

# Chlorotropy of 1-Chlorobenzimidazole

Michael De Rosa,<sup>\*,†</sup> Nieves Canudas,<sup>‡</sup> David Arnold,<sup>†</sup> and Hemant Yennawar<sup>§</sup>

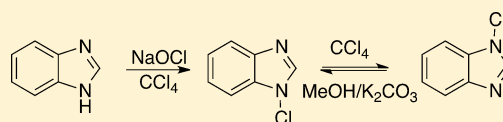
<sup>†</sup>Department of Chemistry, Penn State Brandywine, Media, Pennsylvania 19063, United States

<sup>‡</sup>Departamento de Química, Universidad Simón Bolívar, valle de Sartenejas, Apartado 8900, Caracas 1080-A, Venezuela

<sup>§</sup>Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

## Supporting Information

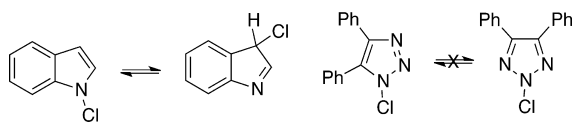
**ABSTRACT:** The chlorotropy observed by NMR in this study occurred by the rapid intermolecular transfer of a chloro group between 1-chlorobenzimidazole and benzimidazole in CCl<sub>4</sub>/CH<sub>3</sub>OH/K<sub>2</sub>CO<sub>3</sub> solution.



## INTRODUCTION

Tautomerism in heteroaromatic compounds involves the movement of an atom or group from one position on the ring to another, typically a proton (prototropy) and usually via an intermolecular mechanism.<sup>1,2</sup> Any atom or group can be part of a tautomeric equilibrium as long as there is sufficient energy to drive the process.<sup>3</sup> The possibility of chlorotropy has been considered.<sup>4</sup> To date, the only known example of this process is the equilibrium between 1-chloroindole and 3-chloro-3H-indole reported in the rearrangement of 1-chloroindole to 3-chloroindole.<sup>5</sup> It has been reported that chlorine exchange was taking place in 1-chloro-4,5-diphenyl-1,2,3-triazole;<sup>6</sup> but a subsequent study<sup>4</sup> indicated that the compound was in fact the symmetrical 2-chloro-4,5-diphenyl-1,2,3-triazole (Scheme 1). In this study, unambiguous evidence is presented for chlorotropy in 1-chlorobenzimidazole.

### Scheme 1. Example of Chlorotropy



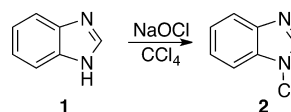
## RESULTS AND DISCUSSION

NMR spectroscopy<sup>7</sup> has been used to study the prototropy of benzimidazole derivatives.<sup>8</sup> As a result of a degenerate (autotrope) equilibrium the six-membered ring of benzimidazole becomes symmetrical and 4-carbon signals are observed by <sup>13</sup>C NMR; in contrast, seven ring carbons are observed in the case of 1-methylbenzimidazole where no tautomeric process is taking place. In the <sup>1</sup>H NMR spectrum, an AA'BB' or A<sub>2</sub> pattern is observed for the benzene ring protons of benzimidazole. Analogous NMR results would confirm chlorotropy in 1-chlorobenzimidazole.

Several examples of 1-chlorobenzimidazole derivatives,<sup>9</sup> including 1-chlorobenzimidazole,<sup>10,11</sup> have been previously reported. In this study, 1-chlorobenzimidazole was prepared by reacting benzimidazole with a solution of sodium

hypochlorite in carbon tetrachloride. The reaction was over (30 min) when all of the benzimidazole, insoluble in CCl<sub>4</sub>, had disappeared. A white solid, which oxidized iodide ion, was obtained in 70–80% yield (Scheme 2). The physical and

### Scheme 2. Synthesis of 1-Chlorobenzimidazole (2)



chemical properties of 1-chlorobenzimidazole obtained in this study differed significantly from those previously reported<sup>10</sup> for this compound.<sup>12</sup> X-ray crystallography definitively demonstrated the structure of **2** obtained in the present study (Figure 1).

Parts a and b of Figure 2 show the <sup>1</sup>H and <sup>13</sup>C NMR spectra, respectively, of 1-chlorobenzimidazole in CCl<sub>4</sub>. Chlorotropy is clearly not evident as the spectra obtained in pure CCl<sub>4</sub> are analogous to 1-substituted benzimidazoles with nonmobile substituents. Similarly, in pure CCl<sub>4</sub>, 1-chloroindole did not exhibit chlorotropy; only when an alcohol containing base (K<sub>2</sub>CO<sub>3</sub>) was added was UV evidence obtained for a chlorine shift.<sup>5</sup> Addition of pure methanol to a CCl<sub>4</sub> solution of **2** caused a slight broadening of the signals of the <sup>1</sup>H NMR spectrum. When a solution of methanol saturated with K<sub>2</sub>CO<sub>3</sub> was added to **2** in CCl<sub>4</sub>, a <sup>1</sup>H NMR spectrum characteristic (a symmetrical pattern) of chlorotropy was obtained (Figure 2c). Washing the CCl<sub>4</sub>/CH<sub>3</sub>OH/K<sub>2</sub>CO<sub>3</sub> solution with water gave the characteristic <sup>1</sup>H NMR spectrum of **2** in pure CCl<sub>4</sub>, indicating that both methanol and K<sub>2</sub>CO<sub>3</sub> were needed for chlorotropy to be observed and that the process was reversible. The <sup>13</sup>C NMR spectrum (Figure 2d) clearly showed evidence of a dynamic process with the expected four signals; as a result of exchange, two of the signals were broadened. Unfortunately, variable-temperature NMR was not possible: when <sup>13</sup>C NMR spectra were taken (CCl<sub>4</sub>/CH<sub>3</sub>OH/K<sub>2</sub>CO<sub>3</sub>) at a higher temperature, **2**

Received: April 15, 2013

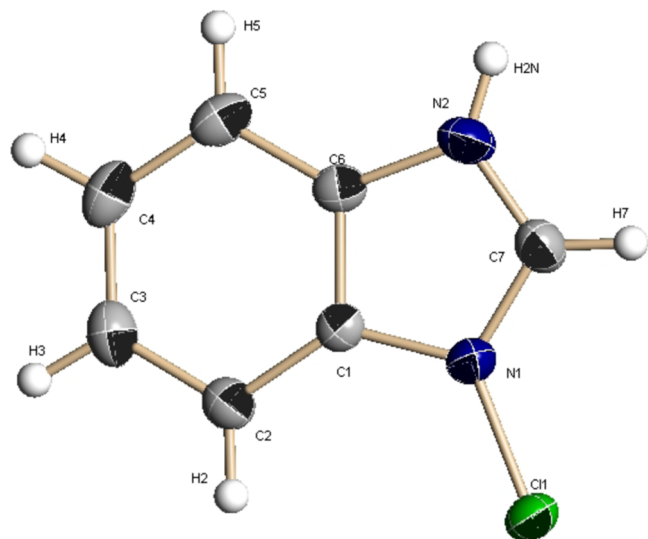


Figure 1. X-ray structure of 1-chlorobenzimidazole.

reacted and a second species was observed; at lower temperature  $\text{CCl}_4$  froze (mp  $-22.9^\circ\text{C}$ ).

If benzimidazole (**1**) was added immediately after the addition of  $\text{CH}_3\text{OH}/\text{K}_2\text{CO}_3$ , the symmetrical  $^1\text{H}$  NMR pattern characteristic of rapid exchange did not change (Figure 3). As the relative amount of benzimidazole (**1**) added increased, all of the signals shifted upfield in the  $^1\text{H}$  NMR spectrum. A plot of the chemical shift of C2H of 1-chlorobenzimidazole (**2**) vs the concentration of added benzimidazole was linear ( $R^2 = 0.991$ ,  $n = 5$ ).<sup>13</sup> Under conditions of fast exchange, the observed chemical shift of C2H is the weighted average of the two exchanging species: 8.237 ppm for benzimidazole (Figure 3g) and 8.353 ppm for 1-chlorobenzimidazole (extrapolation).<sup>13</sup> When the concentration of the two species was equimolar

(Figure 3e), the calculated CH2 chemical shift was 8.30 ppm compared to an experimental value of 8.31 ppm. Similar agreement between calculated and experimental was obtained at the other concentrations.<sup>13</sup> These results, with added benzimidazole, demonstrated that the chlorotropy observed in this study occurred by the rapid intermolecular transfer of a chloro group between 1-chlorobenzimidazole and benzimidazole. If benzimidazole (**1**) were not taking part in the chlorine exchange, its presence would have been detected by  $^1\text{H}$  NMR, either by a broadening of some of the peaks or more likely, by the detection of new peaks. It should be noted that no new peaks were detected even when 2 equiv of benzimidazole (**1**) was added (Figure 3f). The exchange process is illustrated in Scheme 3.<sup>14</sup>

Chlorine exchange can take place in a manner analogous to that observed in other *N*-chloro compounds.<sup>15–17</sup> Mechanistically, this can occur by nucleophilic attack on chlorine by the pyridine-type nitrogen of benzimidazole, a halophilic reaction.<sup>18</sup> It has been proposed that the migration of a group from a pyrrole-type nitrogen to a pyridine-type nitrogen, whether via an intra- or intermolecular process, involved nucleophilic substitution.<sup>19</sup>

Prototropy in benzimidazoles,<sup>1,8g</sup> and imidazoles<sup>1,2</sup> is an intermolecular process involving two or more molecules of the heterocycle.<sup>1,2</sup> Proton exchange, in imidazoles, has also been reported to be subject to general and specific acid and base catalysis.<sup>20</sup> On the basis of analogy to the prototropy studies of benzimidazoles and imidazoles and that the chlorine transfer observed in this study required benzimidazole, methanol, and  $\text{K}_2\text{CO}_3$  to be observed, the base-catalyzed intermolecular mechanism in Scheme 4 is proposed to explain the chlorotropy of 1-chlorobenzimidazole (**2**). Mechanistically, the possibility that the intermolecular exchange was occurring between **2** and the benzimidazole anion could not be eliminated. In this alternative mechanism, the role of  $\text{K}_2\text{CO}_3$  would be to form the

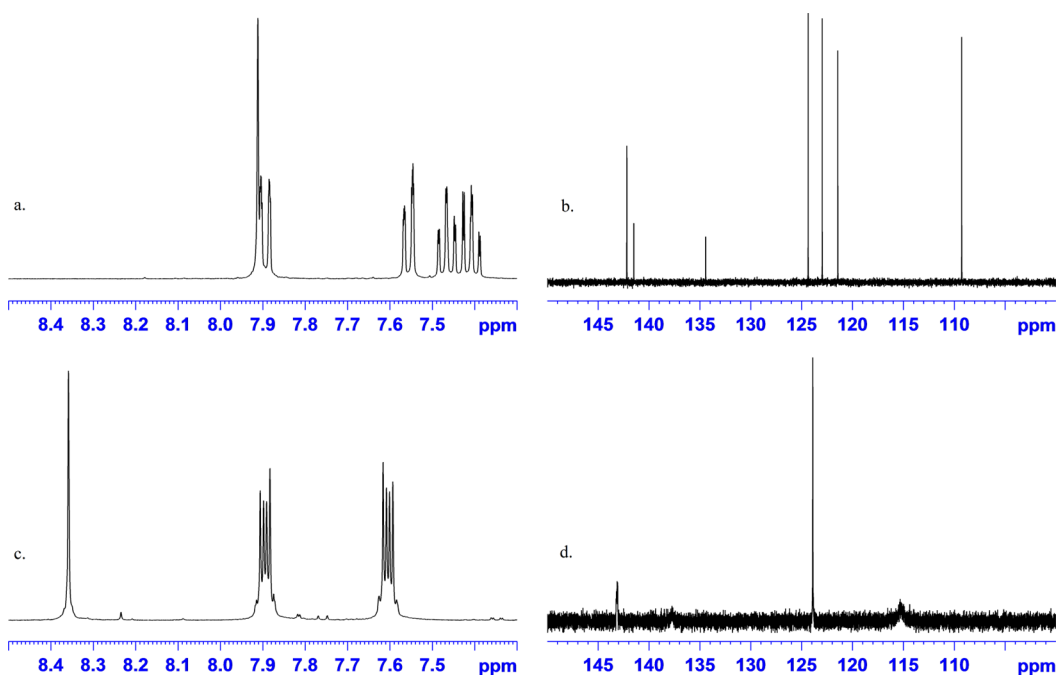
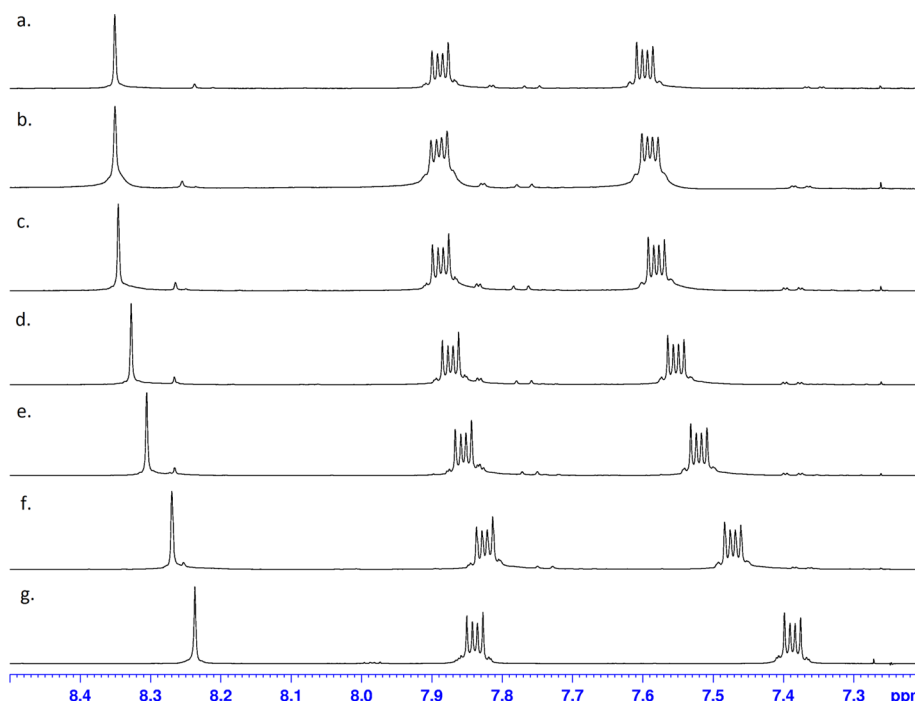
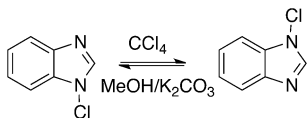


Figure 2. (a)  $^1\text{H}$  NMR (400 MHz) in  $\text{CCl}_4$  of 1-chlorobenzimidazole (0.208 M); (b)  $^{13}\text{C}$  NMR (100 MHz) in  $\text{CCl}_4$  of 1-chlorobenzimidazole (0.208 M); (c)  $^1\text{H}$  NMR (400 MHz) in  $\text{CCl}_4/\text{MeOH}/\text{K}_2\text{CO}_3$  of 1-chlorobenzimidazole (0.15 M); (d)  $^{13}\text{C}$  NMR (100 MHz) in  $\text{CCl}_4/\text{MeOH}/\text{K}_2\text{CO}_3$  of 1-chlorobenzimidazole (0.15 M).

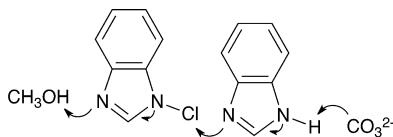


**Figure 3.**  $^1\text{H}$  NMR (400 MHz) spectra taken of 0.15 M 1-chlorobenzimidazole in  $\text{CCl}_4/\text{MeOH}/\text{K}_2\text{CO}_3$ : (a) no added benzimidazole; (b) 10% benzimidazole; (c) 20% benzimidazole; (d) 50% benzimidazole; (e) 100% benzimidazole; (f) 200% benzimidazole; (g) pure benzimidazole (0.15 M) in  $\text{CCl}_4/\text{MeOH}/\text{K}_2\text{CO}_3$ .

### Scheme 3. Chlorotropy of 1-Chlorobenzimidazole



### Scheme 4. Mechanism for Chlorine Migration



conjugate base of benzimidazole.<sup>21</sup> This mechanism would be a stepwise process, in contrast to the concerted mechanism proposed in Scheme 4. Other examples of intermolecular mechanisms<sup>1a</sup> for tautomeric equilibria, other than prototropy, have been reported: thiatropy in 1-(aryltio)benzimidazoles,<sup>22</sup> acylotropy<sup>1a</sup> in 3,5-dimethyl-*N*-phenyl-1*H*-pyrazole-1-carboxamide, and methyltropy<sup>1a</sup> in 2-methylmercaptobenzothiazole. All of these examples occurred by different intermolecular mechanisms.<sup>23</sup>

The NMR results of this study demonstrated chlorotropy in 1-chlorobenzimidazole via an intermolecular transfer of chlorine.

## EXPERIMENTAL SECTION

**Preparation of 1-Chlorobenzimidazole.** To a suspension of 10.0 mmol of benzimidazole (**1**) in 100 mL of  $\text{CCl}_4$  were added 10.0 mL of 1.35 M sodium hypochlorite (commercial bleach) and 10.0 mL of water, and the solution was stirred for 30 min until all solid **1** had disappeared. Solvent was removed under reduced pressure maintaining the temperature no higher than 40 °C. A 70–80% yield of white crystals, mp 61.5–62.0 °C, that oxidized iodide ion was obtained. Solid

1-chlorobenzimidazole decomposed with evolution of chlorine if left in contact with air or if heated above its melting point. Solutions of **2** in  $\text{CCl}_4$  over  $\text{K}_2\text{CO}_3$  were stable for up to a month if kept in the dark at 0 °C.

**1-Chlorobenzimidazole:**  $^1\text{H}$  NMR (400 MHz,  $\text{CCl}_4$ ,  $\text{CDCl}_3$ , external standard)  $\delta$  7.91 (s, 1H), 7.91–7.88 (m, 1H), 7.57–7.54 (m, 1H), 7.49–7.39 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CCl}_4$ , acetone- $d_6$ , external standard)  $\delta$  142.2, 141.5, 134.4, 124.4, 123.0, 121.4, 109.3.

**1-Chlorobenzimidazole with  $\text{MeOH}/\text{K}_2\text{CO}_3$  added:**  $^1\text{H}$  NMR (400 MHz,  $\text{CCl}_4$ ,  $\text{CDCl}_3$ , external standard)  $\delta$  8.36 (s, 1H), 7.92–7.88 (m, 2H), 7.63–7.59 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CCl}_4$ , acetone- $d_6$ , external standard)  $\delta$  143.2, 137.7, 123.9, 115.3.

**Preparation of Crystals for X-ray Analysis.** Solvent evaporation at room temperature did not give crystals useful for X-ray crystallography. A suitable crystal of **2** in  $\text{CCl}_4$  was obtained by evaporation at –10 °C. After 4 days, small crystals were observed. Solvent was added and evaporation allowed two more times. After the third time, the crystal was mounted on a nylon loop with a touch of paratone oil and then frozen in the cryo-stream at –156 °C, for X-ray investigations.

**NMR Study: 1-Chlorobenzimidazole with  $\text{MeOH}/\text{K}_2\text{CO}_3$  and Benzimidazole Incrementally Added.** A 0.208 M solution of 1-chlorobenzimidazole in  $\text{CCl}_4$  was prepared, and a 0.50 mL aliquot was removed and placed in an NMR tube. To this aliquot was added a saturated  $\text{MeOH}/\text{K}_2\text{CO}_3$  solution (0.20 mL). Benzimidazole was then added to the now 0.15 M 1-chlorobenzimidazole (0.104 mmol) solution in increments of: 10% (0.0104 mmol, 1.2 mg), 20% (0.0208 mmol, 2.4 mg total), 50% (0.0520 mmol, 6.0 mg total), 100% (0.104 mmol, 12.0 mg total), 200% (0.208 mmol, 24 mg total). A  $^1\text{H}$  NMR (400 MHz,  $\text{CCl}_4$ ,  $\text{CDCl}_3$ , external standard) was taken after each addition of benzimidazole. A plot of the chemical shift of the C2H resonance of benzimidazole vs percent benzimidazole added was prepared and was found to have a strong linear correlation ( $R^2 = 0.991$ ).<sup>13</sup>

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Complete  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are presented and a crystallographic information file for compound **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [mxd19@psu.edu](mailto:mxd19@psu.edu).

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported, in part, by Grant No. 0910668 from the National Science Foundation. We thank Dr. Scott Van Bramer and Mr. Marty Schultz (Widener University) for NMR spectra. The X-ray structure was determined at the Penn State small molecule crystallographic facility established using funds from an NSF Chemistry Research Instrumentation and Facilities grant (CHE-0131112). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 923215. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

## ■ REFERENCES

- (1) (a) Alkorta, I.; Goya, P.; Elguero, J.; Singh, S. P. *Natl. Acad. Sci. Lett. (India)* **2007**, 30, 139. (b) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *Advances in Heterocyclic Chemistry, Supplement 1: The Tautomerism of Heterocycles*; Academic Press: New York, 1976. (c) Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, 76, 157. (d) Katritzky, A. R.; Hall, C. D.; El-Gendy, B. E.-D. M.; Draghici, B. *J. Comput.-Aided Mol. Des.* **2010**, 24, 475.
- (2) Kereselidze, J. A.; Zarqua, T. S.; Kikalishvili, T. J.; Churgulia, E. J.; Makaridze, M. C. *Russ. Chem. Rev.* **2002**, 71, 993.
- (3) For further discussion see ref 1a and pp 4–6 and 191–200 in ref 1c.
- (4) Canada, J.; Claramunt, R. M.; De, M. J.; Elguero, J. *Heterocycles* **1985**, 23, 2225.
- (5) De Rosa, M.; Triana Alonso, J. L. *J. Org. Chem.* **1978**, 43, 2639.
- (6) Gallagher, T. C.; Sasse, M. J.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1979**, 419.
- (7) Claramunt, R. M.; Lopez, C.; Santa, M. M. D.; Sanz, D.; Elguero, J. *Prog. Nucl. Magn. Reson. Spectrosc.* **2006**, 49, 169.
- (8) (a) Benassi, R.; Lazzeretti, P.; Schenetti, L.; Taddei, F.; Vivarelli, P. *Tetrahedron Lett.* **1971**, 3299. (b) Elguero, J.; Llouquet, G.; Marzin, C. *Tetrahedron Lett.* **1975**, 4085. (c) Pappalardo, L.; Elguero, J.; Fruchier, A. *An. Quim.* **1975**, 71, 598. (d) Marzin, C.; Peek, M. E.; Elguero, J.; Figeys, H. P.; Defay, N. *Heterocycles* **1977**, 6, 911. (e) Fruchier, A.; Pappalardo, L.; Elguero, J. *An. Quim. Ser. C* **1980**, 76, 79. (f) Papadopoulos, E. P.; Hollstein, U. *Org. Magn. Reson.* **1982**, 19, 188. (g) Lee, I.-S. H.; Jeoung, E. H.; Lee, C. K. *J. Heterocycl. Chem.* **1996**, 33, 1711. (h) Mataka, S.; Isomura, K.; Sawada, T.; Tsukinoki, T.; Tashiro, M.; Takahashi, K.; Tori-i, A. *Heterocycles* **1998**, 48, 113. (i) Claramunt, R. M.; Lopez, C.; Alkorta, I.; Elguero, J.; Yang, R.; Schulman, S. *Magn. Reson. Chem.* **2004**, 42, 712. (j) El, K. A.; Ahbala, M.; Essassi, E. M.; Danion-Bougout, R.; Bauchat, P. *Phys. Chem. News* **2005**, 25, 130. (k) Garcia, M. A.; Claramunt, R. M.; Solcan, T.; Milata, V.; Alkorta, I.; Elguero, J. *Magn. Reson. Chem.* **2009**, 47, 100.
- (9) (a) Bamberger, E.; Lorenzen, J. *Ann.* **1893**, 273, 269. (b) Subbotina, N. A.; Gryaznova, N. S.; Belyavskaya, I. V.; Taisova, A. S.; Afonin, V. I.; Zinchenko, E. Y.; Lesovaya, Z. I.; Sazykin, Y. O.; Navashin, S. M. *Antibiot. Khimioter.* **1989**, 34, 358.
- (10) Ramkumar, B. *Asian J. Chem.* **2001**, 13, 777.
- (11) (a) Ramkumar, B. *Afinidad* **2003**, 60, 257. (b) Rukmangathan, M.; Kumar, V. S.; Ramkumar, B. *J. Indian Chem. Soc.* **2010**, 87, 1011.
- (12) In the previous study, a mp of 197–199 °C was reported compared to 61.5–62 °C in this study. It was also reported that it was recrystallized from ethanol, whereas we found that in refluxing methanol benzimidazole and benzimidazole hydrochloride could be isolated. Additionally, by use of preparative TLC fractions were obtained that, by MS, indicated that a complex mixture of monochloro-, dichloro-, trichloro-, and tetrachlorobenzimidazoles had been formed.
- (13) See the Supporting Information.
- (14) That the two species in Scheme 3 are tautomers can be appreciated by mentally substituting one  $^{14}\text{N}$  atom by a  $^{15}\text{N}$  atom.<sup>1a</sup>
- (15) (a) Antelo, J. M.; Arce, F.; Crueiras, J.; Parajo, M. *J. Phys. Org. Chem.* **1997**, 10, 631. (b) Calvo, P.; Crueiras, J.; Rios, A. *J. Org. Chem.* **2009**, 74, 5381. (c) Calvo, P.; Crueiras, J.; Rios, A.; Rios, M. A. *J. Org. Chem.* **2007**, 72, 3171. (d) Dannan, H.; Crooks, P. A.; Dittert, L. W.; Hussain, A. *J. Pharm. Sci.* **1992**, 81, 652. (e) Darwich, C.; Elkhatib, M.; Steinhäuser, G.; Delalu, H. *Helv. Chim. Acta* **2009**, 92, 98. (f) Higuchi, T.; Hasegawa, J. *J. Phys. Chem.* **1965**, 69, 796. (g) Higuchi, T.; Hussain, A.; Pitman, I. H. *J. Chem. Soc. B* **1969**, 626. (h) Higuchi, T.; Ikeda, K.; Hussain, A. *J. Chem. Soc. B* **1968**, 1031. (i) Hussain, A.; Higuchi, T.; Hurwitz, A.; Pitman, I. H. *J. Pharm. Sci.* **1972**, 61, 371. (j) Ramanujam, V. M. S.; Trieff, N. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1275.
- (16) Wille, U. *Sci. Synth.* **2009**, 40b, 893.
- (17) (a) O'Reilly, R. J.; Karton, A.; Radom, L. *J. Phys. Chem. A* **2011**, 115, 5496. (b) Pattison, D. I.; Davies, M. J. *Biochemistry* **2006**, 45, 8152.
- (18) Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, 82, 615.
- (19) See page 191 in ref 1c.
- (20) See page 177 in ref 1c and references therein.
- (21) The formation of  $\text{CHCl}_3$  was not detected by  $^{13}\text{C}$  NMR. This eliminated the possibility that chlorine transfer was occurring between  $\text{CCl}_4$  and the benzimidazole anion.
- (22) Raban, M.; Chang, H.; Craine, L.; Hortelano, E. *J. Org. Chem.* **1985**, 50, 2205.
- (23) Katritzky, A. R.; El-Gendy, B. E.-D. M.; Draghici, B.; Hall, C. D.; Steel, P. J. *J. Org. Chem.* **2010**, 75, 6468.