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MASS SPECTROMETRY OF ONIUM COMPOUNDS

XXI*—SUBSTITUENT EFFECT ON THE EVAPORATION OF ANILINIUM OXIDES

HAMDI M. R. EL-MOUAFI, GEORG HVISTENDAHL and KJELL UNDHEIM Department of Chemistry, University of Oslo, Oslo 3, Norway

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Abstract—The ionisation potentials and characteristic fragmentations of a series of anilinium oxides and their isomeric ethers have been used to assign structures for the gaseous species from the zwitterions. Transmethylation and direct evaporation of the zwitterions are competing processes. A bulky substituent *ortho* to the oxygen or a strongly electron attracting group in the 2-isomer will prevent or reduce the transmethylation. If the volatility is much reduced, however, the temperature increase for evaporation results in transmethylation. The 4-isomer was transmethylated even with two *tert*-butyl groups *ortho* to the oxygen. The appearance potentials for an isomeric pair showed the energy difference between the zwitterion and the ether in the gas phase to be 11.5 kcal/mol.

THE meta- and para- isomers of the N,N,N-trimethylanilinium oxides undergo transmethylation to their respective ethers before evaporation in the mass spectrometer. From the spectra it was found that 75% of the ortho-isomer, however, was evaporated without any prior structural change (Scheme 1).² Subsequently the presence of a gaseous zwitterionic structure was supported by a lower ionisation potential (IP) (6.8 eV) than that found for the isomeric ether (7.59 eV).³



The transmethylation to the isomeric ether and the direct evaporation of the zwitterion are competing processes. The relative amount of the two components in the gas phase is determined by the rate of transmethylation at a given sample temperature compared to the evaporation rate of the zwitterion. Increase in the sample temperature favours ether formation. Complete transmethylation was found to take place when the zwitterion was introduced through the heated inlet system of the mass spectrometer.²

This report deals with substituent effects on the *ortho*-anilinium oxides (I to V, Scheme 2) in these competing reactions. Two derivatives of the *para*-isomer with large groups next to the oxygen atom have also been included (XVI and XVII).

* For Part XX, see Ref. 1.



SCHEME 2

The influence of substituents on the transmethylation reaction may be divided roughly into steric and electronic effects. Transmethylation is an intermolecular nucleophilic displacement reaction² and will as such be subjected to steric interference from bulky substituents next to the oxygen. Electronically a substituent may change the charge distribution in the zwitterion. Thus, an electron withdrawing substituent like the nitro group will reduce the charge density on the oxygen, especially in an *ortho*- or *para*- position, and thereby make the oxygen less nucleophilic.

The effects of substituents on the rate of evaporation of the zwitterion are more complex. The increase in the mass, however, will certainly be important.

For the mechanistic studies homogeneous mixtures of the zwitterion (A) and its perdeuteriomethyl analogue (B) were used.² In the absence of intermolecular transmethylation the two molecular ion peaks are due to the parent gaseous zwitterion (a) (Scheme 3) and its perdeuteriomethyl analogue (b). Isotope effects are considered to be of minor importance relative to experimental errors and are neglected in the treatment below. Making this assumption, the intensity ratio of the molecular ion peaks (a:b) should be equal to the molar ratio (A:B) of the zwitterions. If some intermolecular transmethylation also takes place, four additional gaseous species, will be formed (Scheme 3). Only four peaks will be observed in the spectrum, however, since the mass of the gaseous zwitterions (a) and (b) is equal to the moss of the corresponding ethers (c) and (f). Neglecting any sensitivity differences between the two structurally different molecular ions, the intensity ratio of the molecular ion peaks should be equal to the molar ratio (1).

$$\frac{\mathbf{A}}{\mathbf{B}} = \frac{a+c+d}{b+e+f} \tag{1}$$



The degree of transmethylation α is defined as the ratio between the rate of transmethylation and the rate of formation of the gaseous products (ether and zwitterion). The rates are directly related to the observed peak heights

$$\alpha = \frac{c+d}{a+c+d} \tag{2}$$

The rate of formation of the ethers c and d is dependent on the relative amount of the zwitterions A and B in the mixture

$$\frac{c}{d} = \frac{A}{B}$$
(3)

Combination of Eqns. (2) and (3) gives

$$\alpha = \frac{d(A/B+1)}{a+c+d} \tag{4}$$

The percentage transmethylation is calculated from Eqns. (1) and (4) using the relative peak heights in the spectra of the mixtures of A and B. The values are given in Table 1.

 TABLE 1. IONISATION POTENTIALS AND SPECIES COMPOSITION IN THE GASEOUS STATE

 Compound
 (1)
 (11)
 (12)
 (21)

Compound	(I)	(II)	(III)	(IV)	(V)	(XVI)	(XVII)
Transmethylation	0	10%	100%	60%	85	100%	100%
Direct evaporation	100%	90%	0	40%	15	0	0
IP (eV) of zwitterion	6.30	6.67	7•28	7.27	6.75	7.00	6.80
IP (eV) of ether	7.30	7.52	7.28	7.76	7.45	7.00	6.80

The recorded IP values are also given in Table 1. These values were determined by the semilog plot interpretation of the ionisation efficiency curves.⁴ The ethers needed for reference were either synthesised separately, generated pyrolytically from the zwitterion using the indirect insertion system at 250 to 300 °C, or generated by pyrolytic N-demethylation³ of N, N, N-trimethylanisidinium iodides (XXII, XXIII) during direct insertion in the mass spectrometer. It is seen that in those cases where the isotope technique showed only transmethylation the IP values for the gaseous species from the zwitterions are the same as for the corresponding ethers. On the other hand, the gaseous species from the *tert*-butyl derivative (I) has a very low IP value (6.30 eV) compared to its isomeric ether (XI) (7.30 eV) in agreement with direct evaporation of the zwitterion. This conclusion is further supported by the observed difference in fragmentation between I and XI as discussed below. Thus the steric hindrance from the tert-butyl group next to the oxygen in I effectively prevents transmethylation. No gaseous zwitterion was obtained from the phenyl derivative (III). This is most probably due to the increase in evaporation temperature on substitution. In the 3phenyl derivative (V), however, the phenyl group exerts steric hindrance towards the transmethylation and the zwitterion is the dominating gaseous species.

The 5-nitro derivative (IV) has the highest evaporation temperature (220 °C) in this series. Even so only about 60% of the zwitterions were transmethylated. The lower rate of transmethylation indicates the importance of the nucleophilicity of the oxygen in the process. A chlorine substituent as in II gave a compound which behaved very much as the parent zwitterion. Neither the phenyl groups nor the two *tert*-butyl groups next to the oxygen in the *para*-isomer (XVI) and (XVII) prevented transmethylation. This result supports our assumption that the exceptional behaviour of the parent *ortho*-isomer and certain of its derivatives is due to the short distance between the opposite charges.²

Energetic considerations

In the case of the unsubstituted ortho-isomer (Scheme 1) the energy difference between the gaseous zwitterion and the isomeric ether was calculated from the difference in appearance potential (AP) of the common $[M - CH_3]^+$ fragment in the two processes.³ From the *tert*-butyl derivative (I) more accurate calculations can be made since the zwitterion is the only gaseous species. Owing to interference by methyl group expulsions from the *tert*-butyl groups (Scheme 5) the deuteriated compounds (VI) and (XXIV) were used. Secondary deuterium effects are assumed to be insignificant. The AP's for the $[M - CD_3]^+$ fragment generated from VI and from XXIV were measured. The former corresponds to AP (I) and the latter to AP (XI). Since the $[M - CD_3]^+$ fragment is of common structure (Scheme 4) the following equation can be put forward³

$$\Delta H_{\rm f}({\rm XI}) - \Delta H_{\rm f}({\rm I}) = {\rm AP}({\rm I}) - {\rm AP}({\rm XI}) + E({\rm XI}) - E({\rm I})$$

The value of the AP(I) was found to be 10.44 eV and AP(XI) 10.94 eV. The excess energy terms usually cancel out in such calculations,³ and the difference in AP should correspond to the difference in the heat of formation of the gaseous zwitterion and the isomeric ether. The results show that the gaseous zwitterion (I) has about 11.5 kcal/ mol higher energy than the gaseous ether (XI).

6а—(4 рр.)

(I)		(II)		(III)		(IV)		(V)		(XVI)		(XVII)		(XXIV)	
m/e	% I	m/e	% I	m/e	% I	m e	% I	m e	% I	m e	% I	m e	% I	m/e	% I
263	49	185	100	227	100	194	47	227	100	303	98	263	43	266	69
249	33	170	63	212	66	181	36	226	15	288	100	249	20	251	10
248	100	154	23	196	9	135	100	213	31	273	14	248	100	248	100
234	23	141	16	183	9	58	90	212	100	244	26	57	9	57	26
220	25	58	65	105	10	45	39	196	18	215	8			42	21
58	17	45	30	42	46	44	32	182	27						
57	17	44	32			42	24	58	35						
44	8	42	76					44	26						
42	16							42	78						

TABLE 2. MAJOR PEAKS IN THE MASS SPECTRA OF ANILINIUM OXIDES BY DIRECT INSERTION

Fragmentation

A characteristic feature of the spectra of the gaseous zwitterions (I, II, IV and V; Table 2) are the peaks at m/e 58, 44 and 30. In the deuteriated zwitterions (VI, VII and IX) the corresponding peaks are displaced to m/e 66, 50 and 34. Metastable transitions from the molecular ion to the m/e 58 and m/e 44 species were observed as in the parent 2-isomer.² An intense metastable peak of 'Gaussian' shape was found for the loss of ethylene from m/e 58. The latter probably has the same structure as the $[M - H]^+$ fragment from trimethylamine,^{5.6} thus indicating the presence of three methyl groups on nitrogen (Scheme 4). An important fragmentation process common to both the zwitterions and the ethers is loss of a methyl group from nitrogen and oxygen, respectively, to a common fragment formulated as a quinonoid structure (Scheme 4). The metastable peak associated with the processes is of a very low intensity for the gaseous zwitterions in contrast to the isomeric ethers.

The base peak in the spectra of the *tert*-butyl derivatives of N, N-dimethylanisidine (XI) and (XXI) is due to loss of a methyl group from the molecular ion. This could in principle take place from the *tert*-butyl groups since charge stabilisation on oxygen is possible through quinonoid structures. From the deuteriated ions (VI and XIX),



however, less than 3% of the methyl radical lost was found to be from the *tert*-butyl groups. The deuteriated ether (XXIV) of the *ortho*-isomer showed that about 90%, of the methyl expulsion was from the oxygen (Table 2). Taking into account the statistical factor this clearly demonstrates the preference of nitrogen for charge stabilisation. The zwitterion (I) showed a different behaviour. From the deuteriated compound (VI) it was found that about 70% of the methyl group lost was from the *tert*-butyl groups. Taking the statistical factor into consideration the loss of a methyl group from nitrogen or from the *tert*-butyl groups seems equally favourable. This is not unreasonable since the charge is stabilised on nitrogen in both cases (Scheme 5).



Scheme 5

SYNTHESES

The zwitterions (I to V, XVI and XVII) as hydroiodides were synthesised by methyl iodide methylation of the corresponding aminophenols. Alternatively, the aminophenol was permethylated and the alkyl-ether bond cleaved by hydrogen iodide to give the corresponding zwitterion. The hydroiodides, in contrast to most of the zwitterions, could be dissolved in organic solvents such as acetone and chloroform. Deuteriomethyl reagents in the same way gave the deuteriomethyl analogues (VI to IX, XVIII and XIX). Pyrolysis of the zwitterions above their melting points furnished the corresponding ethers. The mixed deuteriated ether (XXIV) was available by stepwise synthesis from 2,4-di-*tert*-butyl-6-nitrophenol as shown in Scheme 6.

EXPERIMENTAL

The mass spectra were recorded on an AEI MS-902 mass spectrometer attached to an AEI DS-30 data system. The source temperature was kept at 220 °C, the ionising current at 100 μ A and the ionising energy at 70 eV. The high resolution spectra were recorded with a dynamic resolving power of 10,000 and with an ionising current of 500 μ A.



During recording of the ionisation efficiency (IE) curves the repeller was kept at the cage potential and the ionising current was 20 μ A. Perchlorobutadiene served as the reference compound and was present during the whole experiment. The reference compound was calibrated against xenon. The IE curves were interpreted by the semilog plot method.⁴ The recorded IP values are the average from four determinations, the deviation being ± 0.05 eV.

The zwitterions were introduced by direct insertion, the sample temperatures being: I, 155 °C; III, 165 °C; III, 195 °C; IV, 220 °C; V, 190 °C; XVI, 200 °C; XVII, 155 °C. The corresponding ethers were introduced through the heated inlet system.

Syntheses

N-Quaternisation of aminophenols.⁷ A solution of the aminophenol (0.005 mol), methyl iodide (0.018 mol) and anhydrous sodium carbonate (0.005 mol) in methanol (15 ml) was heated under reflux for 10 h. The inorganic material was then filtered off, the residue triturated with a little water and dried. The crude product thus obtained contains small amounts of the O-methylated homologue which was removed on recrystallisation.

The zwitterions were obtained by passage of an aqueous solution over an anion exchanger such as IRA-400 (OH⁻)[.] or neutralisation of a concentrated aqueous solution with sodium carbonate when the zwitterion was precipitated.

3,5-Di-tert-butyl-N,N,N-trimethylanilinium-2-oxide (I) was obtained from 2,4-di-tert-butyl-6aminophenol⁸ in 61% yield, m.p. 283 to 285 °C (water). (Found: C 77.54; H 10.88. Calc. for $C_{17}H_{29}NO$: C 77.56; H 11.02), τ (TFA) 8.4 and 8.6 (CMe₂), 6.1 (NMe₃), 2.0 and 2.2 (2H, arom., J(4H, 6) = 1.5 Hz).

2-Hydroxy-3-chloro-N,N,N-trimethylanilinium iodide (II) was prepared from 2-amino-6-chlorophenol⁹ as described in the literature.⁷ The initial product was found to have the reported m.p. 186 to 188 °C (water) but was found to contain a substantial amount of the O-methylated homologue which was removed by extraction with chloroform; m.p. 210 to 212 °C, τ (TFA) 6·1 (NMe₃), 2·4-2·9 (3H, arom.).

2-Hydroxy-5-phenyl-N,N,N-trimethylanilinium iodide (III) was prepared from 2-amino-4-phenyl-phenol in 60% yield; m.p. 206 to 207 °C (MeOH). (Found C 51.08; H 5.28. Calc. for $C_{15}H_{17}NO$ ·HI: C 50.72; H 5.11), τ (TFA) 6.2 (NMe₃), 2.4 (H-arom.).

2-Hydroxy-5-nitro-N,N,N-trimethylanilinium iodide (IV) was obtained from 2-amino-4-nitros phenol in 30% yield; yellowish red crystals m.p. 188 to 189 $^{\circ}$ C (MeOH). The elemental analysi-indicates mixed crystals of the salt and the zwitterion in the ratio 1:1. (Found: C 41.18; H 4.85.

Calc. for $C_{18}H_{24}N_4O_6$.HI: C 41·55; H 4·84), τ (TFA) 6·0 (N-Me), 2·4 (H³, J(3H, 4H) = 9 Hz), 1·5 (H⁴, J(4H, 6H) = 2·5 Hz), 1·2 (H⁶).

2-Hydroxy-3-phenyl-N,N,N-trimethylanilinium iodide (V) was obtained from 2-methoxy-3phenyl-N,N,N-trimethylanilinium iodide (XXII) which was heated in HI (d. 1.96) solution for 6 h. The product, which crystallised from the cold solution, was dark brown due to complex formation with iodine. The latter was reduced by titration with sodium thiosulphate in the stirred twophase system chloroform: H₂O (1:4). The iodine complex is readily soluble in chloroform but after iodine reduction the iodide is more soluble in water. The aqueous layer was evaporated. The residual material was extracted by heating with chloroform from which the title compound crystallised out on concentration and cooling; yield 64%, m.p. 204 to 205 °C (benzene/chloroform). (Found: C 50.91; H 5.13. Calc. for C₁₅H₁₇NOHI: C 50.70; H 5.07), τ (MeOH-d₄), 6.3 (NMe₃), 2.4–2.9 (H-arom.).

3,5-Diphenyl-4-hydroxy-N,N,N-trimethylanilinium iodide (XVI) was obtained from 2,6-diphenyl 4-aminophenol¹⁰ in 51% yield m.p. 196 to 198 °C (benzene/chloroform). (Found: C 58·43; H 5·16. Calc. for $C_{21}H_{21}$ NOHI: C 58·46; H 5·10), τ (TFA) 6·2 (NMe₃), 2·4 (2Ph, s), 2·3 (H², H⁶, s).

3,5-Di-tert-butyl-4-hydroxy-N,N,N-trimethylanilinium iodide (XVII) was prepared as reported,¹¹ m.p. 222 to 223 °C.

2-Methoxy-3-phenyl-N,N,N-trimethylanilinium iodide (XXII) was obtained in almost quantitative yield on heating 2-phenyl-6-aminophenol for 12 h with excess methyl iodide and the corresponding amount of sodium carbonate in methanol; m.p. 202 to 203 °C (water). (Found: C 52·15; H 5·59. Calc. for $C_{16}H_{20}INO$: C 52·03; H 5·42), τ (TFA) 6·4 (OMe), 6·1 (NMe₃), 2·2-2·8 (H-arom.).

3,5-Diphenyl-4-methoxy-N,N,N-trimethylanilinium iodide (XXIII) was prepared as the ether (XXII) above from 2,6-diphenyl-4-aminophenol,¹⁰ m.p. 231 to 233 °C. (Found: C 59·09; H 5·64 Calc. for $C_{22}H_{24}INO$: C 59·32; H 5·40), τ (TFA) 6·5 (OMe), 6·2 (NMe₃), 2·4 (2Ph, s), 2·2 (H², H⁶, s).

2-Methoxy-3,5-di-tert-butyl-N,N-dimethylaniline(XI). 2-Methoxy-3,5-di-tert-butyl-aniline(XXVII) (1,0 g, 0,004 mol) methyl iodide (1.8 g, 0.013 mol) and anhydrous sodium carbonate (0.45 g, 0.004 mol) in methanol (15 ml) were heated together under reflux for 24 h. The precipitated inorganic material was removed by filtration, the filtrate evaporated and the residual material crystallised from dilute ethanol (colourless needles); yield 60%, m.p. 33 to 34°C. (Found: C 77.43; H 10.70. Calc. for $C_{17}H_{28}NO$: C 77.56; H 11.02), τ (TFA) 8.5 and 8.6 (CMe₃), 6.5 and 6.6 (NMe₂), 6.0 (OMe), 2.6 (H⁴, J(4H, 6H) = 2.0 Hz), 2.2 (H⁶).

2-Trideuteriomethoxy-3,5-di-tert-butyl-N,N-dimethylaniline (XXIV) was prepared as above from 2-trideuteriomethoxy-3,5-di-tert-butylaniline (XXVIII).

2-Methoxy-3,5-di-tert-butylaniline (XXVII). 2,4-Di-tert-butyl-6-nitroanisole (10.5 g, 0.04 mol) was dissolved in ethanol (200 ml). Tin powder (20 g, 0.17 mol) and concentrated HCl (100 ml) were added portion-wise at such a rate that the ethanolic solution was kept boiling. The resultant mixture was then heated under reflux until disappearance of the yellow colour (1.5 h). After filtration the filtrate was concentrated, water added, the suspension neutralised with sodium carbonate and the title compound isolated by ether extraction; yield 68%, colourless needles from dilute ethanol m.p. 80 to 81 °C. (Found: C 76.60; H 10.62. Calc. for C₁₅H₂₅NO: C 76.59; H 10.63), τ (TFA) 8.5 and 8.6 (CMe₃), 2.6 (H⁴, J(4H, 6H) = 1.5 Hz), 2.2 (H⁶).

2-*Trideuteriomethoxy*-3,5-*di*-tert-*butylaniline* (XXVIII) was prepared as XXVII above from 2,4di-*tert*-butyl-6-nitro-1-trideuteriomethoxybenzene (XXVI).

2,4-Di-tert-butyl-6-nitro-1-trideuteriomethoxy-benzene (XXVI) was obtained from 2,4-di-tertbutyl-6-nitrophenol as sodium salt in dilute ethanol using deuteriated dimethyl sulphate as methylating agent; yield 60%. The nondeuteriated title compound has previously been described by nitration of 2,4-di-tert-butylanisole.¹²

O-Methylation by fusion

The zwitterions (I, II and XVII) (0.001 mol) were heated above their melting points and kept at this temperature for 30 min. The cold reaction product was digested with 2N NaOH for a few hours before dissolution in ether. The washed and dried ethereal solution was evaporated and the residue distilled.

2-Methoxy-3-chloro-N,N-dimethylaniline (XII), from II in 51% yield. This compound has previously been prepared by N-methylation of the corresponding aniline.¹³

2-Methoxy-5-phenyl-N,N-dimethylaniline (XIII), from III in 69% yield. XIII was analysed as picrate, m.p. 194 to 195 °C. (Found: C 55.00; H 4.04. Calc. for $C_{21}H_{20}N_4O_8$: C 55.26; H 4.38), τ (TFA) 7.0 and 6.9 (NMe₂), 6.3 (OMe), 2.5 to 3.2 (H-arom.).

3,5-Di-tert-butyl-4-methoxy-N,N-dimethylaniline (XXI), from XVII in 75% yield. The oily product was analysed as picrate, m.p. 181 to 182 °C. (Found: C 56.07; H 6.40. Calc. for $C_{23}H_{32}N_4O_8$: C 56.09; H 6.50), τ (TFA) 8.50 (CMe₃), 6.6 and 6.5 (NMe₂), 6.1 (OMe), 2.5 (H², H⁶, s).

Ether formed by pyrolysis in the mass spectrometer. The ethers (XV) and (XX) were generated from the respective anisidinium derivatives (XXII) and (XXIII) on direct insertion with sample temperature 220 °C. The ether (XIV) was generated from its zwitterion (IV) on direct insertion at 280 to 300 °C.

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