Mass Spectral Behavior of 5(6)-Substituted Benzimidazoles

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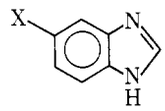
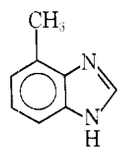
Three general classes of 5(6)-substituted benzimidazoles were compared according to common or similar fragmentation pathways in the mass spectrometer. The 5(6)-alkyl derivatives fragment through a common intermediate of *m/e* 131 as demonstrated by metastable ion ratios for the 2-^{13}C-labeled compounds. It is suggested that this intermediate possesses a ring-expanded structure resembling that of 1,3-diazaazulene whose fragmentation behavior is very similar. For both species, competitive pathways exist for loss of the 2 carbon and carbocyclic ring carbons with HCN or CN· fragments. Moreover, the expected loss of the 2 carbon of the imidazole ring with these fragments is *not* the predominant process. The second general group of derivatives fragments by complete loss of the 5(6) substituent (NO_2, Cl, CO_2H, $COCH_3$) to give a common ion of *m/e* 117. Again, the metastable losses of HCN and H^{13}CN from the 2-^{13}C-labeled derivatives confirms the common structure of this ion and indicates predominant loss of carbocyclic ring carbons. Finally, the similar behavior of several 5(6)-alkenylbenzimidazoles implies fragmentation through a common 143 ion which may result from a ring-expansion process similar to that of styrene. The three main fragmentation pathways observed here should be general for a variety of benzimidazole derivatives. More importantly, the metastable ratio technique for common ion identification is found to be much more reliable for ^{13}C-labeled compounds than for those with ^{2}H labeling. Increased availability of ^{13}C-enriched reagents makes this technique one of broad applicability in mass spectral investigations.

The application of mass spectrometry to the identification and structure determination of heterocyclic compounds has recently been experiencing explosive growth. For such application, the observation of straightforward fragmentation behavior general to a given class of heterocycles would be most desirable. Such is not often the case, however. A recent survey indicates that rearrangements and competitive fragmentation pathways are very common for heterocyclic compounds.[1] These processes make difficult the understanding of the details of the mass spectral behavior. In this paper, we discuss the general and detailed behavior of several 5(6)-substituted benzimidazoles (structures I–XVI). Isotopic labeling is employed to indicate possible fragmentation mechanisms and probable intermediate structures. The techniques presented here are general and should be useful for indicating and establishing ionic structures and fragmentation pathways for other heterocycles.



I, X = CH_3
II, X = CH_2CH_2OH
III, X = CH_2CH_2Cl
VII, X = CO_2H
VIII, X = $COCH_3$
IX, X = NO_2
X, X = Cl
XI, X = $CH(OH)CH_3$
XII, X = $CH{=}CH_2$
XIII, X = $CH{=}CHCO_2H$
XIV, X = $CH{=}CHCO_2CH_3$
XV, X = $CH{=}CHCO_2CH_2CH{=}CH_2$
XVI, X = $CH{=}CHCONHCH_2CH{=}CH_2$



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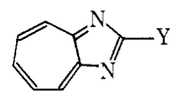
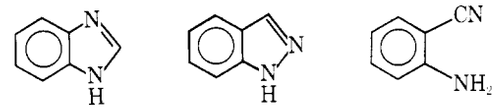


V, Y = SH
VI, Y = SH

An extensive literature investigation of benzimidazoles revealed a paucity of mass spectral information despite widespread industrial and academic interest in this family of heteroaromatics.[2] Only recently, during the course of our work, did reports appear concerning more detailed investigations of the parent benzimidazole[3,4] and 1-ethylbenzimidazole.[5] This work supports our contention that common fragmentation pathways may exist for compounds which are structurally similar or even quite different. For example, for benzimidazole, indazole, and *o*-aminobenzonitrile (below), rearrangement of the molecular ions of all three compounds to a common structure is observed prior to fragmentation of the metastable ions.[3,4] Our work with substituted benzimidazoles and related heterocycles indicates that extensive rearrangement to common structures probably occurs for many daughter ions as well as molecular ions.



In this paper, extensive use is made of ^{13}C labeling in the 2 position of benzimidazoles for two purposes. In our initial observations on unlabeled and ^{2}H-labeled benzimidazoles, it was apparent that rearrangement processes and/or competitive fragmentations were occurring for many derivatives. It was necessary to determine whether either or both of these possibilities involved only hydrogen scrambling or if carbon atoms were involved as well in skeletal rearrangements. The second goal was to develop a technique involving the labeled carbon to confirm common ionic structures. This technique involves metastable ions and requires two or more competitive fragmentations of the ion suspected of a common structure. For two major groups of 5(6)-substituted benzimidazoles, common structures were found for the major daughter ions using this technique. In addition, skeletal rearrangements and competitive fragmentations were found to be quite extensive for all derivatives studied.

The details of the fragmentation behavior are discussed in terms of general pathways and behavior. Three major groups were observed with classification made according to the most intense pathway. Of course, with heterocycles such as benzimidazoles, several competitive pathways may be observed for any given derivative and some of the more interesting and useful of the minor paths will be described on an individual basis.

Procedures

The syntheses of several deuterium-labeled derivatives as well as the 2-^{13}C-labeled compounds are given in the Exper-

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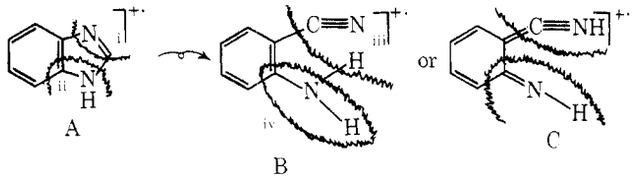
imental Section. The procedure developed for the latter was based on generality as well as conservation of the expensive carbon-13-containing reagent used. Phillip's original synthesis of benzimidazoles[6] employs ring closure of an aromatic ortho diamine with a large excess of formic acid in refluxing 4 N hydrochloric acid. We found that only a slight excess of formic acid is necessary to give almost quantitative yields under similar conditions. Furthermore, rather than using commercially available [^{13}C]formic acid, the much less expensive sodium [^{13}C]formate was employed with in situ liberation of the acid. These two measures brought the cost of 2-^{13}C-labeled benzimidazoles enriched to 90% down to ca. $30 per 200 mg sample.

For replacement of exchangeable hydrogens with deuterium, prior exchange by recrystallization or reprecipitation from $^{2}H_2O$ gave disappointing results. Reexchange of the deuterium in the sample with exchangeable hydrogens absorbed on the walls of the source is the probable explanation, since more than adequate time exists for ca. 50 collisions with the source walls before ionization takes place.[7] This problem was overcome by introducing a $^{2}H_2O$ slurry of the sample into the source on the solid probe. Repeated spectral scans were then made for several minutes after operating pressures were reached. The amount of exchangeable deuterium incorporated into the parent ions varied in a nonregular manner with time, and the spectrum or spectra with the highest isotope incorporation were employed. Deuterium exchange was routinely increased to 90% or better with this method.

The procedure presented here for the comparison of ionic structures in the mass spectrometer is based on two requirements. The ion under consideration must undergo two or more competitive fragmentations and each must exhibit a measurable metastable peak. The comparison is made of the ratio of intensities of the metastable peaks of the competitive fragmentations. For ions of the same structure but from different parent or precursor species, the ratio of metastable intensities will be the same.[8-11]

The requirement of competitive fragmentations is generally satisfied by losses of fragments of different molecular weight and composition.[9,10] However, with nitrogen-containing heteroaromatics such as benzimidazoles, almost all fragmentations involving the skeletal framework result in loss of HCN. The hydrogen, carbon, and nitrogen atoms lost with this fragment may come from different parts of the molecule, however. For example, in the scheme below, two possible intermediates for partial or complete "scrambling" of carbon atoms involved in HCN loss are presented. For structure A,



it is possible that two mutually exclusive, competitive fragmentations occur which do not require prior rearrangement of the benzimidazole nucleus. Thus, fragments i and ii would involve completely different HCN molecules. The second possibility involves rearrangement of the nucleus prior to fragmentation, for example, to structure B or C. Structure B might then lose HCN by competitive loss of fragments iii and iv.

A further consideration is the energy of the species under consideration. Thus, for example, one can envision a situation where the ionic lifetime is comparable to the time required for rearrangement. Competitive losses of HCN could occur from structure A via fragment i and from structure B via fragment iii. A priori, the presence of a ^{2}H or ^{13}C label would not distinguish among these three (and other) possibilities. However, because of energetic requirements, it is possible to eliminate some of these possibilities from consideration.

It is well known that ionization of molecules with 70 eV electrons results in molecular ions with a broad range of energies and lifetimes.[8] For our purposes, it is possible to break this distribution down into three general groups.[8] First, those parent ions with insufficient energy to fragment before arriving at the detector are seen as molecular ions. Second, those parent ions with sufficient energy to fragment in the source are detected as daughter ions. (Qualitatively, the higher the initial ionic energy, the greater the probability of continued fragmentation to daughter ions of lower molecular weight.) Finally, parent ions with intermediate energies and lifetimes fragment between the source and the detector and are observed as metastable peaks. For each daughter ion, of course, similar energetic requirements again lead to observation of the daughter ion, a metastable ion, or a second daughter ion.

Examining the processes discussed above for structures A and B, for example, it is possible to qualitatively relate the type of process with the relative energy and lifetime of the ion under consideration.[12] That is, it has been observed that direct cleavage fragmentations, e.g., loss of i or ii from A, are favored at high energies. Rearrangement processes, e.g., to structure B or C, are favored at lower energies and longer lifetimes. Thus, if competitive fragmentations are occurring from two different structures, e.g., i from A and iii from B, the former should be most evident with the stable (parent and daughter) ion peaks while the latter should predominate almost completely with metastable peaks. To rephrase, if rearrangement is taking place it will generally be complete on the time scale of the metastable peaks.

This conclusion has been widely supported by experimental observations involving both alkanes and heteroatom-containing compounds.[3,4,9-11,13,14] In almost all cases, rearrangement processes which were incomplete for stable ions were found to be complete for the longer lived metastables. An example of special interest involves the monodeuterated derivatives of benzimidazole, indazole, and *o*-aminobenzonitrile previously mentioned.[3,4] For all three isomeric compounds, losses of HCN and ^{2}HCN were competitive for both the stable and metastable ions. With the stable ions, the ratios of HCN to ^{2}HCN lost from the parent ions were widely different for the three compounds. However, the ratios of metastable peaks for these two losses were within experimental error for all three. The two conclusions which may be drawn from the identical isotopic metastable ratios are, first, that the competitive losses of HCN and ^{2}HCN involve rearrangement that may be incomplete for stable ions but complete for metastable ions; and second, the rearranged structures are identical for all three compounds. The obvious corollary to the former is that for the stable ions, fragmentation may be occurring from both the rearranged and unrearranged structures, the amount from each being somewhat dependent on how similar the common rearranged structure is to each of the three parent structures.

In this paper, the confirmation of a common structure relies on the ratio of metastable peak intensities for the competitive losses of $H^{13}CN$ and $H^{12}CN$. While this would be a trivial comparison if no rearrangement processes were taking place and a single fragmentation mechanism were observed, such is definitely not the case for benzimidazoles. The a priori prediction for 2-unsubstituted benzimidazoles in general is that loss of HCN should involve the 2 carbon almost exclusively.[15] In fact, loss of carbocyclic carbons compares favorably or predominates for all the 2-labeled derivatives studied here.[16] Thus, the 2-^{13}C label provides a means of confirming common structure as well as assisting in the elucidation of the nature of the rearranged structures and the types of compet-

Table I. Summary of the Mass Spectral Behavior of 5(6)-Substituted Benzimidazoles

5(6)-substituent	registry no.	base ion (M = parent)	M − HCN	no. of paths[a]	major path	ring exp.[b]	^2H[c]	^{13}C[d]	synth. ref
(VII) CO_2H	15788-16-6	155 M	no	1	M − OH − CO − HCN	no			6
(VIII) $COCH_3$	58442-16-3	145	no	1	M − CH_3 − CO − HCN	no	117	117	*e*
(IX) NO_2	94-52-0	163 M	no	2	M − NO_2 − HCN	no	?	117	6
(X) Cl	4887-82-5	152 M	yes	2	M − Cl − HCN M − HCN − HCN	no	?	117	6
(XI) $CH(OH)CH_3$	66792-92-5	119	no	2	M − CH_3 − CO − HCN				
(XII) $CH{=}CH_2$	4070-35-3	144 M	yes	3	M − C_2H_2 − HCN	144? 143	144 143		23
(XIII) $CH{=}CHCO_2H$	51819-00-2	188 M	no	2	M − OH − CO − HCN	143			27
(XIV) $CH{=}CHCO_2CH_3$	66792-93-6	202 M	no	2	M − CH_3O − CO − HCN	143			*e*
(XV) $CH{=}CHCO_2CH_2$-$CH{=}CH_2$	66792-94-7	171	no	2	M − $CH_2{=}CH$-CH_2O − CO − HCN	143			*e*
(XVI) $CH{=}CHCONHCH_2$-$CH{=}CH_2$	66792-95-8	171	no	2	M − $CH_2{=}CHC$-H_2NH − CO − HCN	143			*e*
(I) CH_3	614-97-1	132 M	yes	2	M − H − HCN	131	131	131	6
(II) CH_2CH_2OH	15788-11-1	131	no	2	M − CH_2OH − HCN	131	131		28
(III) CH_2CH_2Cl	14984-14-6	131	no	2	M − CH_2Cl − HCN	131			28
(IV) 4(7)-CH_3	4887-83-6	132 M	yes	2	M − H − HCN	131	131	131	6
(V) DAA	275-94-5	130 M	yes	2	M − HCN	no	no	no	19
(VI) DAA-2-SH	15852-41-2	162 M	yes	2	M − HCN	no	no	no	19

[a] Number of major, competitive fragmentation pathways at 70 eV. [b] Ring expansion probable in the listed ions. [c] ^2H labeling indicates hydrogen scrambling in the ions listed. [d] ^{13}C labeling indicates skeletal rearrangement in the ions listed. [e] New compounds.

itive fragmentation mechanisms involved in HCN loss from benzimidazoles.

Results and Discussion

Benzimidazole. The details of the fragmentation behavior of the parent benzimidazole will be discussed in a subsequent paper in relation to similar heterocycles. A few general observations are important, however, for comparison with the behavior of the 5(6)-substituted derivatives described here. Both ^2H and ^{13}C labeling[3] indicate that fragmentation of the parent ion occurs by competitive processes apparently involving both unrearranged and rearranged structures. Rearrangement is complete for metastable ions, although competitive loss of labeled and unlabeled HCN is still observed. For metastable ions of benzimidazole, therefore, either the rearrangement process results in specific partial scrambling of both carbon and hydrogen or competitive mechanisms exist for fragmentation of the rearranged species. The latter has been assumed to be the case by Maquestiau and co-workers in their conclusion that the most reasonable common structure for fragmentation of benzimidazole, indazole, and *o*-aminobenzonitrile ions is through the latter structure with loss of the amine nitrogen and a ring carbon predominating. Our work with multiple labeling, i.e., ^2H in the 1 and 2 positions and ^{13}C in the 2 position, clearly confirms competitive mechanisms for the metastable fragmentations. That is, losses of HCN, $^2H^{13}CN$, and either or both ^2HCN and $H^{13}CN$ exhibit significant metastable peaks. Since rearrangement to a common structure is required by the ^2H-labeling experiments,[3] competitive mechanisms for HCN loss from this structure must exist and partial, incomplete hydrogen scrambling is occurring as required by loss of HCN from the trilabeled benzimidazole.

For benzimidazole, then, the following conclusions can be drawn. Metastable ions, and perhaps most of the stable ions, have rearranged completely before fragmentation. This process involves both the rearrangement of the carbon–nitrogen skeleton and scrambling of hydrogens on the imidazole ring with a *limited* number of hydrogens on the carbocyclic ring. Separate mechanisms probably exist for skeletal and hydrogen rearrangements. Competitive loss of labeled and unlabeled HCN may, therefore, result from partial scrambling of the label (^2H) and/or competitive mechanisms for fragmentation involving different atoms of the rearranged structure (^{13}C and ^2H). Evidence for the 5(6)-substituted benzimidazoles studied here indicates that both of these possibilities take place. That is, scrambling and rearrangement processes combine with competitive fragmentation mechanisms for many of these benzimidazoles.

Substituted Benzimidazoles. The 5(6)-substituted benzimidazoles and the two 1,3-diazaazulenes examined here are listed in Table I along with some important features of their mass spectral behavior. The inherent stability to fragmentation of this family of heteroaromatics is attested to by the intensity of the parent ion peak which, for more than half of the derivatives, is the base or most intense peak in the spectrum. In contrast to the fragmentation of benzimidazole, the parent ions of most derivatives do not lose HCN (column four). In fact, the major fragmentation path in all cases (last column) involves initial loss of all or part of the substituent rather than part of the benzimidazole nucleus. These initial steps, then, should be observed generally with similarly-substituted aromatic compounds, while later steps are unique to the benzimidazoles. Three families of derivatives are evident from the major pathways followed: (1) the alkyl derivatives fragmenting through a 131 ion; (2) those derivatives

Table II. Deuterium and Carbon Isotope Ratios for the Competitive Loss of HCN/^{2}HCN and HCN/H^{13}CN, respectively, from Selected Ions [a]

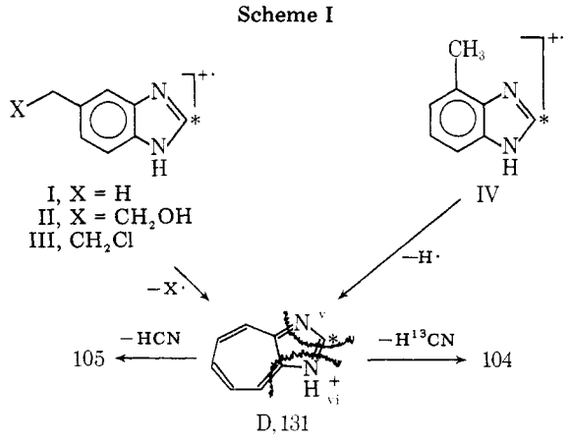
benzimidazole substituent and ions	deuterium		carbon	
	[ion − ^{2}HCN][b]/[ion − ^{2}HCN]	[m^*(HCN)][c]/[m^*(^{2}HCN)]	[ion − HCN][b]/[ion − H^{13}CN]	[m^*(HCN)][c]/[m^*(H^{13}CN)]
H 119 ($M^{+\cdot}$)	1.0[d]	1.4[d]	1.2	2.6
118 ($M^{+\cdot}$ − H·)				(1.8)
92 ($M^{+\cdot}$ − HCN)				5
5(6)-Cl				
153 (^{35}Cl − $M^{+\cdot}$)	1.2	1.5	1.3	3.5
126 (153 − HCN)	(0.3)	0.4		0.6
118 ($M^{+\cdot}$ − Cl)	(1.1)	(0.7)	(0.7)	1.7
91 (118 − HCN)	(0.3)	(0.4)		(2)
5(6)-NO_2				
118 ($M^{+\cdot}$ − NO_2)	0.8	0.7	0.5	1.7
106 ($M^{+\cdot}$ − NO − CO)			(1–2)	(2–3)
91 (118 − HCN)	0.3	0.4	(<1)	(1.3)
5(6)-$COCH_3$				
118 ($M^{+\cdot}$ − CH_3 − CO)			0.6	1.7
91 (118 − HCN)				(1.5)
5(6)-CH_3				
132 ($M^{+\cdot}$ − H·)			<0.6	1.3
105 (132 − HCN)				0.8
4(7)CH_3				
132 ($M^{+\cdot}$ − H)	1.2	2.4	<0.7	1.4
105 (132 − HCN)				0.8
4(7)-CH_3-2-^{13}C-1,2-$^2H_2$[e]				
134 ($M^{+\cdot}$ − H)	$\frac{m^*HCN + m^*H^{13}CN}{m^*HCN + m^*H^{13}CN} = 2.4$		$\frac{m^*H^{13}CN + m^{*2}H^{13}CN}{m^*HCN + m^{*2}HCN} = 1.5$	

[a] Values in parentheses are inexact because of additional daughter ions from competing reactions or from very small m^* intensities. [b] Daughter ion intensity ratios. [c] Metastable ion intensity ratios. [d] Values from ref 3. [e] Combined metastable ratios for both carbon-13 and deuterium.

which lose the substituent completely to give an intermediate 117 ion; and (3) the alkenyl compounds which exhibit a strong 143 ion. While two of the derivatives display a single fragmentation pathway (column five), most exhibit two apparently independent sequences starting from the parent or immediate daughter ions. Nonetheless, the major pathway in almost all cases accounts for most of the total ion current and offers an easily recognized and characteristic feature of the type of substituent present.

Alkyl Substituents. 131 Ions. It is immediately evident from the similarity of the stable ion spectra of the 5(6)-alkyl derivatives (I–III) that the most important fragmentation pathway probably involves a common intermediate.[17] In all cases (Scheme I), the initial loss gives an ion of m/e 131 which is by far the most intense daughter ion. The intensity of this ion may reasonably be ascribed to charge stabilization through extensive delocalization. The ring-expanded structure D was initially postulated in accord with similar ring expansions reported for other heteroaromatics such as the isomeric methyl quinolines.[18] If D is the structure of this intermediate, one would expect the 4(7)-methyl derivative (IV) to also fragment via this structure. Indeed, the mass spectra of I and IV are almost superimposable, strongly supporting common structures and fragmentation pathways for the stable ions of these isomers.

Scheme I



Proof of common structure, however, rests on the 2-^{13}C-labeled derivatives of the methyl isomers I and IV. In Table II are given the metastable ratios for loss of H^{12}CN to H^{13}CN from the 132$^+$ ions (131$^+$ plus the label), i.e., via the two paths in Scheme I. The experimentally equal values for I and IV show that metastable fragmentation must occur through ions of common structure which most probably result from ring expansion. The ratios for the stable ions are also approximately equal, although these values are much less accurate due to the presence of daughter ions of the same m/e values resulting from different fragmentation pathways involving both the parent ion and the (M − H) ion. The necessity of using metastable ions for confirmation of common structure is again indicated here. Stable ion daughter peaks may consist of ions resulting from fragmentation of more than one precursor ion, making comparisons between less similar species, e.g., the other alkyl benzimidazoles, very difficult. Metastable ions, however, identify both the parent and daughter ions unambiguously. Additionally, the similar energy and generally complete rearrangement of metastables ensures comparisons of the same structure and usually eliminates competing direct cleavage processes involving unrearranged ions.

The postulated structure D is assumed to be the common structure for the 131 ions of the other 5(6)-alkyl derivatives II and III as well as for I and IV. Although isotopic labeling was not employed for these derivatives, the preponderance of the

Table III. Comparison of Parent (m_1^+), Daughter (m_2^+), and Metastable (m^*) Ion Intensities for Successive Fragmentations of 131$^+$ Ions[a]

	131/104			104/77			77/51				
	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m^*131/m^*104	m^*104/m^*77
4(7)-CH_3	7.2	6.7	0.9	0.8	1.3	1.6	1.3	6.3	5.1	1.5	3.8
5(6)-CH_3	8.2	7.3	0.9	0.7	1.3	1.8	1.4	7.1	5.3	1.4	3.9
5(6)-CH_2CH_2OH	26	11	0.4	0.5	0.6	1.2	1.5	(12)	(7)	1.4	(10)
5(6)-CH_2CH_2Cl	57	15	0.3	0.4	0.5	1.1	1.4	(12)	(9)	1.7	(11)
diazaazulene				1.4	5.8	4.2	1.9	37	21		9

[a] Values of m_1^+/m^* and m_2^+/m^* times 10^2 units; values are averages of 6–10 consecutive spectra with standard deviations of 6–17%; values in parentheses are estimates with ±50% error.

Table IV. Exact Mass Determination of the 104–102 Peaks of V[a]

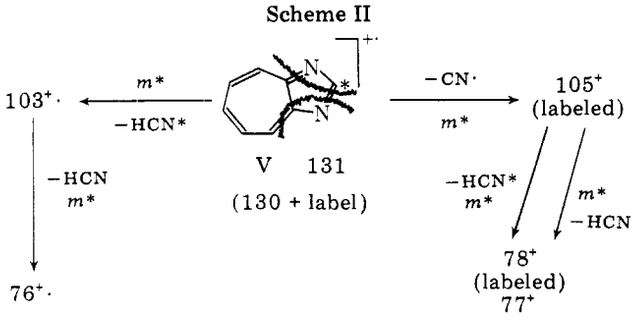
peak	formula	calcd	obsd mass
104	$C_6H_4N_2$	104.0374	
	C_7H_6N	104.0500	104.0494
103	$C_6H_3N_2$	103.0296	
	C_7H_5N	103.0422	103.0424
102	$C_6H_2N_2$	102.0203	
	C_7H_4N	102.0344	102.0355

[a] Obtained by peak matching with a resolution of 5000 at m/e 100 using perfluorotributylamine standard, reference peak at 99.99361.

131 ions in the spectra and the similarity of daughter and metastable ion intensities for subsequent fragmentations of this ion (Table III) strongly support this assumption.[17] With D as the common structure, the loss of H^{12}CN probably involves the two carbons in the seven-membered ring attached to nitrogen. Two competing mechanisms are suggested, one of which involves loss of the 2-^{13}C label, the other results in loss of unlabeled HCN. Alternatively, the rearrangement process involving ring expansion of the carbocyclic ring could also involve rearrangement of the imidazole nucleus to some other structure such as a seven-membered ring analogue of *o*-aminobenzonitrile. The question, then, is whether the common ring-expanded species possesses structure D or further rearrangement takes place involving the imidazole nucleus as found for benzimidazole itself. To help answer this question, an analogue of structure D was examined. The somewhat unstable compound 1,3-diazaazulene (cycloheptimidazole (V)) was synthesized according to the literature procedure[19] and the 2-^{2}H- and 2-^{13}C-labeled derivatives were obtained by slight modification of this synthesis.

The initial fragmentation steps of V (Scheme II) involve the loss of 26 and 28 mass units for both the ^{2}H- and ^{13}C-labeled compounds (26 and 27 for nonlabeled). While the former could a priori involve either H_2C_2 or CN·, exact mass determination of the M − 26 and related daughter ions (Table IV) is consistent with a single nitrogen atom in these ions. Further, the loss of CN· is reasonable in that a cation is formed from the parent radical cation by this process. Surprisingly, the losses of both

Scheme II



CN· and HCN fragments involve no detectable scrambling of either the deuterium or carbon-13 label for either stable or metastable ions.[20] This lack of rearrangement before fragmentation attests to the relative stability of the charged 1,3-diazaazulene nucleus and strongly supports a similar structure for the common 131$^+$ ions of benzimidazoles I–IV. In addition, the observation of two clearly separate fragmentation pathways for V (Scheme II) is excellent support for two analogous paths for the 131 ions of I–IV, i.e., the competitive losses of fragments v and vi from structure D in Scheme I.

It could be argued that a direct comparison of the behavior of the V radical cation (130 m/e) with the 131 cation of I–IV is not justified on the basis of different electronic states for these two ions. It is our feeling that the major differences between the radical cation and cation of similar structure here is that the former should be relatively less stable and undergo losses of small radical molecules as well as neutral molecules. For the 1,3-diazaazulene radical cation, these two differences are evident in relatively greater daughter ion intensities and loss of CN·, respectively. Nonetheless, both loss of CN· and HCN in the spectrum of V display strong metastable peaks. These ions possess energies and lifetimes similar to the 131$^+$ ions, although the (former) radical cations show no evidence of rearrangement prior to fragmentation. Unless such long-lived radical cations are inherently less prone to rearrangement, an unreasonable assumption in view of the extensive rearrangement observed for the benzimidazole radical cation, the 131$^+$ ion, should also be relatively unsusceptible to rearrangement because of the charge delocalization in structure D.

To clarify the nature of the scrambling or rearrangement processes leading to competitive losses of ^{1}H/^{2}H and ^{13}C/^{12}C with HCN, the trilabeled compound [1,2-$^2H_2$-2-^{13}C]-4(7)-methylbenzimidazole was synthesized and examined. Although the major metastable losses from the M − 1 ion of this derivative involve ^{2}H^{13}CN and either ^{2}HCN or H^{13}CN, a significant loss of HCN occurs. Since this loss must involve hydrogens of the carbocyclic ring, limited scrambling of these hydrogens with the imidazole hydrogens is taking place. This suggests a hydrogen scrambling mechanism in addition to that proposed for competitive loss of carbons. Separate mechanisms for hydrogen scrambling and skeletal rearrangement have been reported for benzene[7] and were observed for benzimidazole in this work. It is possible that the exchangeable hydrogen of structure D is responsible for promoting such limited scrambling, especially in view of the lack of scrambling of the 2 hydrogen of V with the carbocyclic ring hydrogens.

Our view of the overall fragmentation behavior of the common 131 ions of I–IV involves the basic nuclear framework of V. The loss of a small radical molecule from the parent ion via β cleavage of the 5(6) substituent occurs with rearrangement to the ring-expanded structure D. Like the parent ion of V, subsequent fragmentation occurs via two competitive mechanisms involving loss of the 2 carbon and either of the

two carbocyclic ring carbons, respectively. Rearrangement of the nuclear framework of structure D or V prior to fragmentation is not evident. A mechanism exists for limited scrambling of the hydrogens of D which is separate from that involving competitive loss of carbon. The existence of common ion D and its subsequent behavior offers a ready means of identifying benzimidazole derivatives with alkyl substituents on the carbocyclic ring. Similar structures are possible for alkylbenzimidazoles with additional substituents on the carbocyclic ring. Derivatives with additional substitution on the imidazole ring, however, exhibit more complicated behavior with the possibility of other ring-expanded intermediates, and these structures will be discussed in a subsequent paper.

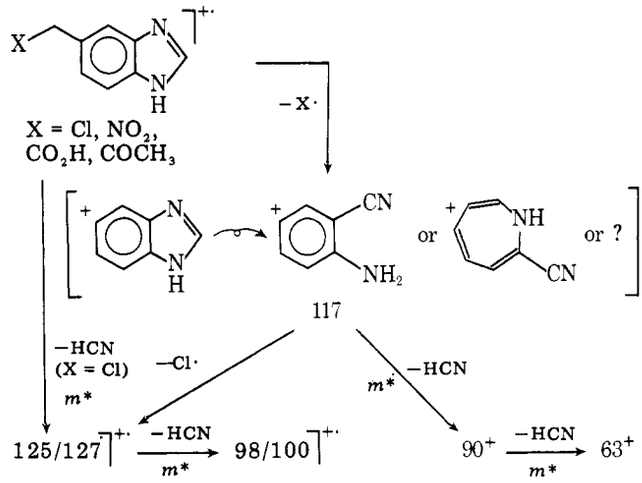
Fragmentation via the 117 Ion. In addition to ring expansion on loss of part of the 5(6) substituent, complete loss of a substituent may occur with formation of a 117 ion, i.e., an ion possibly similar to the M − 1 ion of benzimidazole. The four derivatives which follow this pathway are VII–X. Although the relative intensity of the 117 ions compared to subsequent daughter ions is less than that of the common 131 ions above, this ion is still one of the most intense and is the intermediate in the preferred fragmentation pathway of VII–X. The presence and behavior of the 117 ion, then, represents an identifying characteristic for the benzimidazole nucleus of these derivatives.

Scheme III depicts the general mass spectral behavior of VII–X. For the carboxyl and acetyl derivatives, the two-step loss of the substituent to give the 117 ion is the exclusive fragmentation pathway. For the chloro compound (IX), a competitive pathway exists involving loss of HCN from the parent ion followed by loss of either the chloro group or a second HCN molecule. The nitro derivative (X) also displays a characteristic alternative in the sequential loss of NO and CO.[21] These alternative paths for IX and X will be discussed in more detail later.

It was initially suspected that the 117 ions of VII–X possessed a common structure. The relative intensities of the 117 ions with respect to daughter and metastable ions associated with the sequential loss of two HCN molecules were very similar for VII–X as well as for the M − 1 ion of benzimidazole. Initial ^{2}H-labeling studies involving replacement of the 1 hydrogens of IX and X were disappointing, however. The competitive metastable ratios for losses of HCN and ^{2}HCN were not similar (Table II). Carbon-13 labels were therefore incorporated in the 2 positions of VIII–X and the fragmentations of the labeled 118 ions observed. For all three compounds, the ratios of metastable loss of HCN to H^{13}CN were essentially identical (Table II). Even the benzimidazole M − 1 ion, although much less intense and, therefore, exhibiting weak metastables, displayed an approximately similar ratio. One can conclude, then, that these 117 ions all possess the same structure.

The establishment of a common structure for these 117 ions raises the question of the nature of this structure. A priori, the benzimidazole nucleus might be expected to maintain its integrity prior to fragmentation. The common behavior of benzimidazole, imidazole, and *o*-aminobenzonitrile indicates that skeletal rearrangement occurs even for the parent radical cation.[3,4] Nuclear rearrangement of the 117 ion is therefore quite probable, especially in view of the predominate metastable loss of unlabeled HCN from the 2-^{13}C-labeled 117 ions of VIII–X. Although the *o*-aminobenzonitrile structure is presumed for benzimidazole,[3] a variety of other structures are possible (Scheme III). The present labeling studies allow no differentiation among possibilities and additional suitably labeled models are not readily available. Thus, until further labeling is carried out on the carbocyclic ring of these compounds and appropriate models are constructed, choosing a specific structure for the common 117 ions is not possible.

Scheme III



The success of the carbon-labeling experiment in demonstrating common structure for the 117 ions despite inability of the deuterium label to do so points to an important advantage of this technique. The common ions examined here, both the 131 and 117 species, arise from prior fragmentation of different molecular ions. In the successful application of deuterium labeling to common structure proof,[3,4] only the parent ions of different molecules were examined. It is entirely possible (as shown for the trilabeled derivative of benzimidazole and IV) that facile hydrogen scrambling may occur independent of or in addition to skeletal rearrangements. This may be especially true for compounds such as benzimidazoles which have a labile and exchangeable hydrogen in the 1 position. It is not unreasonable to assume that partial hydrogen scrambling occurs to different extents prior to formation of a common daughter ion for widely different derivatives, i.e., IX and X. Thus, carbon-13 labeling is much more likely to substantiate common structures than deuterium labeling for ions resulting from fragmentation of different parent ions. For parent ions of common structure but different origin, both methods may be effective.

As mentioned previously, both the chloro and nitro derivatives exhibit fragmentation pathways other than via the 117 ion. For the chloro compound, the initial step in two additional paths involves HCN loss and the 2-^{13}C label shows that competitive mechanisms are involved. The M − HCN fragment thus formed may then lose either HCN or Cl· with subsequent fragmentation of the daughter ions thus obtained. While the molecular ion preferentially loses H^{12}CN over H^{13}CN in metastable transitions (with a ratio of 3.5), the M − HCN ion undergoes predominant loss of H^{13}CN. This sequential loss of two HCN molecules seemingly parallels the behavior of benzimidazole, $118^{+\cdot} \rightarrow 91^{+\cdot} \rightarrow 64^{+\cdot}$. However, the M − HCN ion at *m/e* 91 shows complete scrambling of retained carbon-13 before fragmentation. Thus, similar molecular fragments are lost for both carbons, but differences in the amounts of carbon scrambling or in the competitive fragmentation pathways are observed.

The alternate pathway for 5(6)-nitrobenzimidazole (IX) involves the well-documented[21] loss of NO with transfer of an oxygen atom to the ring. Subsequent loss of CO leads here to an ion of *m/e* 106. While it would be interesting to postulate a structure similar to a protonated 1,3-diazapentalene for this ion, the nuclear rearrangements observed for benzimidazole and in I–IV preclude such speculation. It is highly probable that imidazole moiety ring opening is combined with other skeletal rearrangements to give a 106 ion whose structure is quite different from the parent molecule.

Table V.[a] Comparison of 143$^+$ Ions of Vinylbenzimidazoles using the Relative Intensities of m^+ (143$^+$), d^+ (116$^+$), and m^* (94.1)

substituent X	m^+/d^+	$(m^+/m^*) \times 10^{-2}$	$(d^+/m^*) \times 10^{-2}$
H	2.4	1.4	0.6
CO_2H	1.7	1.3	0.7
CO_2CH_3	1.6	0.6	0.4
$CO_2CH_2CH{=}CH_2$	1.8	0.7	0.4
$CONHCH_2CH{=}CH_2$	1.8	0.7	0.4

[a] Values obtained are averages of two or more spectra run consecutively.

The final derivative (XI) classed with these 117 ions is included because of the similarity of its behavior to the acetyl derivative although its base peak and main fragmentation path are through a 119 rather than 117 ion. For this α-hydroxyethyl compound, sequential loss of $CH_3\cdot$ and CO parallels VIII. In this case, however, concomitant transfer of two hydrogen atoms occurs to the benzimidazole nucleus. The 119 ions thus obtained are relatively intense (as the base peak) and its relative stability may well be due to charge delocalization within the benzimidazole framework. However, in view of extensive skeletal rearrangement in the other derivatives, it is quite possible that the subsequent sequential loss of two HCN molecules from the 119 ion involves rearrangement and quite probable that competitive fragmentation mechanisms exist.

Our main interest in this derivative was in the nature of the hydrogen transfer from the side chain. To study this in more detail, the α-deuterio derivative was synthesized by sodium borodeuteride reduction of the acetyl compound. Very little scrambling of the ^2H with the methyl hydrogens is observed prior to $CH_3\cdot$ loss. Almost all of the ^2H is transferred to the nucleus on CO loss, analogous to the general behavior of benzyl alcohols.[21] In contrast to simple benzyl alcohols, however, this 119 ion does not evidence loss of an H_2 molecule but shows sequential loss of two HCN. In addition, the metastable loss of ^2HCN is observed in the statistical amount from both the 119 and 92 ions. Complete hydrogen scrambling is therefore occurring in the metastable ions in contrast to the limited hydrogen scrambling of the benzimidazole 118 ion and the common 131 and 117 ions. This 119 ion, although exhibiting the sequential losses of two HCN, does not behave like other derivative cations and radical cations. This unique behavior must be related to the presence of the additional hydrogen atoms in promoting hydrogen scrambling and perhaps skeletal rearrangements. This possibility may be further investigated using combined ^{13}C and ^2H labeling.

5(6)-Vinyl Derivatives. The vinyl derivatives studied include the parent 5(6)-vinylbenzimidazole (XII) and four derivatives of β-[5(6)-benzimidazole]acrylic acid (XIII–XVI). While the mass spectral behavior of the latter compounds is fairly straightforward, i.e., via initial loss of carboxylic acid fragments, the behavior of the parent is complex. Three major fragmentation pathways are evident involving (in decreasing importance): (a) initial loss of H· followed by HCN, (b) loss of C_2H_2, and (C(c) direct loss of HCN. Although HCN loss is the least important of the three, the fact that this fragmentation of the molecular ion is observed for only two of all the derivatives examined (XII and X) attests to the relative stability of these two substituents to fragmentation. For most derivatives, the initial loss involves all or part of the substituent, while for the chloro and vinyl groups a significant number of molecules lose HCN initially from the benzimidazole framework.

The loss of C_2H_2 is the second most important fragmentation of XII. With ^2H labeling in the α position of the vinyl group, almost complete loss of the label is observed in this process. This is consistent with one of two possibilities with regard to hydrogen scrambling in the side chain. Assuming a four-membered transition state involving transfer of the terminal hydrogen prior to loss of acetylene molecule, either no hydrogen scrambling occurs prior to fragmentation or scrambling does occur and a large deuterium isotope effect greatly favors transfer of hydrogen over deuterium. The latter is consistent with scrambling observed in the major fragmentation path.

The predominant fragmentation of XII involves initial loss of H· from the parent ion followed by two HCN molecules. Incorporation of deuterium in the α position results in loss of both hydrogen and deuterium in the initial step in the ratio of 3.4 and 3.6 for stable and metastable ions, respectively. These values are consistent with complete scrambling of side-chain hydrogens coupled with a deuterium isotope effect of 1.7–1.8 for hydrogen atom loss. Observation of the same hydrogen/deuterium ratios for stable and metastable ions indicates fast hydrogen scrambling before fragmentation, since a slow rearrangement process would be expected to give a significantly different value for the two energetically different types of ions.

In line with the behavior of the alkyl-substituted derivatives and with the behavior of styrenes,[22] it seems reasonable to postulate a ring-expanded structure for the M − 1 (143) ion of XII. The relative stability of this ion is attested to by its intensity compared to other daughter ions and subsequent fragmentation. The observed fragmentations of this ion do not involve the side-chain, but rather sequential loss of two HCN molecules. Further, essentially complete hydrogen–deuterium scrambling occurs in the labeled 143 ions prior to loss of HCN or ^2HCN. While a reasonable structure for this ion would be an eight-membered carbocyclic ring similar to that postulated for styrene,[22] the tendency of many of the benzimidazole derivatives to undergo extensive skeletal rearrangement makes other structures possible.

For the remaining vinyl carboxylic acid derivatives, the initial fragmentation involves loss of all or part of the carboxylic acid group. By far the most important process in all cases is formation of the 143 ion via loss of CO from the low intensity vinyl acrylonium ion. Similar to the behavior of the 143 ion of the parent vinyl compound, fragmentation of these ions involves loss of two HCN molecules. A comparison of relative stable and metastable ion intensities[17] (Table V), as was presented in Table III for the 131 ions, strongly supports a common structure for the 143 ions derived from all five alkenyl compounds. This 143 ion, then, represents a general fragmentation pathway for these derivatives and should serve as an identifying characteristic for related compounds.

Conclusions

The representative 5(6)-substituted benzimidazoles studied here may be classed into three groups according to common fragmentation pathways. Within two of these groups, proof of common intermediate structure is presented for selected 131 and 117 ions employing ^{13}C labeling with the metastable ratio technique. Strong supporting evidence of common structure for the remaining 131 species and for the 143 ions is provided by comparison of relative stable and metastable ion intensities.

The use of ^2H and ^{13}C labeling further indicated that skeletal rearrangements and/or competitive fragmentation mechanisms exist for most, if not all, derivatives for the parent or common intermediate ions of the major fragmentation pathways. The exact nature of these rearrangements and mechanisms is not apparent from this work for most derivatives. For the common 131 ions, however, very good evidence exists for a ring-expanded structure similar to 1,3-diazaazu-

lene with the competitive fragmentations involving the 2 carbon and carbocyclic ring carbons. In addition to skeletal rearrangements, independent hydrogen scrambling takes place for several derivatives and may, indeed, be a general phenomena.

The detailed examination of these benzimidazoles indicates that, in general, their mass spectral behavior is much more complex than previously postulated.[15,16] Nonetheless, the fact that common intermediates and fragmentation pathways exist allows classification into general families of derivatives. These general paths should be valuable for identification and characterization of additional benzimidazoles according to the type of substitution present. Furthermore, the use of the metastable ratio technique developed here for common structure proof of carbon-13-labeled compounds should be generally applicable to many isotopically labeled compounds. Such isotopic labeling (^{13}C, ^{15}N, and ^{17}O) will become increasingly important in elucidating the complex mass spectral behavior of heterocyclic compounds.

Experimental Section

All aromatic diamines (except 2,3-diaminotoluene) used in the synthesis of the various benzimidazoles were commercially available or previously described in the literature. DCME (α,α-dichloromethyl methyl ether) was purchased from Aldrich; this material may be carcinogenic and must be handled with due precautions. The carbon-13-labeled compounds used in the synthesis of ^{13}C-labeled derivatives (sodium [^{13}C]formate and [^{13}C]thiourea) were 90% enriched and purchased from Merck Isotopes. All other reagents and solvents were commercially available and purified as needed.

General Synthesis of Benzimidazoles. A. Phillip's Procedure (Formic Acid). The appropriate aromatic diamine (Aldrich) (0.01 mol) was slurried with excess formic acid in 20 mL of 4 N HCl. The mixture was heated at reflux for 6–8 h and charcoal added carefully to the dark reaction mixture. After filtering and cooling, the strongly acidic mixture was neutralized with dilute NaOH or $NaHCO_3$ to pH 7. The precipitated benzimidazole was collected by filtration and air dried. Generally, recrystallization from water or aqueous ethanol gave the desired pure product. Several of the derivatives, such as the 5(6)-chloro, 5(6)-methyl, and 5(6)-acetyl compounds, are extremely hydroscopic. These materials could be readily purified by column chromatography on silica with ethyl acetate solvent. All mp's and IR data agreed with those previously reported.

B. Alternative Procedure (DCME). One equivalent of the reagent α,α-dichloromethyl methyl ether (DCME) was added dropwise to a cooled (0 °C) mixture of 1 equiv of aromatic ortho diamine plus 1 equiv of tri-*n*-butylamine in dry THF. After complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 4–24 h. The pure product precipitated as the hydrochloride salt, and may be neutralized with dilute $NaHCO_3$. This procedure gave the following isolated yields of benzimidazoles (substituent and percent yield): H, 100%; 5(6)-CH_3, 61%; 4(7)-CH_3, 80%; 5(6)-NO_2, 70%; 5(6)-$COCH_3$, 62%; 5(6)-Cl, 74%.

Complete characterization of the previously unreported 5(6)-acetylbenzimidazole is given in ref 23.

2,3-Diaminotoluene. A suspension of 2-nitro-6-methylaniline (1.0 g, 0.007 mol) in 45 mL of 3 N sodium hydroxide containing 9 g of sodium dithionite was heated at 80 °C with stirring for 3 h. The orange starting material gradually dissolved to give a clear, colorless solution which was filtered hot and allowed to cool. Extraction with ether, which was then dried with 4A molecular sieves and evaporated, gave the desired product as tan crystals in 90% yield, mp 77–78 °C.

[2-^{13}C]-4(7)-Methylbenzimidazole (IV). A mixture of 2,3-diaminotoluene (0.244 g, 0.002 mol) and sodium [^{13}C]formate ^{13}C (0.167 g, 0.0024 mol) was added to 2–3 mL of 5 N hydrochloric acid. The mixture was heated at 90 °C for 4 h, diluted to 6 mL, and made slightly basic with concentrated ammonium hydroxide. The oil which initially separated rapidly solidified to give a light yellow product in 85% yield, mp 142–144 (lit.[24] mp 145 °C).

The following compounds were obtained with the above procedure and quantities from commercially available diamines which were first purified by sublimation in vacuo at 80 °C.

[2-^{13}C]Benzimidazole. An 80% yield of needles was obtained on cooling the hot neutralized reaction mixture, mp 170 °C (lit.[24] mp 170 °C).

[2-^{13}C]-5(6)-Chlorobenzimidazole (X). An 85% yield of off-white precipitate was obtained from the neutralized reaction mixture, mp 125 °C (lit.[25] mp 125–126 °C).

[2-^{13}C] 5(6)-Nitrobenzimidazole (IX). The reddish-brown crude material was obtained in 90% approximate yield. A small sample was recrystallized from water, mp 199–200 °C (lit.[26] mp 209–210 °C).

[2-^{13}C]-5(6)-Acetylbenzimidazole (VIII). This material was isolated in the same manner as the 5(6)-methyl derivative above. Synthesis of the starting diamine has been described.[23]

[α-^{2}H]-5(6)-(α-Hydroxyethyl)benzimidazole (XI). 5(6)-Acetylbenzimidazole was reduced with a 10% excess of $NaBD_4$ in ethanol. This material was isolated as described.[23] The NMR of this material exhibited no α-hydrogen resonance, while the methyl group was observed as a singlet.

[α-^{2}H]-5(6)-Vinylbenzimidazole. Dehydration of the α-deuterio derivative described above was carried out in the manner described.[23] The NMR of this material showed no splitting of the terminal methylene hydrogens by an α hydrogen.

β-[5(6)-Benzimidazole]acrylic Acid Chloride. β-[5(6)-Benzimidazole]acrylic acid[27] (1.0 g, 0.005 mol) was refluxed with 10 mL of thionyl chloride for 4 h. The slurry thus obtained was dried in vacuo to remove excess thionyl chloride to give an off-white dry solid which was used as obtained.

Methyl β-[5(6)-Benzimidazole]acrylate (XIV). To a cooled (0 °C) 5-mL sample of methanol was added the acid chloride prepared above (0.5 g, 0.002 mol). After stirring 4 h, the grey precipitate was filtered, dissolved in water, and neutralized with $NaHCO_3$. Extraction with chloroform twice followed by solvent evaporation gave an off-white product in 89% yield which was used as obtained.

Allyl β-[5(6)-Benzimidazole]acrylate (XV). This material was obtained in 68% yield in the same manner as XIV using allyl alcohol. A small analytical sample was prepared by sublimation at 80 °C and 0.5 mm Hg: mp 100 °C; NMR (Me_2SO-d_6) δ 7.4 (H_2, s), 7.12–6.73 (3 aromatic H + 1 vinyl H, m's), 5.68 (1 vinyl H, J_{trans} = 16 Hz), 5.08 (1 allyl H, m), 4.52 (2 allyl H, m), 3.85 (2 allyl H, ~d, $J \simeq 5$ Hz).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 67.82; H, 5.39; N, 11.87.

***N*-Allyl-β-[5(6)-benzimidazole]acrylamide (XVI).** This material was obtained in 75% yield from the acid chloride and excess allyl amine. The crude reaction mixture was cooled to −5 °C overnight to give golden needles of product. Recrystallization from 50% aqueous methanol gave pale yellow needles: mp 232–238 °C (thermal polymerization); NMR (Me_2SO-d_6) δ 8.10 (H_2, s), 7.85–6.85 (4 H, m's), 6.68 (1 vinyl H, d, J = 16 Hz), 5.9 (1 H, m), 5.15 (2 H, m), 3.9 (2 H, m); IR (KBr pellet) 3320, 3100–2600, 1660, 1615, 1540, 1465, 1420, 1350, 1315, 1300, 1285, 1260, 1225, 1210, 1035, 1005, 970, 950, 890, 860, 820 cm^{-1}.

[2-^{13}C]-1,3-Diazaazulene-2-thiol (VI). This material was prepared according to the procedure of Nozoe, Makai, and Murato,[19] except that [^{13}C]thiourea was used instead of thiourea in the condensation with methyl tropolone.

[2-^{13}C]-1,3-Diazaazulene (V). Using the above carbon-13-labeled material, the literature procedure[19] was used for the oxidative desulfurization in dilute nitric acid. After neutralization of the product solution, the desired material could be isolated in very pure form by chloroform extraction, drying over 4A sieves, and solvent evaporation to give bright yellow crystals. Rapid air oxidation of this material requires cold storage under argon or nitrogen.

[2-^{2}H]-1,3-Diazaazulene. The unlabeled thiol derivative VI was slurried with D_2O containing 10% HNO_3 and normal desulfurization carried out to give the desired material with greater than 90% deuterium incorporated in the 2 position.

Mass Spectra. All spectra were obtained on the AIE-MS902 operating at low resolution unless otherwise noted for specific exact mass determinations. Spectra of compounds with deuterium-replaced exchangeable hydrogens were obtained by repeated scanning of a D_2O slurry of the compound introduced on the probe directly into the source. For labeled compounds, the amount of isotope incorporation was determined by using a minimal ionizing potential (~8–14 eV) to directly observe the parent ions. Spectral comparisons involving ratios of parent, daughter, and metastable peaks (e.g., Table V) were carried out on a series of spectra run consecutively for each compound. The compounds being compared were run in rapid succession under conditions as nearly identical as possible. It should be noted that these ratios, i.e., p^+/m^* and d^+/m^*, have no absolute significance and may vary greatly with small changes in operating conditions or machine configurations.

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Registry No.—2,3-Diaminotoluene, 2687-25-4; 2-nitro-6-methylaniline, 570-24-1; β-[5(6)-benzimidazole]acrylic acid chloride, 66792-91-4; 5(6)-chlorobenzotriazole, 94-97-3.

Supplementary Material Available: Table of mass spectra data for benzimidazole substituents (6 pages). Ordering information can be found on any current masthead page.

References and Notes

(1) Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds", Wiley-Interscience, New York, N.Y., 1971.
(2) P. N. Preston, *Chem. Rev.*, **74**, 279 (1974).
(3) A. Maquestiau, Y. Van Haverbeke, R. Flammang, M. C. Pardo, and J. Elquero, *Org. Mass Spectrom.*, **9**, 1188 (1974).
(4) A. Maquestiau, Y. Van Haverbeke, R. Flammang, M. C. Pardo, and J. Elquero, *Org. Mass Spectrom.*, **10**, 558 (1975).
(5) A. Maquestiau, Y. Van Haverbeke, R. Flammang, M. C. Pardo, and J. Elquero, *Org. Mass Spectrom.*, **10**, 313 (1975).
(6) M. H. Phillips, *J. Chem. Soc.*, 2395 (1928); 1143 (1931).
(7) J. H. Beynon and R. G. Cooks, *Adv. Mass Spectrom.*, **6**, 835 (1974).
(8) R. G. Cooks, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 137 (1969).
(9) T. W. Shannon and F. W. McLafferty, *J. Am. Chem. Soc.*, **88**, 5021 (1966).
(10) J. L. Occolowitz, *J. Am. Chem. Soc.*, **91**, 5202 (1969).
(11) A. Selva, U. Vettori, and E. Gaetani, *Org. Mass Spectrom.*, **9**, 1161 (1974).
(12) D. H. Williams and R. G. Cooks, *Chem. Commun.*, 663 (1968).
(13) S. Meyerson and P. N. Rylander, *J. Chem. Phys.*, **27**, 901 (1957).
(14) S. Meyerson and P. N. Rylander, *J. Am. Chem. Soc.*, **78**, 5799 (1956).
(15) T. Nishiwaki, *J. Chem. Soc. C*, 428 (1968).
(16) S.-O. Lawesson, G. Schroll, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 1875 (1968).
(17) D. H. Williams, R. G. Cooks, and I. Howe, *J. Am. Chem. Soc.*, **90**, 6759 (1968).
(18) S. Safe, W. D. Jamieson, and O. Hutzinger, *Org. Mass Spectrom.*, **6**, 33 (1972).
(19) T. Nozoe, I. Makai, and I. Murato, *J. Am. Chem. Soc.*, **76**, 3352 (1954).
(20) Compound VI is the intermediate in the synthesis of V, and the mass spectra of labeled and unlabeled derivatives were obtained. With both the S-^{2}H and 2-^{13}C derivatives, two fragmentation pathways were observed involving competitive loss of HCN and HNCS in which no scrambling was observed. The ^{2}H was cleanly lost with both fragments while the ^{13}C was lost *only* with the HNCS. Thus, the same two fragmentation mechanisms are observed for V and VI.
(21) H. Budziklewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry, Organic Compounds", Holden-Day, San Francisco, Calif., 1967.
(22) A. Venema, N. M. M. Nibbering, and T. J. de Boer, *Org. Mass Spectrom.*, **3**, 1584 (1970).
(23) C. G. Overberger and L. J. Mathias, *J. Polym. Sci., Polym. Chem. Ed.*, in press.
(24) R. C. Weast, Ed., "Handbook of Chemistry and Physics", 53rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1972.
(25) D. J. Rabiger and M. M. Joullie, *J. Chem. Soc.*, 915 (1964).
(26) J. Ridd and B. Smith, *J. Chem. Soc.*, 1363 (1960).
(27) C. G. Overberger and C. J. Podsiadly, *Bioorg. Chem.*, **3**, 16, 35 (1974).
(28) C. G. Overberger, B. Kösters, and T. St. Pierre, *J. Polym. Sci., Part A-1*, **5**, 1987 (1967).

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Substituted Benzimidazoles and 1,3-Diazaazulene

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The ^{13}C NMR chemical shifts of a variety of substituted benzimidazoles and two 1,3-diazaazulenes are presented. Peak assignment is made with substituent-induced chemical shifts (SCS) and long-range ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants. The SCS of benzimidazole derivatives are compared to those of benzenes. Excellent correlations of $\delta(C_2)$ are observed with σ_p and σ_6 for 5(6) substituents. Similar correlations involving the para carbon (C_8) exhibit greater scatter than those of the 2 carbon. The $\delta(C_2)$ values also correlate well with pK_a, and this correlation is used to predict a pK_a of 3.4 for 5(6)-acetylbenzimidazole. The ^{13}C spectrum of 1,3-diazaazulene is unambiguously assigned. The chemical shifts do not agree with previously calculated charge densities. The average chemical shifts of the carbocyclic carbons indicate decreasing electron density in the seven-membered ring in the series azulene, 1,3-diazaazulene, protonated 1,3-diazaazulene, and tropylium ion.

The determination and assignment of ^{13}C NMR chemical shifts is rapidly becoming routine in many laboratories. This routine use is dependent on the confirmation of shift assignments by techniques such as partial or complete coupling of carbons to hydrogens. Increases in instrument sensitivity as well as the development of gated decoupling has made the acquisition of completely coupled spectra readily feasible. The interpretation of these coupled spectra is simplified by the fact that first-order analysis is generally sufificient for determination of not only one-bond but two- and three-bond coupling constants at the resolutions normally available. These long-range coupling constants should be characteristic of specific molecular subunits as are long-range hydrogen–hydrogen coupling constants in ^{1}H NMR spectroscopy.

One of the most obvious and useful examples of long-range ^{13}C–^{1}H coupling involves the methyl group. Unlike the small to negligible ^{1}H–^{1}H coupling of ring and methyl hydrogens, ring carbons exhibit large exocyclic coupling constants to methyl hydrogens. For both pyridine[2] and quinoline[3] derivatives, the $^{2}J_{^{13}C-^{1}H}$ of the ipso carbon is found to be approximately 6 Hz, while the $^{2}J_{^{13}C-^{1}H}$ of the ortho carbons generally falls between 4 and 5 Hz. These coupling constants should be characteristic for methyl-substituted compounds and should allow ready identification of both the ipso and ortho carbon resonances in coupled spectra. Furthermore, the relatively small effect of a methyl substituent on the chemical shift of carbons other than the ipso carbon should allow identification of the ^{13}C resonances of the unsubstituted compounds once the spectrum of the methyl derivative is assigned. Thus, the examination of the spectrum of a methyl analogue is useful for the assignment of the spectrum of the parent compounds.

The ^{13}C NMR spectrum of benzimidazole has been reported previously in comparison with the spectra of purine derivatives.[4] The spectra of the benzimidazole HCl salts and the sodium salt of the anion were also given. Protonation of either the anion or the neutral benzimidazole resulted in downfield shifts of $C_{5,6}$ along with upfield shifts of C_2, $C_{4,7}$, and $C_{8,9}$. These characteristic protonation shifts were then applied to purine spectra to determine the site of protonation of this material.[4]

In this paper, we report the ^{13}C chemical shifts of a number of substituted benzimidazoles. The long-range coupling of methyl hydrogens is used to more completely assign the

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