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The role of ion/neutral complexes in the fragmentation of *N*-benzyl-(alkylpyridinium) ions

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Dedicated to Professor Tino Gäumann on the occasion of his 85th birthday.

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ABSTRACT

N-Benzylpyridinium ions bearing an alkyl group at the pyridine nucleus were studied as potential precursors of gaseous ion/neutral complexes. The occurrence of I/N complexes [$C_6H_5CH_2^+$ ··· alkylpyridine] was probed by the reactivity of the potential benzylic hydride donor sites present in the *ortho*-, *meta*- and *para*-alkyl groups (R = methyl, ethyl, isopropyl and benzyl). Collision-induced dissociation of the ions, carried out in an electrical ion cage mass spectrometer, revealed that hydride transfer strongly depends both on the energy requirements of the hydride transfer but also on the position of the hydride donor. Hydride transfer, giving rise to the loss of toluene, was found to occur exclusively with those *N*-benzylpyridinium ions which bear an isopropyl or a benzyl substituent in the *ortho* position of the pyridine ring, thus reflecting the intermediacy of I/N complexes. All of the putative hydride donor alkyl groups were found to be non-reactive in the *meta* and *para* positions, as were methyl and ethyl groups even in the *ortho* positions. Density functional calculations (B3LYP/6-311+G/3d,2p)//(B3LYP/6-31+G(d)) on the hydride-transfer and simple-cleavage channels were carried out to help rationalizing these observations. The results suggest that the intra-complex hydride abstraction from the 3- and 4-isopropyl- and from the 3- and 4-benzylpyridine neutrals, although being thermodynamically favorable, is suppressed by substantial intra-complex rotational (or reorientation) barriers.

1. Introduction

N-Benzylpyridinium ions are well known in mass spectrometry for their role as suitable species to probe the internal energy deposition on ions generated under various ionization conditions [1–11]. The propensity of such "thermometer ions" to cleanly undergo dissociation of the benzylic C–N bond depends not only on the external conditions of the ion source but, in particular, on the electronic properties of the reactant. Therefore, various electron-releasing and electron-withdrawing substituents have been introduced into the benzylic moiety of the *N*-benzylpyridium ion to affect the energy requirements of the C–N bond cleavage. The readiness to release the corresponding $C_7H_6X^+$ ions, which should mostly retain their (original) benzylic structure but are also believed to partially rearrange by ring expansion to tropylium ions [9,10], provides a suitable indicator for the mildness or roughness of the ionization conditions.

However, gaseous *N*-benzylpyridinium ions could be ideal species to study another important probe reaction, namely, intramolecular hydride transfer. This process has been used extensively to probe the formation of ion/neutral complexes [12–21] as reactive intermediates during mass spectrometric fragmentation [22–30]. As has been shown, a large number of metastable *tert*-butylbenzenium and related $[M+H]^+$ ions eliminate isobutane, necessarily formed via an intra-complex hydride transfer, rather than just releasing the *tert*-$C_4H_9^+$ ion or eliminating isobutene by intra-complex proton transfer. Similar to the *N*-benzylpyridinium ions, even tiny differences in the "electronic" conditions of the reactants strongly affect the relative weight of the hydride transfer process [24,25,27].

Recently, the fragmentation of various di-, tri- and tetrabenzylammonium ions was found to occur predominantly via I/N complexes, reflecting the intra-complex reactivity of benzyl cations towards the aromatic π-systems and benzylic hydride donor sites of the neutral constituent [31]. A very recent paper reported on the substituent effects on the fragmentation of *N*-benzylpiperidinium and *N*-benzylpiperazinium ions bearing various electronically active substituents (X) in the benzylic moiety of the reactants [32]. Again, hydride transfer leading to the loss of the corresponding toluene derivatives was indicative of I/N complexes, such as [X–$C_6H_4CH_2^+$ ···· *c*-$(CH_2)_5NH$], as reactive intermediates during the fragmentation of such relatively simple cyclic ammonium ions.

In view of all these findings, we raised the question whether suitable *N*-benzyl-(alkylpyridinium) ions, bearing alkyl groups as potential hydride donor sites at the heterocyclic moiety, would represent useful model ions for probing the intermediacy of I/N

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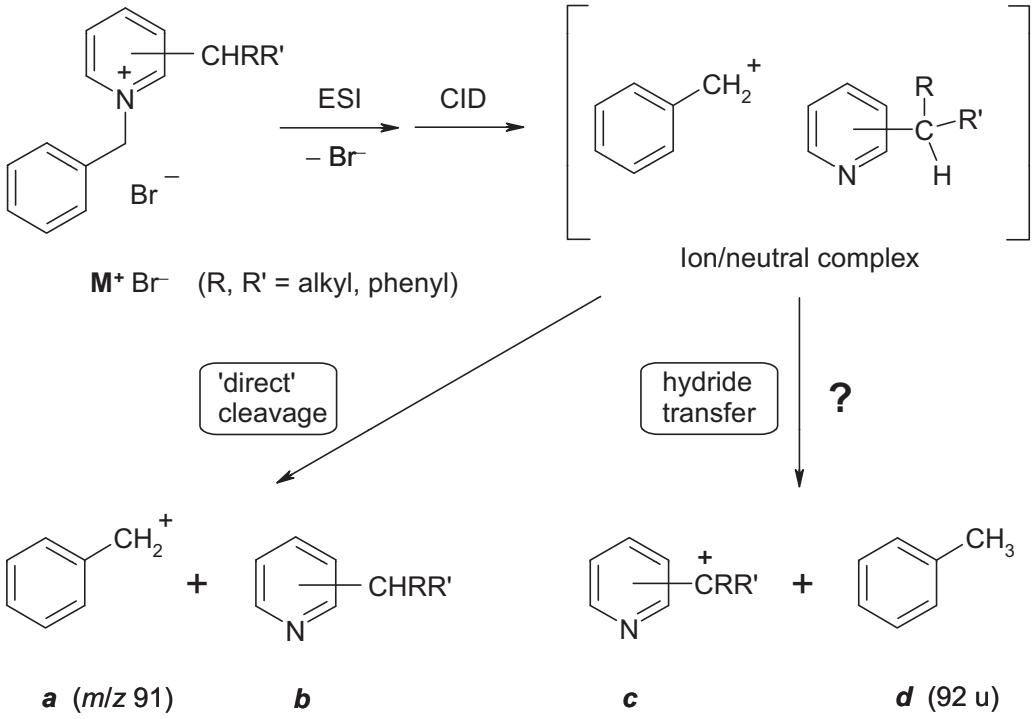


Scheme 1. Fragmentation of *N*-benzyl-(alkylpyridinium) ions, generated by ESI from the corresponding bromides, via two competing channels under ESI/CID conditions:. Benzylic cleavage (left) and rearrangement via an I/N complex (right).

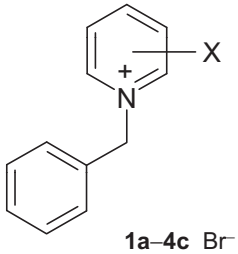
complexes during fragmentation (Scheme 1). To the best of our knowledge, this variant has never been applied to benzylpyridinium thermometer ions. In the present work, we report our results on the fragmentation of a set of *N*-benzyl-(alkylpyridinium) ions ($\mathbf{M^+}$) which, after collisional activation in an ion cage mass spectrometer, should be able to undergo the 'direct' dissociation reaction giving the (parent) $C_7H_7^+$ ions (***a***) and the neutral alkylpyridines ***b*** and, in competition, the elimination reaction generating the corresponding (α-substituted) azabenzylium ions ***c*** and toluene (***d***) by intra-complex hydride transfer. In this case, different from all the previous studies, the electronic properties of the alkyl-substituted pyridine moiety as a leaving group and/or as a hydride donor should govern the course of the fragmentation and, in particular, the role of the putative ion/neutral complexes.

2. Experimental

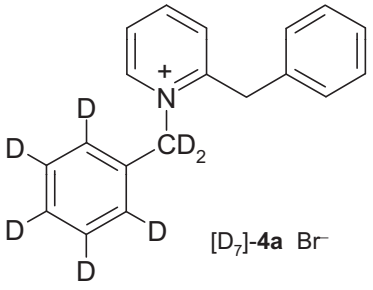
2.1. Compounds

The *N*-benzyl-(alkylpyridinium) bromides (Scheme 2) were synthesised by heating solutions of the appropriate alkylpyridines (10 mmol) (see below) and freshly distilled benzyl bromide (10 mmol) in dichloromethane (15 mL) for 5–6 h. Stirring was continued overnight. The reaction was monitored by TLC and mostly driven to completion. Removal of the solvent under reduced pressure gave crystalline products or viscous oils. These crude products were subjected to the ESI measurements in most cases.

Some of the alkylpyridines were not commercially available. The 2-, 3- and 4-isopropylpyridines were prepared by Grignard reaction of the respective picolinic acid methyl or ethyl esters with methyl magnesium iodide. The resulting pyridyl carbinols were reduced by use of hydroiodic acid and red phosphorous at 150–160 °C [33]. Work-up including kugelrohr distillation (85–90 °C, 7 mbar) gave the corresponding isopropylpyridines in moderate yields (*ortho*, 43%; *meta* 20%; and *para*, 44%) as colorless liquids. 3-Benzylpyridine was synthesized by Wolff–Kishner reduction of 3-benzoylpyridine (675 mg, 3.7 mmol) with hydrazine hydrate (600 μL) and powdered potassium hydroxide (800 mg) in diethylene glycol (10 mL). The mixture was heated to reflux (130 °C) for 5 h and then the temperature was slowly increased to 195 °C and kept for 2.5 h. Work-up gave a crude product (650 mg) and subsequent kugelrohr distillation yielded the product (385 mg, 62%) as a colorless liquid. ^{1}H NMR spectroscopy confirmed the purity of the compound. The *N*-[D_7]benzyl-2-benzylpyridinium



	X		X
1a	2-methyl	**3a**	2-isopropyl
1b	3-methyl	**3b**	3-isopropyl
1c	4-methyl	**3c**	4-isopropyl
2a	2-ethyl	**4a**	2-benzyl
2b	3-ethyl	**4b**	3-benzyl
2c	4-ethyl	**4c**	4-benzyl



Scheme 2. Compounds and ions studied.