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Gas-phase reaction: alkyl cation transfer in the dissociation of protonated pyridyl carbamates in mass spectrometry

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ABSTRACT

In the mass spectrometry of pyridyl carbamates, alkyl cation transfer is one of the major fragmentation reactions of the protonated molecules. Literature results and theoretical calculations indicate that the pyridine nitrogen is the most favorable site for protonation in these structures. Substituent and comparison experiments run to elucidate the fragmentation patterns reveal that the proton is localized at the pyridine nitrogen and the reaction center is charge-remote when the alkyl cation transfer occurs. The mechanism involving configuration inversion via an ion-neutral complex is favorable in energy for the alkyl cation transfer in these structures.

1. Introduction

Mass spectrometry combined with collision-induced dissociation (CID) can be used not only to determine the structures of gas-phase organic molecules but also to determine the sites of protonation.[1–4] Determination of the protonation site aids the elucidation of reaction mechanisms, because the cleavages are commonly directed by the charge resulting from the protonation.[1,5–8] The mobile proton model describes the proton transfer across the MH^+ ion during the mass spectrometry of peptides and proteins.[1,5–8] The proton first attaches to the protonation site, and then triggers the cleavages by migrating to the reactive center.[9,10] The carbonyl oxygen is the preferred protonation site in many amides, but the dissociation reactions triggered by the proton transfer take place elsewhere.[10–13] These models are applicable to both flexible peptides and rigid molecules owing to the formation of a charge center after the reaction has occurred.[14–16] A new charge center is generally necessary for fragmentation to occur.

Proton transfer,[1,8–20] benzyl cation transfer,[21–23] benzoyl cation transfer,[24] charge transfer,[25] hydride transfer,[26] methyl transfer,[27–31] and other transfers[32] are universal in gas-phase reactions. Reactions of organic ions in the gas phase, as well as the transfer of various groups, can lead to the formation of many different types of reactive intermediates such as σ-, π-, or proton-bonded complexes, and ion-neutral complexes.[33–38] Group transfers and rearrangements can proceed in various ways, and their comprehensive understanding is required before the gas-phase reactions can be fully understood.

Intermolecular and intramolecular alkyl cation transfer is of particular interest in both solution chemistry and gas-phase chemistry, and has thus been studied experimentally and modeled theoretically.[39–48] In the solution phase, the transfer of a methyl cation can be used to investigate the disproportionation reactions of methylamines,[49] homogeneous, and heterogeneous catalysis[50] and organic syntheses for organometallic chemistry.[51,52] Methyl cation transfer is a well-studied gas-phase reaction; topics of interest include the measurement of the methyl cation transfer equilibria,[53,54] the alkylation of esters, and the formation of π-complexes with benzene,[55–60] methylation of some pyridine derivatives and amino acids via ion-molecule reactions,[61–63] and methylation of the nitrogen atom in different hybridization states.[64] Gas-phase reactions in the collision cell involving the transfer of a methyl group at the charge center have been observed during both low-energy[27,29–31,65] and high-energy[28,66] collision processes. Wysocki's group also reported the effect of alkyl substitution at the amide nitrogen on amide bond cleavage by ESI/SID, thereby yielding a deeper understanding of the mobile proton model. They proposed a charge-remote mechanism for the proton

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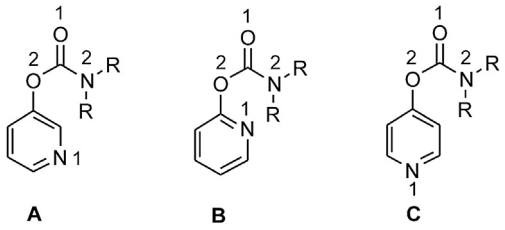
transfer in the formation of b ions; however, the alkyl group transfer would not occur following this pattern.[67]

Insights into proton transfer and alkyl cation transfers are indispensable for illustrating the reaction patterns of mass spectrometry and understanding the detailed mechanisms of gas-phase chemistry. Here we report a combined experimental and theoretical investigation of the remote charge-induced alkyl cation transfer during the dissociation of pyridyl dialkylcarbamates and their alkylated analogs, which are important units in various pharmaceutical products and pesticides.[68–70]

2. Results and discussion

The structures of the pyridyl carbamates of interest here are given in Scheme 1. The dissociation reactions of these molecules were investigated by tandem mass spectrometry (Table 1). Methyl cation transfer, as well as ethyl and *n*-butyl cation transfer—which result in the formation of the ion $\mathbf{RC_5H_5NO^+}$—can be observed during the fragmentation of these compounds. The $[A+H]^+$ ions dissociate to the most abundant $\mathbf{RC_5H_5NO^+}$ ion among the pyridyl carbamates. As an example, Fig. 1 shows the spectrum for compound A1 that bears a dimethylcarbamate substituent on the *meta* position of pyridine. The major product ions, with *m*/*z* 72, 110, and 123, are formed as a result of the elimination of pyridinol, isocyanatomethane, and CO_2, respectively.



Scheme 1. Structures of pyridyl carbamates (R=methyl, ethyl, *n*-butyl).

Table 1
Major product ions of protonated pyridyl carbamates in the CID mass spectra (excitation amplitude is 0.5 V)[a]

Compd	R	MH^+(*m*/*z*)	R_2NCO^+	$\mathbf{RC_5H_5NO^+}$	Other ions
A1	CH_3	167(50.8)	72(24.6)	110(100)	123(1.8)
B1	CH_3	167(0.8)	72(100)	110(0.6)	123(0)
C1	CH_3	167(8.9)	72(100)	110(25.6)	123(64.1)
A2	Ethyl	195(10.5)	100(100)	124(44.8)	96(11.4)
B2	Ethyl	195(2)	100(100)	124(0)	96(0)
C2	Ethyl	195(6.3)	100(100)	124(25.8)	96(7.6)
A3	*n*-Butyl	251(91.1)	156(100)	152(14.1)	100(6.1)
B3	*n*-Butyl	251(0.2)	156(100)	152(0)	100(2.4)
C3	*n*-Butyl	251(4.4)	156(100)	152(0.1)	100(2.6)

[a] *m*/*z* (Relative intensity, %).

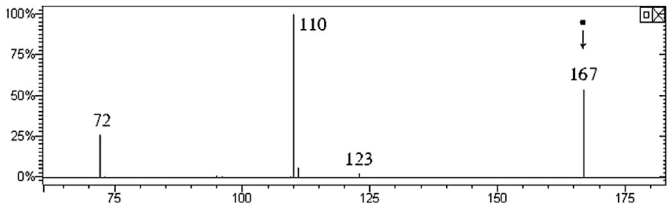


Fig. 1. CID spectrum of the MH^+ ion (*m*/*z* 167) of compound A1.

The protonation site is very important to the reaction mechanism. The pyridyl carbamates may be protonated at a variety of positions, including the pyridine nitrogen, the amide nitrogen, the ester oxygen, and the carbonyl oxygen. The preferred protonation site of these molecules is yet to be determined. The gas-phase basicities and proton affinities of related molecules given in Table 2 suggest that the pyridine nitrogen is much more favorable than the carbonyl oxygen, the amide nitrogen, or the ester oxygen. Table 3 shows that the calculated relative gas-phase proton affinity energies of pyridine nitrogen are much higher than those of other sites (from 63.75 kJ mol^{-1} to 207.54 kJ mol^{-1}), thus suggesting the pyridine nitrogen to be the most favorable site for protonation giving rise to the MH^+ ions.

Table 2
Gas-phase basicity and PA values and possible site of protonation of selected compounds[71]

Compound	GB (kJ/mol)	PA (kJ/mol)	Protonation site
Pyridine	898.1	930.0	N
3-CH_3O–pyridine	902.8	937.4	N
2-CH_3O–pyridine	910.9	942.7	N
4-CH_3O–pyridine	929.8	961.7	N
$C_6H_5OCH_3$	807.2	839.6	O
$(CH_3)_2NCOOCH_3$	847.3	878.3	O(C=O)
$C_6H_5CO_2CH_3$	819.5	850.5	O(C=O)

Table 3
Calculated relative energies of A1, B1, and C1 with different protonation sites[a,72]

Site	A1	B1	C1
N1	0	0	0
N2	113.34	92.79	133.61
O1	76.87	63.75	98.23
O2[a]	193.01	156.72	207.54

[a] The ester bond is cleaved when the proton attaches to the oxygen. All structures were optimized at the B3LYP/6-31G++ (d, p) level of theory in kJ mol^{-1}.

Nevertheless, the role of the proton attached to the pyridine nitrogen in the gas-phase reaction is unclear. Alkyl cation transfer occurs distant from the thermodynamically preferred protonation site. The MH^+ ions of B and C have relatively stable pyridinone structures, and alkyl cation transfer appears to be possible subsequent to the formation of the complex of pyridinone and ion R_2NCO^+. While compound A does not have a pyridinone structure to generate ion R_2NCO^+ directly. Established research on proton transfer suggests that the proton may be mobile during the CID: it could transfer to another reactive site to trigger the fragmentation.

To fix the 'proton' on the nitrogen, we considered less flexible alkyl groups, which allowed us to investigate whether the protonation site would be localized during the fragmentation. Pyridostigmine (*m*/*z* 181) and pyridostigmine-d_3 (*m*/*z* 184) are quaternary ammoniums that hold the methyl or methyl-d_3 group on the pyridine nitrogen. As shown in the CID spectra in Fig. 2, pyridostigmine exhibits a similar loss of C_2H_3NO to protonated pyridyl dimethylcarbamates to produce ion *m*/*z* 124. Pyridostigmine-d_3 generates an ion at *m*/*z* 127, whose CID-MS^3 spectrum matches the CID-MS^2 of the *N*-CD_3–3-methoxypyridine cation. This demonstrates that the methyl cation on the pyridine nitrogen remains at its original site during the fragmentation. Moreover, as shown in Fig. 3, the dissociation behaviors of the *N*-ethyl-pyridyl dimethylcarbamate cation (*m*/*z* 195) and the *N*-methyl-pyridyl diethylcarbamate cation (*m*/*z* 209) explicitly exhibit the pattern of alkyl cation transfer. The *N*-ethyl-pyridyl dimethylcarbamate cation produces ions at *m*/*z* 151, *m*/*z* 138, and *m*/*z* 110 through collision-induced activation. The ion at *m*/*z* 138,