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Gas-phase reactions of the oxygen radical anion with arylalkylamines

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Abstract

The gas-phase reactions of the oxygen radical anion $O^{\cdot -}$ with a number of biologically active arylalkylamines of general formula $R^1C_6H_4CHR^2$ $(CH_2)_nNHR^3$, where R^1=H, F, NO_2, OH, or OCH_3, R^2=H or OH, and R^3=H or CH_3, have been studied by means of chemical ionization mass spectrometry, using a mixture of N_2O and N_2 (1:9) to generate the $O^{\cdot -}$ reagent ions. The collision-induced dissociation spectra of the $[M-H+O]^-$ adduct ions formed in the ion source of the mass spectrometer have been interpreted in terms of the aliphatic chain length and the presence of different functional groups in the molecule. The analysis of data indicates that the preferred site of oxygen radical anion attachment is the benzylic carbon atom, except for the amines with a benzylic hydroxy group (octopamine and synephrine), where a competition between the aromatic ring and the benzylic carbon atom, becomes evident. The fragmentation pathways observed for octopamine and synephrine are unique as compared with all the other amines, in which the chain length also exerts an important influence on the observed decompositions. (Int J Mass Spectrom 210/211 (2001) 563–568) © 2001 Elsevier Science B.V.

Keywords: Oxygen radical anion; Negative chemical ionization; Arylalkylamines; Fragmentation mechanisms

1. Introduction

The oxygen radical anion, $O^{\cdot -}$, reacts with organic molecules in the gas phase in a variety of ways that may be classified as: hydrogen atom abstraction; proton abstraction; $H_2^{\cdot +}$ abstraction; hydrogen atom displacement; and alkyl group displacement [1].

These reactions have been reviewed by Grabowski and co-worker [2]. The organic compound structurally similar to the arylalkylamines of the present study (Table 1), that were the subject of earlier works include aliphatic amines, xylenes, fluoroidivenes, alkylpentafludeophenyl ethers, halogen derivatives of benzene, and several simple aromatic compounds.

Tiernan and co-worker [3] reported OH^- as the only product arising from reaction with simple aliphatic amines, using a tandem mass spectrometer. On the other hand, de Koning and co-worker [4] found that an amino-hydrogen is preferentially abstracted from methyl-amine, and that small quantities of an intriguing $H_2O^{\cdot -}$ were formed as a product ion in the reactions with methyl, ethyl, and di-methylamine.

With xylenes, Bruins et al. [5] were able to conclude that the major product was the $[M-H]^-$ ion and that in the para-xylene reaction 16% of a $[M-H+O]^-$ product was formed. Also they showed

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Dedicated to Professor Nico Nibbering on the occasion of his retirement.

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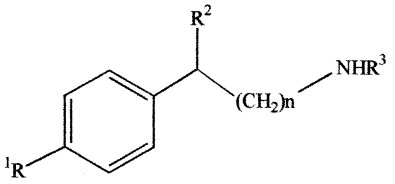


Table 1
Arylalkylamines

Amine	*n*	R^1	R^2	R^3
Benzylamine	0	H	H	H
2-Phenylethylamine	1	H	H	H
N-Methyl-2-phenylethylamine	1	H	H	CH_3
3-Phenylpropylamine	2	H	H	H
4-Phenylbutylamine	3	H	H	H
2-(4-Fluorophenyl)-ethylamine	1	F	H	H
2-(4-Nitrophenyl)-ethylamine	1	NO_2	H	H
2-(4-Methoxyphenyl)-ethylamine	1	CH_3O	H	H
Tyramine	1	OH	H	H
Octopamine	1	OH	OH	H
Synephrine	1	OH	OH	CH_3

that the removal of an hydrogen atom or proton from each of the methyl groups accounted for the formation of a $[M-2H]^{\cdot -}$ product. With the fluorotoluenes the amount of this latter product was higher than with toluene itself.

Ingemann et al. [6] reported that in the reaction with $C_6F_5OCH_3$ an ipso substitution is observed on the carbon atom bearing the methoxyl group, and a S_N2 reaction takes place on the carbon of the methyl group. Also a charge-transfer process is probably observed.

The reaction of the oxygen radical anion with C_6H_5X compounds (X=F, Cl, CN) was found by Matimba et al. [7] to take place, to some extent, by $H_2^{\cdot +}$ transfer, and they thus estimated the acidities of the $C_6H_4X^{\cdot}$ radicals.

Vouros and co-woker [8] have studied, among others, the reaction of the oxygen radical anion with toluene, and concluded that not only a benzyl-oxide anion but also a ortho-methyl-phenoxide anion was generated. For the second of these products they proposed a mechanism that involved the same benzylic hydrogen atom abstraction observed with the first product, followed consecutively by a ring expansion to form a cyclic seven membered radical, reaction with the hydroxyl anion, and finally a ring-contraction process to return to a benzenic ring.

Following previous studies on the gas-phase deprotonation reactions of arylalkylamines [9], the present work describes the fragmentation pathways of the adduct ions $[M-H+O]^-$, generated by reaction of arylalkylamines with $O^{\cdot -}$ produced by a mixture of N_2O and N_2 in a chemical ionization source. The amines were chosen with the objective of being able to understand the influence of each of several specific features on the course of the reactions, namely: the length of the alkyllic chain, the type of substitution on the aromatic ring, the presence or absence of a benzylic hydroxyl group, and methyl substitution on the amino group.

2. Experimental

Arylalkylamines (Table 1) were of commercial origin and were introduced into the ion source of the mass spectrometer by way of an unheated direct insertion probe. Mass spectrometric experiments were performed with a VG Autospec Q instrument (Micromass, Manchester, UK) of EBEqQ geometry equipped with a chemical ionization source. A gaseous mixture of N_2O and N_2 (1:9), at source pressures of about 3×10^{-5} Torr, was used to generate the $O^{\cdot -}$ ions, with a source temperature of 175 °C. The electron energy was 70 eV and the accelerating voltage 8 kV. Collision-induced dissociation spectra were obtained by mass selection of the ion to be studied with the magnetic sector of the instrument and scanning the second electrostatic analyser, using Ar as the collision gas to produce a reduction of ~50% of the main beam intensity.

3. Results and discussion

3.1. Chemical ionization spectra

The intensities of the peaks observed in the chemical ionization mass spectra of the arylalkylamines presented

Table 2
Oxygen radical anion chemical ionization mass spectra of arylalkylamines

Amine	M_r	$[M - 2H]^-$	$[M - H]^-$	$[M - H + O]^-$
Benzylamine	107	70	30	74
2-Phenylethylamine	121	16	79	43
N-Methyl-2-phenylethylamine	135	7	28	32
3-Phenylpropylamine	135	3	25	<1
4-Phenylbutylamine	149	<1	2	<1
2-(4-Fluorophenyl)-ethylamine	139	36	<1	3
2-(4-Nitrophenyl)-ethylamine	166	<1	<1	<1
2-(4-Methoxyphenyl)-ethylamine	151	11	51	15
Tyramine	137	10	100	<1
Octopamine	153	4	100	<1
Synephrine	167	2	44	2

in Table 2 show that the $[M-H]^-$ ions are formed in the ion source in fairly high abundance, which can be correlated with the availability of acidic protons. It is predictable that the order of decreasing acidities of the different types of protons present in the molecule of the arylalkylamines studied must be roughly: phenolic, alcoholic, and finally the group including benzylic, aminic, benzenic, and alkylic protons, which are far less acidic then the former ones. The particularly high intensities of the $[M-H]^-$ peaks observed for tyramine and octopamine are in accordance with this prediction, synephrine being an exception. The relative abundances of the $[M-H+O]^-$ ions seem to follow those of the $[M-2H]^{\cdot -}$ ions more closely than those of $[M-H]^-$ ions.

3.2. Collision-induced dissociation spectra of the $[M-H+O]^-$ adduct ions

The analysis of the collision-induced dissociation spectra of the $[M-H+O]^-$ anions of the arylalkylamines studied (Table 3) shows two sharply distinct types of behaviour, dependent on the absence or presence of a benzylic hydroxyl group.

3.2.1. Amines without a benzylic hydroxyl group

The $[M-H+O]^-$ adduct ions of the primary arylalkylamines show important losses of 17 Da (relative intensities of product ion signals in the collision-induced dissociation spectra ranging from 6% to 40%) that might be due to loss of NH_3 or $OH^{\cdot}$. The observation of CH_3NH_2 loss and absence of 17 Da loss in the spectrum of the secondary amine 2-phenyl-N-methylethylamine, is a strong indication that elimination of ammonia is taking place for the primary amines. The mechanism proposed for this reaction is exemplified in Scheme 1 for tyramine and involves the formation of an ion−neutral complex between an epoxide [10] and the NH_2^- ion, followed by proton abstraction.

Loss of the radical $^{\cdot}CH_2NH_2$ (or $^{\cdot}CH_2NHCH_3$ for the secondary amine) generates the most abundant product ion in the spectra of 2-phenylethylamine, 2-(4-fluorophenyl)ethylamine, and 2-(4-nitrophenyl) ethylamine. When the size of the aliphatic chain increases, as in 3-phenylpropylamine and 4-phenylbutylamine, loss of the radicals $^{\cdot}(CH_2)_2NH_2$ and $^{\cdot}(CH_2)_3NH_2$, respectively, is observed instead, although they are no longer the most abundant ions. The driving force for this fragmentation reaction will be the formation of a resonance stabilized benzaldehyde radical anion.

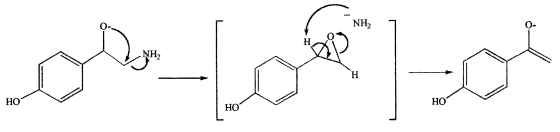
The influence of the size of the aliphatic chain is also present in two other observations, namely: (1) the observation of NH_3, CH_3NH_2, and $CH_3CH_2NH_2$ losses when n increases from 1 to 3; (2) the loss of 36 Da observed only for $n=2$ and 3; and (3) the loss of 16 Da when $n=0$. The mechanism of metil- and etilamine eliminations, mentioned in (1) might be analogous to the one shown in Scheme 1, or alternatively, the reaction might proceed by way of a 1,2-elimination, resulting in either case in a stabilized

Table 3
Collision induced dissociation spectra of the $[M - H + O]^-$ adduct ions of arylalkylamines

Benzylamine	– 16 63%	– NH_3 24%	– CH_2=NH 13%			
2-Phenylethylamine	– CH_2NH_2 32%	*m/z* 92 30%	– NH_3 23%	– CH_2=NH 15%		
N-Methyl-2-phenylethylamine	– CH_2NHCH_3 55%	– CH_3NH_2 45%				
3-Phenylpropylamine	*m/z* 114 79%	– $(CH_2)_2NH_2$ 9%	– CH_3NH_2 6%	– NH_3 6%		
4-Phenylbutylamine	*m/z* 128 59%	– NH_3 10%	– $(CH_2)_3NH_2$ 11%	*m/z* 126 11%	– $CH_3CH_2NH_2$ 9%	
2-(4-Fluorphenyl)-ethylamine	– CH_2NH_2 34%	*m/z* 118 32%	– NH_3 19%	*m/z* 116 12%	*m/z* 110 3%	
2-(4-Nitrophenyl)-ethylamine	– CH_2NH_2 51%	– NH_3 28%	*m/z* 135 14%	*m/z* 121 7%		
2-(4-Methoxyphenyl)-ethylamine	– CH_3 39%	– CH_3-CH_2=NH 18%	– $CH_3-CH_2NH_2$ 15%	– CH_2NH_2 10%	*m/z* 128 7%	– NH_3 6%
Tyramine	– NH_3 40%	– CH_2NH_2 23%	– CH_3NH_2 23%	*m/z* 118 7%		
Octopamine	– H_2O 52%	– CH_3NH_2 31%	– CH_3NH_2-CO 10%	*m/z* 123 7%		
Synephrine	– H_2O 55%	– $(CH_3)_2NH$ 32%	– $(CH_3)_2NH-CO$ 13%			

anion. Loss of 36 Da mentioned in (2) is an unique fragmentation for 3-propylamine and 4-butylamine, generating the most abundant ions (*m/z* 114 and 128, respectively) in both spectra. The data presently available point to consecutive eliminations of NH_3, $^{\cdot}OH$, and 2H, not necessarily in this sequence, but are not sufficient to enable us to propose a mechanism. The reason why this fragmentation only occurs for these two amines is the size of the aliphatic chain, which for all the other arylethylamines, does not contain enough hydrogen atoms. Finally loss of 16 Da, mentioned in (3) might correspond to loss of the oxygen atom or NH_2

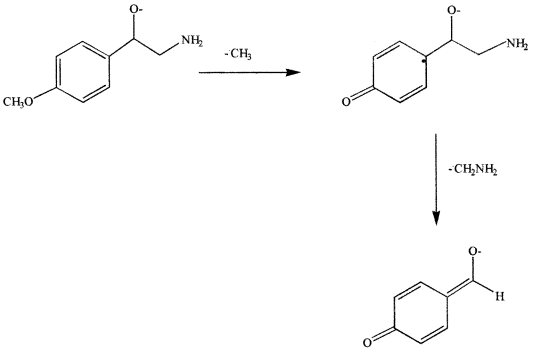
The presence of a methoxyl group in the aromatic ring of 2-(4-metoxyphenyl)ethylamine, induces a different fragmentation pattern for the $[M-H+O]^-$ adduct ion of this amine, namely loss of methyl radical followed by loss of $^{\cdot}CH_2NH_2$ (Scheme 2). The fragmentation pathways discussed previously, strongly indicate that, with the exception of benzylamine, the site of preferred oxygen radical anion attachment is the benzylic carbon atom.



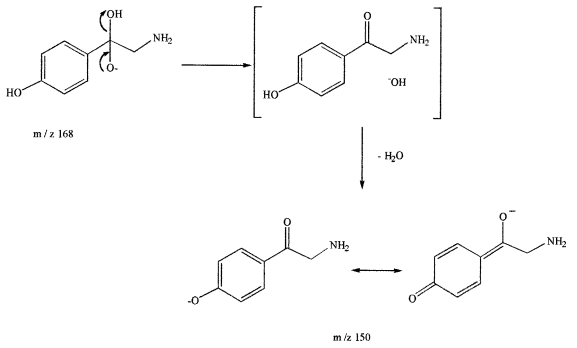
Scheme 1.

3.2.2. Amines with a benzylic hydroxy group

For the two amines with a benzylic hydroxy group (octopamine and synephrine), losses of H_2O produce the most intense peak in their spectra. The mechanism proposed for this reaction involves oxygen atom



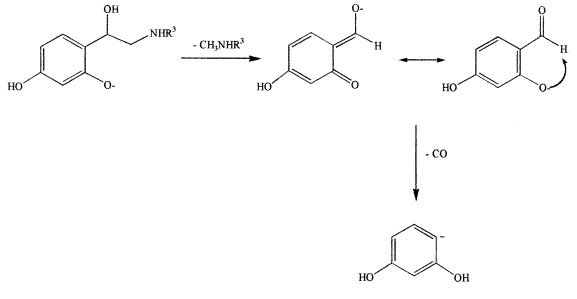
Scheme 2.



Scheme 3.

incorporation at the benzylic position, followed by the formation of an ion−molecule complex between the hydroxyl anion and an arylcetoamine, and the final abstraction of a proton from the phenolic group (Scheme 3). The mechanism is supported by the observed shift of the peak due to H_2O loss (*m/z* 150) to *m/z* 152 due to D_2O loss, in the collision-induced dissociation spectrum of octopamine-d_4.

The second interesting feature in the spectra of octopamine and synephrine is the elimination of, respectively, methylamine and ethylamine from the $[M-H+O]^-$ ions, incorporating the β-carbon in the neutral, whereas for the amines without a benzylic hydroxy group that atom is retained in the product ion formed. The reason for this difference must be looked for in the stability of the product ion thus, which further decomposes with loss of carbon monoxide (Scheme 4). This consecutive fragmentation suggests significant oxygen atom incorporation in the aromatic ring probably due to the fact that the benzylic position is, for these two amines, already occupied with a bulky hydroxy group rendering the attack of the oxygen radical anion less favorable.



Scheme 4.

4. Conclusions

The collision-induced decomposition spectra of the $[M-H+O]^-$ adduct ions formed in the ion source of the mass spectrometer have been interpreted in terms of the aliphatic chain length and the presence of different functional groups in the molecule. The analysis of the spectra indicate that the preferred site of oxygen radical anion attachment is the benzylic carbon atom, except for the amines with a benzylic hydroxy group (octopamine and synephrine), where a competition between the aromatic ring and the benzylic carbon, becomes evident. The fragmentation pathways observed for the $[M-H+O]^-$ ions of octopamine and synephrine are unique (loss of water, loss of methyl- and ethylamine followed by loss of carbon monoxide) as compared with all the other amines, in which the chain length also exerts an important influence on the decompositions observed. Loss of ammonia/amine from the $[M-H+O]^-$ ions is common to all the amines without a benzylic hydroxy group, as well as loss of the radical containing the β-carbon of the aliphatic chain, while loss of 16 Da only occurs for benzylamine.

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