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Proximity effects in the electron impact mass spectra of 2-substituted benzazoles

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Dedicated to Professor Dudley H. Williams on the occasion of his retirement in recognition of his outstanding contribution to understanding the principles of mass spectrometry and developing its applications in organic chemistry and biology.

Abstract

The 70 eV electron impact mass spectra of a wide range of 2-substituted benzazoles are reported and discussed. Particular attention is paid to the mechanistic significance and analytical utility of $[M–H]^+$ and $[M–X]^+$ signals in the spectra of benzazoles in which the 2-substituent contains a terminal aryl group with one or more substituents, X. Loss of $H^•$ or $X^•$ occurs preferentially from an *ortho*-position from ionized 2-benzylbenzimidazoles, 2-phenethylbenzimidazoles, 2-styrylbenzimidazoles, 2-styrylbenzoxazoles and 2-styrylbenzothiazoles. In the three styrylbenzazole series, the $[M–H]^+$ and/or $[M–X]^+$ signals dominate the spectra. This unusually facile loss of $H^•$ or $X^•$ may be attributed to a proximity effect, in which cyclization of the ionized molecule is followed by elimination of an *ortho*-substituent to give an exceptionally stable polycyclic ion. Formation of a new five- or six-membered ring by the proximity effect occurs rapidly; cyclization to a seven-membered ring takes place rather less readily; but formation of a ring with only four atoms or more than seven atoms is not observed to a significant extent. The proximity effect competes effectively with loss of a methyl radical by simple cleavage of an ethyl, isopropyl and even a *t*-butyl group in the pendant aromatic ring of ionized 2-(4-alkylstyryl)benzazoles.

Keywords: Benzimidazoles; Benzoxazoles; Benzothiazoles; Proximity effect; Rearrangement; Hydrogen atom elimination; Doubly-charged

1. Introduction

The general application of mass spectrometry in elucidating the structure of organic compounds dates from the late 1950s, was emphasized by seminal textbooks [1,2], and is taken for granted today. However, its value in deducing the relative position of substituents in aromatic rings took rather longer to recognize and is still not fully appreciated by some organic chemists.

An interesting example of how specific rearrangements may reveal valuable analytical information arose from the observation that ionized cinnamaldehyde and similar species contain unusually strong $[M–H]^+$ peaks in their electron impact (EI) spectra [3]. In the case of ionized cinnamaldehyde itself, this facile loss of a hydrogen atom could have been attributed to simple cleavage to form a conjugated acylium ion, Eq. (1). However, the EI spectra of related species of general structure PhCH=CHCOX (X = OH, CH_3 or Ph), for which there was no obvious site from which the hydrogen atom could be lost, also showed strong $[M–H]^+$ signals. Isotopic labelling revealed that the hydrogen atom actually originates from the aromatic ring, via a process that became known as a proximity effect, Scheme 1. Similar signals in the spectra of a wide range of compounds, including natural products such as aurones [4], were subsequently uncovered and interpreted by parallel mechanisms. More recently, analogies have been drawn

Abbreviations: BBI, 2-benzylbenzimidazole; PBI, 2-phenethylbenzimidazole; SBI, 2-styrylbenzimidazole; ArBI, 2-arylbenzimidazole; ω*n*PhBI, 2-(ω-phenylalkyl)benzimidazole [*n* = number of connecting (CH_2) groups]; AlkBI, 2-(alkenyl)benzimidazole or 2-(alkyl)benzimidazole; SBO, 2-styrylbenzoxazole; PBO, 2-phenethylbenzoxazole; SBT, 2-styrylbenzothiazole; PBT, 2-phenethylbenzothiazole

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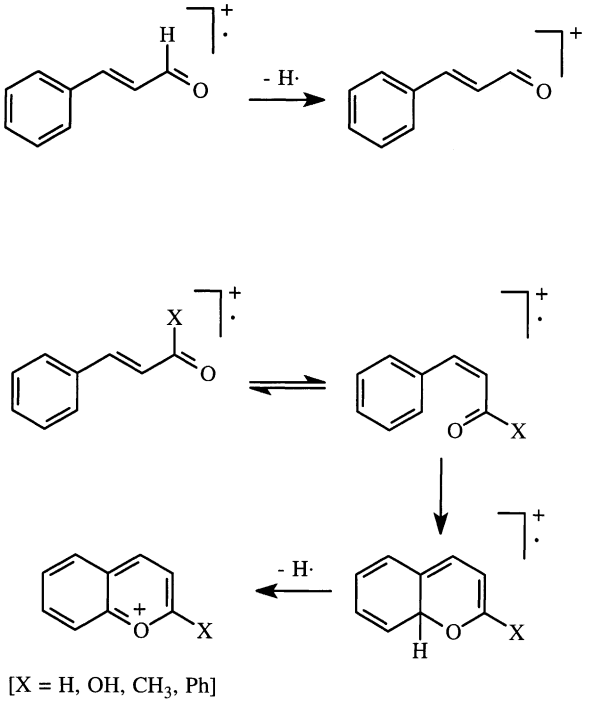
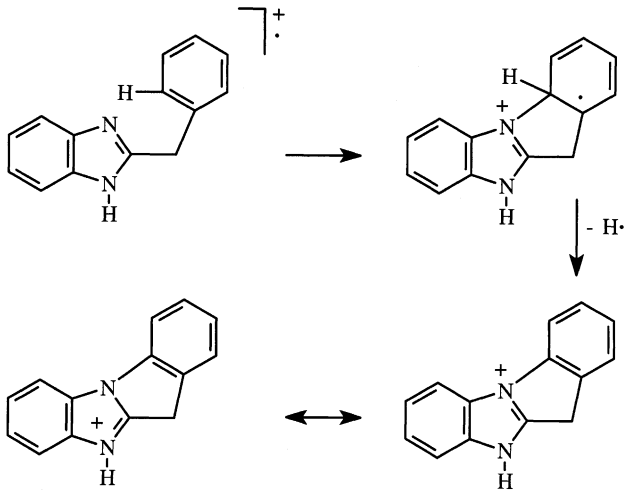


Scheme 1.

between these fragmentations and aromatic substitutions [5].

An intense $[M–H]^+$ peak appears in the EI spectrum of 2-benzylbenzimidazole. This signal may be ascribed to a proximity effect, Scheme 2, in which an extremely stable conjugated tetracyclic cation is formed. This fragmentation also occurs for several other ionized 2-substituted benzylbenzimidazoles. Consequently, a systematic study of the EI spectra of several classes of 2-substituted benzazoles has been undertaken to investigate the generality and analytical utility of this process.



Scheme 2.

2. Experimental

2.1. Synthesis

Most of the substituted 2-benzylbenzimidazoles and 2-phenethylbenzimidazoles were prepared by the acid catalyzed condensation of 1,2-phenylenediamine with the appropriate substituted phenylacetic acid or hydrocinnamic acid, respectively [6,7]. After refluxing the reagents together in aqueous hydrochloric acid, basification of the cooled reaction mixture with concentrated ammonia solution precipitated the crude substituted benzimidazole, which was collected by filtration and recrystallized from aqueous ethanol [7]. Typical yields were 20–60%. The required phenylacetic acids were commercially available. Most of the hydrocinnamic acids were obtained by palladium catalyzed hydrogenation of the corresponding cinnamic acids in methanol or acetic acid [8] to give essentially quantitative yields of almost pure products. The cinnamic acids were synthesized by heating a solution of the appropriate substituted benzaldehyde with excess malonic acid in pyridine in the presence of a catalytic amount of piperidine [9]. After acidification of the reaction mixture with dilute hydrochloric acid, the crude product was collected by filtration and recrystallized from aqueous ethanol. Typical yields were 75–95%. Pentadeuteriocinnamic acid was prepared by treating pentadeuteriophenyl magnesium bromide with triethyl orthoformate in diethyl ether solution at 5 °C to give the diethyl acetal of pentadeuteriobenzaldehyde [10], which was decomposed with cold 2.5 M sulphuric acid to liberate the labelled benzaldehyde in 90% yield. Condensation of pentadeuteriobenzaldehyde with excess malonic acid gave pentadeuteriocinnamic acid, some of which was hydrogenated to give pentadeuterio hydrocinnamic acid in 85% yield, which was converted in the usual manner to 2-(pentadeuteriobenzyl)benzimidazole.

The corresponding 2-styrylbenzimidazoles were made by stirring an equimolar mixture of 1,2-phenylenediamine dihydrochloride (prepared from commercial diamine [11]) and the appropriate substituted cinnamic acid in ethylene glycol at 120 °C for 15–48 h; after cooling, dilution with water and basification with aqueous ammonia, the precipitated crude product was collected and recrystallized from aqueous ethanol. Typical yields were 65–85%. This method resembles that discovered independently [12] in which the same reagents were refluxed for 5 h.

Although other means of preparing 2-styrylbenzimidazole itself have been reported [13–17], most are tedious and few may be readily extended to substituted derivatives. The use of ethylene glycol as solvent not only circumvented the problems in preparing 2-styrylbenzimidazoles, but also greatly improved the yield in other cases, especially the substituted 2-arylbenzimidazole series.

The remaining 2-substituted benzimidazoles were prepared in similar fashion from the requisite carboxylic acid in either aqueous hydrochloric acid (ω-phenylalkyl and

Table 1
Partial 70 eV electron impact mass spectra of 2-benzylbenzimidazoles of general structure $(C_7H_5N_2)CH_2C_6H_4X$

Assignment[b]	X																	
	H		F	2	3	4	Cl	2	3	4	Me	2	3	4	MeO	2	3	4
	m/z	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]
	209	14	227	15	16	14	243	1	33[c]	34[c]	223	16	16	15	239		11	17
$M^{\bullet+}$	208	**95**	226	**97**	**100**	**99**	242	**7**	**100**	**100**	222	**100**	**100**	**100**	238	**6**	**70**	**100**
$[M–H]^+$	207	100	225	50	91	100	241	2	60	58	221	26	87	85	237	4	100	48
$[M–H_2]^{\bullet+}$	206	21	224	12	24	19	240		11	11	220	4	12	12	236		8	2
$[M–X]^{2+}$			207	100	2	1	207	100	21	21	207	60	9	10	207	100	11	2
$[M–HX]^{\bullet+}$			206	28	2	<1	206	18	36	36	206	16	17	15	206	12	8	
$[M–H_2–X]^+$			205	11	3	1	205	9	11	10	205	5	4	4	205	5	3	
$C_7H_5N_2CH_2^+$	131	9	131	7	8	4	131	1	7	7	131	6	6	6	131	3	8	3
$ArCH_2^+$	91	26	109	24	12	12	125	4	6	12	105	9	5	4	121	4	2	14
M^{2+}	104	15	113	5	6	5	121		<1	<1	111	5	2	2	119	1	7	5
$[M–H]^{\bullet2+}$	103.5	9	112.5	1	2	2	120.5	1	2	3	110.5	3	4	2	118.5			<1
$[M–H_2]^{2+}$	103	27	112	6	6	7					110	13	17	11	118		1	
$[M–X]^{\bullet2+}$			103.5	1	<1	<1	103.5	5	9	9	103.5	3	3	1	103.5	2	2	
$[M–HX]^{2+}$			103	9	7	5	103	20	39	33	103	15	12	9	103	6	7	
$[M–H_2–X]^{2+}$			102.5	1	<1	<1	102.5	3	4	4	102.5	1	1	<1	102.5	<1	<1	

[a] RI: relative intensity, normalised to a value of 100 units for the most intense peak. Data in bold type denote molecular ion signals; only selected ^{13}C and other isotope signals are quoted.

[b] The data are arranged so that the *m/z* values in each row correspond to a common assignment. Some assignments are only tentative. The notation does not necessarily imply the order in which the neutral fragments are lost. Similarly, some signals assigned as loss of a molecule could arise by loss of two radicals; thus, $[M–CH_4]^{\bullet+}$ may be $[M–CH_3\text{-}H]^{\bullet+}$.

[c] This signal contains a strong contribution from the $^{13}C^{37}Cl$-satellite of $[M–H]^+$.

2-alkenyl series) or ethylene glycol (substituted 2-aryl series).

The 2-styrylbenzoxazoles and 2-styrylbenzothiazoles were obtained by adding 50% aqueous sodium hydroxide solution to a stirred equimolar mixture of the requisite substituted benzaldehyde and 2-methylbenzoxazole and 2-methylbenzothiazole, respectively, in the presence of benzyltriethylammonium chloride as a phase transfer catalyst [18]. After stirring for 1–48 h, the crude styrylbenzazole was isolated by diluting the reaction mixture with water,

Table 2
Partial 70 eV electron impact mass spectra of 2-benzylbenzimidazoles of general structure $(C_7H_5N_2)CH_2C_6H_3X_2$ and $(C_7H_5N_2)CH_2C_6H_3XY$

Assignment[b]	X, Y										
	H, 4-NO_2		2,3-C_4H_2[d]		Cl_2	2,3	2,4	2,6	3,4	3,4-$(MeO)_2$	
	m/z	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]
	254	16	259	16	277	3[c]	2[c]		33[c]	269	18
$M^{\bullet+}$	253	**100**	258	**92**	276	**10**	**13**	**<1**	**100**	268	**100**
$[M–H]^+$	252	37	257	100	275	23	15	<1	71	269	54
$[M–H_2]^{\bullet+}$	251	5	256	41	274				4	268	
$[M–X]^{2+}$	207	33			241	100	100	100	23	237	15
$[M–HX]^{\bullet+}$	206	46			240	7	6	5	38	236	
$[M–H_2–X]^+$	205	19			239	3	2	2	6		
$[M–X–Y]^+$					206	84	70	55	42		
$[M–X–HY]^{\bullet+}$					205	19	1	7	22		
$ArCH_2^+$	136	<1	139	3	159	6	5	3	9	151	5
$C_7H_5N_2CH_2^+$	131	4	131	1	131	2	1	1	11	131	18
M^{2+}	126.5		129	11	138	2	2		2	134	6
$[M–H]^{\bullet2+}$	126	<1	128.5	2	137.5				<1	133.5	
$[M–X]^{\bullet2+}$	103.5	4			120.5	8	5	10	[11]	133.5	
$[M–HX]^{\bullet2+}$	103	21			120	11	9	5	17	118.5	
$[M–H–HX]^{2+}$	102.5	4			119.5	1	<1	<1	2	118	
$[M–X–Y]^{2+}$					103	28	19	31	29	103	
$[M–HX–Y]^{\bullet2+}$					102.5	9	9	3	8	102.5	
$[M–HX–HY]^{2+}$					102	10	7	3	15	102	

For (a, b, c), see footnote to Table 1.

[d] 2(1-Naphthylmethyl)benzimidazole.

Table 3
Partial 70 eV electron impact mass spectra of 2-phenethylbenzimidazoles of general structure $(C_7H_5N_2)CH_2CH_2C_6H_4X$

Assignment[b]	X																	
	H		F	2	3	4	Cl	2	3	4	Me	2	3	4	MeO	2	3	4
	m/z	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]
	223	16	241	18	17	17	257	2[c]	36[c]	33[c]	237	16	16	15	253	<1	16	9
$M^{\bullet+}$	222	**100**	240	**100**	**100**	**100**	256	**2**	**100**	**92**	236	**100**	**100**	**100**	252	**3**	**100**	**53**
$[M–H]^+$	221	86	239	56	72	74	255	4	71	62	235	41	79	81	251	7	83	16
$[M–H_2]^{\bullet+}$	220	4	238	4	4	4	254		4	6	234		7	3				
$[M–H–H_2]^{\bullet+}$	219	7	237	3	5	5	253		3	3	233	1	5	4				
$[M–X]^+$			221	21			221	100	6	3	221	36	6	4	221	100	1	1
$[M–HX]^{\bullet+}$			220	3			220	4	3	2	220	3	9	4	220	3		
$[M–H_2–X]^+$			219	8	1	1	219	8	6	5	219	7	12		219	7	1	
$C_9H_9N_2^+$	145	46	145	43	51	38	145	8	79	57	145	39	10	38	145	8	58	6
$C_7H_5N_2CH_2^+$	131	43	131	69	73	69	131	20	97	100	131	34	5	26	131	8	31	5
$ArCH_2^+$	91	22	109	11	12	29	125	4	8	23	105	36	34	75	121	15	9	100
M^{2+}	111	1	120	5	4	2	128	<1	<1	<1	118	2	<10		126	3	1	2
$[M–H]^{\bullet 2+}$	110.5	1	119.5	<1	<1	<1					117.5	2	<4	<6				
$[M–X]^{\bullet 2+}$							110.5	1	2	1					110.5	<1		
$[M–HX]^{2+}$							110	3	14	6					110	1		
$[M–H_2–X]^{\bullet 2+}$			109.5	1	<1		109.5	1	6	3					109.5	<1		

For (a, b, c), see footnote to Table 1.

Table 4
Partial 70 eV electron impact mass spectra of 2-phenethylbenzimidazoles of general structure $(C_7H_5N_2)CH_2CH_2C_6H_3X_2$ and $(C_7H_5N_2)CH_2CH_2C_6H_3XY$

Assignment[b]	X, Y																	
	C_4H_2	2,3[d]	3,4[e]	Cl_2	2,3	2,4	2,6	3,4	3,4-$(MeO)_2$		3,4-(OCH_2O)		4-C_2H_5		4-$CH(CH_3)_2$		4-$C(CH_3)_3$	
	m/z	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]
	273	12	5	291	3	4	<1	28	283	8	267	9	251	19	265	19	279	20
$M^{\bullet+}$	272	**65**	**31**	290	**1**	**3**	<1	**55**	282	**48**	266	**58**	250	**100**	264	**100**	278	**100**
$[M–H]^+$	271	49	24	289	4	5	<1	32	281	7	265	19	249	84	263	53	277	48
$[M–H_2]^{\bullet+}$	270	2	<1	288				2	280		264	1	248	1	262	7		
$[M–H–H_2]^{\bullet+}$	269	4	2															
$[M–CH_3]^{\bullet+}$									267	15			235	5	249	14	263	25
$[M–X]^+$				255	100	100	100	4	251	2			221	<1	221	7	221	3
$[M–HX]^{\bullet+}$				254	2	3	3	2	250	1								
$[M–X–H_2]^+$				253	3	5	9	3							219	1		
$[M–X–Y]^{\bullet+}$				220	3	1	64	<1										
$[M–X–HY]^+$				219	3	2	3	1										
$[M–HX–HY]^{\bullet+}$				218	4	2	7	1	218	3								
$C_9H_9N_2^+$	145	29	8	145	13	16	10	56	145	<1	145	10	145	31	145	27	145	25
$C_7H_5N_2CH_2^+$	131	12	6	131	30	55	36	100	131	9	131	7	131	19	131	26	131	19
$ArCH_2^+$	141	100	100	159	9	6	2	6	151	100	135	100	119	40	133	31	147	17
M^{2+}	136	2	1	145	(13)[f]	(16)[f]	(10)[f]	(56)[f]	141	2	133	<1	125	<1	132	4	139	<2
$[M–H]^{\bullet 2+}$	135.5	1		144.5	<1	<1	<1											
$[M–H_2]^{2+}$				144	2	<1	<1	2										
$[M–X]^{\bullet 2+}$				127.5	1	1	<1	4	125.5	1								
$[M–HX]^{2+}$				127	1<	<1	<1	1										
$[M–X–Y]^{\bullet 2+}$				110	1	2	1	2										
$[M–HX–Y]^{2+}$				109.5	2	3	2	2										

For (a, b, c), see footnote to Table 1.
[d] 2-[2-(1-Naphthylethyl)]benzimidazole.
[e] 2-[2-(2-Naphthylethyl)]benzimidazole.
[f] Signal isobaric with $C_9H_9N_2^+$.

extracting the product with dichloromethane and evaporating the dried organic extracts. Recrystallization from ethanol or aqueous ethanol gave the desired styrylbenzazole in 50–95% yield. 2-Methylbenzoxazole was prepared by careful distillation of a mixture of 2-aminophenol and excess acetic anhydride [19]; 2-methylbenzothiazole was obtained from commercial sources.

Only a few members of the substituted phenethylbenzoxazole series could be prepared in a pure state by palladium catalyzed hydrogenation of the corresponding styrylbenzoxazole. Hydrogenation either tended not to go to completion, or else was accompanied by some hydrogenolysis to 2-methylbenzoxazole. These difficulties were not noticeable in the styrylbenzothiazole series, representative examples of which were hydrogenated in methanol to give the corresponding phenethylbenzothiazole.

2.2. Mass spectrometry

The mass spectra were obtained on a refurbished AEI MS902 double-focusing mass spectrometer, in which the ions were transmitted through the electric sector before entering the magnetic analyzer. Samples were introduced on the probe and allowed to evaporate at such a rate that a pressure of $\sim 10^{-6}$ Torr developed in the source. The accelerating voltage was 8 kV, the source block temperature was 200 °C and the nominal energy of the ionising electrons was 70 eV.

3. Results and discussion

The 70 eV EI spectra of an extensive range of 2-benzylbenzimidazoles are summarized in Tables 1 and 2. Analogous data for 2-phenethylbenzimidazoles and 2-styrylbenzimidazoles are shown in Tables 3–6. The spectra of a few 2-phenethylbenzoxazoles, 2-phenethylbenzothiazoles, 2-arylbenzimidazoles, 2-(ω-phenylalkyl)benzimidazoles and 2-alkylbenzimidazoles or 2-alkenylbenzimidazoles are summarized in Tables 7–11, respectively. The spectra of the 2-styrylbenzoxazoles and 2-styrylbenzothiazoles resembled those of the analogous benzimidazoles and are not reproduced, but full details are available on request. In the following discussion, the names of the heterocycles are abbreviated as illustrated below, with a conventional prefix to indicate the nature and position of any substituent(s) in the pendant aryl ring.

Thus, Nap2BI, 2-Cl-6-F-SBO, and ω3PhSBI denote, respectively, 2-(2-naphthyl)benzimidazole, 2-(2-chloro-6-fluorostyryl)benzoxazole and 2-(3-phenylpropyl)benzimidazole.

3.1. Molecular ion signals

With the exception of a few compounds with substituents in both the 2- and 6-positions of the pendant aryl ring, all the 2-substituted benzazoles show appreciable molecular ion

Table 5
Partial 70 eV electron impact mass spectra of 2-styrylbenzimidazoles of general structure $(C_7H_5N_2)CH{=}CHC_6H_4X$

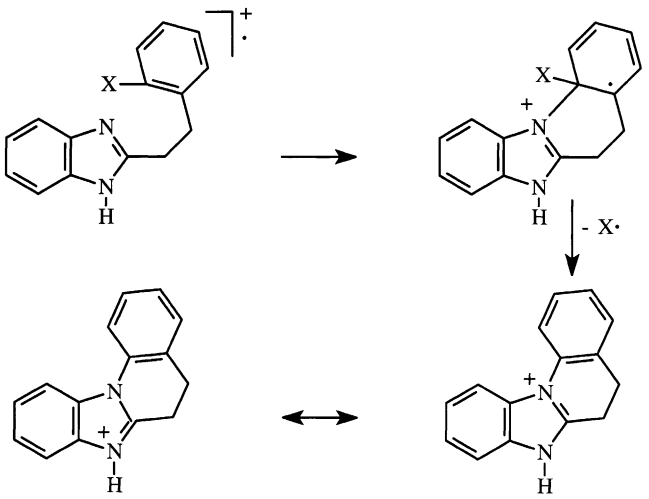
Assignment[b]	X																					
	H		F		2	3	4	Cl	2	3	4	Br	2	3	4	Me	2	3	4	MeO	2	3	4
	m/z	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]
	221	5	239	5	5	5	4	255	12[c]	36[c]	36[c]	299	11[d]	99[d]	100[d]	235	5	6	5	251	<1	7	5
$M^{\bullet+}$	220	**36**	238	**41**	68	100	**34**	254	**22**	**40**	**38**	298	**15**	**47**	**40**	234	**33**	**39**	**36**	250	**2**	**48**	**33**
$[M–H]^+$	219	100	237	68	100	100	100	253	27	100	100	297	8	100	98	233	38	100	100	249	3	100	100
$[M–H_2]^{\bullet+}$	218	15	236	10	13	12	12	252	2	7	7	296	<1	1	3	232	7	10	11	248		5	3
$[M–X]^+$			219	100	1			219	100	8	5	219	100	11	9	219	100	4	3	219	100	4	1
$[M–HX]^{\bullet+}$			218	12				218	18	14	16	218	3	12	10	218	11	7	3	218	7	3	<1
M^{2+}	110	6	119	13	8	7	127	2	2	2						117	3	4	1	125	<1	2	
$[M–H]^{\bullet 2+}$	109.5	9	118.5	14	11	9	126.5	<1	<1	<1	1					116.5	3	3	21				
$[M–H_2]^{2+}$	109	3	118	5	5	4	126	<1	<1	<1	<1					116	15	13	11				
$[M–X]^{\bullet 2+}$			109.5	6	<1	<1	109.5	12	9	7	109.5	20	39	29	109.5	6	4	3	109.5	3		
$[M–HX]^{2+}$			109	4				109	13	11	9	109	8	11	9	109	2	1	1	109	1		

For (a, b, c), see footnote to Table 1.
[d] This signal is mainly the ^{81}Br satellite of $[M–H^+]$.

Table 6
Partial 70 eV electron impact mass spectra of 2-styrylbenzimidazoles of general structure $(C_7H_5N_2)CH{=}CHC_6H_3X_2$ and $(C_7H_5N_2)CH{=}CHC_6H_3XY$

Assignment[b]	X, Y																				
	C_4H_2	2,3[d]	3,4[e]	2,6-F_2		2,6-F,Cl		Cl_2	2,3	2,4	2,6	3,4	3,4-$(MeO)_2$		3,4-(OCH_2O)		4-Et		4-*i*-Pr		4-*t*-Bu	
	m/*z*	RI[a]	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]	RI[a]	RI[a]	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]	*m*/*z*	RI[a]
	271	7	7	257	6	273	5	289	17	15	1	68	281	8	265	5	249	6	263	6	277	7
$M^{\bullet+}$	270	**40**	**43**	256	**27**	272	**19**	288	**18**	**18**	**7**	**43**	280	**42**	264	**36**	248	**39**	262	**38**	276	**41**
$[M–H]^+$	269	100	100	255	11	271	7	287	24	20	<1	100	279	100	263	100	247	100	261	100	275	100
$[M–H_2]^{\bullet+}$	268	14	13					286	1	1		6	278	4	262	4	246	5	260	4	274	4
$[M–CH_3]^+$													266				233	4	247	4	261	9
$[M–X]^+$				237	100	253	54	253	100	100	100	15	249	1			219	7	219	6	219	7
$[M–HX]^{\bullet+}$				236	3	252	7	252	10	11	7	11	248	1			218	2	218	<1	218	<1
$[M–Y]^+$						237	100															
$[M–HY]^{\bullet+}$						236	21															
$[M–X–Y]^{\bullet+}$						218	6	218	9	12	13	5										
$[M–X–HY]^{\bullet+}$						217	3	217	14	7	5	10										
M^{2+}	135	4	7	128	6	136	1	144	<1	<1		1	140		132	1	124	<1	131	<1	138	<1
$[M–H]^{\bullet 2+}$	134.5	6	10					143.5			<1		139.5		131.5	3						
$[M–X]^{\bullet 2+}$				118.5	4	126.5	1	126.5	12	13	10	15										
$[M–HX]^{2+}$								126	3	4	3	4										
$[M–HX–Y]^{\bullet 2+}$								108.5	9	8	7	6										
$[M–Y]^{\bullet 2+}$						118.5	15															
$[M–HY]^{2+}$						118	9															

For (a, b, c), see footnote to Table 1.
[d] 2-[2-(1-Naphthylstyryl)]benzimidazole.
[e] 2-[2-(2-Naphthylstyryl)]benzimidazole.



Scheme 3.

signals, most of which are of at least moderate relative intensity (RI). Mass spectrometry is, therefore, a very convenient analytical method for detecting these compounds, many of which possess pharmacological activity or have potential applications as optical bleaching agents or in photography.

3.2. $[M–H]^+$ and $[M–X]^+$ signals

The spectra of almost all the benzazoles contain strong $[M–H]^+$ and/or $[M–X]^+$ signals. In many cases, one of these signals is the base peak in the spectrum. This trend is especially pronounced in the SBI, SBO and SBT series, in which the spectrum of every benzazole without a substituent in the 2-position of the pendant aryl ring is dominated by $[M–H]^+$, which is typically three times as intense as the next strongest signal (usually $M^{\bullet+}$). If allowance is made for the proportion (roughly half) of the apparent $M^{\bullet+}$ peak that may be ascribed to the ^{13}C-satellite signal of $[M–H]^+$, the extraordinary ease of hydrogen atom elimination from these ionized benzazoles is even more striking. Similarly, the spectra of members of the SBI, SBO and SBT series with a 2-substitutent, X, in the aryl ring are dominated by $[M–X]^+$, regardless of the nature of X. Parallel, though less noticeable, trends are found in the spectra of the BBIs and PBIs and, to a lesser degree, the limited range of PBOs and PBTs. The variations in the RIs of $M^{\bullet+}$, $[M–H]^+$ and $[M–X]^+$ in the spectra of a wide range of benzazoles are summarized in Table 12.

These data attest to the importance of the proximity effect in the fragmentation of ionized 2-substituted benzazoles, as shown in Scheme 3 for ionized 2-X-PBI. Even substituents like a fluorine atom or a methoxy group that are rarely lost from ionized aryl systems are easily eliminated by this mechanism. In the case of the fluoroderivatives, the RI of $[M–F]^+$ is 2% or less if the substituent is in the 3- or 4-position. In contrast, when a 2-fluorosubstituent is present, $[M–F]^+$ is either the base peak or of comparable RI in the SBI, SBO

Table 7
Partial 70 eV electron impact mass spectra of 2-phenethylbenzoxazoles of general structure $(C_7H_4NO)CH_2CH_2C_6H_4X$

Assignment[b]	X or X, Y																			
	H		Cl	2	3	4	MeO	2	4	3,4-$(MeO)_2$		3,4-(OCH_2O)		4-Me		4-Et		4-*i*-Pr		4-*t*-Bu	
	m/z	RI[a,d]	*m/z*	RI[a,d]	RI[a,d]	RI[a,d]	*m/z*	RI[a,d]	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]
	224	16	258	1[c]	30[c]	14[c]	254	2	2	284	4	268	3	238	4	252	4	266	6	280	9
$M^{\bullet+}$	223	**100**	257	**2**	**100**	**51**	253	**20**	**12**	283	**20**	267	**22**	237	**34**	251	**40**	265	**46**	279	**64**
$[M–H]^+$	222	86	256	3	37	19	236	10	<1	282	<1	266	1	236	8	250	5	264	5	278	2
$[M–H_2]^{\bullet+}$	221	4	255		2																
$[M–H–H_2]^+$	220	7	251		1	1															
$[M–X]^+$			222	100	32	8	222	90	<1	252	<1			222	<1			222		222	5
$[M–HX]^{\bullet+}$			221	7	2	1												221	2		
$[M–X–H_2]^+$			220	3	4	2															
$[M–CH_3]^+$					<2	<1	238	2	<1	268	9			222	<1	236	<1	250	3	264	45
$C_7H_4NOCH_2^+$	132	43	132	10	68	12	132	3	<2	132	2	132	2								
$ArCH_2^+$	91	22	125	25	67	100	105	100	100	151	100	135	100	105	100	119	100	133	100	147	100

For (a, b, c), see footnote to Table 1.
[d] Spectrum also contains a signal at *m/z* 133, assumed to be the molecular ion of a trace of 2-methylbenzoxazole, formed by hydrogenolysis of the precursor.

Table 8
Partial 70 eV electron impact mass spectra of 2-phenethylbenzothiazoles of general structure $(C_7H_4NS)CH_2CH_2C_6H_4X$

Assignment[b]	X											
	H		Me	2	3	4	4-Et		4-*i*-Pr		4-*t*-Bu	
	m/z	RI[a,d]	*m/z*	RI[a,d]	RI[a,d]	RI[a,d]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]
	241	4	255		3	1	269	3	283	3	297	4
	240	19	254	16	16	9	268	14	282	11	296	18
$M^{\bullet+}$	239	**100**	253	**98**	**100**	**56**	267	**66**	281	**46**	295	**97**
$[M–H]^+$	238	59	252	13	43	19	266	21	280	16	294	13
$[M–H_2]^{\bullet+}$	237	1										
$[M–H–H_2]^{\bullet+}$	236	2										
$[M–X]^+$			238	11	4	2				4	238	5
$[M–CH_3]^+$			238	(11)	(4)	(2)	252	3	266	21	280	37
	162	49	162	16	68	12	162	12	162	8	162	6
	149	2	149	39	6	<1	149	1	149	<1	149	<1
$C_7H_4NSCH_2^+$	148	24									148	14
$ArCH_2^+$	91	98	105	100	83	100	119	100	133	100	147	100
			79	17	67	100						
			77	21	67	100	91	21			117	29

For (a, b, c), see footnote to Table 1.

Table 9
Partial 70 eV electron impact mass spectra of 2-arylbenzimidazoles

Assignment[b]	Ar								
	C_6H_5		C_6H_4Cl	2	3	4	$C_{10}H_7$	1	2
	m/z	RI[a]	*m/z*	RI[a]	RI[a]	RI[a]	*m/z*	RI[a]	RI[a]
	195	15	229	17	17	17	245	9	16
$M^{\bullet+}$	194	**100**	228	**100**	**100**	**100**	244	**59**	**100**
$[M–H]^+$	193	16	227	7	6	7	243	100	41
$[M–H_2]^{\bullet+}$	192	5	226	1	1	1	242	18	10
$[M–Cl]^+$			193	15	15	16			
$[M–HCl]^{\bullet+}$			192	8	7	8			
Ar^+	77	7	111	<1	3	6	127	2	11
M^{2+}	97	6	114	5	6	2	122	9	6
$[M–H]^{\bullet 2+}$	96.5	2	113.5	<1	<1	<1	121.5	12	5
$[M–Cl]^{\bullet 2+}$			96.5	7	8	8			
$[M–HCl]^{2+}$			96	6	5	6			

For (a, b, c), see footnote to Table 1.

Table 10
Partial 70 eV electron impact mass spectra of 2-benzimidazoles of general structure $C_7H_5N_2(CH_2)_nC_6H_5$

Assignment[b]	*n*									
	0[d]		1[d]		2[d]		3		4	
	m/z	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]
	195	15	209	14	223	16	237	<1	251	9
$M^{\bullet+}$	194	**100**	208	**95**	222	**100**	236	**3**	250	**50**
$[M–H]^+$	193	16	207	100	221	86	235	1	249	3
$[M–H_2]^{\bullet+}$	192	6	206	21	220	4				
$[M–H–H_2]^{\bullet+}$	191	1<	205	7	220	7				
$C_9H_{10}N_2^+$	146		146		146	5	146		146	69
$C_9H_9N_2^+$	145		145		145	43	145	2	145	100
$C_7H_8N_2^+$	132		132	1	132	4	132	100	132	36
$C_7H_5N_2CH_2^+$	131	9	131	9	131	69	131	8	131	9
$C_6H_5CH{=}CH_2^{\bullet+}$					104	6	104	2	104	3
$C_6H_5CH_2^+$			91	26	91	21	91	4	91	8
M^{2+}	97	9	104	15	111	1	118	1	125	1
$[M–H]^{\bullet 2+}$	96.5	4	103.5	9	110.5	1				
$[M–H_2]^{2+}$			103	26						

For (a, b, c), see footnote to Table 1.
[d] The data for $n = 0$, 1 and 2 also appear in Tables 9, 1 and 3, respectively, but are included for purposes of comparison.

Table 11
Partial 70 eV electron impact mass spectra of 2-alkylbenzimidazoles and 2-alkenylbenzimidazoles of general structure ($C_7H_5N_2$)R

Assignment[b]	R																			
	H		CH_3		C_2H_5		C_3H_7		C_4H_9		C_5H_{11}		2-C_3H_5		3-C_4H_7		4-C_5H_9		2-C_5H_9	
	m/z	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]	*m/z*	RI[a]
	119	8	133	9	147	5	161	3	175	2	189	3	159	7	173	7	187	17	187	6
$M^{\bullet+}$	118	**100**	132	**100**	146	**60**	160	**31**	174	**11**	188	**19**	158	**73**	172	**58**	186	**100**	186	**30**
$[M–H]^+$	117	3	131	62	145	100	159	16	173	3	187	2	157	100	171	100	185	62	185	14
$[M–H^{\bullet 2+}$			130	3	144	1	158	<1					156	19	170	4	184	2	184	1
$[M–H–H_2]^{\bullet+}$													155	3	169	12	183	5	183	2
$[M–HCN]^{\bullet+}$	91	24	105	2	119	3														
$[M–CH_3]^+$					131	18	145	24	159	6	173	1	143	5	157	19	171	2	171	22
$[M–C_2H_4]^{\bullet+}$							132	100	146	6	160	2			144	6	158	22	158	34
$[M–C_2H_5]^+$							131	24	145	23	159	12			143	4	157	44	157	100
$[M–C_3H_6]^{\bullet+}$									132	100	146	16					144	10	144	2
$[M–C_3H_7]^+$									131	15	145	49					143	6	143	1
$[M–C_4H_8]^{\bullet+}$											132	100								
$[M–C_4H_9]^+$											131	15								
$[M–C_4H_6]^{\bullet+}$																	132	98	132	46
$C_7H_5N_2CH_2^+$			131	62	131	18	131	24	131	14	131	15	6	10	131	53	131	3	131	13
$[C_6H_5]^+$			77	4	77	6	77	9	77	4	77	1	77	7	77	21	77	10	77	9

For (a, b), see footnote to Table 1.

and SBT series. From an analytical perspective, the value of these of $[M–X]^+$ signal is clear: pendant rings with a 2-substituent may be readily distinguished from the isomeric 3- and 4-substituted species. The remarkable change in the overall appearance of the spectra, most of which contain very few other significant fragment ion signals, is illustrated in Fig. 1 for the three isomeric F-SBIs.

The spectra of BBIs and PBIs allows the relative ease of formation of five- and six-membered rings by the proximity effect to be compared by considering the ratio of the RIs of

Table 12
Relative intensities of $M^{\bullet+}$, $[M–H]^+$ and $[M–X]^+$ signals in the mass spectra of 2-substituted benzazoles with a pendant C_6H_4X or $C_6H_3X_2$ aromatic ring

X	Ratio of relative intensity of $M^{\bullet+}$:$[M–H]^+$:$[M–X]^+$ signals				
	SBI	SBO	SBT	BBI	PBI
H	36:100	37:100	38:100	95:100	100:86
2-F	41:68:100	62:54:100	44:66:100	97:50:100	100:56:21
3-F	35:100:1	39:100:<1	43:100:<1	100:91:2	100:72:<1
4-F	34:100:<1	40:100:<1	41:100:<1	99:100:1	100:74<1
2-Cl	22:27:100	38:33:100	15:7:100	7:2:100	2:3:100
3-Cl	40:100:8	63:100:15	50:100:21	100:60:21	100:71:6
4-Cl	38:100:5	46:100:5	45:100:14	100:58:21	92:62:3
2-Br	15:8:100	15:8:100	9:3:100		
3-Br	47:100:11	47:100:11	47:92:17		
4-Br	40:98:11	40:98:9	48:93:20		
2-CH_3	33:38:100	29:27:100	29:28:100	100:26:60	100:41:36
3-CH_3	39:100:4	71:100:7	43:100:9	100:87:9	100:79:6
4-CH_3	36:100:3	34:100:4	41:100:7	100:85:10	100:81:4
2-OCH_3	2:3:100	13:7:100	10:2:100	6:4:100	3:7:100
3-OCH_3	48:100:4	47:100:3	46:100:5	70:100:1	100:83:1
4-OCH_3	33:100:1	48:100:2	62:100:2	100:48:2	53:16:1
2,6-F_2	27:11:100	28:11:100	29:14:100		
2,3-Cl_2	18:24:100	25:19:100	16:11:100	10:23:100	1:4:100
2,4-Cl_2	18:20:100	18:15:100	13:5:100	13:15:100	3:5:100
2,6-Cl_2	7:<1:100	11:<1:100	8:<1:100	<1:<1:100	<1:<1:100
3,4-Cl_2	43:100:15	44:100:14	65:100:13	100:71:23	53:32:2
3,4-$(CH_2O)_2$	41:100:1	61:100:1	76:100:3	100:54:15	43:7:15
3,4-(OCH_3O)	36:100	45:100	56:100		56:19
2,3-(C_4H_2)	40:100	39:100	44:100	92:100	65:49
3,4-(C_4H_2)	43:100	47:100	53:100		31:24

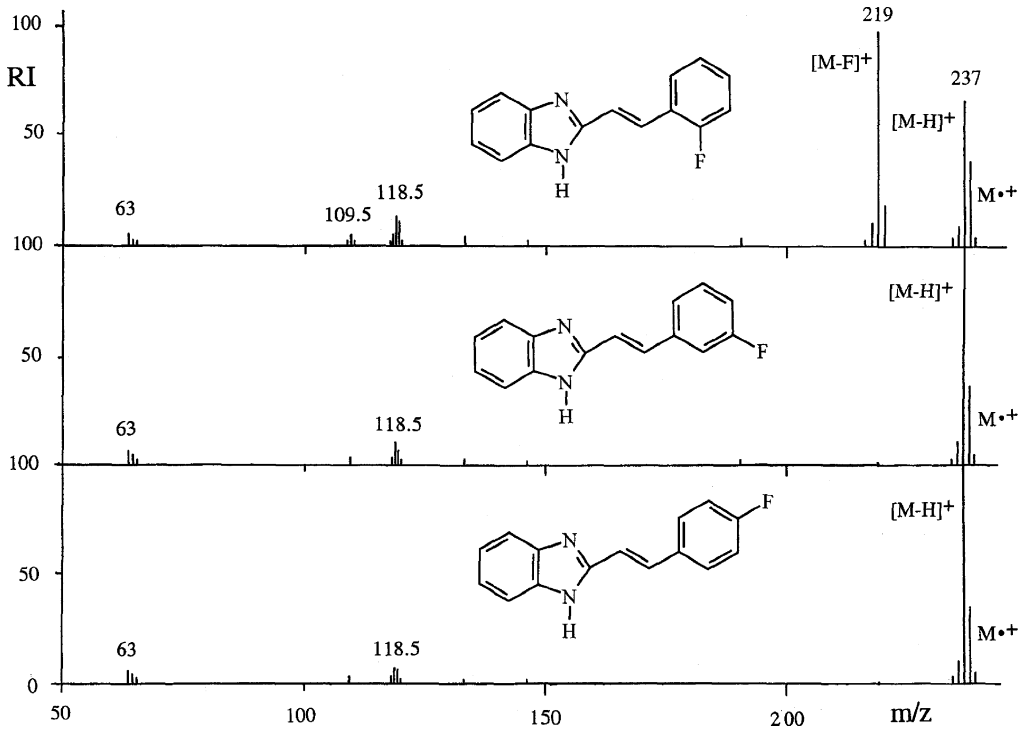


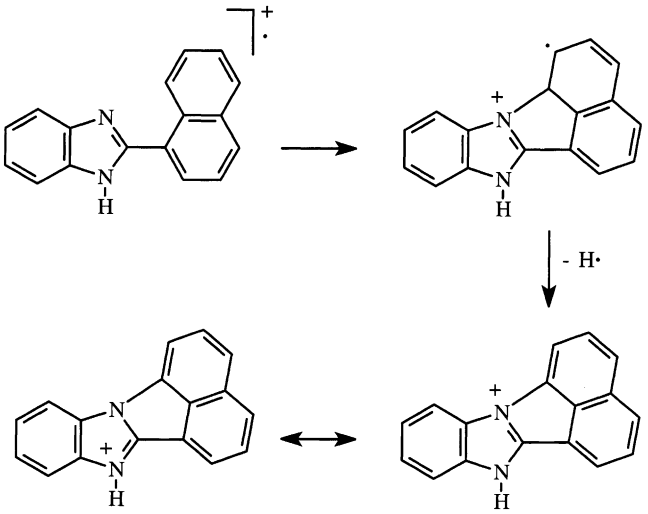
Fig. 1. EI mass spectra (70 eV) of isomeric 2-(fluorostyryl)benzimidazoles.

the $[M–H]^+$ and M^+ peaks. The same trends are observed; moreover, the variations in the ratio are usually only slight. Consequently, the proximity effect occurs with similar ease when the initial cyclization involves formation of a five- or six-membered ring when the carbon atoms of the connecting chain are sp^3 hybridized.

Analysis of the rate of the cyclization step may be extended by considering the spectra of the ωnPhBIs. The ratio of the RIs of the $[M–H]^+$ and $M^{\bullet+}$ peaks is 0.16:1, 1.05:1, 0.86:1, ~0.3:1 and 0.06:1, respectively, for $n = 0$, 1, 2, 3 and 4. There is a greater uncertainty about the ratio for $n = 3$, chiefly because facile fragmentation of the ionized molecule by a new pathway becomes possible, thus greatly reducing the RI of both the $[M–H]^+$ and $M^{\bullet+}$ peaks. Nevertheless, it is clear that the rate of cyclization is significantly slower when a seven-membered ring is involved. Larger rings are formed even more slowly; indeed, the proximity effect is not really significant if it entails the formation of an eight-membered ring.

A brief comment is necessary on the case when $n = 0$. Although there is an appreciable $[M–H]^+$ peak in the spectrum of PhBI, it is unlikely that this signal reflects a proximity effect with formation of a four-membered ring. Few processes other than loss of a hydrogen atom or hydrogen (iso)cyanide from ionized PhBI seem plausible. Moreover, the spectra of the isomeric 2-(chlorophenyl)benzimidazoles and the two 2-(naphthyl)benzimidazoles [Nap1BI and Nap2BI) suggest that at least part of the $[M–H]^+$ and $[M–X]^+$ signals in the spectra of 2-arylbenzimidazoles may arise by mechanisms other than a proximity effect. Thus, the spectra of the three isomeric ClC_6H_4BIs are almost superimposable: the RI of $[M–Cl]^+$ does not depend on the position of the chloro substituent. This finding contrasts sharply with the strong correlation between the ratio of the RIs of the $[M–Cl]^+$ and $M^{\bullet+}$ peaks in the spectra of the corresponding sets of ClBBIs and ClPBIs and the position of the chlorine atom in the pendant ring. Similarly, the ratio of the RIs of the $[M–H]^+$ and $M^{\bullet+}$ signals in the spectra of Nap1BI and Nap2BI is ~1.7:1 and 0.4:1, respectively. The larger ratio in the former system is explained by the greater ease of hydrogen atom elimination by a proximity effect involving cyclization to the peri-position, with formation of a five-membered ring, Scheme 4. The corresponding process in the ionized Nap2BI would entail forming a four-membered ring, so it is far less facile, if it occurs at all.

A comparison of the ratio of the RIs of the $[M–H]^+$ and $M^{\bullet+}$ peaks in the SBI and PBI series indicates that the proximity effect to form a new six-membered ring occurs even more readily for ionized BIs in which the two carbon atoms connecting the aromatic entities are sp^2 hybridized. A parallel trend is also evident in the ratio of the RIs of the $[M–X]^+$ and $M^{\bullet+}$ signals. These trends, which are also observed for the corresponding SBOs and SBTs, are more remarkable than appears at first sight. The cation produced by the proximity effect in the SBI and analogous series would be expected to be especially stable because the extra ring which is formed is aromatic; this difference might provide a thermodynamic factor favouring the proximity effect in the SBI series compared to the analogous ionized PBIs. However, NMR shows clearly that the SBIs contain a *trans*-olefinic



Scheme 4.

C=C linkage, which is not compatible with the initial cyclization. It has long been known that many acyclic C=C bonds do not retain their stereochemical integrity after EI, as is illustrated by the very similar behaviour of $C_nH_{2n}^{\bullet+}$ radical-cations formed from isomeric *cis*- and *trans*-alkenes [20–23]. Consequently, isomerization of the C=C bond in the ionized SBIs may be facile.

Any *trans*/*cis*-isomerism of the ionized SBIs would have to compete with other processes, including cleavage of a linkage in the alkyl chain connecting the two aryl entities. This fragmentation by σ-cleavage would be far more difficult for the ionized SBIs (in which a C=C bond must be broken to form an unstable vinyl cation and radical) than for the analogous PBIs (in which fission of only a C–C bond need take place to give a more stable benzylic cation and radical). Moreover, although the proximity effect must entail rearrangement of the initial ionized SBI to a species with a *cis*-C=C bond, the geometry of this species is almost ideal for the cyclization step. Indeed, molecular models indicate that the sp^2 hybridized atoms in an ionized *cis*-SBI are unlikely to assume the co-planar geometry that would maximize the overlap of atomic orbitals in an extended π-system. The six atoms of the ring that would be formed by the proximity effect are more likely to form a single turn of a helix. This geometry brings the nitrogen atom and the *ortho*-carbon atom of the pendant ring into contact, in such a way that bonding may naturally occur. Thus, although the C=C bond in the ionized SBIs might seem to be unsuited for cyclization because it would normally have *trans* stereochemistry, it may actually be a most effective "tether" in the first step of a proximity effect. Cleavage of this double bond is energetically undesirable, but rearrangement to a stereoisomer with a *cis*-C=C leads almost inevitably to cyclization. In contrast, when the connecting hydrocarbon chain contains only σ-bonds, the "tether" is less robust because σ-cleavage of the central C–C linkage is relatively facile. This combination of factors appears to favour the proximity effect in ionized SBIs (and SBOs and SBTs), relative to the analogous ionized PBIs (and PBOs and PBTs).

Another indication of the ease of the proximity effect for ionized SBIs (and, to a similar extent, for the analogous SBOs and SBTs) is provided by the relative rate of this rearrangement compared to that of methyl radical elimination by σ-cleavage of a 4-alkyl group (Table 13). Simple cleavages tend to have much higher maximum rates than rearrangements because the latter have additional geometric restraints that do not apply to the former [24–26]. Rearrangements often have lower appearance energies (AEs), partly because they tend to involve bond formation, as well as bond breaking. If a simple cleavage has a lower AE than a competing rearrangement, the former generally dominates at both high and low internal energies, corresponding to fast and slow reactions. The AE for the characteristic fragmentation (the primary fragmentation with the lowest AE) of many monosubstituted benzenes is known [27]. Thus, the AE for loss of a methyl radical from ethylbenzene, isopropyl benzene and *t*-butylbenzene is just 11.25, 10.65 and 10.26 eV, respectively. The last two cleavages are amongst the most facile of all characteristic fragmentations. Consequently, elimination of a methyl radical by σ-cleavage of a 4-alkyl group ought to occur exceptionally readily. Yet it competes only very ineffectively with a rearrangement that entails isomerization of a C=C bond, formation a new ring and eventual hydrogen atom expulsion. Therefore, the proximity effect must have a substantially lower AE than even these exceptionally favourable simple cleavages. The ratio of the intensities of $[M–H]^+$ (via the proximity effect) to $[M–CH_3]^+$ (by simple cleavage of the 4-alkyl group) always exceeds 10:1 in the SBI series; it is somewhat smaller (reaching a minimum value of ∼3:1) in the SBO and SBT analogues, with the smallest ratio for a 4-*t*-butyl group. The ratio is significantly reduced in the PBI series, though it remains comparable to that in the corresponding SBO and SBT systems. Only on progressing to the PBO and PBT series does the simple cleavage occur faster than the proximity effect (ratio of 0.06:1 and 0.08:1, respectively, for 4-*t*BuPBO and 4-*t*BuPBT). These trends, which are summarized in Fig. 2, also suggest that the increased basicity and greater electron density of the imidazole ring favours the proximity effect.

The competition between elimination of a different substituent from the 2- and 6-positions of the pendant aryl ring is informative. The ratio of the intensities of the $[M–H]^+$ and $[M–X]^+$ signals varies systematically with the nature of the substituent, X, in the 2-position of the monosubstituted benzazoles. Substituents with a −I inductive effect generally decrease the ratio, especially compared to substituents that have a +I effect. Thus, the ratio is much smaller when $X = CH_3O$ than when it is CH_3 (Fig. 3).

Moreover, in general, the more electronegative the atom attached to the 2-position, the greater the selectivity with which a strong $[M–X]^+$ is associated with the 2-substituent. Thus, in the halogenoseries, the $[M–H]^+$:$[M–X]^+$ ratio declines as the electronegativity of the halogen declines. This

Table 13
Relative intensities of $M^{\bullet+}$, $[M–H]^+$ and $[M–CH_3]^+$ signals in the mass spectra of 2-substituted benzazoles with a pendant $C_6H_4CH_n(CH_3)_{3-n}$ aromatic ring

n	Ratio of relative intensity of $M^{\bullet+}$:$[M–H]^+$:$[M–CH_3]^+$ signals					
	SBI	SBO	SBT	PBI	PBO	PBT
2 [CH_2CH_3]	39:100:4	41:100:7	45:100:6	100:84:5	40:5:<1	66:21:3
1 [$CH(CH_3)_2$]	48:100:4	38:100:9	48:100:12	100:53:14	46:5:3	46:16:21
0 [$C(CH_3)_3$]	41:100:9	41:100:30	56:100:41	100:48:25	64:2:45	54:5:60

trend is the opposite of what would be expected if an electronegative substituent in the 2-position favoured the cyclization step by increasing the electrophilicity of the carbon atom to which it is attached. Similarly, the smaller size of the more electronegative halogen atom would be expected to impose less steric hindrance on the initial cyclization. On the other hand, if the stability of the eliminated radical or atom were important or if relief of steric crowding in the intermediate formed by cyclization were significant, more facile loss of a chlorine (or bromine) rather than a fluorine atom might be anticipated. Consequently, this trend could be taken as evidence that the initial cyclization is not rate-limiting. In general, the first step is rate limiting in electrophilic aromatic substitution and in proximity effects.

The $[M–F]^+$:$[M–Cl]^+$ ratio for 2-Cl–6-F-SBO and 2-Cl–6-F-SBT is especially interesting in this connection. This ratio is 0.54:1, 0.19:1 and 0.61:1, respectively, in the SBI, SBO and SBT series. The preference for expelling a chlorine atom is surprising, at least at first sight. Attachment of the basic nitrogen atom in the benzazole system to the 6-position, which bears the more electronegative and smaller fluorine atom, and which would lead to $[M–F]^+$, might have been expected to be more favourable. Yet $[M–Cl]^+$ is the more intense peak. This curious trend is intelligible if loss of the halogen atom is actually slower than (perhaps at least partially reversible) cyclization to the 2- or 6-position. The preference for eliminating a chlorine atom, rather than a fluorine atom, appears to apply in the 2,6-X_2-series: the spectra of 2,6-F_2-SBI, 2,6-F_2-SBO and 2,6-F_2-SBT all contain appreciable $M^{\bullet+}$ signals (RI ∼ 28%); the corresponding peaks in the spectra of the analogous 2,6-Cl_2-compounds are significantly weaker (RIs in the range 7–11%), suggesting that chlorine atom loss occurs more readily from these ionized 2,6-X_2-species.

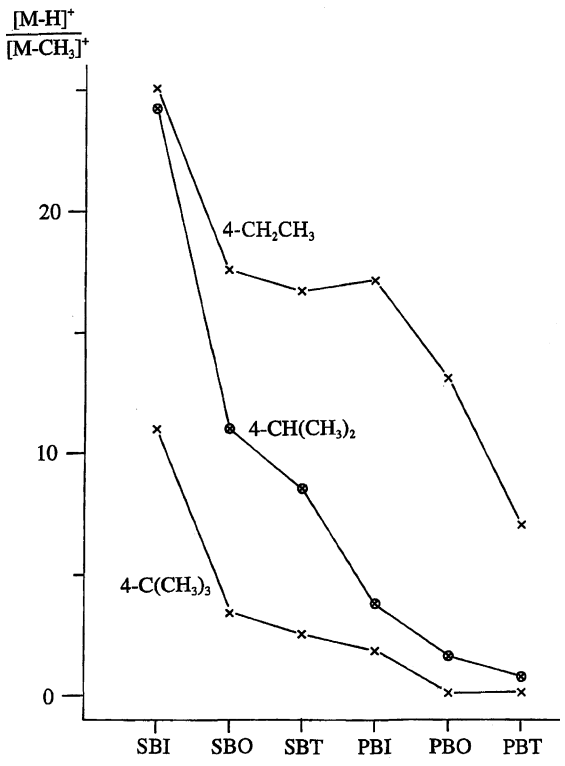


Fig. 2. Ratio of relative intensities of $[M–H]^+$:$[M–CH_3]^+$ signals in 70 eV EI mass spectra of 2-(4-alkylaryl)benzazoles with a $CH_n(CH_3)_{3-n}$ substituent ($n = 2$, 1 and 0).

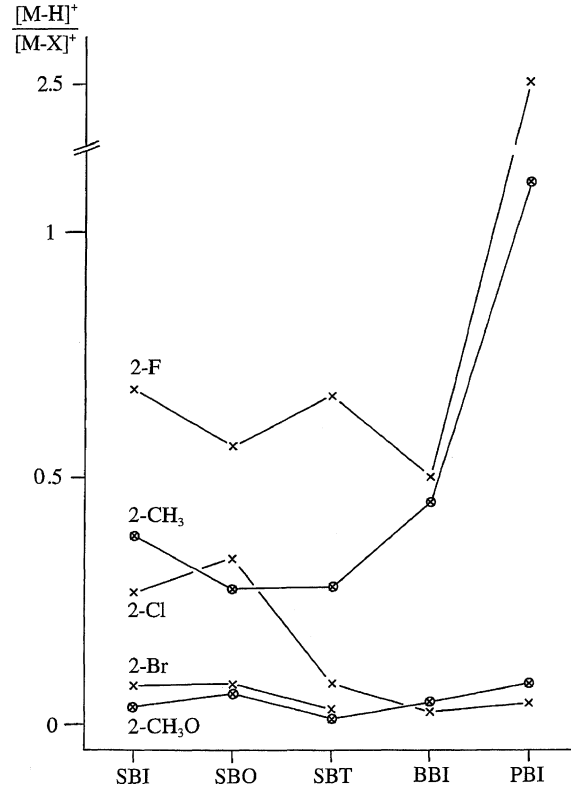
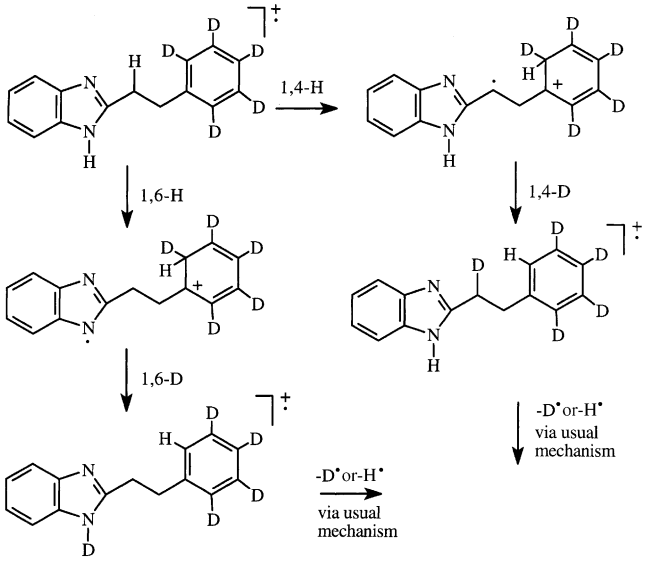


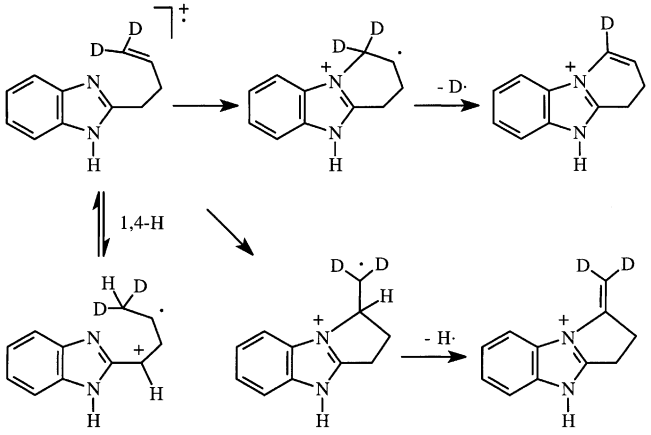
Fig. 3. Ratio of relative intensities of $[M–H]^+$:$[M–X]^+$ signals in 70 eV EI mass spectra of 2-substituted benzazoles.



Scheme 5.

A final point concerning the spectra of 2,6-disubstituted benzazoles is that weak $[M–H]^+$ signals appear when a fluorine atom is present in either or both positions. These minor peaks may indicate that fluorine possesses a slight mobility within the aromatic ring, so that it may migrate to another site, thus enabling a hydrogen atom to be lost from the vacated 2-position. This anomaly, which does not occur in the dichloroseries, is unfortunate because it detracts slightly from the otherwise specific correlation between the presence of a substituent in both the 2- and 6-position and the absence of an $[M–H]^+$ signal.

Further supporting evidence for the mechanism of the proximity effect is found in the $[M–D]^+$:$[M–H]^+$ ratios for the benzazoles with a pentadeuteriophenyl ring. The greatest selectivity is found for $^2H_5$-SBI, $^2H_5$-SBO, $^2H_5$-SBT, where the ratio is 3.3:1, 4.3:1 and 3.2:1, respectively. In the SBO system, after correction for the contribution of the ^{13}C-isotope satellite of $[M–D]^+$ to the apparent "$[M–H]^+$" signal, the actual ratio of deuterium to protium atom loss is approximately 14:1. A slightly lower selectivity (about 7:1) applies in the benzimidazole and benzothiazole cases. In contrast, the ratio of $[M–D]^+$:$[M–H]^+$ in the case of $^2H_5$-PBI and $^2H_5$-PBT is much smaller (0.31:1 and 0.27:1, respectively, corresponding to a corrected ratio of deuterium to protium atom loss of about 0.15:1, which is so small that it suggests that an isotope effect must favour elimination of a protium atom). A similar trend appears to apply for $^2H_5$-PBO, but accurate data are not available because clean hydrogenation of $^2H_5$-SBO could not be achieved. This dramatic reduction in the selectivity of deuterium atom loss from ionized $^2H_5$-PBI suggests that at least limited exchange of the hydrogen atoms of the pendant ring with those of the two connecting methylene groups and/or that on the nitrogen atom occurs before hydrogen atom elimination, Scheme 5. Such processes would be expected to be less facile in the styrylbenzazole series.



Scheme 6.

Additional evidence that hydrogen transfers may precede loss of a hydrogen atom is found in the fragmentation of ionized labelled 2-alkenylbenzimidazoles. Cyclization followed by expulsion of a hydrogen atom or alkyl radical by a proximity effect often appears to be important. Thus, for ionized 2-(but-3-enyl)benzimidazole, cyclization to form a six-membered ring, followed by loss of a hydrogen atom from what was initially the terminal carbon atom of the butenyl chain, is a logical explanation for the formation of $[M–H]^+$, Scheme 6. However, $[M–H]^+$ is decidedly stronger than $[M–D]^+$ in the spectrum of 2-(4,4-$^2H_2$-but-3-enyl)benzimidazole. Specific elimination of a deuterium atom might have been expected on the basis of cyclization of the original structure. It seems likely that at least some hydrogen exchange precedes cyclization, as is supported by the similarity of the molecular ion regions of the spectra of 2-(1,1-$^2H_2$-but-3-enyl)benzimidazole and 2-(4,4-$^2H_2$-but-3-enyl)benzimidazole, both of which contain stronger $[M–H]^+$ than $[M–D]^+$ signals (RIs in the ratio ~2.5:1 in each case). Alternatively, the initial cyclization may not be 6-endo-trig, but 5-exo-trig. If the latter is favoured [28], $[M–H]^+$ could arise by loss of the hydrogen atom originally attached to the penterminal carbon atom of the butenyl chain. Other 2-alkenylbenzimidazoles with a terminal double bond also show strong $[M–H]^+$ signals, for which analogous explanations can be devised. Similarly, the presence of $[M–C_nH_{2n+1}]^+$ ions in the spectra of these and other alkenylbenzimidazoles may be rationalized by related mechanisms. Thus, the base peak corresponding to $[M–C_2H_5]^+$ in the spectrum of 2-(pent-2-enyl)benzimidazole may be explained by a 5-endo-trig cyclization, followed by loss of the ethyl group. In contrast, benzimidazoles with a saturated 2-alkyl group tend to show $[M–C_nH_{2n}]^{\bullet+}$ signals in their spectra.

3.3. Benzylic ions

Apart from the ubiquitous $[M–H]^+$ and $[M–X]^+$ signals, few fragment ions are of general importance in the spectra

of 2-substituted benzazoles with a terminal aryl group. One significant category is σ-cleavage of a bond to a methylene group in the connecting alkyl chain in the BBI, PBI, PBO and PBT series. Charge retention could, in principle, occur on either aryl fragment, to give a benzylic cation.

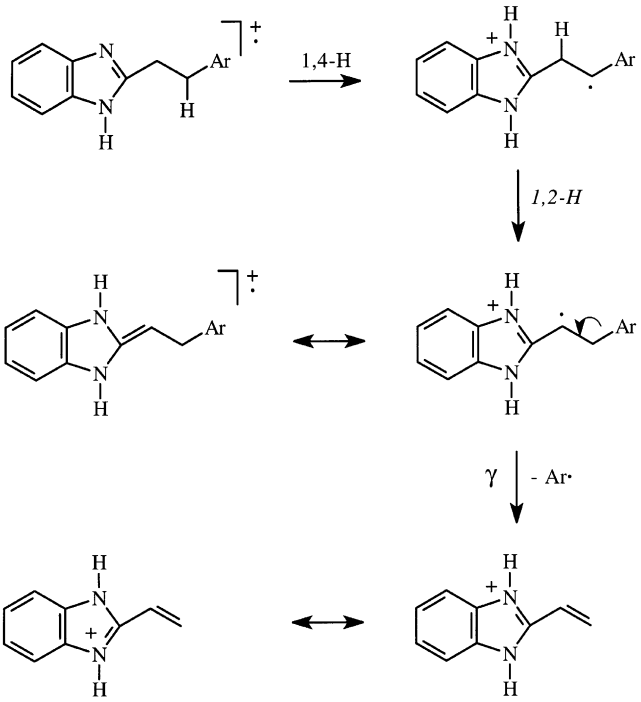
In the BBI series, formation of a benzylic cation is accompanied by elimination of an aryl radical. The RIs of the $C_6H_5N_2C–CH_2^+$ (or $C_6H_4NZC–CH_2^+$, Z = O, S) and $^+CH_2–Ar$ signals formed by these σ-cleavages rarely exceed 10%. In contrast, far stronger $C_6H_5N_2C–CH_2^+$ (or $C_6H_4NZC–CH_2^+$) and $^+CH_2–Ar$ peaks are found in the PBI, PBO and PBT series, where both cationic and radical fragments are benzylic if the bond between the two methylene groups is broken. Thus, $C_6H_5N_2C–CH_2^+$ accounts for the base peak in the spectrum of 4-ClPBI; moreover, the RI of the corresponding signal for the other five FPBIs and ClPBIs lies in the range 20–97%. On the other hand, the complementary $^+CH_2–Ar$ signal accounts for the base peak in the spectrum of 4-MeOPBI, 3,4-$(MeO)_2$PBI, 2- and 4-MeOPBO, 2- and 4-MePBT, and many members of the 4-alkylPBO and 4-alkylPBT series. These trends may be understood in terms of the influence of the substituent in the aryl ring on the stability of the $^+CH_2–Ar$ cation: a halogen atom, with a powerful −I effect, destabilizes this cation, whereas a methoxy group, with a powerful +M effect to offset the −I effect, stabilizes it.

3.4. $C_9H_9N_2^+$ ions

Appreciable signals (typical RI 20–60% in systems with no 2-substituent) are present at *m/z* 145 in the spectra of many of the PBIs. The formation of $C_9H_9N_2^+$ may be explained by a mechanism involving consecutive 1,2-H shifts, followed by loss of an aryl radical by γ-cleavage to give protonated 2-vinylbenzimidazole, Scheme 7. The resultant cation is extensively stabilized by conjugation. There is much precedent for this kind of mechanism in simpler systems, including ionized carboxylic acids [29–31], alkenols [32] and alkenyl methyl ethers [33,34].

3.5. Doubly-charged ions

A final noteworthy feature of the spectra of the benzazoles is the presence of comparatively abundant doubly-charged ions, especially in the BBI and SBI series. Although some of these signals could be attributed to singly charged ions that have the correct *m/z* ratio to coincide with M^{2+} and $[M–X]^{\bullet 2+}$ species, the "half mass" peaks at non-integral *m/z* values must correspond to doubly-charged ions. Thus, the signal at *m/z* 103 (RI in the range 5–33%) which is present in the spectrum of BBI and all members of the sets of three isomeric FBBIs, ClBBIs and MeBBIs may not be entirely $[M–HX]^{2+}$. On the other hand, the weaker signal at *m/z* 103.5 (RI 5–9%) in the spectrum of BBI and the three isomeric ClBBIs must be $[M–H]^{\bullet 2+}$ and $[M–Cl]^{\bullet 2+}$, respectively. Similarly, the peak at 102.5 (RI 3–9%) in the spectrum



Scheme 7.

of the three isomeric ClBBIs and the four isomeric Cl_2BBIs can be attributed to $[M–H–HCl]^{\bullet 2+}$ {or $[M–H_2–Cl]^{\bullet 2+}$} and $[M–Cl–HCl]^{\bullet 2+}$ {or, perhaps, $[M–Cl_2–H]^{\bullet 2+}$}, respectively. The opposite "parity" applies in the SBO and SBT series, in which there is no doubt that the M^{2+} peaks, which appear at *m/z* values midway between two integers, correspond to doubly-charged species. Further confirmation of the identity of doubly-charged ions with integral *m/z* values is sometimes possible on the basis of their ^{13}C-isotope satellites. Thus, the weak signal (RI ∼ 0.5%) at *m/z* 111.5 in the spectrum of 2-MeBBI may be attributed to the ^{13}C-isotope satellite of M^{2+}.

The presence of these M^{2+}, $[M–H]^{\bullet 2+}$, $[M–X]^{\bullet 2+}$, $[M–H–HX]^{\bullet 2+}$ and $[M–X–HX]^{\bullet 2+}$ signals presumably reflects the unusually stable polycyclic ions that may be formed by the removal of two electrons from such extensively conjugated heterocycles. It is not possible to establish whether some or all of these ions contain the additional ring that is formed by the proximity effect in the singly-charged systems. Curiously, the doubly-charged ions are much less significant in the spectra of the PBIs, perhaps because fragmentation by fission of the connecting alkyl chain is more facile. Alternatively, the doubly-charged ions may simply be more stable in the five-membered ring series.

4. Conclusions

Proximity effects in the electron impact ionization spectra of a very wide range of 2-substituted benzazoles are mechanistically interesting and analytically useful. Cycliza-

tion occurs readily when the new ring contains five, six and, to a somewhat lesser degree, seven atoms. In contrast, eight membered rings are formed much more slowly and there is no firm evidence for the formation of four-membered rings. Preferential elimination of a 2-substituent occurs, regardless of the nature of this substituent, which may be a hydrogen, fluorine, chlorine or bromine atom, or a methyl, methoxy or nitro group. The presence of a C=C double bond in the hydrocarbon chain connecting the two aryl entities enhances the importance of the proximity effect. The rearrangements that precede expulsion of the 2-substituent must have a very low critical energy, as is emphasized by the dominance of the proximity effect over simple cleavage of a 4-alkyl substituent in the pendant aryl ring. There is evidence that the cyclization is not the rate-limiting step in elimination of at least some halogeno substituents.

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References

[1] H. Budzikiewicz, K. Djerassi, D.H. Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day, San Francisco, 1964.
[2] H. Budzikiewicz, K. Djerassi, D.H. Williams, Mass Spectra of Organic Compounds, Holden-Day, San Francisco, 1967.
[3] J. Royayne, D.H. Williams, J.H. Bowie, J. Am. Chem. Soc. 88 (1966) 4980.
[4] R.J. Goldsack, J.S. Shannon, Org. Mass. Spectrom. 15 (1980) 545.
[5] H.-F. Grutzmacher, Org. Mass. Spectrom. 28 (1993) 1375.
[6] M.A. Philips, J. Chem. Soc (1928) 2393.
[7] A. Vogel, in: B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell (revisers), Textbook of Practical Organic Chemistry, fourth ed., Longman, London, 1978, p. 888.
[8] A. Vogel, in: B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell (revisers), Textbook of Practical Organic Chemistry, fourth ed., Longman, London, 1978, p. 880.
[9] A. Vogel, in: B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell (revisers), Textbook of Practical Organic Chemistry, fourth ed., Longman, London, 1978, p. 882.
[10] C.E. Wood, M.A. Comley, J. Soc. Chem. Ind. 43 (1923) 429T.
[11] A. Vogel, in: B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell (revisers), Textbook of Practical Organic Chemistry, fourth ed., Longman, London, 1978, p. 662.
[12] K.P. Dubey, R. Kumar, J.S. Grossert, D.L. Hooper, Ind. J. Chem. B 38 (1999) 1211.
[13] R. Weidenhagen, Chem. Ber. 69 (1936) 2263.
[14] S. Moore, K.P. Lunk, J. Org. Chem. 5 (1940) 637.
[15] S. Roseman, J. Am. Chem. Soc. 75 (1953) 3854.
[16] D.W. Hein, R.J. Alheim, R.J. Leavitt, J. Am. Chem. Soc. 79 (1957) 427.
[17] F. Patzold, F. Zeuner, Th. Heyer, H.-J. Niclas, Synth. Commun. 22 (1992) 281.
[18] D.V. Ramana, N.V.S. Rama Krishna, Ind. J. Chem. (B) (1990) 247.
[19] M.A. Philips, J. Soc. Chem. Ind. 56 (1937) 302T.
[20] W.A. Bryce, P. Kebarle, Can. J. Chem. 34 (1956) 1249.
[21] G.G. Meisels, J.Y. Park, B.G. Giessner, J. Am. Chem. Soc. 91 (1969) 1555.
[22] G.A. Smith, D.H. Williams, J. Chem. Soc. (B) (1972) 1529.
[23] R.D. Bowen, D.H. Williams, Org. Mass Spectrom. 12 (1977) 453.
[24] R.G. Cooks, J.H. Beynon, R.M. Caprioli, G.R. Lester, Metastable Ions, Elsevier, Amsterdam, 1973.
[25] I. Howe, D.H. Williams, R.D. Bowen, Mass Spectrometry: Principles and Applications, McGraw-Hill, New York, 1981.
[26] F.W. McLafferty, F. Turecek, Interpretation of Mass Spectra, fourth ed., University Science Books, Mill Valley, California, 1993.
[27] I. Howe, D.H. Williams, J. Am. Chem. Soc. 91 (1969) 7137.
[28] J.E. Baldwin, J. Chem. Soc. Chem. Commun. (1976) 734.
[29] T. Weiske, H. Schwarz, Chem. Ber. 116 (1983) 323.
[30] T. Weiske, H. Halim, H. Schwarz, Chem. Ber. 118 (1985) 495.
[31] T. Weiske, H. Schwarz, Tetrahedron 42 (1986) 6245.
[32] C.E. Hudson, D.J. McAdoo, Tetrahedron 46 (1990) 331.
[33] R.D. Bowen, A.D. Wright, J. Chem. Soc. Chem. Commun. (1992) 96.
[34] A.D. Wright, R.D. Bowen, Can. J. Chem. 71 (1993) 1073.