JOURNAL OF MASS SPECTROMETRY, VOL. 32, 1133–1136 (1997)

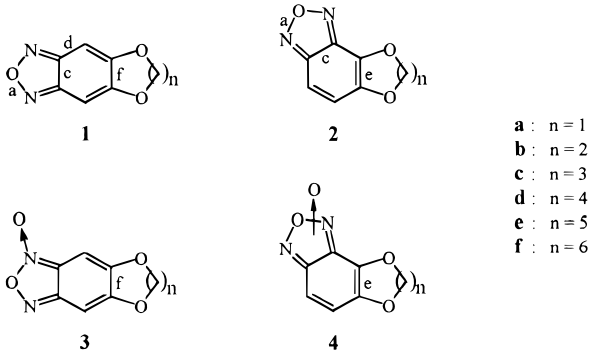
JMS Letters

Dear Sir,

Distinction between Linear and Angular 1,2-Alkylenedioxy-benzofurazans and -benzofuroxans by Mass Spectrometry

Benzofurazans (2,1,3-benzoxadiazoles)[1a,b] and benzofuroxans (2,1,3-benzoxadiazole 1-oxides) are well known for their pharmacological properties.[1c] Considering that some of these compounds exhibit biological activity while others do not, we recognize the importance of distinguishing between related isomers. We present herein evidence from mass spectrometry that permits differentiation between the linear* benzofurazans **1** and the angular* isomers **2** on the basis of a single fragment ion, that of *m/z* 80. This ion may also serve to distinguish between the linear and the angular benzofuroxan isomeric pairs **3** and **4** respectively.

The synthesis of all the compounds **1**–**4** was previously reported.[2] Low-resolution electron-ionization (EI) mass spectra were recorded at 70 eV with a Hitachi Perkin-Elmer RMU-6L or a VG Tritech TS-250 mass spectrometer. High-resolution EI mass spectra (HREI-MS) and tandem mass spectra (MS/MS) were acquired with a Kratos MS-50 three-sector instrument under conditions similar to those described elsewhere.[3] The pertinent ions are listed in Table 1 and exact masses are given in Table 2. Clearly the angular derivatives show a greater propensity for forming the product ion of *m/z* 80 (ion **5**, see Scheme 1) than do their linear counterparts.



* The compounds in which the alkylenedioxy heterocyclic ring is fused to the pseudoaromatic ring with an 'f-' and 'e-bond' are arbitrarily referred to as linear and angular, respectively.

To probe in more detail the origin, composition, structure and mechanism of formation of this ion, we employed the six-membered **1b**, **2b**, **3b**, **4b** (b-series) and, partly, the seven-membered **3c**, **4c** heterocycles as model compounds. The linear isomers formed the product ion **5** with a relative abundance range of 1.2%–1.6% as compared with the higher relative abundance level of 21%–47% for the angular derivatives (see Table 2). Ion **5** is assigned the molecular formula C_4H_2ON on the basis of exact mass measurements and is common to all the compounds (Table 2).

Metastable ion (MI) decompositions of source-produced molecular ions $M^{\cdot+}$ of the model b-series and **3c**, **4c** indicate that none afforded a detectable fragment ion **5**, preferring other known[3c,4] lower-energy channels of fragmentation.

Collisionally activated decomposition (CAD) performed on the source-produced ions of the linear furazan **1b** did not show any observable formation of ion **5**, whereas CAD of the angular isomer **2b** revealed formation of **5** with 88% relative abundance. Similar results were found for the analogous linear **3b**, **3c** and angular **4b**, **4c** benzofuroxans, the former giving no observable ion **5**, whereas the latter produced ion **5** at 11% (**4b**) and 7% (**4c**) relative abundances.

CAD and MI experiments were also carried out on a number of source-produced ions of the model compounds to deduce the origin of ion **5**. The MI fragmentations of the source-produced $[M - CH_3]^+$ ions of furazans **1b** and **2b** did not produce observable levels of ion **5**. Collisional activation of $[M - CH_3]^+$, however, produced **5** in 20% (**1b**) and 60% (**2b**) relative abundances. Formation of **5** from the activated $[M - CH_3]^+$ ion[5] of the linear compound must be the result of extensive rearrangements. CAD and MI data on the source-produced ions $[M - C_2H_4]^{\cdot+}$ of **2b** and $[M - NO]^+$ of **1b** and **2b**[4] did not produce any observable ion **5**. **1b** does not give sufficient loss of C_2H_4 from $M^{\cdot+}$ to afford a product to activate.

The CAD and MI spectra of the source-produced $[M - O]^{\cdot+}$ ions[3c,4] of the furoxans **3b** and **4b** are essentially the same as those observed for $M^{\cdot+}$ of the corresponding furazans **1b** and **2b** respectively. Furthermore, the source-produced $[M - N_2O_2]^{\cdot+}$ ion[3c,4] and the ion of *m/z* 119 (either $[M - CH_3 - N_2O_2]^+$ or $[M - N_2O_2 - CH_3]^+$) did not decompose to the product ion **5**.

To insure that the *m/z* 80 ion is common to the angular benzofurazan **2b** and the angular benzofuroxans **4b** and **4c**, we

Table 1. Characteristic ions of benzofurazans 1, 2 and benzofuroxans 3, 4 [nominal *m/z* (% relative abundance)]

Linear compound	$M^{\cdot+}$	*m/z* 80	Angular compound	$M^{\cdot+}$	*m/z* 80
1a	164 (100)	(3)	**2a**	164 (99)	(87)
1b	178 (70)	(3)	**2b**	178 (100)	(80)
1c	192 (86)	(2)	**2c**	192 (100)	(52)
1d	206 (100)	(4)	**2d**	206 (37)	(8)
1e	220 (42)	(5)	**2e**	220 (42)	(27)
1f	234 (26)	(1)	**2f**	234 (28)	(16)
3a	180 (100)	(0)	**4a**	180 (75)	(20)
3b	194 (95)	(3)	**4b**	194 (64)	(41)
3c	208 (100)	(1)	**4c**	208 (100)	(41)
3d	222 (91)	(1)	**4d**	222 (69)	(9)
3e	236 (100)	(2)	**4e**	236 (68)	(24)
3f	250 (34)	(2)	**4f**	250 (28)	(11)

CCC 1076–5174/97/101133–04 $17.50

Received 23 April 1997
Accepted 23 June 1996

Table 2. High-resolution data on characteristic ions of benzofurazans 1b, 2b and benzofuroxans 3b, 3c, 4b, 4c [*m/z* deviation in ppm (% relative abundance)][a]

Compound	Composition	M$^{\cdot+}$		*m/z* 80	
1b	$C_8H_6O_3N_2$	178.0375	−1.7 (100)	80.0136	0.3 (1.4)
2b	$C_8H_6O_3N_2$	178.0379	+0.6 (100)	80.0133	−3.1 (47)
3b	$C_8H_6O_4N_2$	194.0331	+1.8 (100)	80.0130	−7.2 (1.6)
4b	$C_8H_6O_4N_2$	194.0322	−2.5 (73)	80.0142	+7.6 (23)
3c	$C_9H_8O_4N_2$	208.0492	+3.9 (100)	80.0145	+11.9 (1.2)
4c	$C_9H_8O_4N_2$	208.0485	+0.4 (90)	80.0138	+3.0 (21)

[a] Although errors for determination of the experimental exact masses of *m/z* 80 are sometimes large, they are sufficiently small to distinguish C_4H_2ON from all other possibilities. (The mass of the elemental composition $C_3^{13}C_2H_2O$, the most similar possibility derived from the precursors, differs from that of C_4H_2ON by 45.4 ppm.)

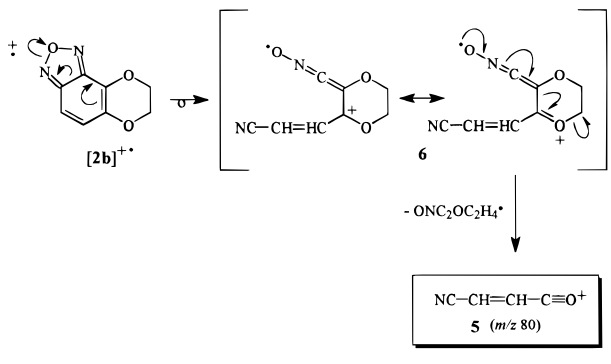
obtained MI and CAD spectra of this ion from these sources. The three sets of experiments furnished similar results, thus indicating a common structure for **5**. The only detectable MI decomposition of **5** is loss of CO to give an ion of *m/z* 52. This is expected for an acylium ion. Upon collisional activation, source-produced ion **5** fragments by losses of CO and CO plus H to give the ions of *m/z* 52 and 51 (100% and 62% relative abundances, respectively).

We also carried out a precursor ion scan[6] of ion **5** from furazan **2b**; this experiment would tell us, under comparable conditions, what precursor ion(s) form ion **5**. The only detectable precursor ion leading to **5** is the molecular ion of **2b**, indicating that the route to **5** via $[M - CH_3]^+$ is not important. From all the above information we propose the mechanistic rationale shown in Scheme 1. Ion $[\mathbf{2b}]^{\cdot+}$ rearranges directly to ion **6**, which furnishes ion **5** through a radical-driven process.

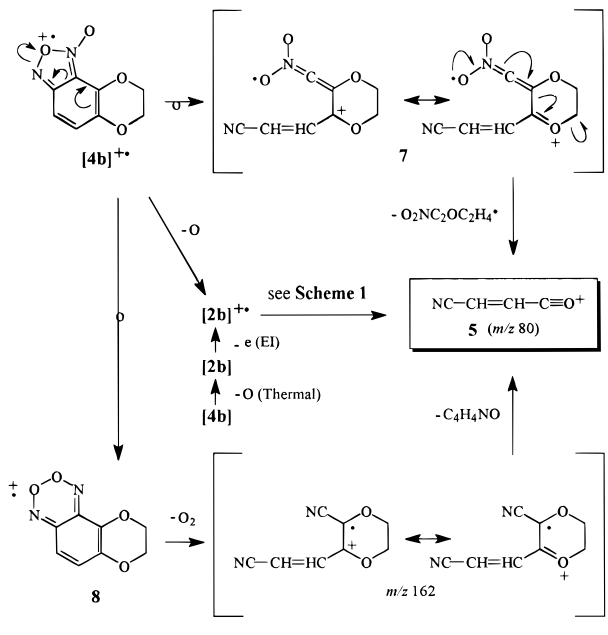
Similarly, a precursor ion scan for product ion **5** from the furoxan **4b** indicates that **5** was derived from three principal source-produced ions: $M^{\cdot+}$, $[M - O]^{\cdot+}$ and $[M - O_2]^{\cdot+}$ (see Fig. 1). It is no surprise that $[M - O]^{\cdot+}$, either by loss of O from $M^{\cdot+}$ or by EI of a thermal degradation product of neutral **4b**, affords **5**, because the former ion is the same as the $M^{\cdot+}$ of the corresponding furazan **2b** (see Scheme 1). A plausible mechanism for the process $M^{\cdot+} \rightarrow \mathbf{5}$ via **7** is depicted in Scheme 2 and is analogous to that proposed in Scheme 1 for the decomposition of $[\mathbf{2b}]^{\cdot+}$. Rearrangement of $[\mathbf{4b}]^{\cdot+}$ to the peroxidic ion **8** followed by expulsion of O_2 rationalizes the formation of $[M - O_2]^{\cdot+}$. Because we do not have evidence for the generality of $[M - O_2]^{\cdot+} \rightarrow \mathbf{5}$, we prefer not to speculate on a mechanism for its formation. There is an ion, $[M - O_2]^{\cdot+}$ (*m/z* 162), at a relative abundance of less than 1% in HREI-MS, and its exact mass is within 5 ppm of that expected for $C_8H_6O_2N_2$. Before the structures of the furoxans had been definitively resolved, structures similar to **8** were proposed to represent stable, ground state furoxans.[1a,b]

To test the generality of using the *m/z* 80 ion to distinguish isomers, we prepared several non-heterocyclic substituted benzofurazans (**9a–9f**) and benzofuroxans (**10a–10f**) that contain at least one alkoxy group. We reasoned *a priori* that the furazans **9b**, **9d**, **9f** and the corresponding furoxans **10b**, **10d**, **10f** should afford enhanced relative abundances for ion **5** compared with **9a**, **9c**, **9e** and **10a**, **10c**, **10e**. The former two series are analogous to those seen for the previously discussed angular derivatives **2** and **4**, which contain unit **11**, on which EI decomposition to give the product ion **5** depends. In contrast, compounds **9a**, **9c**, **9e** and **10a**, **10c**, **10e** are not expected to produce ion **5**. Indeed, the low-resolution EI mass spectra confirmed our prediction (Table 3). Additional support comes from the previously reported[4d] mass spectrum of the methoxy-substituted benzofurazan **9b**, which fragmented to ion **5** (~22% relative abundance), whereas **9g** did not.

The ion of *m/z* 80 (**5**) appears to serve as a differentiating tool generally applicable to alkoxy-substituted benzofurazan and benzofuroxan compounds. In a sequel full article we will describe the synthesis and full characterization of the novel benzofurazans and benzofuroxans discussed in this letter.



Scheme 1



Scheme 2

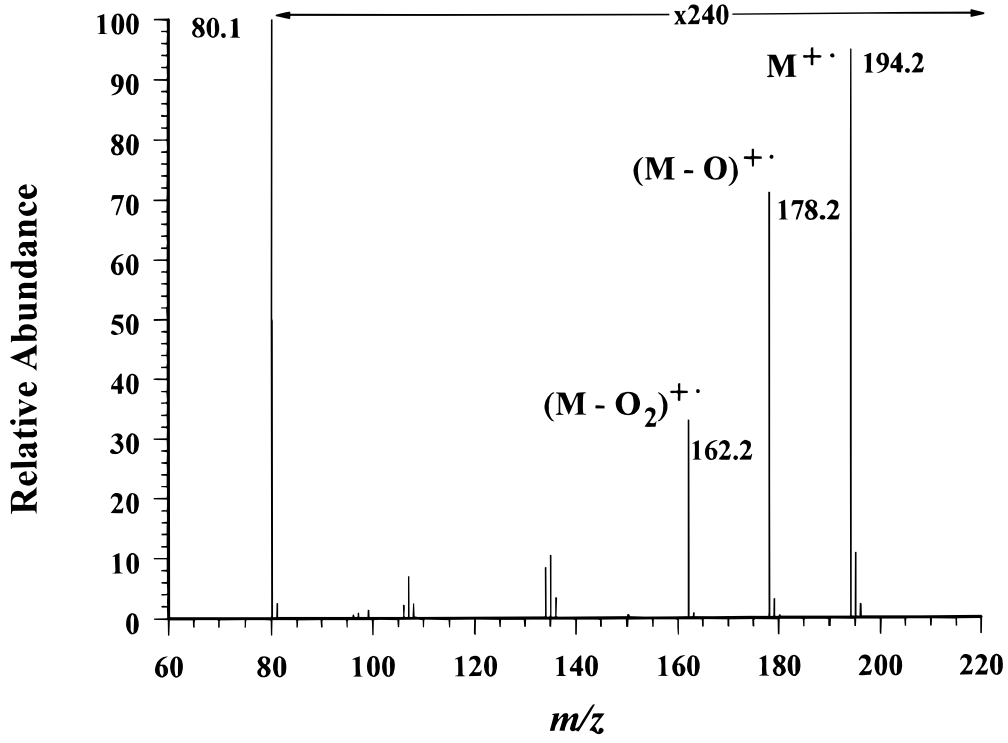
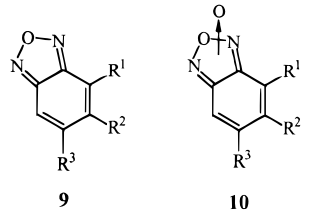


Figure 1. Precursor-ion mass spectrum of ion **5** (of *m/z* 80) from benzofuroxan **4b**.



9 **10**

	R^1	R^2	R^3
a	OMe	H	H
b	H	OMe	H
c	OMe	Me	H
d	Me	OMe	H
e	H	OMe	OMe
f	OMe	OMe	H
g	OMe	H	Me

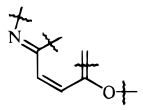


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Table 3. Characteristic ions of benzofurazans 9 and benzofuroxans 10 [nominal *m/z* (% relative abundance)]

Compound	$M^{\cdot+}$	*m/z* 80	Compound	$M^{\cdot+}$	*m/z* 80
9a	150 (63)	(11)	**9b**	150 (47)	(69)
9c	164 (27)	(9)	**9d**	164 (28)	(72)
9e	180 (100)	(3)	**9f**	180 (100)	(57)
10a	166 (100)	(5)	**10b**	166 (100)	(13)
10c	180 (43)	(1)	**10d**	180 (100)	(7)
10e	196 (100)	(7)	**10f**	196 (100)	(45)

One of us (G.G.T) wishes to thank the 'Leonidas Zervas' Foundation for a two-year (1994–1996) scholarship. The US group acknowledges the NIH (Grant P41 RR00954) for support and Professor Kevin Moeller for discussions.

Yours,

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Contract grant sponsor: 'Leonidas Zervas' Foundation.
Contract grant sponsor: NIH; Contract grant number: P41 RR00954.

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