Mechanism of Formation of Doubly Charged Fragments from Bis-benzyltetrahydroisoquinolines under Electron Impact

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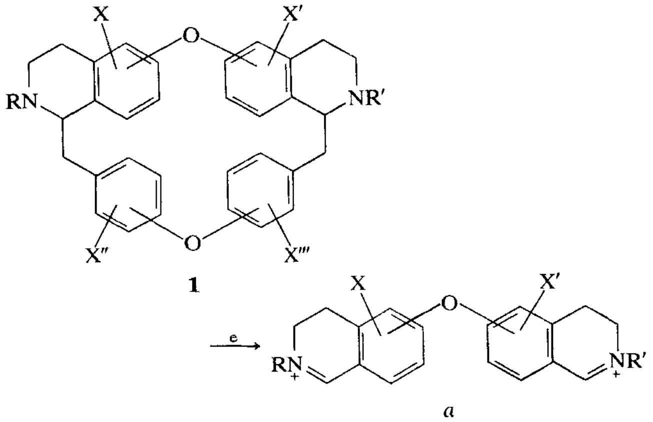
Some bis-benzyltetrahydroisoquinolines [α,α′-di-*N*,*N*-(1-benzyl-1,2,3,4-tetrahydroisoquinoline)-*p*-xylene and various substituted analogues] give rise to very abundant doubly charged fragment ions under electron impact, corresponding to the loss of the two benzyl groups. Substituent effects, ionization and appearance energy measurements and metastable transitions show that these doubly charged ions are formed (at least in part) from singly charged precursors by a heterolytic cleavage (charge separation).

INTRODUCTION

While the chemistry of singly charged organic gas phase cations has rapidly developed into a very active branch of science in the last two decades, little attention has been paid to the behavior of organic multiply charged ions in the mass spectrometer. The reason for this neglect is that they give rise to low intensity peaks (if any) in the mass spectra of the majority of organic compounds. The relatively low abundance of the doubly charged ions may result from the low efficiency of the second ionization as well as from the instability of many organic systems carrying two positive charges in the gas phase.[1,2] Both these factors may explain the very low abundance of these ions in the mass spectra of aliphatic hydrocarbons[1] in contrast to their much higher abundances in the case of polycyclic aromatic systems.[3] The unusual combination of instability of the singly charged and relative stability of the doubly charged ions has sometimes resulted in the apparently rare phenomenon of $[M]^{2+}$ having greater abundance than $[M]^{+\cdot}$.[4–6]

Interesting findings concerning the formation and fragmentation of doubly charged ions by unimolecular and collision induced processes have been obtained by measurements of phenomena occurring in the field free regions of mass spectrometers.[7,8] In these investigations the removal of the singly charged spectrum allows reliable measurements of the doubly charged ions even if their abundance is very low.

Bis-benzylisoquinoline systems



1

a

In view of the above introduction it is surprising to find that doubly charged fragments are the most abundant ions in the mass spectra of some bis-benzylisoquinoline alkaloids, **1**.[9] The structure of these ions *a* in which the two charges reside on quaternary nitrogen atoms, is consistent with their high abundance. Doubly charged fragment ions are usually believed to be generated by the decomposition of doubly charged parents:

$$[\text{Parent}]^{2+} \rightarrow [\text{Fragment}]^{2+} + \text{Neutral} \qquad (1)$$

If this were the only mode of formation of ions *a* from the alkaloids **1**, namely $[M]^{2+} \rightarrow$ ion *a*, the high abundance of ions *a* would indicate a very high efficiency of the second ionization. It is possible to suggest an alternative (or additional) pathway for the formation of abundant doubly charged fragments by the loss of an anion from the singly charged parent ion:

$$[\text{Parent}]^{+} \rightarrow [\text{Fragment}]^{2+} + [\text{Anion}]^{-} \qquad (2)$$

This pathway seems attractive in the case of the bis-benzylisoquinoline alkaloids **1** because it may explain the very high abundance of ions *a* without assuming an exceptionally high efficiency of the second ionization. This charge separation process has been suggested as the mechanism of formation of $[M-Cl]^{2+}$ from 1,3,5-trichlorobenzene.[10]

The bis-benzylisoquinoline system **2** was synthesized in order to explore the occurrence of pathway (2). This system has been chosen because it has some characteristic features of the bis-benzylisoquinoline alkaloids which allow expectation of high abundance for the doubly charged ions *b*. It has two possible positive

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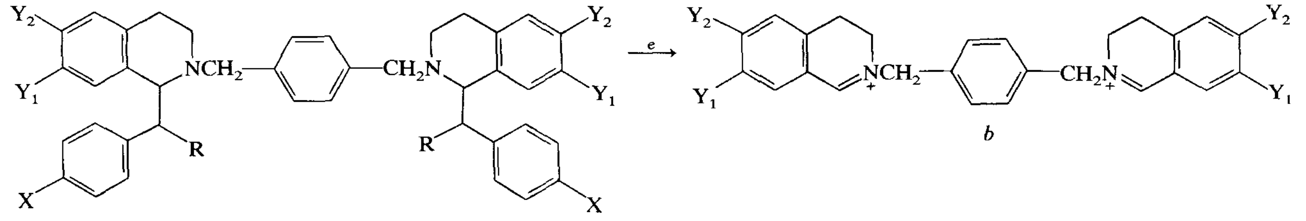


2

2a: $R=Y_1=Y_2=H;\ X=NO_2$
2b: $R=Y_1=Y_2=H;\ X=Br$
2c: $R=Y_1=Y_2=H;\ X=Cl$
2d: $R=Y_1=Y_2=H;\ X=F$
2e: $R=Y_1=Y_2=H;\ X=H$
2f: $R=Y_1=Y_2=H;\ X=OCH_3$
2g: $R=Y_1=Y_2=H;\ X=NH_2$
2h: $R=X=Y_2=H;\ Y_1=Cl$
2i: $R=X=H;\ Y_1=Y_2=OCH_3$
2j: $R=CH_3;\ X=Y_1=Y_2=H$

charge sites, which may be stabilized by immonium structure formation resulting from the cleavage of the two benzylic bonds. The two remote sites are separated by the *p*-xylyl moiety which should withstand the repulsion of the two charges. The two benzylic groups are not connected to one another, which allows study of their consecutive cleavages.

The mass spectra of compounds **2** are relatively simple (Fig. 1). They exhibit neither singly nor doubly charged molecular ions. Most abundant are the singly charged ions *c* $[M-XC_7H_6]^+$ formed by the loss of one benzyl (or substituted benzyl) radical from $[M]^{+\cdot}$, and the expected doubly charged ions *b* corresponding to the loss of the two benzyls. The suggested pathway (2) for the formation of ions *b* from the singly charged molecular ion by the sequential loss of a benzyl radical and a benzyl anion is shown in Scheme 1. The occurrence of this pathway was studied by three independent techniques, namely substituent effects, appearance energy measurements and by metastable transitions.

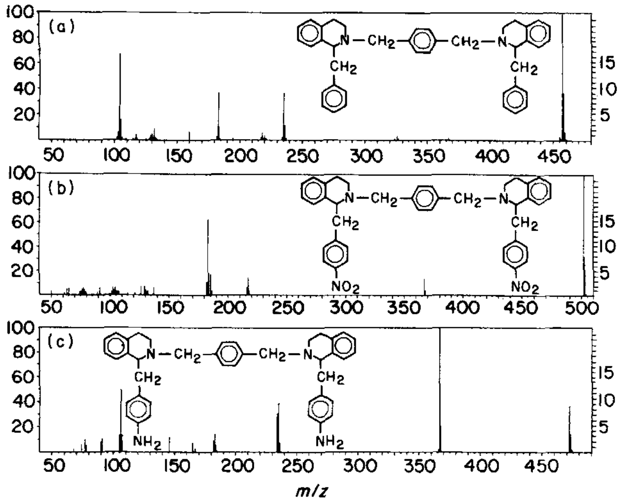


Figure 1. Mass spectra of (a) **2e**; (b) **2a**; (c) **2g**.

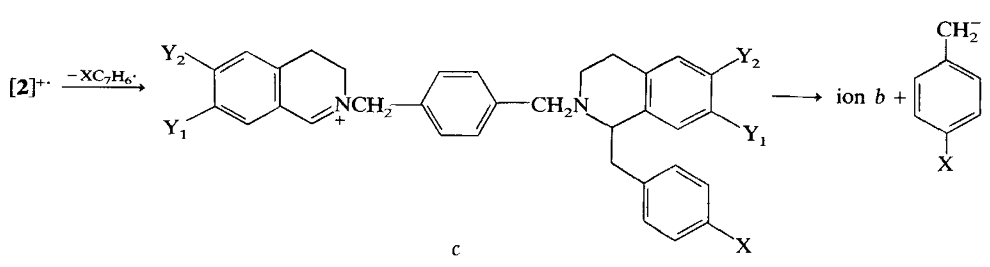
Table 1. Abundance data for ions *b* and *c* in the mass spectra of substituted bis-benzylisoquinoline derivatives 2

Compound	X	Rel. ab. (ion *b*)[a]	Rel. ab. (ion *c*)[a]	[ion *b*]/[ion *c*]
2a	NO_2	63	100	0.63
2b	Br	72[b]	100[b]	0.72
2c	Cl	40[b]	100[b]	0.68
2d	F	58	100	0.58
2e	H	36	100	0.36
2f	OCH_3	27	100	0.27
2g	NH_2	14	37[c]	0.38

[a] Relative abundance % of the most abundant ion.
[b] Based on the sum of abundances of the isotopic species.
[c] The most abundant ion at *m/z* 367 corresponds to the loss of C_7H_7N from ion c.

Substituent effect

The abundance data of ions *b* and *c* in the mass spectra of bis-benzyltetrahydroisoquinolines substituted in the benzyl groups are listed in Table 1. It is not possible to find a linear correlation of the abundances of ion *b* with any substituent constant. However, the data show a small but significant substituent effect: the abundance of ion *b* is higher for electron withdrawing substituents ($X=NO_2$, Br, Cl, F) than for the electron donating ones ($X=NH_2$, CH_3O). This behavior is consistent with the proposed mechanism (Eqn (2) and Scheme 1) in which the benzyl group is expelled as an anion. The expulsion of a radical would result in increased abundance for electron donating substituents as compared with the electron withdrawing ones. The small effect and the non-linearity of the data may be explained by competitive fragmentation processes of the variously substituted ions *c* as well as by the possible occurrence of an additional mechanism of formation of ion *b*. It should also be noted that the compounds are non-volatile, and it was impossible to

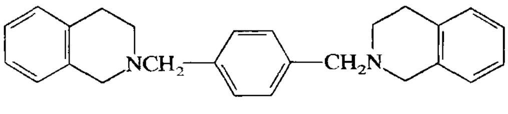


Scheme 1

measure their mass spectra under identical conditions. The mass spectrum of **2j**, which has a methyl group in both benzylic positions, provides further support for the proposed mechanism (Eqn (2) and Scheme 1). In this case the abundance of the doubly charged ion *b* ([ion *b*]/[ion *c*] = 0.41) is very similar to that of the unsubstituted **2c** ([ion *b*]/[ion *c*] = 0.36). The expulsion of a radical (Eqn (1)) would be expected to result in a much higher abundance of ion *b* for **2j**, because of the greater stability of α-phenylethyl radical as compared with the benzyl radical.

Appearance energy measurements

The values of the appearance energies of the doubly charged ions *b* (listed in Table 2) are around 20 eV. The first and second ionization energies of the bis-benzylisoquinoline derivatives **2** could not be measured directly due to the absence of the molecular ions from their mass spectra. The unsubstituted bis-tetrahydroisoquinoline **3** gave rise to a doubly charged molecular ion which enabled the measurement of the second ionization energy, 22.1 eV. A similar value, 21.8 eV was obtained for the quinoline analogue **4**. The second ionization energies of the bis-benzyltetrahydroisoquinoline derivatives **2** are expected to be very close to that of the unsubstituted **3**, since they should not be affected by the benzyl groups in view of the relatively lower ionization energy of the tetrahydroisoquinoline moiety.[11] In analogy, the ionization energy of methyldibenzylamine (7.85 eV[12]) is unaffected by the benzyl groups being practically identical with that of trimethylamine (7.80 eV[13]).



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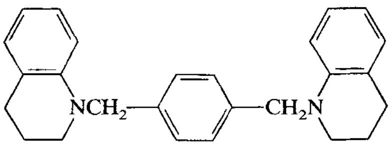

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The above data show that the appearance energies of ions *b* (~20 eV) are lower by ~2 eV than the second ionization energies of the parent compounds **2** (~22 eV). These results lead to the conclusion that at least in the range of energies of 20–22 eV, ions *b* cannot be formed from the doubly charged molecular ions (Eqn (1)), and consequently must be generated from the singly charged $[M]^{+\cdot}$ by the elimination of a benzylic anion (Eqn (2) and Scheme 1).

Table 2. Appearance energies of ions *b* formed from substituted bis-benzylisoquinolines 2

Compound	Appearance energy (eV)	Compound	Appearance energy (eV)
2b	19.8	**2e**	20.0
2c	20.3	**2f**	20.1
2d	19.8	**2j**	20.3

Metastable transitions

Direct evidence for the formation of the doubly charged ions *b* from the singly charged ions *c* by the loss of a benzylic anion (Scheme 1) is provided by the measurement of metastable transitions occurring in the first field free region (1st FFR) of a double focusing mass spectrometer. It can be shown easily that the doubly charged daughter ion $[m_2]^{2+}$ generated in the 1st FFR by the charge separation process $[m_1]^{+} \rightarrow [m_2]^{2+} + [m_3]^{-}$ will be detected by increasing the accelerating voltage to the value

$$V_1 = 2\frac{m_1}{m_2}V_0$$

(m_1 and m_2—the masses of the ions $[m_1]^{+}$ and $[m_2]^{2+}$, V_0—the accelerating voltage at which processes occurring in the ion source are detected). The accelerating voltage scans of ions *b* showed in each of the bis-benzylisoquinoline derivatives **2a**–**2j** a single metastable transition corresponding to their formation from the singly charged ions *c*. This finding unambiguously indicates that ions *b* are formed exclusively from the singly charged ions *c* (Scheme 1) in the 1st FFR by a relatively slow process ($k \sim 10^5\ s^{-1}$). It does not exclude the possibility of a fast process occurring in the high energy doubly charged molecular ions by the consecutive loss of two benzylic radicals:

$$[M]^{2+} \rightarrow [M-\text{benzyl}]^{2+\cdot} \rightarrow [M-2\ \text{benzyl}]^{2+}$$

$$b$$

It should be noted, however, that the intermediate doubly charged $[M-\text{benzyl}]^{2+\cdot}$ ion has not been detected in any of the compounds **2** examined.

In several bis-benzyltetrahydroisoquinoline alkaloids **1**, the reported metastable transitions indicate formation of the doubly charged ions *a* from the doubly charged molecular ions: $[\mathbf{1}]^{2+} \xrightarrow[*]{} a$.[9c,9d] The absence of analogous metastable transitions in **2** may be attributed to the instability of the intermediate doubly charged $[M-\text{benzyl}]^{2+\cdot}$ *radical* cations. A single cleavage of a benzylic bond in the doubly charged molecular ions of the alkaloids **1** results in *even-electron* species (molecular ions in which only one benzylic bond is retained), which may yield ions *a* by a slow process that can be detected by a metastable transition.

CONCLUSION

The data presented show unambiguously that the abundant doubly charged ions *b* in the mass spectra of **2** are formed by a charge separation process from the singly charged ions *c*. No evidence could be found for their formation from the doubly charged molecular ions of **2** by a sequential loss of two benzyl radicals. If such a process does occur it must involve high energy $[M]^{2+}$ ions, in the absence of metastable transitions and of the intermediate $[M-\text{benzyl}]^{2+\cdot}$ ions.

It is generally accepted that only one decomposition mode is available for even-electron singly charged ions: $[\text{even}_1]^+ \rightarrow [\text{even}_2]^+ + [\text{neutral even}]$. It has been shown recently that in numerous cases the previously forbidden (by the 'even-electron rule') processes $[\text{even}]^+ \rightarrow [\text{odd}]^{+\cdot} + [\text{radical}]^{\cdot}$ are observed.[14] It has been shown here that in some specific cases an additional mode of decomposition is available for an even-electron ion, namely the charge separation process leading to doubly charged ions: $[\text{even}]^+ \rightarrow [\text{even}]^{2+} + [\text{even}]^-$.

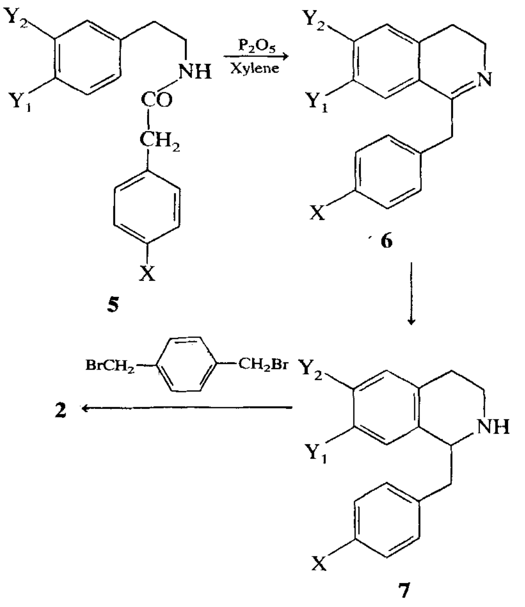
EXPERIMENTAL

Mass spectra were measured with a Varian MAT 711 double focusing mass spectrometer, at an electron beam energy of 70 eV. The source temperature was 250 °C. The pressure in the drift tube was lower than 5×10^{-8} Torr in all measurements. Samples were introduced by the direct inlet probe, heated until the vapour pressure enabled reproducible measurements. The ionization and appearance energies were measured by the energy compensation technique (voltage difference at 0.1% of ion current at 50 eV)[15] using argon (IE 15.7 eV) as the calibrating material. The estimated error is ±0.3 eV.

Preparation of compounds 2

The bis-benzyltetrahydroisoquinoline derivatives were synthesized following the route summarized in Scheme 2. The substituted 1-benzyl-3,4-dihydroisoquinolines **6** were synthesized following the reported procedure.[16] They were reduced to the corresponding 1-benzyl-1,2,3,4-tetrahydroisoquinolines **7** with lithium aluminum hydride in ether, with the exception of **6a** (X=NO_2), which was treated instead with sodium cyanoborohydride: methanolic HCl was added to 1-(4-nitrobenzyl)-3,4-dihydroisoquinoline (**6a**) (266 mg) and sodium cyanoborohydride (62 mg) in methanol (10 cm^3) until bromocresol green turned blue. After stirring for 4 h the solvent was evaporated off, and 6 N NaOH was added until the residue dissolved. Extraction (CH_2Cl_2) yielded **7a** as an oil (0.2 g), which solidified on standing and was used for the synthesis of **2** without further purification.

The physical properties of compounds **6** and **7** were in agreement with the reported data.[16–19]



Scheme 2

Compounds **2** were obtained by refluxing the tetrahydroisoquinolines **7** with an equivalent amount of α,α'-dibromo-*p* xylene in ethanol (benzene for **2b**) for 12 h, flash-evaporating the solvent and crystallization.

2a M.p. 233–235 °C (methylene chloride).
2b M.p. 223–224 °C (ethyl acetate).
2c M.p. (dec.) 198 °C (ethanol). Anal. calc. for $C_{40}H_{38}N_2Cl_2$: C, 77.79; H, 6.15. Found: C, 77.62; H, 5.93.
2d M.p. (dec.) 188 °C (hexane–methylene chloride). Anal. calc. for $C_{40}H_{38}N_2F_2$: C, 82.19; H, 6.51; Found: C, 82.58; H, 6.86.
2e M.p. 195–197 °C (hexane–chloroform). Anal. calc. for $C_{40}H_{38}N_2$: N, 5.11. Found: N, 5.29.
2f M.p. 247–249 °C (ethyl acetate).
2h M.p. 203–205 °C (hexane–ethyl acetate). Anal. calc. for $C_{40}H_{38}N_2Cl_2$: C, 77.79; H, 6.15. Found: C, 78.02; H, 6.19.
2i M.p. (dihydrobromide) 222–224 °C (hexane–chloroform). Anal. calc. for $C_{44}H_{48}N_2O_4 \cdot 2HBr$: C, 63.76; H, 6.02. Found: C, 63.38; H, 5.99.
2j M.p. 217–219 °C (methylene chloride). Anal. calc. for $C_{42}H_{44}N_2$: C, 87.45; H, 7.69; Found: C, 87.23; H, 7.83.
2g was prepared by hydrogenation of **2a** on Raney nickel. Due to difficulties in crystallization the crude material was used for measurements.

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