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Structural Elucidation of Sulfur Derivatives of Benzimidazoles by Density Functional Calculations, and Vibrational and NMR Spectral Analyses

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Abstract

The room temperature structural as well as vibrational (IR and Raman) and NMR (^{1}H and ^{13}C) spectral studies have been performed on 1-methyl-benzimidazole-2-thione, 2-(methylthio)benzimidazole, and 1-methyl-2-mercaptobenzimidazole tautomers at B3LYP/6-311++G** level of theory. 1-methyl-benzimidazole-2-thione is the most stable tautomer with significant energetic separations than the other two tautomers and with too high transition barriers to the other tautomers. This suggests that 1-methyl-benzimidazole-2-thione is the main species at the room temperature. Comparison of experimental and calculated room temperature vibrational and NMR spectra suggests the presence of the 2-(methylthio)benzimidazole and 1-methyl-2-mercaptobenzimidazole tautomers in the solid and solution phases as minor species.

Keywords: Benzimidazole; Infrared; Raman; Density functional theory (DFT); Potential energy surface scan

Introduction

The bicyclic organic compound benzimidazole (BI) consists of benzene-fused imidazole. Design and synthesis of BI derivatives have been greatly advanced over the last few decades due to their resemblance with the naturally occurring nucleotide bases, their structural and functional features, and their rich chemical behaviors. They play significant roles in organic and coordination chemistries as a result of their several potential donor centers [1-3], in medicinal chemistry as antibacterial, antifungal [4-6], antitumor [7-10], and anthelmintic (antiparasitic for humans, pets, livestock, and plants) [11] agents, in materials' applications as dyes, photographs, and catalytic agents [12-14]. Hence, structural investigations on BI derivatives are of great importance to understand their structure-function relationships better.

When a $-SCH_3$ group is bound to the position 2 of the imidazole moiety of BI [2-(methylthio)benzimidazole, abbreviated as BI-NSMe (Figure 1), an interesting chemistry emerges: The methyl moiety may migrate to the deprotonated nitrogen of the imidazole moiety (1-methyl-benzimidazole-2-thione, abbreviated as BI-NMeS). Then, the proton of the imidazole nitrogen may be transferred to the sulfur atom (1-methyl-2-mercaptobenzimidazole, abbreviated as BI-NMeSH). These three isomers together with their conformations due to the orientations of methyl hydrogens and the $S–CH_3$ bond may coexist, or some of them may dominate over the others. In this study, the tautomerism and conformational stability of these isomers will be analyzed in terms of density functional theory (DFT) based ground-state energetics and potential energy surface (PES) scans that connect the isomers to each other. Their computed IR, Raman, and NMR spectra will be compared with the previously available experimental spectra to identify the existent form of these species at the room temperature.

Computational details

Optimized gas-phase structures/energetics and vibrational/NMR spectral characteristics of the isomers were obtained at the B3LYP/6-311++G** level by using Gaussian03 program package [15]. Since the computational methods overestimate the vibrational frequencies systematically, the frequencies have been scaled with the previously derived factors [16,17]. These factors are 0.955 and 0.988 for the frequencies above and below 2500 cm^{-1}, respectively. The computational room temperature vibrational spectra were plotted in terms of the scaled computational frequencies and computed IR/

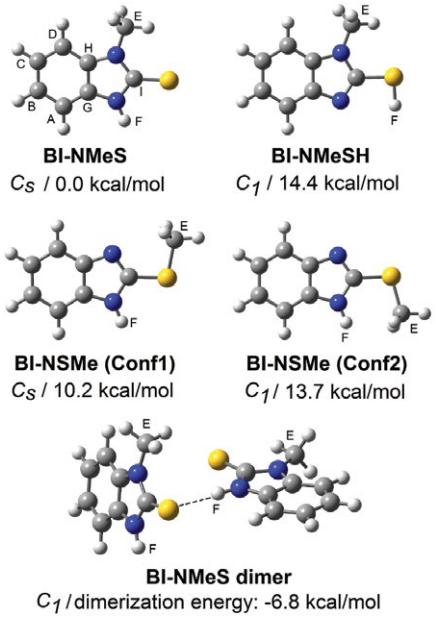

Figure 1: The geometrical structure, symmetry, and energetic stability of the investigated BI derivatives.

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Raman intensities by using pure Lorentzian band shapes with FWHM of 10 cm^{-1}. The Raman intensities were obtained by using the computed Raman activities, the scaled frequencies, and the laser wavelength (1064 nm=9398.5 cm^{-1}) [18]. Isotropic NMR shielding constants were also calculated at the same computational level but with Gauge Including Atomic Orbital (GIAO) method [19]. Isotropic NMR chemical shifts were then obtained by subtracting the computational shielding constants from those of TMS calculated with the same protocol (184.07 ppm for C and 31.97 ppm for H).

Results and Discussion

All possible structures of SCH_3 derivatives of BI at position 2 including their all tautomers (BI-NMeS, BI-NMeSH, and BI-NSMe (Figure 1), conformers, and rotamers have been fully optimized. BI-NMeS has been found to have only one stable structure with C_s symmetry. BI-NMeSH has two isoenergetic rotamers with C_1 symmetry, in which the methyl hydrogen closer to the sulfur atom is out of the ring plane by ± 17°. BI-NSMe has two stable conformers due to the orientation of the S–CH_3 bond. The conformation with the methyl group closer to the deprotonated nitrogen of BI (Conf1) is only 3.5 kcal/mol more stable than the one with the methyl group closer to the protonated nitrogen of BI (Conf2). Conf1 and Conf2 have C_s and C_1 symmetries, respectively. All other structures due to methyl orientations have at least one imaginary frequency and thus are not stable. BI-NMeS is the ground-state isomer and 10-15 kcal/mol more stable than the lowest energy forms of BI-NMeSH and BI-NSMe (Figure 1). Therefore, BI-NMeS is the main species in the gas phase at the room temperature.

To assess if BI-NMeS is converted to the other isomers, two separate PES scans moving H of N to S, and the methyl carbon to S have been performed (Figure 2). The remaining coordinates were fully relaxed during these PES scans. In both cases, the transition barrier is too high (above 30 kcal/mol). Therefore, if existed, BI-NMeSH and BI-NSMe are too minor in the gas phase at the room temperature.

A previously found X-ray structure of this molecule [20] is actually consistent with these energetic findings, demonstrating the presence of only BI-NMeS in solid phase with intramolecular NH···S hydrogen bonds (Figure 1 for the orientation of the two units of BI-NMeS). However, a recent comparative experimental and density functional study [21] on vibrational and NMR spectra considered only the presence of the BI-NSMe conformer that appeared in this study 10 (Conf1) and 14 (Conf2) kcal/mol above the most stable BI-NMeS (Figure 1). Therefore, we reanalyze the previous experimental spectra [21,22] in terms of the present B3LYP calculations considering all possible isomers. The experimental [21,22] and simulated IR and Raman spectra of BI-NMeS, BI-NMeS dimer, BI-NMeSH, and BI-NSMe (Conf1 and Conf2) are as given Figures 3 and 4.

The X-H stretchings (X=N, S, and C) of the 3600-2500 cm^{-1} region were labeled on the spectra (Figures 3 and 4) with a-e. The N-H stretching of BI-NMeS (bare and dimeric) and BI-NSMe (Conf1 and Conf2) that does not involve with any H-bonding (a) appears around 3500 cm^{-1} in both experimental and theoretical spectra. Its H-bonding partner (b) appears in 3250-3150 cm^{-1} region of the experimental and calculated spectra of BI-NMeS dimer. This ensures the presence of H-bond forming BI-NMeS molecules in the powdered sample. The ring (c) and methyl (d) C-H stretchings appear in both experimental and calculated (for all isomers) spectra in the 3150-2800 cm^{-1} region. The S-H stretching (e) of BI-NMeSH appears as a weak band in 2700-2500 cm^{-1} region, indicating the presence of this isomer as a minor species.

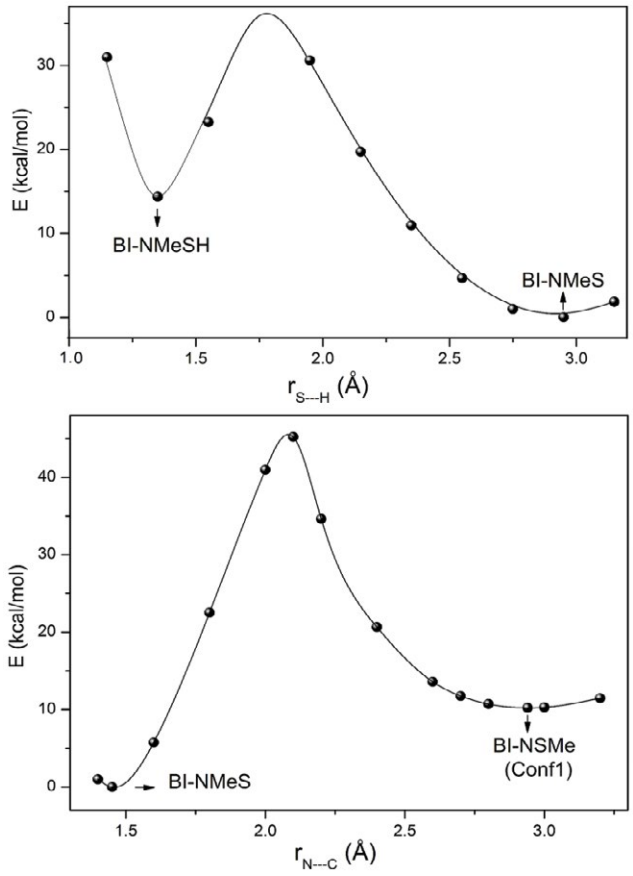

Figure 2: Relaxed PES scans that connect BI-NMeS to BI-NMeSH and BI-NMeS.

The intensity pattern of the experimental IR spectrum due to methyl in and out-of plane bendings at around 1000 cm^{-1} is more consistent with that of Conf1 and Conf2 of BI-NSMe. Therefore, IR spectrum suggests the presence of the minor BI-NSMe in the powdered sample, as well.

Although the overall shapes of the experimental vibrational spectra resemble more to BI-NMeS and its H-bonding partners, some characteristic bands of the other isomers exist also in the experimental spectra. Therefore, BI-NSMe and BI-NMeSH are present in the powdered sample as minor species in addition to the main BI-NMeS at the room temperature.

The calculated and experimental (in $CdCl_3$) [21] room temperature ^1H and ^{13}C chemical shifts of the isomers are as given in Tables 1 and 2. The assignments of the NMR signals to the specific hydrogens and carbons are given according to the labeling system (A-I) of Figure 1. The experimental chemical shifts are not fully consistent with those calculated any single isomer but better represented with the average values of the five species considered. This suggests the presence of all isomers in the room temperature solution.

Conclusion

When a –SCH_3 group is bound to the position 2 of BI, three tautomeric forms exist (Figure 1). Consistent with a previous X-ray study [20], the present DFT calculations find that the most stable tautomer has the methyl moiety at the ring nitrogen with the other ring nitrogen being protonated, i.e., BI-NMeS. Although the other

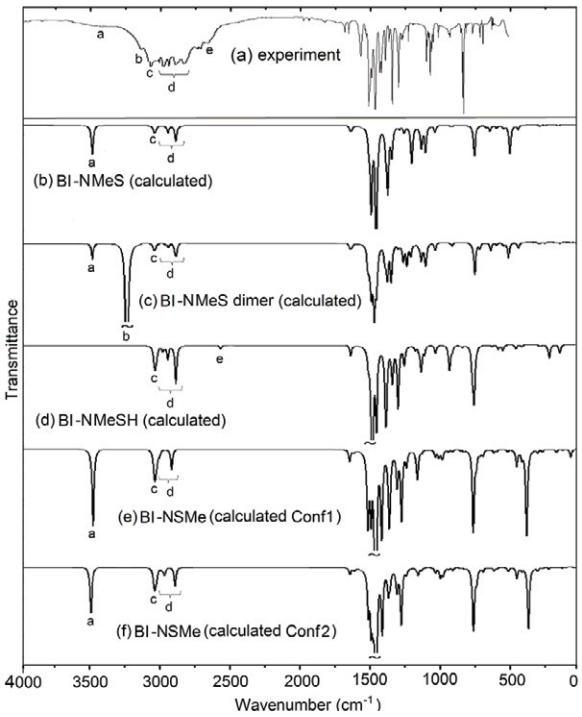

Figure 3: Experimental (KBr) [21,22] and calculated IR spectra of the investigated isomers.

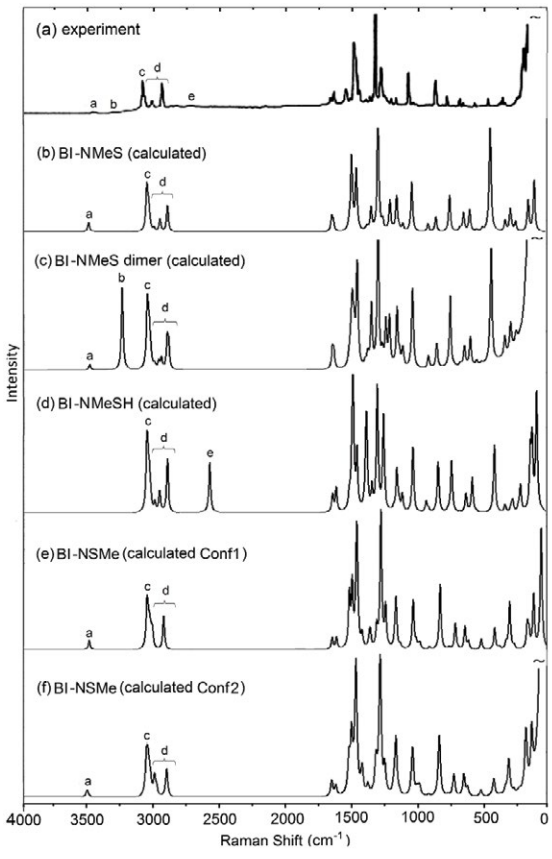

Figure 4: Experimental [21,22] and calculated Raman spectra of the investigated isomers.

	Calculated							Exp.
	BI-NMeS	BI-NMeS dimer		BI-NMeSH	BI-NSMe (Conf1)	BI-NSMe (Conf2)	Average	
A	7.0	7.1	7.3	7.8	7.2	7.4	7.3	7.2
B	7.3	7.4	7.3	7.4	7.3	7.3	7.3	7.2
C	7.3	7.4	7.2	7.3	7.4	7.4	7.3	7.2
D	7.0	7.3	7.0	7.2	7.8	7.8	7.4	7.3
E*	3.7	4.1	3.6	3.6	2.7	2.4	3.3	2.8
F	7.9	8.1	11.2	4.9	7.7	7.8	7.9	7.5

*Averaged values for the methyl hydrogens

Table 1: The calculated and experimental [21] ^{1}H NMR chemical shifts in ppm.

	Calculated						Exp.
	BI-NMeS	BI-NMeS dimer		BI-NMeSH	BI-NSMe (Conf1)	BI-NSMe (Conf2)	Average	
A	112.2	113.0	114.1	125.4	112.3	112.2	114.9	115.4
B	128.7	129.0	128.5	128.3	127.8	127.4	128.3	122.4
C	128.5	128.9	127.6	127.7	127.8	128.3	128.1	122.4
D	112.7	114.9	112.0	111.3	125.0	125.8	116.9	115.4
E	30.9	32.7	30.4	31.9	20.6	18.2	27.4	14.8
G	137.4	137.2	138.3	152.1	142.0	141.6	141.4	140.5
H	141.6	142.4	141.0	144.0	151.5	153.3	145.6	140.5
I	181.4	180.3	180.6	156.5	160.6	156.7	169.4	151.5

Table 2: The calculated and experimental [21] ^{13}C NMR chemical shifts in ppm.

two tautomers are lying significantly higher than BI-NMeS with too high transition barriers that connect the tautomers to each other, the comparison of the experimental and calculated room temperature vibrational and NMR spectra suggests that they also exist in the solid and solution phases as minor species. These results are quite analogous to the previous findings on the sulfur derivatives of the benzoxazole and benzothiazole isomers [16,17].

In pharmacological studies, the proper determination of conformational, tautomeric, and protonation state preferences of compounds is extremely important to reveal the drug-receptor interaction mechanisms, and thus to devise more effective drugs. It is apparent from the present study on pharmacologically important BI derivatives that the comparison of the experimental and theoretical spectra allows one to determine such critical structural details.

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