

In-Sook Han Lee* and Eun Hee Jeoung

Department of Science Education, Kangweon National University, Chuncheon 200-701, Korea

Chang Kiu Lee

Department of Chemistry, Kangweon National University, Chuncheon 200-701, Korea

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Benzimidazoles containing furyl and thienyl substituents at C-2 were prepared by condensation of *o*-phenylenediamine and corresponding carboxylic acids in the presence of polyphosphoric acid. The 2-heteroarylbenzimidazoles showed tautomerism in dimethyl sulfoxide solution while 2-phenylbenzimidazole did not. The tautomerism appeared to be taking place by intermolecular relay of protons between stacked molecules.

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Tautomerism in imidazole has been widely investigated in literature [1]. The mechanism of this phenomenon in neutral organic solvents has been explained, in general, as an intermolecular process involving two or more imidazole molecules. In aqueous solution, however, a water molecule participates in the process by giving its own H atom to N-3 and accepting an H atom from N-1-H of imidazole [2]. Black and Heffernan [3] used ^1H nmr spectroscopy to investigate the tautomerism of benzimidazole [3]. Spectroscopy (^{13}C nmr) can also be used as a tool for verifying the occurrence of tautomerism in the imidazole skeleton [4]. For example, C-4 and C-5 show a single peak at 121.9 ppm for imidazole and 120.0 ppm for imidazolium ion [5], which is strong evidence of the tautomerism of the N-H in solution. Similarly, C-4 and C-5 of 2-phenylimidazole show an identical ^{13}C chemical shift value (122.7 ppm). Studies of the tautomerism in some 2-substituted imidazoles and benzimidazoles by ^{13}C nmr were also reported [6]. Benzimidazole also exists as tautomeric forms, and its ^{13}C -nmr spectrum shows only four peaks in spite of seven carbon atoms being present. On the other hand, 2-phenylbenzimidazole does not show tautomerism. Out of 11 carbon peaks in 2-phenylbenzimidazole, four of them correspond to carbons in the 2-phenyl ring and seven to benzimidazole carbons [7]. 2-(2-Pyridyl)benzimidazole also shows 12 peaks, one for each carbon atom present [8]. On the other hand, the ^1H nmr spectrum of 2-(4-pyridyl)benzimidazole was interpreted as a result of the tautomerism although its ^{13}C nmr spectrum seemed to indicate the opposite [9].

The contrasting observation from 2-phenylimidazole and 2-phenylbenzimidazole led us to investigate the phenomena of tautomerism in this system. First, we have prepared 2-heteroarylbenzimidazoles **3a-d** and found that these compounds show tautomerism in contrast to 2-phenylbenzimidazole (**3e**) in dimethyl sulfoxide solution. We report herein our results of the preparation of

compound **3** and the effect of 5-membered heteroaromatic substituents on the tautomeric behavior of the benzimidazole ring as well as spectral characteristics of benzimidazole and benzimidazolium ion derivatives.

Results and Discussion.

Synthesis of 2-Aryl Benzimidazoles.

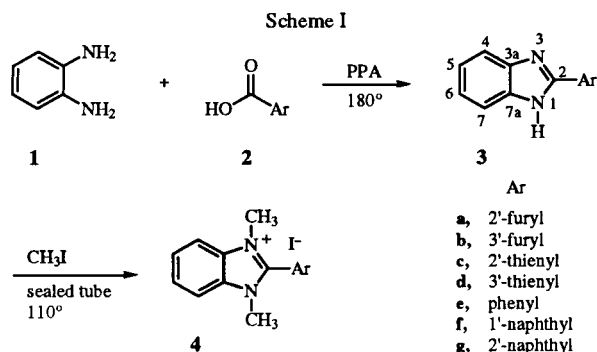
The synthesis of 2-aryl substituted benzimidazole was reported more than a century ago [10]. Although there are several ways leading to 2-arylbenzimidazole, a typical procedure is heating *o*-phenylenediamine with a substituted benzoic acid in the presence of a mineral acid [11]. However, whether or not 2-furoic acid and 2-thiophenecarboxylic acid gives an analogous product has not been investigated. A reaction to prepare 2-substituted benzimidazoles was heating *o*-phenylenediamine and 2-furylacetic acid in the presence of polyphosphoric acid for 3-4 hours [12]. Although there is a report in the literature describing the preparation of 2-(2'-furyl)benzimidazole, we were not able to obtain the detailed procedure and any physical constants such as the melting point [13]. Heating *o*-phenylenediamine with benzaldehyde gave, in addition to several other products, 2-phenylbenzimidazole [14]. When we repeated the procedure we obtained *o*-diphenylbenzalimide as the major product. When *o*-phenylenediamine was treated with benzoyl chloride in pyridine a diamide formed.

There are other reports of the preparation of **3** from **1**: condensation with esters in the presence of trimethylaluminum [15] or with *N*-ethoxycarbonylthioamides in tetrahydrofuran [16]. However, the former procedure requires transformation of carboxylic acids into esters and the latter requires preparation of the *N*-ethoxycarbonylthioamides from heterocycles and ethoxycarbonylisothiocyanate.

We have prepared **3** by the procedure reported by Craig *et al.* [12] with a slight modification. Polyphosphoric acid seems to be the suitable acid for the procedure because it

behaves as a strong catalyst as well as a good dehydrating agent. The furan ring is known to be labile to acids, transforming to a ring-opened product [17]. Therefore, use of polyphosphoric acid provides conditions mild enough to retain the ring.

When 2- and 3-furoic acids **2a** and **2b** were heated together with **1** and polyphosphoric acid at 180° for three hours, 2-(2'- and 3'-furyl)benzimidazoles, **3a** and **3b** were formed in 40% and 90% yields, respectively. The yields were higher with the thiophene series, giving **3c** and **3d** in



80% and 90% yields, respectively. The reaction mixtures, which were dark brown solid masses, were usually suspended in ammonium hydroxide solution and filtered, and recrystallized from ethanol. However, 2-pyrrolicarboxylic acid did not give a benzimidazole derivative under similar conditions. Our attempts to prepare various 2-pyrrolylbenzimidazoles were unsuccessful.

Methylation of benzimidazoles **3** was carried out in a sealed stainless-steel tube by heating with excess of methyl iodide at 110° to prepare the *N,N*-dimethylbenzimidazolium iodide salts **4**. Another methylation procedure,

such as stirring a mixture of the benzimidazole, sodium hydroxide and methyl iodide in dimethyl sulfoxide, was not successful and the starting material was recovered nearly quantitatively.

Spectroscopy and Tautomerism.

As described in the introduction, the striking similarity between the ¹³C nmr chemical shift values of imidazole and imidazolium ion led us to examine the effect of 5-membered heteroaromatic substituents on the ¹H and ¹³C chemical shifts of **3a-d** in dimethyl sulfoxide. As shown in Table I, the chemical shift values of protons in the 2-heteroarylbenzimidazoles are slightly shifted upfield compared to those of benzimidazole itself. For example, signals corresponding to H-5 (and H-6) of **3a-d** appear at δ 7.15-7.17. The differences between the 2-substituted and unsubstituted benzimidazoles are 0.03-0.05 ppm. Similarly, those of H-4 (and H-7) appear at δ 7.52-7.55, which are shifted upfield by 0.15-0.18 ppm from the value of unsubstituted benzimidazole. Effects of 2-aryl substituents in **3e-g** were even less significant. Apparently, furyl, thienyl, and phenyl substituents have very small, and similar effects on the chemical shifts of the protons in the benzimidazole ring.

In contrast to the minimal effect of the 2-aryl substituents, the opposite effect of the 2-benzimidazolyl group on the chemical shift values of furyl and thienyl rings is quite striking. For example, the signals corresponding to 3'-, 4'-, and 5'-H of the furan ring in **3a** appear at δ 7.18, 6.70, and 7.92, respectively. These correspond to downfield shifts of 0.88, 0.40, and 0.54 ppm, respectively. Similar magnitudes of downfield shifts are observed with the thiophene compound **3c** which show a difference of 0.74, 0.25, and 0.60 ppm for 3'-, 4'-, and

Table I

¹H NMR Chemical Shift Values (δ) of 2-Substituted Benzimidazole Derivatives in Dimethyl Sulfoxide-d₆ (0.1 M) at 25°

Compound	4/7	5/6	2'	Position 3'	4'	5'	N-Me (N-H)
3a	7.53	7.17	-	7.18	6.70	7.92	13.00
3b	7.54	7.15	8.36	-	7.06	7.83	12.70
3c	7.54	7.17	-	7.70	7.21	7.84	13.05
3d	7.55	7.17	8.22	-	7.69	7.71	12.70
3e	7.54	7.19	8.10	7.50	7.66	-	12.90
3f	7.68	7.30	[a]	[a]	[a]	[a]	12.95
3g	7.65	7.27	[b]	[b]	[b]	[b]	13.07
4a	8.10	7.71	-	7.87	7.82	8.40	4.30
4b	8.09	7.71	8.65	-	7.17	8.17	3.99
4c	8.09	7.73	-	7.92	7.49	8.31	3.95
4d	8.11	7.75	8.55	-	7.68	8.07	3.97
4e	8.12	7.75	7.88	7.79	7.82	-	3.90
Benzimidazole [c]	7.65	7.22	-	-	-	-	12.50
2-Methylbenzimidazole [d]	7.48	7.10	-	2.50 [e]	-	-	12.18

[a] Other peaks are: 7.72 (m, 2 H), 7.82 (m, 1 H), 8.06 (m, 2 H), 8.13 (d, 1 H, J = 8.8 Hz), 9.15 (d, 1 H, J = 8.0 Hz). [b] Other peaks are: 7.67 (m, 2 H), 8.02 (d, 1 H, J = 8.0 Hz), 8.13 (m, 2 H), 8.35 (dd, 1 H, J = 1.7 and 8.6 Hz), 8.79 (s, 1 H). [c] Benzimidazole. [d] 2-Methylbenzimidazole. [e] Signal of 2-CH₃.

Table II
¹³C NMR Chemical Shift Values (ppm) for 2-Substituted Benzimidazole Derivatives in Dimethyl Sulfoxide-d₆ (0.1 M) at 25°

Compound	Position								Me
	2	3a/7a	4/7	5/6	2'	3'	4'	5'	
3a [a]	146.0	135.3	114.9	117.7	145.1	112.8	110.9	144.1	
[b]	145.6	136.5	121.8	117.2	144.5	112.3	110.4	143.6	
3b [a]	145.8	135.0	107.6	118.0	144.7	121.8	107.6	142.4	
3c [a]	146.9	134.0	115.2	122.7	139.3	128.8	127.3	129.3	
[b]	145.9	134.0	121.1	121.1	141.9	127.2	125.7	127.7	
3d [a]	148.4	132.6	115.0	121.2	128.1	139.5	125.5	126.1	
3e [a]	156.4	135.0	118.8	121.6	126.4 [c]	128.9 [c]	129.8 [c]	[d]	
[e]	151.2	130.4	115.5	122.0	126.6[c]	128.7 [c]	129.5 [c]	[f]	
3f [a]	152.2	135.3	120.0	123.5	[g]	[g]	[g]	[g]	
[a]	134.5	112.2	122.5						
3g [a]	152.1	134.3	119.8	123.5	[h]	[h]	[h]	[h]	
[a]	133.7	112.3	122.7						
4a	147.7	132.3	113.8	122.4	149.8	127.3	113.7	147.8	34.1
4b	143.2	134.5	111.4	119.9	146.4	124.7	105.4	143.8	31.1
4c	146.0	132.3	113.8	119.3	137.0	129.0	127.3	135.8	33.5
4d	147.3	132.1	113.8	120.9	129.8	135.1	127.1	128.9	33.4
4e	150.4	133.0	113.4	121.1	129.5 [c]	130.8 [c]	126.7 [c]	[i]	32.8

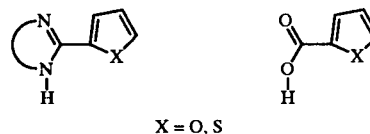
[a] 0.1 M solution. [b] 0.01 M solution. [c] Assignment may not be accurate. [d] C-1' is at 143.8. [e] 0.1 M solution at 100°. [f] C-1' is at 144.7. [g] Other peaks are: 126.2, 127.2, 128.0, 128.4, 128.7, 129.3, 131.0, 131.4, 135.8, 144.8. [h] Other peaks are: 124.8, 126.7, 127.8, 128.0, 128.5, 128.7, 129.3, 129.4, 136.0, 144.9. [i] C-1' at 131.8.

5'-H, respectively. The effects of 3'-furyl and 3'-thienyl substituents on 3', 4', and 5'-Hs are almost the same as those of 2'-furyl and 2'-thienyl substituents (Table I).

As shown in Table II the ¹³C chemical shift values of C-2 in the benzimidazole ring are very close (145.8-148.4 ppm) regardless of the identity and position of the heteroatom in 5-membered ring systems in **3a-d** when the spectra were obtained with 0.1 M solution in dimethyl sulfoxide at 25°. Furthermore, the tautomerism of benzimidazole seems to be taking place fast enough to give the skeleton C₂ symmetry on the nmr time scale. The ¹³C nmr spectral patterns of **3a-d** are very similar to those of 1,3-dimethylbenzimidazolium ions **4a-d**, respectively, which are C₂ symmetric themselves. Therefore, only four peaks corresponding to the benzimidazole carbons appear in each of the ¹³C nmr spectra of **3a-d**. This is in definite contrast to the observed ¹³C nmr spectrum of 2-phenylbenzimidazole (**3e**), which shows 11 peaks, suggesting that here tautomerism is unfavorable, as mentioned in the introduction. The ¹³C nmr spectra of **3a-g** have been obtained in 0.1 M concentration at 25° and the results are listed in Table II.

Although the mechanism of tautomerism in imidazole has been generally believed to be an intermolecular relay of protons, there has not been a reported example of the phenomenon that would rule out the transfer mediated by solvent or other impurities present [18]. One conceivable explanation for the different tautomeric behaviors among 2-phenyl and 2-heteroaryl benzimidazoles may come

from the increase in acidities of N-H by the presence of 2-heteroaryl rings. There are structural similarities between **3** and aryl carboxylic acids as shown below. Although we did not attempt to determine the pK_a values of **3a-d** in dimethyl sulfoxide, it seems reasonable to assume that the order of pK_a of N-H may be **3a** < **3c** < **3e** considering the pK_a of furan-2-carboxylic acid (**2a**), thiophene-2-carboxylic acid (**2c**), and benzoic acid (**2e**) are 3.15, 3.5, and 4.2, respectively, at 25° in water [19]. But the pK_a values of furan-3-carboxylic acid (**2b**, 4.0) and thiophene-3-carboxylic acid (**2d**, 4.1) are very close to that of benzoic acid (4.2). Since only 2-arylbenzimidazoles **3e-g** do not show tautomerism, the phenomena occurring in **3a-d** may not be affected by pK_a's.



An alternative explanation for the process of tautomerism in heteroaryl benzimidazoles **3a-d** may be an intermolecular relay of the proton taking place in a spatial arrangement shown in I. Although the molecule is essentially planar the arrangement depicted in I is feasible because of a low rotational energy barrier about the C-2-C-2' bond. The PCMODEL calculations of the rotational energy barriers for **3a** and **3c** give 3.96 and 3.64 kcal/mole, respectively. Therefore, the repulsion between the C-3'-H of furan (or

thiophene) and the C-4-H of benzimidazole can be avoided without raising the molecular energy by rotating the furan (or thiophene) ring. Consequently, N-1-H-N-3' may lie on a straight line, which may facilitate the tautomerism. The calculated rotational energy barriers for C-3' derivatives **3b** and **3d** are 3.75 and 3.49 kcal/mole, respectively, and the tautomerism is feasible here also by similar argument. However, the arrangement shown in **II** should also be possible with 2-phenyl-, **3e**, and 2-(2-naphthyl)-, **3g**, derivatives because their rotational energy barriers are 2.98 and 2.97 kcal/mole, respectively. Although the differences in rotational barriers between 2-heteroaryl, **3a-d**, and 2-aryl, **3e** and **3g**, are not significant, the smaller barrier in **3e** should make a linear arrangement such as **II** more favorable than **I**, which would make the tautomerism more feasible in **3e**. However, the observation is opposite of our prediction. Therefore, we have ruled out the linear relay of protons as the process of tautomerism in the current system.

An alternative arrangement of two or more 2-substituted benzimidazole skeletons may be a face-to-face approach which may result in a stacked association as illustrated in **III** and **IV**. The two rings in **3** are essentially planar and the 2-aryl ring may lie on the top of the benzene ring of benzimidazole. Such an association may be feasible if a π ring system is polarized by the presence of a heteroatom [20] and consequently, a stacked structure such as **III** is likely to exist in solution whereas **IV** may be difficult to form.

The rationale can be supported by the observation of 11 peaks corresponding to all carbon atoms in **3c** in the ^{13}C nmr spectrum of a 0.01 *M* solution of the compound (Figure 1). Compound **3a** also showed similar phenomena. Decreasing the concentration of the solution seems to reduce the probability of the arrangements **III**. On the other hand, tautomerism in **3e** can be observed at 100° in a 0.1 *M* solution of dimethyl sulfoxide. Apparently, arrangement **IV** can be achievable at a higher temperature. When the hot solution of **3e** was cooled to 25°, an identical ^{13}C nmr spectrum to the spectrum of the freshly prepared solution was obtained, indicating that such an association is not likely with **3e**. The spectrum did not change when the solution was left for 3 days at 25° or the concentration was increased to 0.2 *M*.

Another notable observation is that neither conjugation nor the inductive effect of the heteroatom causes any significant effect on the ^{13}C chemical shifts of the benzimidazole carbons. This may also be an indication that the free rotation of the two rings about the C-2-C-2' (or C-2-C-3') bond occurs. As mentioned earlier, ^{13}C chemical-shift values of the 2-heteroaryl-1,3-dimethylbenzimidazolium iodides **4** are very similar to those of the benzimidazoles **3**. As expected, the presence of a positive charge in the imidazole ring causes a slight upfield shift of the peaks corresponding to the carbons in the benzimidazole skeleton except for those in **4a**; however, those carbons in the 5-membered rings showed slight downfield shifts.

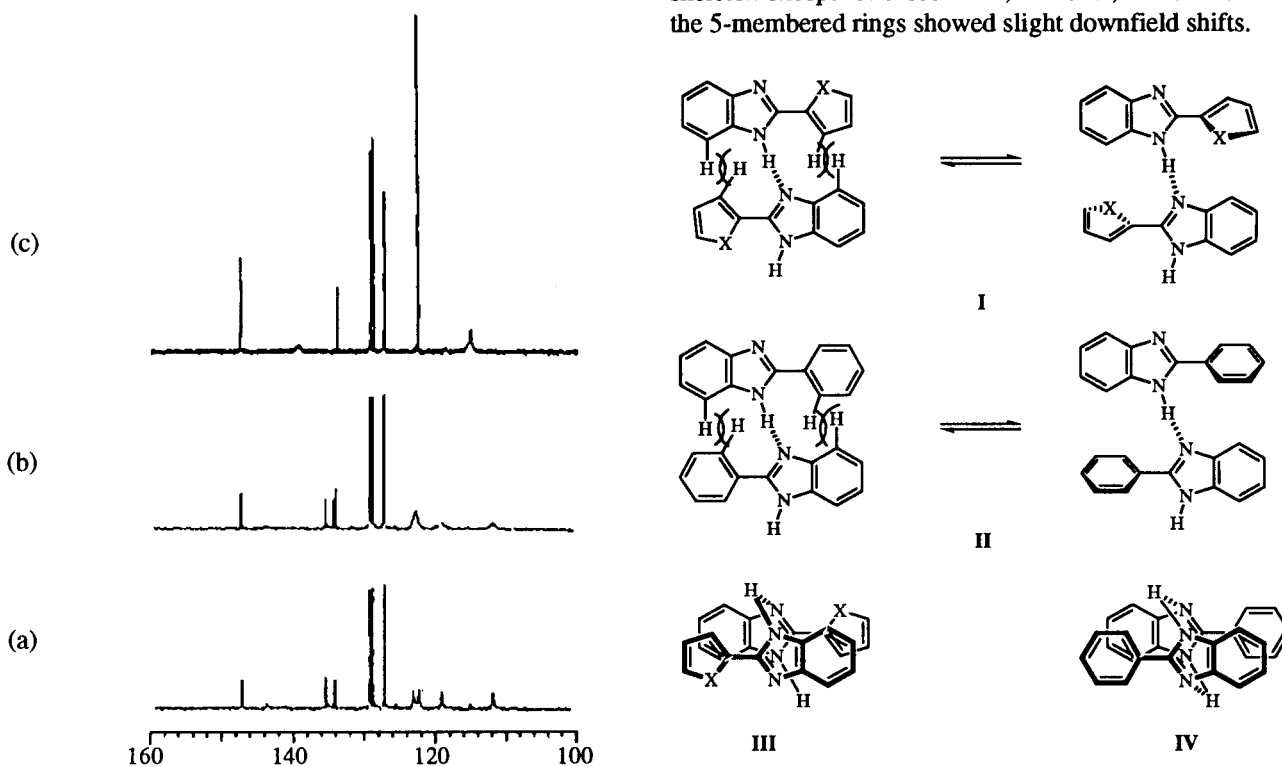


Figure 1. Spectra (^{13}C nmr) of **3c** in dimethyl sulfoxide- d_6 at 25°: (a) 0.01 *M*; (b) 0.05 *M*; (c) 0.1 *M*.

The ^{13}C chemical-shift values of C-3a in the benzimidazoles **3** and the benzimidazolium iodides **4** were about

Table III
Infrared, UV-Visible and Mass Spectral Data for the 2-Substituted Benzimidazoles

Compound	ν_{\max} (KBr), cm^{-1}	λ_{\max} , nm (log ϵ) [a]	m/z (%)
3a	3100-2500 m, 1433 s 745 vs	246 (4.07), 248 (4.05), 299 (4.21) 307 (4.28), 322 (4.17)	184 (M^+ , 57) 113 (100)
3b	3100-2500 w, 1620 m 1470 m, 760 s	292 (4.02), 303 (3.98)	184 (M^+ , 100) 156 (30)
3c	3100-2500 w 1450 s, 1425 s, 745 m	249 (3.82), 316 (4.18), 319 (4.18)	200 (M^+ , 100) 156 (8)
3d	3100-2500 m, 1432 s 750 s	222 (4.32), 301 (4.39), 313 (4.26)	200 (M^+ , 100) 91 (44)
3f	3100-2500 w, 1600 m 750 s, 730 s	226 (4.57), 308 (4.15)	244 (M^+ , 100) 156 (10)
3g	3100-2500 w, 1620 m 810 s, 750 s	242 (3.58), 282 (4.53) 319 (4.44)	244 (M^+ , 100) 156 (12)
4a	2950 w, 1605 s, 1520 s 1490 s, 760 s	223 (4.26), 252 (3.81), 257 (3.80) 304 (4.13), 354 (3-37)	212 (M - HI, 100) 147 (40)
4b	3140 m, 1600 m, 1385 ms 1170 s, 760 s	220 (4.36), 288 (3.91), 358 (3.12) 184 (20)	212 (M - HI, 100)
4c	2920 w, 2450 s, 1425 s 745 m	244 infl (4.01), 293 (4.21) 297 (4.21)	228 (M - HI, 100)
4d	3050 m, 1572 ms, 1480 ms, 771 vs	222 (4.84), 285 (4.57), 354 (2.47)	228 (M - HI, 100) 147 (60)

[a] In 2-propanol-water (4:1 by volume).

Table IV
Analytical Data for the 2-Substituted Benzimidazoles

Compound (Formula)	Yield (%)	Mp, ° dec	Found (%) (Required)		
			C	H	N
3a ($C_{11}H_8N_2O$)	40	315-320 [a]	71.6 (71.8)	4.5 (4.4)	15.4 (15.2)
3b ($C_{11}H_8N_2O$)	95	>320	71.7 (71.8)	4.4 (4.4)	15.3 (15.2)
3c ($C_{11}H_8N_2S$)	78	>320 [b]	66.1 (66.0)	4.3 (4.0)	13.9 (14.0)
3d ($C_{11}H_8N_2S$)	95	320 dec [c]	66.1 (66.0)	3.9 (4.0)	13.8 (14.0)
3f ($C_{17}H_{12}N_2$)	90	284	83.4 (83.6)	4.9 (4.9)	11.6 (11.5)
3g ($C_{17}H_{12}N_2$)	90	209	83.5 (83.6)	4.8 (4.9)	11.8 (11.5)
4a ($C_{13}H_{13}IN_2O$)	70	238-240	45.6 (45.9)	4.0 (3.9)	8.0 (8.2)
4b ($C_{13}H_{13}IN_2O$)	67	200 dec	45.7 (45.9)	3.9 (3.9)	8.1 (8.2)
4c ($C_{13}H_{13}IN_2S$)	62	290-291	43.6 (43.8)	3.7 (3.7)	7.6 (7.9)
4d ($C_{13}H_{13}IN_2S$)	40	264-266	44.0 (43.8)	3.6 (3.7)	7.8 (7.9)

[a] Lit [22] 305-307°. [b] Lit [6] 332-334°. [c] Lit [22] 336-338°.

130-135 ppm regardless of substituents at C-2. The aryl substituents at C-2 also did not have any significant effect on the ^{13}C chemical shifts of *N*-methyl groups (31.1-34.1 ppm) in **4**. This may be additional evidence that furyl, thienyl, or phenyl rings cause little electronic effect to the benzimidazoles or benzimidazolium ions.

The dihedral angle along C-2-C-1' in 2-(1-naphthyl)benzimidazole (**3f**) was calculated to be 43° using the PCMODEL. This, along with high rotational barrier (12.68 kcal/mole) may prohibit linear or face-to-face arrangement of **3f**. As a result, tautomerism is difficult to take place. The fact that tautomerism is dependent on concentration as shown in **3a-d** and concentration-independent in benzimidazole and 2-methylbenzimidazole seems to suggest that the process is not influenced by solvent. Instead, intermolecular relay of protons is involved in the present system.

EXPERIMENTAL

Melting points were determined on a Fischer MEL-TEMP apparatus and are uncorrected. PCMODEL calculations were performed on a Macintosh Quadra 610 with molecular modeling software from Serena Software, Bloomington, Indiana. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian VXR-FT NMR spectrometer with dimethyl sulfoxide- d_6 as the solvent at 500 MHz for 1H and 125 MHz for ^{13}C and were referenced to internal tetramethylsilane. Solutions for nmr analyses were prepared by weighing in the appropriate amount of the solid into a 1.0 ml-volumetric flask and filled from a freshly opened bottle of the solvent to make 0.1 *M* solution. The mixture was sonicated, if necessary, to ensure complete dissolution. Each solution (0.6 ml) was taken into an nmr tube (5 mm) and spectrum was obtained immediately. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 1410 IR spectrophotometer

as potassium bromide pellets. Ultraviolet and visible (uv) spectra were obtained in 2-propanol-water (4:1 v/v) on a Hitachi 1300 single-beam spectrophotometer. Electron-impact mass spectra (ms) were obtained using a Finnigan MAT-95 at the Mass Spectrometry Laboratory in the University of Minnesota. Elemental analyses were performed by the M-H-W Laboratories, Phoenix, Arizona.

Starting Materials.

o-Phenylenediamine (**1**), 2(and 3)-furoic acids, **2a** and **2b**, 2(and 3)-thiophenecarboxylic acids, **2c** and **2d**, 1(and 2)-naphthoic acids, **2f** and **2g**, benzimidazole, 2-methylbenzimidazole, and polyphosphoric acid were purchased from the Aldrich Chemical Co. and used without further purification. 2-Phenylbenzimidazole (**3e**), and 1,3-dimethyl-2-phenylbenzimidazolium iodide (**4c**) were prepared by following the method given in the literature [21].

2-(2'-Furyl)benzimidazole (**3a**).

An Illustrative Procedure for the Preparation of 2-Heteroarylbenzimidazoles.

A mixture of **1** (2.06 g, 19.1 mmoles), **2a** (2.30 g, 20.5 mmoles), and polyphosphoric acid (5.52 g) was stirred in an oil bath at 180° for 1.5 hours. The solution was cooled to room temperature and the pH was adjusted to 10 with 6%-ammonium hydroxide. The tarry solid was collected by filtration and recrystallized from ethanol to give **3a** (1.34 g, 40%) as a white solid.

1,3-Dimethyl-2-(2'-furyl)benzimidazolium Iodide (**4a**).

An Illustrative Procedure for the Preparation of 1,3-Dimethyl-2-Heteroarylbenzimidazolium Iodides.

A solution of sodium hydroxide (0.28 g, 7 mmoles) in methanol (7 ml) was prepared first in a pressure tube to which were added **3a** (1.27 g, 6.89 mmoles) and methyl iodide (6.75 g, 47 mmoles). The tube was sealed and was heated in an oil bath at 110° for 12 hours. After cooling to room temperature the mixture was suspended in acetone and filtered. The residue was dissolved in ethanol (200 ml) by heating, decolorized with charcoal, and recrystallized to give **4a** (1.60 g, 70%).

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REFERENCES AND NOTES

- [1] A. R. Katritzky and J. M. Lazowski, *Adv. Heterocyclic Chem.*, **1**, 311 (1963); *Adv. Heterocyclic Chem.*, **2**, 1 (1963).
- [2] K.-C. Chang and E. Grunwald, *J. Am. Chem. Soc.*, **98**, 3737 (1976).
- [3] P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18**, 353 (1965).
- [4] F. W. Wehrli, A. P. March and S. Wehrli, *Interpretation of Carbon-13 NMR Spectra*, 2nd Ed, John Wiley & Sons, New York, NY, 1988, pp 309-310.
- [5] E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy*, 3rd Ed, VCH, Weinheim, Germany, 1990, p 282.
- [6] E. P. Papadopoulos and U. Hollstein, *Org. Magn. Reson.*, **19**, 188 (1982).
- [7] C. J. Pouchert and J. Behnke, *The Aldrich Library of ¹³C and ¹H FT NMR Spectra*, Vol 3, 1993, 180A.
- [8] Ref [6], 181A.
- [9] C. Marzin and M. E. Peek, *Heterocycles*, **6**, 911 (1977).
- [10] For comprehensive references, see K. Hofmann, *Imidazole and Its Derivatives*, Interscience Publishers, Inc., New York, NY, 1953, pp 260-265.
- [11] D. W. Hein, R. J. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).
- [12] J. C. Craig, N. N. Ekwuribe, C. C. Fu, and K. A. M. Walker, *Synthesis*, 303 (1981).
- [13] M. M. Elichaninov, L. Y. Oleinikova and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 1047 (1979); *Chem. Abstr.*, **92**, 42836v (1980).
- [14] J. G. Smith and J. Ho, *Tetrahedron Letters*, 3541 (1971).
- [15] G. Neef, U. Eder, and G. Sauer, *J. Org. Chem.*, **46**, 2824 (1981).
- [16] B. George and E. P. Papadopoulos, *J. Org. Chem.*, **42**, 441 (1977).
- [17] L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, W. A. Benjamin, Inc, New York, NY, 1968, p 105.
- [18] A. N. Nesmeyanov, N. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, *Tetrahedron*, **31**, 1461 (1975).
- [19] C. W. Bird and G. W. H. Cheeseman, in *Comprehensive Heterocyclic Chemistry*, Vol 4, A. R. Katritzky and C. W. Rees eds, Pergamon Press, New York, 1984, p 71.
- [20] C. A. Hunter and J. K. M. Sanders, *J. Am. Chem. Soc.*, **112**, 5525 (1990).
- [21] Z. N. Timofeeva and A. V. El'tsov, *Zh. Obshch. Khim.*, **37**, 2590 (1967).
- [22] Merck & Co., Inc., BP 966 796/1964; *Chem. Abstr.*, **62**, 2779 (1965).