Gas-phase Studies on Reductive Cyclization to a Benzotriazole Derivative from its Precursors by Liquid Chromatography/Thermabeam Tandem Mass Spectrometry

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Liquid chromatography/Thermabeam mass spectrometry/mass spectrometry was carried out on the starting material, 2-nitro-2'hydroxy-5'-acetylazobenzene (1) and the intermediate N-oxide (2) formed by dithionite reduction of the starting material (1). The mass spectra of (1) and the intermediate (2) showed an abundant fragment ion that corresponds to that of 2-(2'-hydroxy-5'-acetylphenyl)benzotriazole (3). These results show that 3 could be formed from both 1 and 2. The formation of 3 in the gas phase is analogous to the chemical reduction processes of the 2-nitroazobenzene derivative 1 and the N-oxide 2 in solution.

INTRODUCTION

Benzotriazoles, especially 2-(2'-hydroxyphenyl)-2*H*benzotriazoles with various substituents on the hydroxy-substituted phenyl ring or the aromatic ring of the benzotriazole group, are an important class of compounds owing to their applications as ultraviolet absorbers for the protection of synthetic fibers against sunlight¹ and stabilizers, especially for plastic materials.² The intact intramolecular hydrogen bond is of great importance for the photostability of these compounds.²⁻⁸

Benzotriazoles are usually prepared by different chemical reduction processes of the azo derivatives with a structure similar to that of 2-nitro-2'-hydroxy-5'acetylazobenzene (1).9 Vogl and co-workers¹⁰ reported the synthesis of 2-(2'-hydroxy-5'-acetyl-phenyl)benzotriazole (3), by reducing (1), a coupling product of diazotized 2-nitroaniline and 4-hydroxyacetophenone, with Zn/NaOH.¹⁰ Other derivatives of benzotriazole were similarly synthesized by this group. Rosevear and Wilshire¹¹ performed the reductive cyclization of 2nitrophenylazo dyes, with the structures similar to that of 1, in ethanolic sodium hydroxide solution with thiourea S,S-dioxide (formamidinesulfinic acid), ammonium sulfide or sodium dithionite as the reductant. However, to our knowledge, the formation of benzotriazole species from its precursors in the gas phase has not been studied. In this paper, we report the gas-phase reductive cyclization of (1) and the intermediate N-oxide (2)(obtained by partial reduction of 1) to 3 by using liquid chromatography/Thermabeam/mass spectrometry/mass spectrometry (LC/TAB-MS/MS).

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EXPERIMENTAL

The 2-nitroazobenzene derivative 1 was prepared by a coupling reaction of diazotized 2-nitroaniline and 4-hydroxyacetophenone (4-HAP) as reported previously.^{9,10} A cooled diazonium salt solution of 2-nitroaniline, prepared by reaction with concentrated HCl and sodium nitrite, was added dropwise to the stirred solution of 4-HAP, NaOH pellets and anhydrous Na₂CO₃. The isolated solid 1 was used as such for different analyses and for reductive cyclization to 3.

The chemical reduction of 1 was carried out with the reducing agent sodium dithionite $(Na_2S_2O_4)$ under alkaline conditions as reported by Rosevear and Wil-

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LC/MS

Chromatography of samples of the azo compound 1, the N-oxide 2 and the benzotriazole 3 was carried out on a phenyl column (Phenomenex Bondex, 10 μ m; 300 mm × 3.9 mm i.d.) using isocratic elution with acetonitrile/tetrahydrofuran/water (20:20:60, v/v/v). HPLC-grade acetonitrile and tetrahydrofuran were obtained from Fisher; water was either doubly distilled or of Millipore quality. All solvents were filtered through Micro Separations 0.22 μ m nylon filters before use. A Waters 600-MS LC system equipped with Waters 486-MS tunable-wavelength UV detector was used to separate the mixtures before they entered the mass spectrometer; a flow rate of 0.5 cm³ min⁻¹ was used throughout the LC/MS work.

An Extrel Thermabeam (TAB) system was employed as the LC/MS interface. Analyses of all samples were carried out by nebulizing the respective LC peaks followed by removal of the solvent molecules. The remaining solute particles (as particle beams) continued to travel into the vacuum chamber;¹² they were subsequently desorbed by the hot ionizer and bombarded by an electron beam at 70 eV. An Extrel (Pittsburgh, PA, USA) ELQ-400-3 QQQ tandem mass spectrometer was used for mass spectral detection. Fragment ion MS/MS scans¹³ were performed by flow injection of samples containing 1 and 2 at a collision energy of 11.3 eV and 2×10^{-5} Torr (1 Torr = 133.3 Pa) or argon. These ions are unique molecular ions and have no interference from other components in the mixture as indicated by LC/MS.

RESULTS AND DISCUSSION

The mass spectra of the samples enriched with 1 and 2, obtained by LC/TAB-MS, are shown in Fig. 1(a) and



Figure 1. LC/Thermabeam MS of (a) 2-nitro-2'-hydroxy-5'-acetylazobenzene (1) and (b) 2-(2'-hydroxy-5'-acetylphenyl)benzotriazole N-oxide (2).



Figure 2. LC/Thermabeam MS of an authentic sample of 2-(2'-hydroxy-5'-acetylphenyl)benzotriazole (3)

(b), respectively. The formation of the fragment ion at m/z 253 in both cases suggests that 1 and 2 are probably reduced to 3, as the rest of the fragmentation pattern in Fig. 1 is identical with the LC/TAB mass spectrum of an authentic sample of 3, as shown in Fig. 2.

In order to understand the gas-phase reductive cyclization, we considered the energetics of different cyclization processes, as shown in Fig. 3. The enthalpy of the reactions were calculated on the basis of group equivalent methods.¹⁴ Our model also includes the non-cyclic *N*-oxide, 2' which is transformed into 2. While the formation of 2' from 1 is favorable by $\Delta H = -582$ kJ mol⁻¹, the formation of the cyclic *N*-oxide 2 is further exothermic by $\Delta H = -301$ kJ mol⁻¹. In contrast, the formation of 3 from 2 is an endothermic process ($\Delta H = 749$ kJ mol⁻¹). However, the overall process for the formation of 3 from 1 is favorable by $\Delta H = -138$ kJ mol⁻¹.



Figure 3. Energy diagram for the formation of 3 from the starting material 1 through the intermediates 2 and its non-cyclic form 2' (see text for details). The energies given are in kJ mol⁻¹.

To support further the ring closure processes, tandem mass spectrometry (MS/MS) was applied to study the structures of the molecular ions of 1 (m/z 285), 2 (m/z269) and 3 (m/z 253), and also the structures of the fragment ions at m/z 253 from 1 and 2 (Fig. 1). The tandem mass spectra of the molecular ion of 1 (m/z 285) and its fragment ion (m/z 253) are shown in Fig. 4(a) and (b), respectively. The fragment ions at m/z 163 and 135 in Fig. 4(a) are probably formed by the fragmentation of nitrobenzene and nitrophenylazo groups from the molecular ion. Note that the tandem mass spectrum of the ion at m/z 285 is different from the LC/TAB mass spectrum of 1 [Fig. 1(a)]. This presumably arises from different average energies deposited into the ion, i.e. in MS/MS and LC/TAB-MS. The relative abundances of the ions at m/z 163 and 135 in Fig. 4(a) suggest that the bonding (i.e. double bond character) between the azo group (-N=N-) and 4-hydroxyacetophenone is stronger than that between the azo group and nitrobenzene. The fragment ion scan of the fragment ion at m/z 253 [Fig. 4(b)], on the other hand, only yielded a fragment ion at m/z 238 due to loss of the methyl group. The absence of the fragment ion at m/z 253 in Fig. 4(a) suggests that the molecular ion of 1 requires greater excitation to overcome the energy barrier for the formation of the molecular ion of 3.

The MS/MS scans of the molecular ion of the intermediate 2 (m/z 269) and of the fragment ion at m/z 253 are shown in Fig. 5(a) and (b), respectively. Under the same collision conditions as used for 1 (Fig. 4), the molecular ion of 2 seems more stable than that of 1 since the fragment ions from 2 are less abundant (lower peak intensity) than those from 1. These two fragment ions at m/z 254 and 226 are presumably formed by loss of a methyl and an acetyl group from the molecular ion, respectively. These results are consistent with the stability of the cyclic N-oxide 2 presented in Fig. 3.



Figure 4. Fragment ion tandem mass spectra of the ions at (a) m/z 285 and (b) 253 [as shown in Fig. 1(a)].

The structure of the fragment ion of m/z 253, which is observed with both compounds 1 and 2, can be further confirmed by an MS/MS scan of the molecular ion (m/z253) from an authentic sample of 3 under identical experimental conditions. The relative abundances of the fragment ions (Fig. 6), are comparable to those in the tandem mass spectra in Figs 4(b) and 5(b). These results strongly suggest that the fragment ion with m/z 253 from 1 and 2 has the structure of 3.

The fragmentation patterns observed in Figs 4(a) and 5(a) along with the data presented in Fig. 1 clearly suggest that the energy deposited into the system is a critical factor for the formation of the peak at m/z 253. The greater stability of 2 further implies that stronger reduction conditions are necessary to convert 2 into 3. Thus, the gas-phase reductive cyclization is in accordance with that observed in solution.⁹⁻¹¹

In conclusion, the reductive cyclization of 2-nitro-2'hydroxy-5'-acetylazobenzene to 2-(2'-hydroxy-5'-acetylphenyl)benzotriazole occurs in the gas phase. The nitrogen atom of the nitro group of 1 attacks the azo nitrogen immediately bonded to the 4-hydroxyacetophenone moiety to form 2 under mild reduction conditions. Further reduction removes the residual nitroso-oxygen to produce 3. These results are consistent with those reported for the reactions in solution. Reductive cyclization of other benzotriazole derivatives in the gas phase is expected to follow steps similar to those observed in the formation of 3.

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Figure 5. Fragment ion tandem mass spectra of the ions at (a) m/z 269 (b) m/z 253 [as shown in Fig. 1(b)].



Figure 6. Fragment ion tandem mass spectrum of the molecule ion of 3 at m/z 253 (as shown in Fig. 2).

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