**179.** *The Ionization Constants, and Ultraviolet and Infrared Spectra of 4(7)- and 5(6)-Halogenated Benzimidazoles.*

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For a series of 4(7)- and 5(6)-halogenated benzimidazoles, the ionization constants show that for compounds with a halogen atom in either the 4(7)- or the 5(6)-position the basicity decreases in the order F > I > Cl > Br. Attempts have been made to correlate the effect of substituents on the $pK_a$ values of benzimidazoles by means of the Hammett equation; no relationship could be established for 5(6)-substituted compounds, presumably because of the tautomeric nature of the ring, but a satisfactory correlation was obtained for the 4(7)-halogenated benzimidazoles. The ultraviolet data indicate that the implied order of overall electron-release for halogen atoms in both the 4(7)- and the 5(6)-position is I > Br > Cl > F. The infrared spectra of these halogenated benzimidazoles are discussed.

THE ionization constants of benzimidazole [1] and various substituted benzimidazoles have been reported. The most complete study of $pK_a$ values is that of Davies *et al.*[2] who determined the values for a large number of substituted benzimidazoles both in water and in

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[1] (a) Taylor, *J.*, 1948, 765; (b) Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162; (c) Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

[2] Davies, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420.
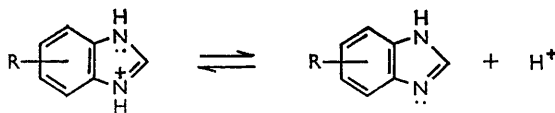
50% ethanol. Values obtained under different conditions vary considerably, and in order to establish any correlations for a series of compounds the same conditions must be used. Water is a satisfactory solvent but too few benzimidazoles are sufficiently soluble in it. Although 50% ethanol is a good solvent for most benzimidazoles, $pK_a$ determinations in organic solvents are not very accurate. To overcome this difficulty we used just enough alcohol to dissolve the benzimidazoles completely and some sodium chloride to keep the ionic strength constant during titrations.[3] The same small amount of alcohol was used in all cases and the values obtained were in good agreement with values previously determined in aqueous media.

It is well known that halogen atoms can exert inductive $(-I)$ and mesomeric $(+M)$ effects that oppose each other. Since all halogenated benzimidazoles are less basic than benzimidazole, regardless of position of substituent, the halogen atoms must exhibit a predominantly base-weakening inductive effect $(-I)$. The order of basicity for compounds with a halogen atom in either the 4(7)- or the 5(6)-position is $F > I > Cl > Br$. Although fluorine is the most electronegative atom, it is also the most likely to donate electrons by a base-strengthening mesomeric effect $(+M)$. Chlorine and bromine show a smaller $(+M)$ mesomeric effect, and their inductive effect $(-I)$ is more noticeable. Since iodine shows the least base-weakening inductive effect, iodobenzimidazoles are more basic than their chloro- or bromo-analogues.

A 4(7)-halogenated benzimidazole is always less basic than one having the same halogen in the 5(6)-position, as would be expected, since inductive withdrawal $(-I)$ falls off with increasing distance from the site affected. The greatest difference in basicity is between the 5(6)- and the 4(7)-fluoro-isomers. This supports the belief that mesomeric effects should be more important in the 5(6)-position and inductive effects should be stronger in the 4(7)-position.

The polar effects of substituents on rates or equilibria may be correlated with the nature of the substituents by means of the Hammett equation, $\log (k/k_0) = \rho\sigma$, where $k$ is a rate, or equilibrium, constant for a substituted compound, $k_0$ that for the corresponding unsubstituted compound, $\rho$ is the reaction constant and is a measure of the susceptibility of a given reaction series to polar substituents, and $\sigma$ is the substituent constant, independent of the nature of the reaction. The transmission of electrical effects from one ring to a position on an adjacent ring of a fused ring system has been studied by Jaffé.[4] These studies have been extended to fused ring systems which contain nitrogen, such as the quinoline system [5] and the indole system.[6] However, no reports could be found of an attempt to study the transmission of electrical effects from a benzene ring to a fused ring containing two heteroatoms such as the imidazole ring. Such a correlation would not be expected to hold unless tautomerism was restricted and the substituent could be considered either *meta* or *para* to the reactive centre.

The reaction studied was the ionization of the conjugate acid of a benzimidazole. The Hammett equation held only in cases where a halogen atom was in the 4(7)-position.



In these cases, if Jaffé's $\sigma_m$ values were used, a reaction constant of $+2\cdot13$ was obtained. This value shows that the ionization of the conjugate acid of a benzimidazole is facilitated by a low electron-density at the reaction site. The results indicate that for the 4(7)-halogenated benzimidazoles electronic effects are transmitted to the basic nitrogen of the

[3] Irwin and Irwin, *J. Amer. Chem. Soc.*, 1947, **69**, 1091.
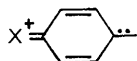[4] Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 4261.
[5] Baciocchi and Illuminoti, *Gazzetta*, 1957, **87**, 981.
[6] Melzer, *J. Org. Chem.*, 1962, **27**, 496.

imidazole ring through the carbon *meta* to the 4(7)-carbon. Thus, the tautomeric form in which the halogen is *ortho* to the NH group of the imidazole ring appears to be the one which plays an important role in the transmission of electronic effects. This tautomeric form could be stabilized by electrostatic attractions between the halogen atom and the hydrogen atom of the N–H bond. In the case of 4(7)-fluorobenzimidazole support for such an electrostatic attraction derives from the fact that this compound sublimes under reduced pressure above 100°, and the 5(6)-isomer does not.

The most comprehensive study of ultraviolet spectra of substituted benzimidazoles is that of Leandri *et al.*[7] A qualitative study of inductive and mesomeric effects on the ultraviolet spectra of substituted benzimidazoles may be found in this work. Recent studies[8] of the ultraviolet absorption spectra of a large number of halogenated benzenes support the view that the implied order of overall electron release for the halogens is I > Br > Cl > F. This order is not in agreement with the accepted order of mesomeric effects, since ground-state calculations have shown that the resonance integrals, which are a measure of the orbital overlap of two bonded atoms, decrease in the order F > Cl > Br > I for –C=C–X systems. This apparent discrepancy is attributed to the fact that excited states involved in electronic absorption spectra are not identical with activated complexes involved in chemical reactions and, therefore, should be affected differently by the halogen atoms. Excited states for the heavier halogens are said to be more energetically stable and this is offered as an explanation for the order observed from ultraviolet spectra data.[8]

The effect of a single halogen substituent on the selective absorption of pyridine was studied by Brown and McDaniel,[9] who found that the absorbancy index of the maxima in the 250—300 mμ region was in the order F > Cl > Br > I for both the free and the protonated 3-halogenopyridines. However, the corresponding maxima in the spectra of the free and the protonated 2-halogenopyridines gave the opposite order, I > Br > Cl > F. The apparent mesomeric effect of halogens observed from ultraviolet data has been attributed[8] to the release of electrons in an electronic state such as (I).


(I)

While it is clear from $pK_a$ values that halogen atoms exert predominantly an inductive effect, since they all decrease the basicity of benzimidazole, the ultraviolet data support the existence of resonance effects similar to those observed for the halogenated benzenes. The introduction of a halogen atom causes bathochromic displacements of the characteristic bands of the benzimidazole ring. The wavelength at which a particular absorption band occurs for a 4(7)- or a 5(6)-halogenated benzimidazole, as compared to benzimidazole, decreases in the order I > Br > Cl > F. The formation of excited electronic states such as (I) would be expected to produce a bathochromic displacement in the bands associated with the benzene ring. The smaller inductive effect of chlorine or bromine would be less apt to hinder the formation of electronically excited states which depend on donation of electrons by the substituent. The introduction of an iodine atom in the 5(6)-position causes a more noticeable displacement of all bands towards longer wavelengths than the other halogens. This supports the view that there is an apparent increased mesomeric effect of iodine in the excited electronic state.

The relevant molecular vibrations of heterocyclic compounds are the subject of recent reviews,[10] but these contain few references to the benzimidazole ring. Although infrared absorption values for various substituted benzimidazoles are available, the first systematic work reported is that for simple alkyl- and perfluoroalkyl-benzimidazoles.[11] Some definite

[7] Leandri, Mangini, Montanari, and Passerini, *Gazzetta*, 1955, **85**, 769.
[8] Forbes, *Canad. J. Chem.*, 1959, **37**, 1977; 1960, **38**, 1104; 1961, **39**, 1131, 2295.
[9] Brown and McDaniel, *J. Amer. Chem. Soc.*, 1955, **77**, 3752, 3756.
[10] Katritzky, *Quart. Rev.*, 1959, **13**, 353; Katritzky, " Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, 1963.
[11] Morgan, *J.*, 1961, 2343.

assignments of infrared bands for the out-of-plane CH deformations of the benzene ring fused to the five-membered ring have also been reported.[12]

The infrared spectra of benzimidazoles are very complex, and difficult to obtain since the compounds are not very soluble in the usual solvents. Because of this, all spectra were determined as potassium bromide discs in spite of the fact that in this medium certain bands originate from some type of crystal interaction rather than to a vibration of the molecule itself. Although in dilute solutions benzimidazoles are reported [2] to show a single sharp band near 3400 cm.$^{-1}$ the spectra of all our compounds showed strong broad bands from 3300 to 2800 cm.$^{-1}$ due to polymeric association through intermolecular hydrogen bonding. The 1650—1500 cm.$^{-1}$ region is a very characteristic one in the benzimidazole spectrum. The 5(6)-halogenated benzimidazoles show two bands of about the same intensity in this region, one *ca.* 1620 cm.$^{-1}$ and the other *ca.* 1590 cm.$^{-1}$; the latter is usually fairly intense because of conjugation between the benzene and imidazole rings. The frequencies and intensities of these bands decrease in the order F > Cl ∼ Br > I. The 4(7)-substituted benzimidazoles show similar bands in this region. The band *ca.* 1580 cm.$^{-1}$ is more intense than the one *ca.* 1600 cm.$^{-1}$ for all 4(7)-halogenated benzimidazoles. The out-of-plane CH bending frequencies of some substituted benzimidazoles have been definitely assigned in the 850—800 and 900—830 cm.$^{-1}$ regions. The spectra of 5(6)-halogenated benzimidazoles show broad strong bands in these regions and it is difficult to make specific assignments. The out-of-plane CH bending frequencies of 4(7)-substituted benzimidazoles should cause absorption in the 800—700 and 720—685 cm.$^{-1}$ regions. The infrared spectra of the 4(7)-halogenated benzimidazoles show two intense bands *ca.* 783—774 and 773—728 cm.$^{-1}$ which could be ascribed to the out-of-plane bending frequencies of 4(7)-substituted benzimidazoles.

EXPERIMENTAL AND RESULTS

The Phillips reaction [13] is not a good method for the preparation of pure halogenated benzimidazoles although it had been used for 5(6)-fluoro-,[14] 4(7)- and 5(6)-chloro-,[15,16] and 4(7)- and

TABLE 1.

Ionization constants and melting points of 4(7)- and 5(6)-halogenated benzimidazoles.

| Benzimid- azole | p$K_a$ in 5 : 95 ethanol–water (0·1M in NaCl) at 30° ± 0·5° | Lit. pK$_a$ in water | in 50% ethanol | M. p. | Lit. m. p. |
|---|---|---|---|---|---|
| Unsubst. ...... | 5·52 | 5·53 [1b,c] | 4·98 * | 169—170° | 170—172° * |
| 5(6)-F ......... | 5·21 | 5·11 [19] | — | 132—133 | 132 [18] |
| 5(6)-Cl ......... | 4·98 | — | 3·92 * | 117—118, 125—126 | 124—126 * |
| 5(6)-Br ...... | 4·89 | — | — | 130—131 | 137 * |
| 5(6)-I ......... | 5·03 | — | — | 144—145 | 144—145 [19] |
| 4(7)-F ......... | 4·80 | 4·40 [19] | — | 189—190 | 180—185 [18] |
| 4(7)-Cl ......... | 4·73 | — | — | 170—171 | 170—171 [15] |
| 4(7)-Br ...... | 4·70 | — | — | 167—168 | 168 [15] |
| 4(7)-I ......... | 4·75 | — | — | 188—189 | 188—189 [19] |

* K. Hofmann in " Imidazole and its Derivatives. Part I," ed. Weisberger, Interscience, New York, 1953, p. 379.

5(6)-bromobenzimidazole.[15,17] Both 4(7)- and 5(6)-fluorobenzimidazole had been previously prepared by the decomposition of the corresponding diazonium fluoroborates.[18]

[12] O'Sullivan, *Spectrochim. Acta*, 1960, **16**, 764.
[13] Phillips, *J.*, 1928, 2393.
[14] Smith, jun., and Steinle, jun., *J. Amer. Chem. Soc.*, 1953, **75**, 1292; Takatori, Yamada, Arai, and Nakagawa, *Yakugaku Zasshi*, 1958, **78**, 108.
[15] Montanari and Passerini, *Boll. sci. Fac. Chim. ind. Bologna*, 1953, **11**, 42.
[16] Fischer, *Ber.*, 1904, **37**, 556; Steck, Nachod, Ewing, and Gorman, *J. Amer. Chem. Soc.*, 1948, **70**, 3406; Crowther, Curd, Davey, and Stacey, *J.*, 1949, 1260.
[17] Fischer and Mouson, *Ber.*, 1905, **38**, 325; Phillips, *J.*, 1930, 2400.
[18] Fisher and Joullié, *J. Org. Chem.*, 1958, **23**, 1944.
[19] Rabiger and Joullié, *J. Org. Chem.*, 1961, **26**, 1649.

4(7)- and 5(6)-Iodobenzimidazole were prepared by the reaction of the corresponding diazonium fluoroborates with potassium iodide,[19] and 4(7)- and 5(6)-chloro- and 4(7)- and 5(6)-bromobenzimidazole by modified Sandmeyer reactions.

TABLE 2.

Absorption maxima (m$\mu$) and (in parentheses) molecular extinction coefficients for 4(7)- and 5(6)-halogenated benzimidazoles.

| | | | |
|---|---|---|---|
| Unsubst. ...... | 277(3·65), 270(3·67), 242(3·72) | 4(7)-F ... | 273(3·30), 263(3·37), 242(3·71) |
| 5(6)-F ......... | 280(3·67), 275(3·73), 242(3·72) | 4(7)-Cl ... | 280(3·55), 272(3·63), 253(3·86), 248(3·63) |
| 5(6)-Cl ......... | 284(3·63), 279(3·69), 246(3·68) | 4(7)-Br ... | 280(3·56), 271(3·66), 253(3·87) |
| 5(6)-Br ...... | 286(3·79), 280(3·78), 235(3·99) | 4(7)-I ... | 282(3·65), 274(3·82), 255(4·00) |
| 5(6)-I ......... | 288(3·65), 281(3·70), 249(3·69) | | |

*4(7)-Chlorobenzimidazole.*—4(7)-Aminobenzimidazole dihydrochloride [18] (6·9 g.) was suspended in water (5 ml.) and concentrated hydrochloric acid (8·3 ml.), and a solution of sodium nitrite (2·3 g.) in water (7 ml.) was added to it with stirring at 0°. Freshly prepared cuprous chloride was dissolved in concentrated hydrochloric acid (15 ml.) and cooled to 0°, and the solution of the diazonium chloride added to it from a separatory funnel with the stem below the surface of the liquid. The cuprous salt of 4(7)-chlorobenzimidazole was filtered off, suspended in 4N-hydrochloric acid, and hydrogen sulphide passed through the suspension. The precipitate formed was filtered off and the filtrate neutralized with ammonium hydroxide, to precipitate 4(7)-chlorobenzimidazole, which was recrystallized from benzene–light petroleum (b. p. 60—80°) (yield 24%).

TABLE 3.

Characteristic bands (cm.$^{-1}$) in the spectra of 4(7)- and 5(6)-halogenated benzimidazoles.

| Unsubst. | 5(6)-F | 5(6)-Cl | 5(6)-Br | 5(6)-I | 4(7)-F | 4(7)-Cl | 4(7)-Br | 4(7)-I |
|---|---|---|---|---|---|---|---|---|
| 1622m | 1630s | 1620m | 1620m | 1614m | 1636m | 1621m | 1620m | 1617w |
| 1604m | 1602m | 1584w | 1587w | 1573m | 1592s | 1587s | 1579s | 1573s |
| 1591ms | 1517m | 1464s | 1510s | 1495m | 1517s | 1504m | 1505w | 1507w |
| 1550w | 1467s | 1456s | 1481s | 1472s | 1484m | 1481s | 1481s | 1484s |
| 1498w | 1435s | 1440m | 1461m | 1458s | 1461s | 1460s | 1458m | 1451s |
| 1480s | 1422m | 1420s | 1409m | 1443s | 1423s | 1414s | 1440m | 1404s |
| 1462s | 1361s | 1396m | 1381w | 1430m | 1369s | 1357s | 1410m | 1361m |
| 1409s | 1353s | 1348m | 1340s | 1406s | 1325w | 1294s | 1408s | 1351s |
| 1367s | 1292s | 1341m | 1290s | 1346m | 1301s | 1273s | 1348s | 1294s |
| 1348m | 1269w | 1288s | 1271s | 1334m | 1293m | 1226s | 1291s | 1274s |
| 1302s | 1242s | 1274s | 1256w | 1288s | 1284s | 1192s | 1270s | 1227s |
| 1272s | 1201w | 1253s | 1238w | 1267s | 1274s | 1153m | 1226m | 1194s |
| 1240s | 1177w | 1236s | 1191w | 1254s | 1265w | 1143m | 1181m | 1150w |
| 1197s | 1156s | 1195m | 1148w | 1241m | 1240s | 1085w | 1143w | 1132s |
| 1191m | 1128s | 1170s | 1124w | 1204w | 1211w | 1048m | 1109w | 1060w |
| 1165w | 1103s | 1150m | 1066m | 1195w | 1170s | 1015w | 1048w | 1047m |
| 1131s | 945s | 1125w | 1047w | 1173w | 1151s | 965s | 962s | 958s |
| 1113w | 934w | 1075w | 952s | 1151m | 1049s | 928s | 909s | 893s |
| 1004s | 852s | 1055w | 891s | 1132m | 953s | 855m | 855m | 863s |
| 956s | 834s | 1018w | 831m | 1124m | 929w | 835s | 826m | 827s |
| 936m | 823s | 957s | 791s | 1039m | 866s | 778s | 791w | 774s |
| 890ms | 806s | 902s | 736m | 957s | 850s | 728s | 776m | 733s |
| 849m | 762m | 849s | | 943m, 885s, | 783s | | 733s | |
| 769s | | 797s | | 876s, 862s, | 733s | | | |
| 742s | | 756w | | 839w, 805s, | | | | |
| | | 703m | | 798s, 785m, | | | | |
| | | | | 756w | | | | |

5(6)-Chlorobenzimidazole, prepared by the reaction of 1,2-diamino-4-chlorobenzene with formic acid, was obtained in two forms, that which was precipitated first having m. p. 125—126°. When the filtrate was set aside, material of m. p. 117—118° was obtained. This phenomenon had been reported previously.[20] The two forms were similar in all respects except for their melting points and *X*-ray patterns; they may be polymorphs. The procedure described for the preparation of 4(7)-chlorobenzimidazole, when used to prepare 5(6)-chlorobenzimidazole, yields only one form, m. p. 120—122°. 4(7)- and 5(6)-Bromobenzimidazole were prepared as for 4(7)-chlorobenzimidazole, but using cuprous bromide and the dihydrobromides. The 4(7)-isomer, after several recrystallizations from benzene–light petroleum (b. p.

[20] Crowther, Curd, Davey, and Stacey, *J.*, 1949, 1260.

60—110°) and hexane, had m. p. 166—168° (1%); the 5(6)-*isomer* had m. p. 130—131° (26%). Since this melting point did not agree with the literature values, the compound was analysed (Found: C, 42·9; H, 2·7; Br, 40·3; N, 14·4. $C_7H_5BrN_2$ requires C, 42·6; H, 2·5; Br, 40·6; N, 14·2%).

*Potentiometric Titrations.*—A Leeds and Northrup pH-meter equipped with glass and saturated calomel electrodes was used in the titrations. The meter was calibrated against two buffers: (1) 0·05M-potassium hydrogen phthalate (pH 4·00 at 30°); (2) 0·025M-potassium dihydrogen phosphate and 0·025M-disodium hydrogen phosphate (pH 6·85 at 30°). The solutions to be titrated were prepared by dissolving the compound ($10^{-5}$ mole) in distilled water (5 ml.) and absolute ethanol (5 ml.). This solution was then mixed with 0·4M-sodium chloride solution (25 ml.) and distilled water (65 ml.). The resulting solution (100 ml.) was $10^{-4}$M with respect to the compound analysed and was titrated with $10^{-3}$M-hydrochloric acid standardized against sodium carbonate with Methyl Purple as indicator. The results are shown in Table 1.

*Ultraviolet Spectra.*—The ultraviolet spectra were obtained on a Beckman DU spectro-photometer modified by Process and Instruments Co. with an attached Leeds and Northrup Speedomax Type G recorder with 1-cm. quartz cells. The optical densities used to calculate the molecular extinction coefficients were corrected values.[21] The results are shown in Table 2.

*Infrared Spectra.*—Infrared measurements were made for potassium bromide discs on a Perkin–Elmer model 421 spectrophotometer, calibrated against a polystyrene film; all values are corrected (Table 3).

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   [21] G. Rao, " Ultraviolet and Visible Spectroscopy, Chemical Applications," Butterworths, London, 1961, p. 6.