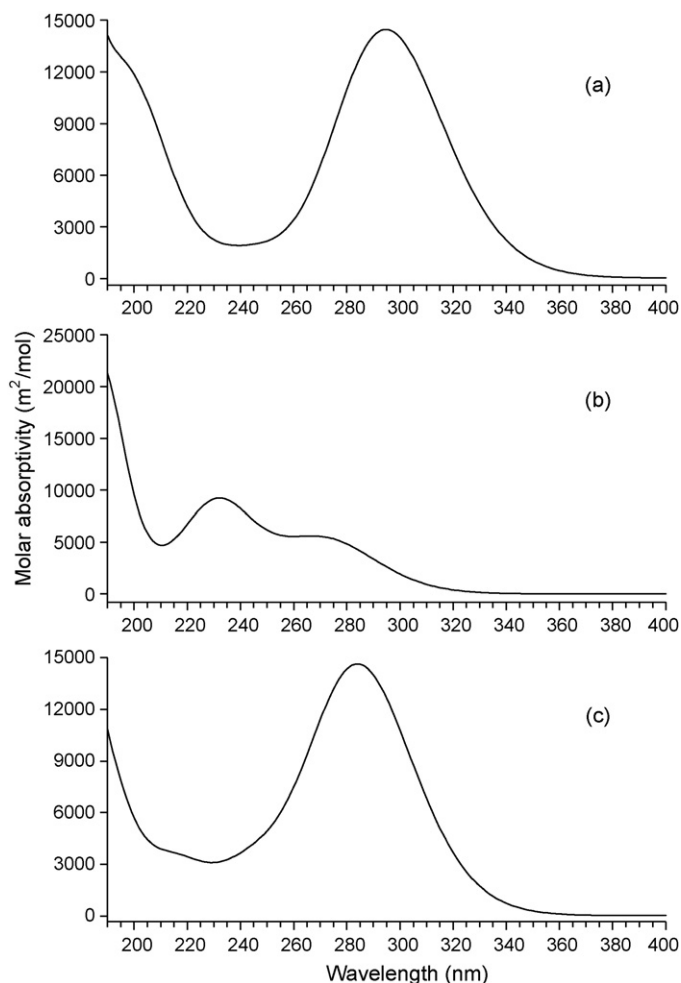


Fig. 3. Calculated TDDFT UV spectra for (a) S-(thiobenzoyl)thioglycolic acid, (b) structure **A**, and (c) structure **B**.

with the UV DAD spectrum of impurity **I**, because the changes in the UV spectrum relative to S-(thiobenzoyl)thioglycolic acid might be caused by the disturbance of the conjugation between the thione (C=S) moiety and the phenyl ring. This possibility was further studied using TDDFT calculations of the UV spectra of S-(thiobenzoyl)thioglycolic acid and structures **A** and **B** at the B3LYP/6-311G(d,p) level of theory. As seen in Fig. 3(a), the calculated spectrum of S-(thiobenzoyl)thioglycolic acid shows a λ_{max} of 295 nm and a shoulder at 200 nm, in agreement with the experi-

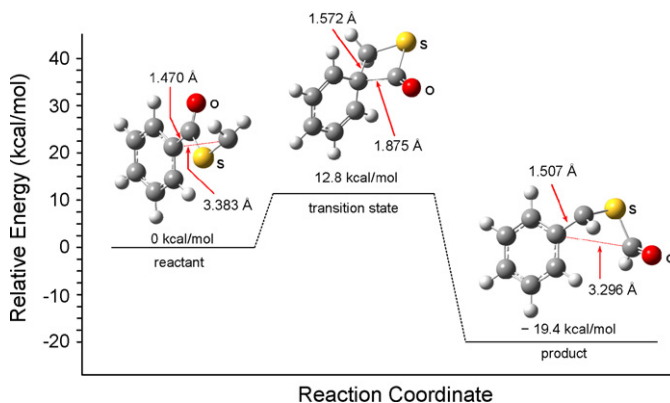
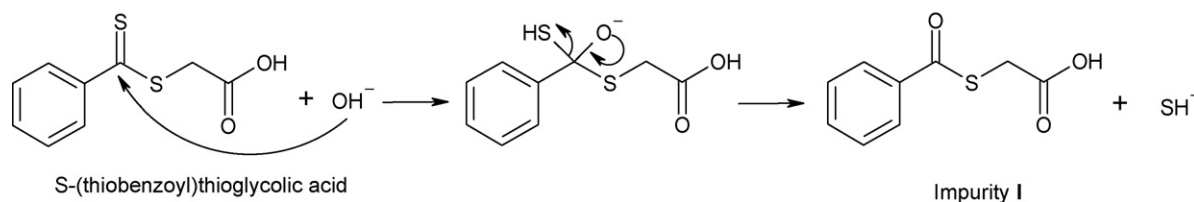


Fig. 4. Schematic potential energy surface for the Smiles rearrangement reaction of the benzoylthiomethyl anion of *m/z* 151.



Scheme 5. Proposed mechanism for the formation of impurity I under basic conditions.

mental spectrum in Fig. 1(b). This helps to verify that the chosen level of theory is adequate for the prediction of the UV spectra for structures **A** and **B**. The calculated spectrum of structure **A**, shown in Fig. 3(b), results in two peaks with λ_{max} of 232 and 267 nm. These peaks are within 8 and 3 nm respectively of the observed λ_{max} values in the experimental spectrum of impurity **I**, shown in Fig. 1(a); this agreement helps to confirm structure **A** as the identity of impurity **I**. In contrast, the calculated spectrum of structure **B** in Fig. 3(c) is clearly not in agreement with the experimental spectrum of impurity **I**. It should be noted that both S-(thiobenzoyl)thioglycolic acid and structure **B** showed additional electronic transitions between 420 and 480 nm, while structure **A** did not; the use of this visible-wavelength transition is not explored further here, but is in general agreement with the observed pink color of S-(thiobenzoyl)thioglycolic acid solutions.

In order to fully confirm that the impurity possesses structure **A**, an authentic sample of (benzoylthio)acetic acid was synthesized to repeat the LC-UV analysis (including the spiking experiment) and LC-MS/MS analysis. It was found that (benzoylthio)acetic acid exhibits the same retention time and MS/MS fragmentation pathways in both positive ion and negative ion modes; thus confirming the proposed structure of impurity **I**.

3.4. Theoretical calculation of the Smiles rearrangement reaction

DFT calculations at the B3LYP/6-311G(d,p) level of theory were performed to better understand the transition state and reaction intermediate as well as their relative energies in the Smiles rearrangement reaction. The DFT calculation for the benzylthio(oxo)methyl anion gives a bond-breaking ion-neutral complex, implying that this product ion (benzylthio(oxo)methyl anion) of m/z 151, which directly results from the Smiles rearrangement, is not sufficiently stable to survive. The detection of the ion of m/z 151, as illustrated in Scheme 4(a), is believed to be the proton-transfer product of the formylthio(phenyl)methyl anion from the benzylthio(oxo)methyl anion. The transition state for the Smiles rearrangement was calculated based on the optimized structures of the benzoylthiomethyl anion and the formylthio(phenyl)methyl anion as the reactant and the product, respectively. Fig. 4 displays the schematic potential energy surface showing that the Smiles rearrangement reactant (the benzoylthiomethyl anion of m/z 151) must overcome an energy barrier of 12.8 kcal/mol to undergo the Smiles rearrangement reaction to yield thermodynamically favorable the benzylthio(oxo)methyl anion (with 19.4 kcal/mol lower than that of the benzoylthiomethyl anion). This is probably because, for the benzoylthiomethyl anion, the carbonyl group (C=O) is less efficiently able to delocalize the negative charge at $-\text{CH}_2^-$ through the phenyl ring. For the transition state, although the negative charge can be readily delocalized in the phenyl ring [18], this is believed to be compensated by the higher energy resulting from the expansion force of the four-membered ring. As for the formylthio(phenyl)methyl anion, in contrast, the negative charge at the alpha-carbon can be efficiently delocalized via the phenyl ring, resulting in the more stable Smiles rearrangement product.

3.5. Formation mechanism of the oxidative impurity I

During the stability study of S-(thiobenzoyl)thioglycolic acid at 40 °C/75% RH (relative humidity), no obvious increase of impurity **I** was observed for up to 3 months. However, in a forced degradation study of S-(thiobenzoyl)thioglycolic acid in 1.5 eq. of NaOH (0.1N) aqueous solution, a significant growth at a level of about 1% of impurity **I** was observed promptly. This strongly indicates that the formation of impurity **I** occurs via a base-mediated process. The proposed mechanism of the formation of impurity **I** is depicted in Scheme 5, involving an initial OH^- nucleophilic attack at the thione carbon of S-(thiobenzoyl)thioglycolic acid ($\text{S}_{\text{N}}2$ reaction) followed by the loss of HS^- . Based on this mechanism, a proper process control (e.g. by controlling the rate of adding sodium (chloro)acetate salt) could be successfully designed and implemented to minimize the formation of impurity **I**.

4. Conclusions

The pseudo-oxidative by-product in S-(thiobenzoyl)thioglycolic acid has been characterized by accurate MS and MS/MS as well as the H/D exchange experiments. The negative ion MS/MS data provides the complementary structural information to the positive ion MS/MS data. The understanding of the gas-phase Smiles rearrangement upon CID in the negative ion MS/MS mode allowed thorough data interpretation and hence played an important role in structural elucidation. As demonstrated in the present case, this information allowed the fragmentation patterns to be rationalized and, consequently, the structure of impurity **I** to be elucidated. In addition, LC-UV DAD and TDDFT calculations offered another dimension of structural information about this unknown impurity. The DFT calculations at the B3LYP/6-311G(d,p) level of theory show the energy profile and transition state of the thermodynamically favorable Smiles rearrangement reaction. Impurity **I** was confirmed using an authentic sample of (benzoylthio)acetic acid. This pseudo-oxidative impurity is proposed to be generated by an initial OH^- nucleophilic attack at the thione carbon followed by the loss of HS^- , accounting for the major process impurity observed under basic conditions. Unambiguous structural identification of impurity **I** provided useful information for designing proper procedures to minimize its formation.

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