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JMS Letters

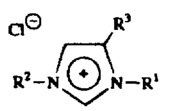
Dear Sir,

Rearrangement with Formaldehyde Extrusion in the Electrospray Mass Spectra of Alkoxymethylimidazolium Cations

In the course of a search for improved methods of histidine side-chain protection in peptide synthesis, we have prepared numerous alkoxymethyl-imidazole and -histidine derivatives. We find that the electrospray mass spectra of alkoxymethyl-imidazolium cations show a facile rearrangement resulting in the extrusion of formaldehyde. Little has so far appeared in the literature on the formation of fragment ions in electrospray mass spectrometry, so the spectra of compounds **1**–**5** (Fig. 1; Table 1) are reported as typical examples. Even at low cone voltages, where little collisional activation occurs, **1** and **2** show loss of a molecule of formaldehyde (Scheme 1), and as the voltage is raised and collisional activation increases the loss of a second appears; ultimately $[M - 2CH_2O]^+$ becomes the base peak (see Fig. 2). Compound **3** shows the same phenomenon, but higher voltages than with **1** and **2** are required. In a range of similar salts, the ease of formaldehyde extrusion correlates qualitatively with the solution stability as a carbocation of the migrant group. The *tert*-butoxymethylimidazolium salt **4** does not undergo rearrangement as in Scheme 1, but shows simultaneous loss of formaldehyde and isobutene with concomitant hydrogen transfer (Scheme 2), a pathway not available to **3** because of Bredt's rule.

These remarkable processes are not peculiar to dialkylimidazolium salts: the cation of the protected histidine hydrochloride **5** also appears to extrude a molecule of formaldehyde at one stage of its fragmentation, which can be rationalized as in Scheme 3.

The preparation and characterization of the salts **1**–**4** (which were pure crystalline solids) will be reported elsewhere. The protected histidine derivative **5** is from previous work.[1] The electrospray mass spectra were determined on a Fisons Instruments VG Bio-Q triple quadrupole atmospheric pressure ionization mass spectrometer equipped with an electrospray ionization interface. Spectra were recorded from acetonitrile–water (1 : 1) solutions at a concentration of 2–5 pmol μl^{-1}.



	R^1	R^2	R^3
1	$4\text{-}MeOC_6H_4CH_2OCH_2$	$= R^1$	H
2	$2,4,6\text{-}Me_3C_6H_2CH_2OCH_2$	$= R^1$	H
3	Adamant-1-yloxymethyl	$= R^1$	H
4	Bu^tOCH_2	$C_6H_5COCH_2$	Me
5	$C_6H_5CH_2OCH_2$	H	$Bu^tOCONHCH(CO_2Me)CH_2$

Table 1. Electrospray mass spectral data for 2–5

		Relative abundance (%) at various cone voltages								
Compound	*m/z*	25 V	30 V	40 V	50 V	60 V	65 V	70 V	80 V	100 V
2	393[a]	—	100	—	100	49	—	16	—	—
	363[b]	—	0	—	22	29	—	11	—	—
	333[c]	—	0	—	32	100	—	100	—	—
3	397[a]	—	—	—	100	100	—	—	100	9
	367[b]	—	—	—	0	5	—	—	31	8
	337[c]	—	—	—	0	2	—	—	54	100
4	287[a]	100	—	100	44	—	3	—	—	—
	201[d]	4	—	27	100	—	100	—	—	—
5	390[a]	—	100	—	100	23	—	10	—	—
	334[e]	—	0	—	33	25	—	11	—	—
	304[f]	—	0	—	20	100	—	100	—	—
	260[g]	—	0	—	0	12	—	16	—	—

[a] M^+
[b] $[M - CH_2O]^+$
[c] $[M - 2CH_2O]^+$
[d] $[M - CH_2O, -Me_2C{=}CH_2]^+$
[e] $[M - Me_2C{=}CH_2]^+$
[f] $[M - Me_2C{=}CH_2, -CH_2O]^+$
[g] $[M - Me_2C{=}CH_2, -CH_2O, -CO_2]^+$

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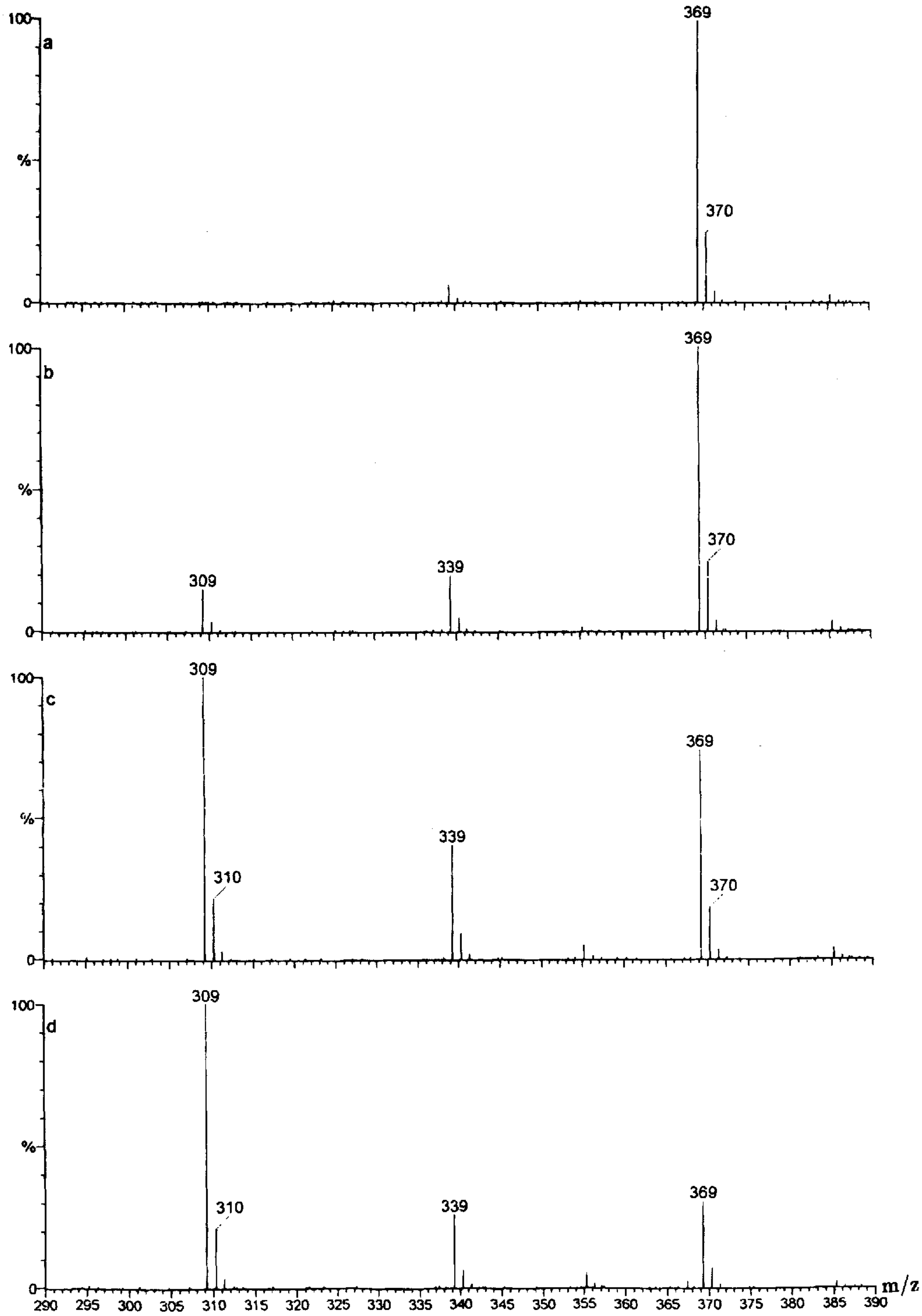
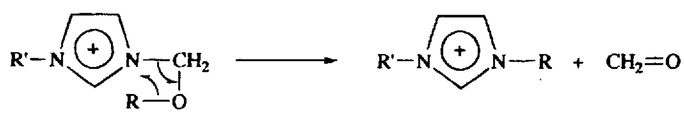


Figure 1. Electrospray mass spectrum of **1** at cone voltages of (a) 20, (b) 50, (c) 60 and (d) 70 V.



Scheme 1.

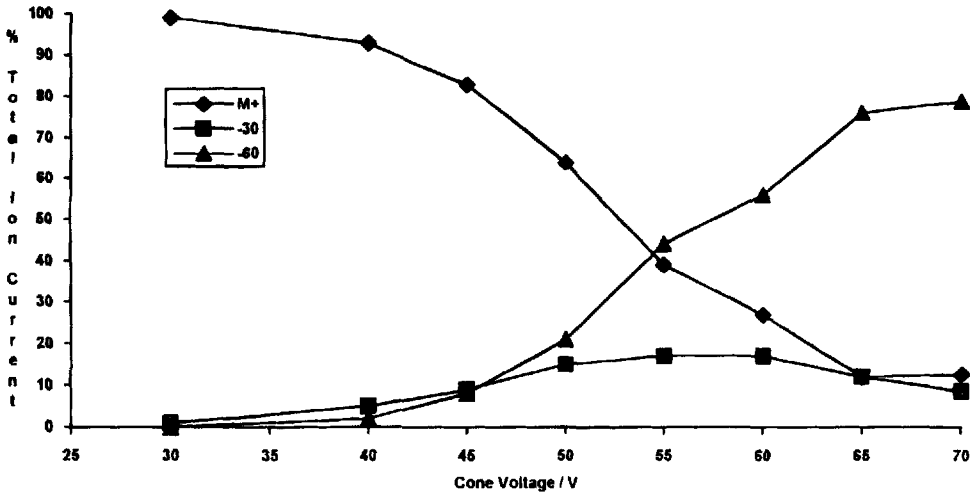
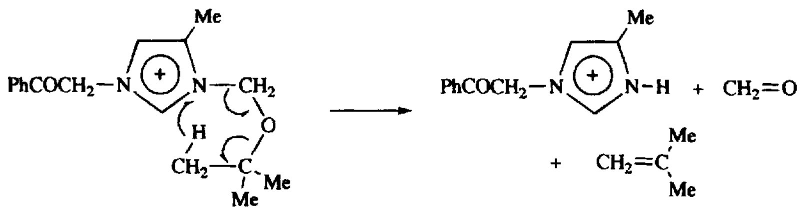


Figure 2. Percentage of the total ion current carried by M^+, $[M-CH_2O]^+$ and $[M-2CH_2O]^+$ in the electrospray mass spectrum of **2** as the cone voltage is raised from 30 to 70 V.



Scheme 2.

$$m/z390(M^+) \xrightarrow{-CH_2{=}C(CH_3)_2} m/z334 \xrightarrow{-CH_2O} m/z304 \xrightarrow{-CO_2} m/z260$$

Scheme 3.

Yours

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Reference

1. T. Brown, J. H. Jones and J. D. Richards, *J. Chem. Soc., Perkin Trans. 1* 1553 (1982).