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Elucidating H/D-Exchange Mechanism of Active Hydrogen in Aniline and Benzene-1,2-dithiol

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Abstract : In this study, the hydrogen/deuterium (HDX) exchange mechanism of active hydrogen, nitrogen, and sulfur-containing polycyclic aromatic hydrocarbon (PAH) dissolved in toluene and deuterated methanol by atmospheric pressure photoionization (APPI) is investigated. The comparison of the data obtained using APPI suggests that aniline and benzene-1,2-dithiol contain two exchanging hydrogens. The APPI HDX that best explains the experimental findings was investigated with the use of quantum mechanical calculations. The HDX mechanism is composed of a two-step reaction: in the first step, analyte radical ion gets deuterated, and in the second step, the hydrogen transfer occurs from deuterated analyte to de-deuterated methanol to complete the exchange reaction. The suggested mechanism provides fundamentals for the HDX technique that is important for structural identification with mass spectrometry. This paper is dedicated to Professor Seung Koo Shin for his outstanding contributions in chemistry and mass spectrometry.

Keywords : atmospheric pressure photoionization (APPI), hydrogen/deuterium exchange (HDX), potential energy surface, quantum mechanical calculation.

Introduction

In the early stages of the development of mass spectrometry (MS), hydrogen/deuterium exchange (HDX) mechanism has proved to be one of the efficient methods used in mass spectrometric studies to determine the number of acidic hydrogens in a molecule.[1-6] In the recent years, HDX results obtained from high-resolution MS have been assisting in the elucidation of complex molecular structures.[7-13] Thus, it is very important to study the HDX mechanism in order to contribute extensively in the analyses of complex molecular structures.

There have been some experimental studies on the HDX mechanism of organic compounds. HDX with electron rich carbanions groups through the interaction of deuterated reagents occurs in gas phase.[14-16] It has been also reported that at first the analyte and deuterated reagent form intermediate complex and/or the analyte got deuterated and then HDX occurs.[17-19] The mechanism of HDX between arenium ions and D solvents was reported using ion cyclotron techniques. The HDX occurs through intramolecular proton transfer within the collision complex.[20] Using quadrupole collision cell, the HDX of enolate ions with CH_3OD and C_2H_5OD through the transfer of enolic hydrogen atom was demonstrated.[21] HDX reactions involving protonated aromatic species and D_2O through the exchange of ring hydrogen in a high-pressure mass spectrometer were reported by Martinsen and Buttrill.[22] Hunt et al. studied HDX reactions using correlation ion mobility spectrometry.[1] HDX of all ring H atoms by D atoms was observed when ring-protonated aromatic compounds and D-solvents were used.[23] The mechanism of intra- and intermolecular proton transfer in alkylbenzenes was also reviewed.[24]

Employing theoretical calculations, several research groups have extracted the information of HDX reaction mechanism. For example, in solution, HDX of biomolecules was

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This Article is dedicated to Professor Seung Koo Shin in commemorating his retirement and contribution to the Korean Society for Mass Spectrometry.

employed to understand the mechanisms of protein folding.[25,26] HDX of simple molecules directly in the gas phase has been used extensively to deduce reaction mechanism of complex molecules.[1,18,27] For the occurrence of HDX of aromatic compounds, two major criteria should be fulfilled according to the previous reports. One is ring protonation, which could lead to the HDX of the reagent ions in the ion source.[1] Another is ring deuteration, which can form deuterated reagent ions before HDX reaction takes place.[17] Beauchamp[17] et al. suggested that occurrence of a proton transfer reaction in the complex is the prerequisite for the mechanism of the isotope exchange reaction. According to Stone[28] and Ranasinghe et al.,[29] a complex is formed between the reagent ion bearing exchangeable H atom and the D solvent before HDX takes place. This phenomenon is related with the proton affinity difference between the reagent ion and the D solvent. Here, the transfer of the labile proton to D solvent forms an activated complex with the reagent ion after ring deuteration.[17] Then, the exchanged products are regenerated by dissociating the activated complex.

The formation of a strong H-bond between the reactant ion and the HDX reagent initiates HDX processes. The energetics of this process was shown by the potential energy surface (PES) by Jaroszewdki et al.[30] Hunt et al.[1] reported that the extent of HDX is dependent on the exothermicity of the ion-molecule reaction involved and increasing the endothermicity of the proton transfer reaction diminished the efficiency of HDX reactions. By applying this simple mechanistic picture, the HDX mechanism of a dimer containing a protonated amine and an oxygen or nitrogen donor base was also explained.[31] Thus, it could be useful to have some approach of the PESs for HDX with the model compounds in order to understand the mechanism.

Because of the complex structure of crude oil, it is difficult to unambiguously interpret HDX results. Therefore, to interpret them correctly, it is important to consider the compounds of crude oil with a deuterium donor, the structure of the reaction complex, and the mechanism of HDX. With the limited range of studies performed to date to address the earlier mentioned difficulty, very little is known about the mechanism and energetics of HDX processes for heteroatom compounds. This motivated us to investigate thoroughly the gas-phase HDX reactions of heteroatom compounds with deuterium agent.

In this study, we have undertaken a systematic HDX mechanism by combining atmospheric pressure photoionization (APPI)-HDX-MS technique and quantum mechanical calculations, focusing our attention on simple nitrogen and sulfur compounds. Experiments were performed to explore the possibility of HDX with CH_3OD according to the number of exchangeable hydrogen atoms at $–NH_2$ and –SH groups using APPI-HDX-MS system. Using theoretical calculations, we illustrated the dynamic pathways for HDX exchange between nitrogen/sulfur compounds and CH_3OD.

Experimental

Chemicals

All the standard compounds, HPLC-grade solvent toluene and deuterated methanol (CH_3OD) were purchased from J.T. Baker (Center Valley, PA, USA) and Sigma-Aldrich (St. Louis, MO, USA).

Sample preparation

The standard compounds were dissolved in toluene to prepare 1 mM stock solution. The HDX MS experiments were performed by diluting each stock solution with 10:90 (v/v) deuterated methanol-toluene solvent to a final concentration of 10 μM just before the MS analysis. The direct infusion of analyte solution was performed at 100 μL/min.

Mass spectrometry

Q Exactive quadrupole Orbitrap mass spectrometer (Thermo Fisher Scientific Inc., Rockford, IL, USA) equipped with APPI source was used to perform the HDX experiments of aniline and benzene-1,2-dithiol. A Harvard stainless steel syringe pump model 11 (Harvard, Holliston, MA, USA) was used to supply the solution of standard compounds aniline and benzene-1,2-dithiol to the APPI source.

The APPI source (+) conditions used in this study were as follows: tube lens radio frequency (RF) level, 20 Hz; tube lens voltage, 25 V; skimmer voltage, 15 V; C-Trap RF, 550 V; sweep gas flow, 0 (arbitrary units); sheath gas flow, 10 (arbitrary units); and auxiliary gas flow, 5 (arbitrary units). High-purity (99.99%) nitrogen was obtained by the evaporation of liquid nitrogen and used as the source gas. External positive calibration was performed by using Pierce LTQ Velos ESI Positive Ion Calibration Solution (Thermo Fisher Scientific Inc., Rockford, IL, USA) into the ESI source. The data acquisition parameters were as follows: m/z range, 50–750; maximum injection time, 60 ms; microscan, 1; automatic gain control (AGC), ON; and resolution, 140,000.

Computational details

The Gaussian 09 suite program[32] was used to optimize the stable geometry of compounds and their relative energies in gas phase and to explore the PES of the reaction systems with the Berny analytical gradient optimization method. Gradient-corrected density functional theory with the Becke three-parameter exchange functional[33] and the Lee–Yang–Parr correlation functional (B3LYP)[34] with an all-electron 6-311+G(df,2p) basis set was used to compute the reaction pathways. Each stationary point (minimum on the PES) was tested by a harmonic vibrational analysis. Transition state structures were verified by harmonic frequency analysis and by intrinsic reaction coordinate analysis for the reaction pathways.

Notation for exchanged peaks

In this study, the following notation is used to indicate the HDX ions: d_nMD^+ where d_n is number of HDXs (n = 0,1,2,3…), M is analyte and D^+ is deuterium ion.

Results and Discussion

Analysis of nitrogen and sulfur compounds by APPI-HDX-MS

Aromatic amine containing one $–NH_2$ and aromatic thiol containing two –SH groups were considered as model compounds in this study. The model compounds contain only one aromatic ring and their side chains do not contain other active sites except $–NH_2$ in nitrogen compound and –SH in sulfur compound that can exchange hydrogen(s) or participate in the formation of additional hydrogen bonds within the reaction complex.

Aniline and benzene-1,2-dithiol were analyzed by (+) APPI-HDX-MS. The studied compounds exchanged all labile hydrogens, but no significant exchange of aromatic ring hydrogen was observed, consistent with the previous results of HDX of nitrogen and sulfur compounds.[13,35] The mass spectra are shown in Figure 1. As shown in Figure 1a, aniline containing one $–NH_2$ group performed two exchanges. The two HDXs were confirmed by $d_2M^{+\cdot}$ and d_2MD^+ ions, where the d_2MD^+ ion was the most abundant. The exchange of two nonactive hydrogen atoms (d_3MD^+ and d_4MD^+) was also observed, but their abundance is very low compared to the exchange of active hydrogen atoms. In Figure 1b, benzene-1,2-dithiol containing two –SH groups performed two exchanges, denoted by $d_1M^{+\cdot}$ and $d_2M^{+\cdot}$. The nonactive hydrogens of benzene-1,2-dithiol did not take part in HDX reactions during APPI-MS analysis.

To assure the nonoccurrence of HDX of aromatic or nonactive hydrogens even at elevated temperatures, the corresponding mass spectra of aniline and benzene-1,2-dithiol were also collected at high capillary and vaporizer temperatures (refer to Figure 2). Figure 2a shows the influence of capillary temperature on the abundance of HDX ions. In the case of aniline, the abundance of HDX ions (d_3MD^+ and d_4MD^+) for nonactive hydrogen atoms did not improve further as the capillary temperature increases from 100 to 400°C. For benzene-1,2-dithiol, the only HDX of aromatic hydrogen was observed at the highest capillary having negligible abundance. Figure 2b shows the influence of vaporizer temperature (from 100 to 400°C) on the abundance of HDX ions of the analyzed compounds. It is also interesting to observe the differential behaviors of molecular and protonated ions of Aniline. These ions specially $d_2M^{+\cdot}$ and d_2MD^+ showed different trends upon increasing capillary and vaporizer temperatures. The intensity of $d_2M^{+\cdot}$ ions increases upto 300°C capillary

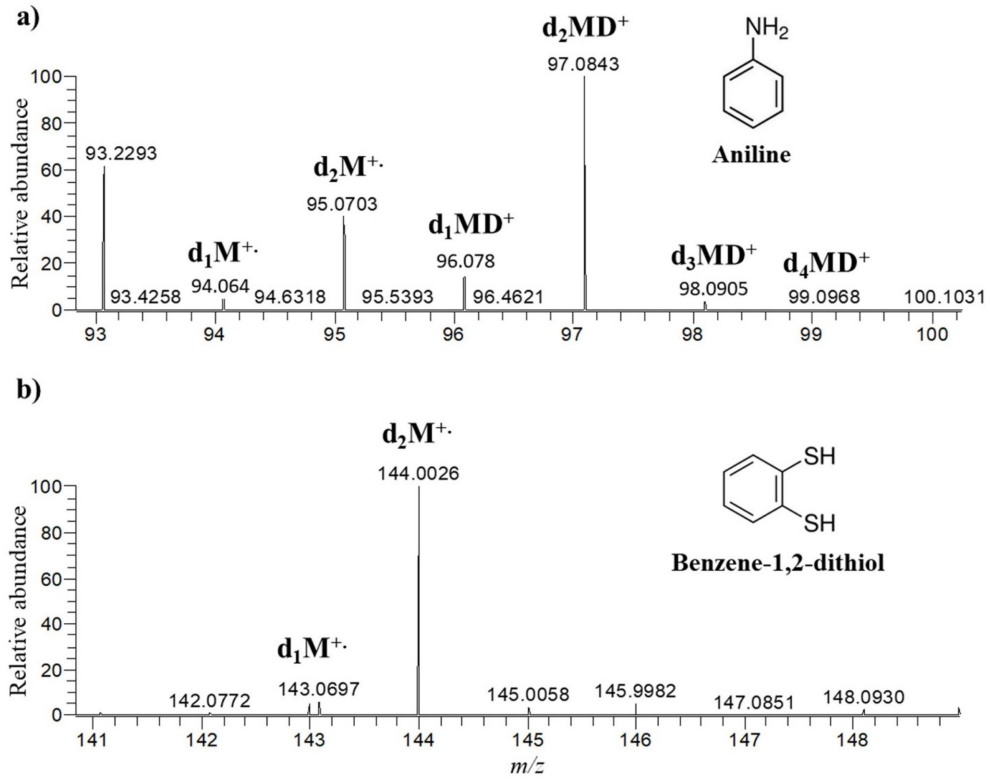

Figure 1. APPI-HDX mass spectra of (a) aniline and (b) benzene-1,2-dithiol.

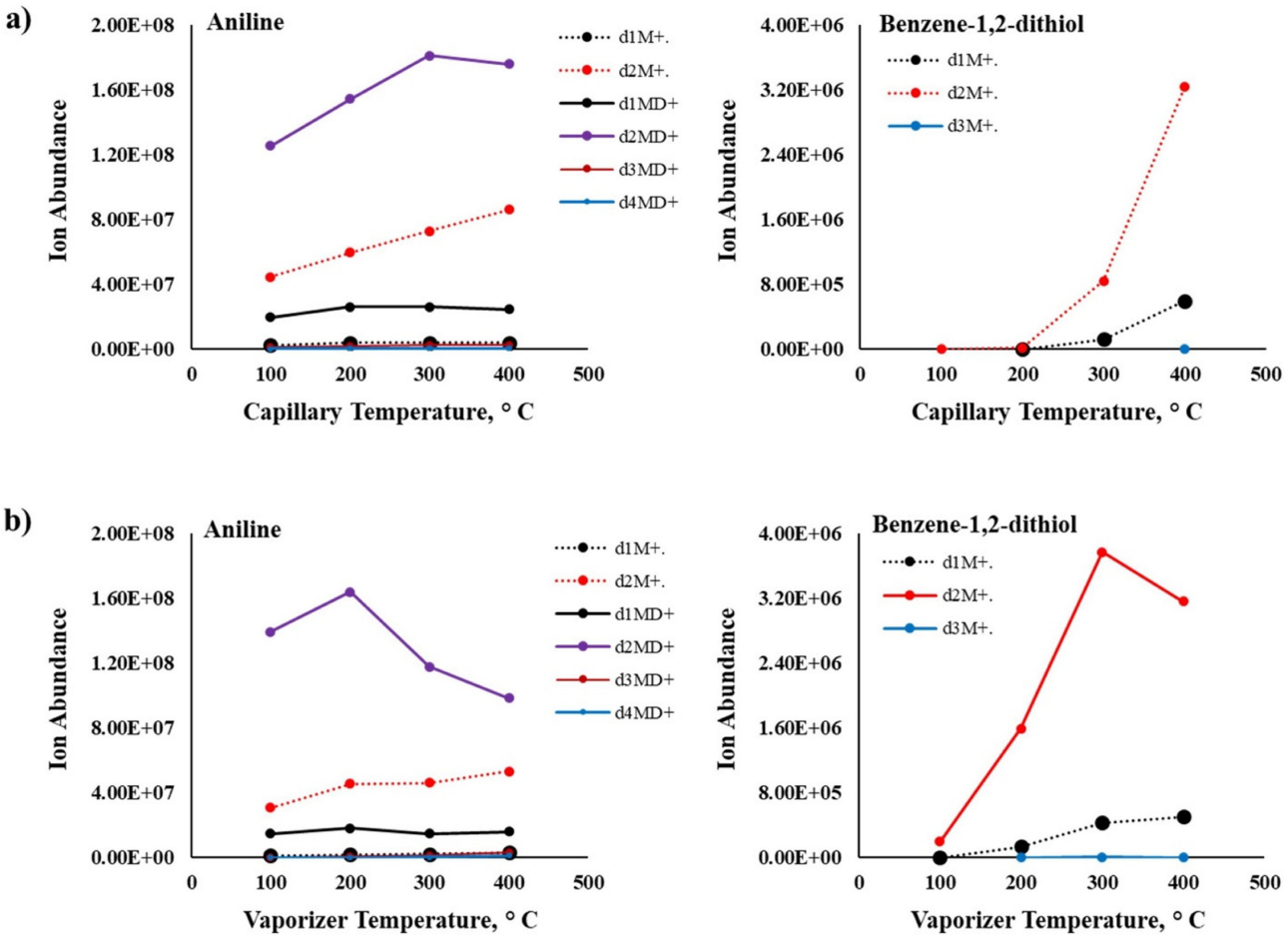

Figure 2. Influence of (a) capillary temperatures and (b) vaporizer temperatures on the abundance of HDX ions in APPI-HDX-MS.

temperature and then dropped. However, in case of vaporizer temperature, it increases upto 200°C and then dropped. The possible reason for that might be the vaporizer temperatures has relatively less impact on ions formation than capillary temperatures. It is also noticeable that the sum intensity of these two ions are greater at capillary temperatures than the vaporizer temperatures. Both aniline and benzene-1,2-dithiol showed insignificant HDXs of one or two aromatic hydrogens although the temperature was allowed to increase until 400°C.

From the APPI-HDX-MS analysis, it was confirmed that aniline and benzene-1,2-dithiol contain two exchanging hydrogens. In agreement with the previous results, the –NH_2 and –SH groups in the analyzed nitrogen and sulfur compounds are indeed the most reactive, thus causing the initial HDX to occur at the exchanging site.[36]

Proposed mechanistic considerations for HDX mechanism

The quantum mechanical calculations for HDX of aniline and benzene-1,2-dithiol were carried out in order to elucidate the exact HDX mechanism for the compounds analyzed by APPI-HDX-MS. The experimental results discussed in the previous section provide support for computing the reaction pathways for HDX of the analyzed compounds. Therefore, only HDX reactions on the exchangeable hydrogen atom-bearing functional groups (–NH_2/–SH) were considered in the theoretical calculations.

Two reaction mechanisms have been considered to find out the feasible HDX reaction mechanism for sulfur compounds. For easy understanding, an example for aniline is presented in the following equations:

$$[[C_6H_5NH_2] + [CH_3OD]]^{\bullet+} \rightarrow [[C_6H_5NHD]^{\cdots}[CH_3OH]]^{\bullet+}$$
(single-step reaction)

$$[[C_6H_5NH_2] + [CH_3OD]]^{\bullet+} \rightarrow [[C_6H_5NH_2{+}D]^{\cdots}[CH_3O]]^{\bullet+}$$
$$\rightarrow [[C_6H_5NHD] + [CH_3OH]]^{\bullet+}$$ (double-step reaction)

In single-step reaction, HDXs occur at the same time. However, for double-step reaction, at first step, the analyte ion gets deuterated and form intermediate complex, where the deuterium ion is supplied by CH_3OD. And in the

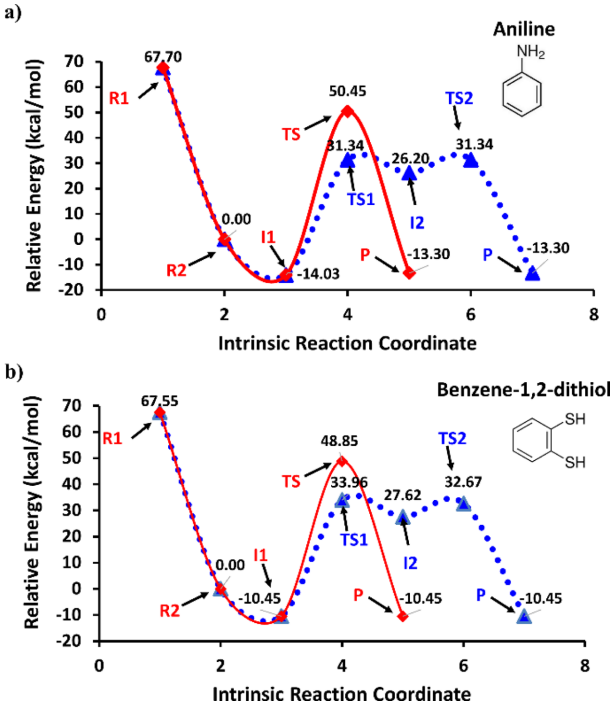

Figure 3. Proposed APPI-HDX mechanism for (a) aniline and (b) benzene-1,2-dithiol.

second or final step, the hydrogen transferred from deuterated analyte ion to de-deuterated methanol ion ($[CH_3O]^{\bullet+}$) to make the de-deuterated methanol ion to neutral methanol.

The simulated results for aniline and benzene-1,2-dithiol are presented in Figure 3a and Figure 3b, respectively, where R1 is the summed molecular energy of neutral analyte and CH_3OD radical ion, R2 is the energy of analyte radical ion plus neutral CH_3OD, and I1 represents the first intermediate, which is a bound structure of analyte and CH_3OD with positively charged radical. Optimized structures of Benzene-1,2-dithiol along with CH_3OD during HDX reaction obtained at the B3LYP/6-311+G** level were presented in the supporting information (Fig. 1S). For single-step reaction (straight line), TS is the hydrogen and deuterium transfer transition state and P is the final product (protonated analyte deuterium ion plus CH_3OH). However, for double-step reaction, TS1 is the deuterium transfer state to analyte from CH_3OD; I2 is the product intermediate, which is a bound structure of deuterated analyte ion and deprotonated $CH_3O\bullet$ ion; TS2 is the hydrogen transfer state to de-deuterated $CH_3O\bullet$ from protonated analyte ion; and P is the final product, the same as the single-step reaction.

According to the data presented in Figure 3a and Figure 3b, the single-step reaction (red line in both figures) required higher energy than the double-step reaction (dotted line). More specifically, single step reaction requires 19.11 and 14.89 kcal/mol more energy than the double-step reaction for aniline and benzene-1,2-dithiol, respectively. Therefore, double-step reaction is the preferable reaction path for HDX to occur.

In addition, the energetics of reactants, products, and stable intermediates were estimated in constructing these reaction coordinate diagrams. Since almost all nitrogen and sulfur containing PAHs compounds exhibit similar reactivity and participate in n number of HDX (n is number of hydrogen/deuterium exchanged), these mechanisms may apply for all nitrogen and sulfur containing PAHs compounds.

Conclusions

In this study, APPI-HDX experiments and quantum mechanical calculations were performed to illustrate the dynamic pathways for HDX between nitrogen/sulfur compounds and deuterated methanol. The experimental results assured that the HDX occurred at the $–NH_2$/–SH groups and that hydrogens bonded to nitrogen or sulfur atom can be counted by the HDX methodology. Also, the quantum mechanical calculations clearly showed that the APPI-HDX mechanisms are composed of a two-step reaction: first step, the radical ion of analyte gets deuterated, and second, the hydrogen transfer takes place to complete the exchange reaction from deuterated analyte to de-deuterated methanol. The mechanism described in this study can provide fundamental understanding of the HDX process that can be helpful for further development of the technique.

Supplementary Information

Supplementary information is available at https://docs.google.com/presentation/d/1RdLMaGtq4XpH0JgD62yIBrh6v-6ghi6a/edit?usp=sharing&ouid=111353140014732050956&rtpof=true&sd=true.

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Conflict of Interest

The authors declare that they have no competing interests.

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