

Substituent effects in the gas-phase pyrolysis of 4-(*N*-arylamino)-1-butyl acetate and 5-(*N*-arylamino)-1-pentyl acetate

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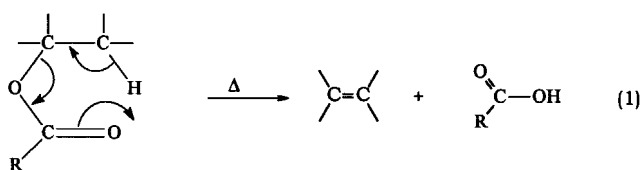
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ABSTRACT: A kinetic study of the gas-phase pyrolysis of 4- and 5-(*N*-arylamino)-1-butyl and -1-pentyl acetate was made. Each ester was pyrolysed at five or six different temperatures and over a temperature range not less than 50 °C. These reactions were homogeneous and unimolecular. The reactivities of these compounds were compared with those of the parent compounds 4- and 5-(*N*-phenyl)-1-butyl and -1-pentyl acetate and with each other. The products of the decomposition reaction of these compounds suggest an anchimeric assistance of the amino substituent for a *trans* elimination, indicating that an ion-pair type of mechanism may be operating during the process of elimination. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: gas-phase pyrolysis; 4-(*N*-arylamino)-1-butyl acetate; 5-(*N*-arylamino)-1-pentyl acetate; substituent effects

INTRODUCTION

Esters containing non-vinyl β -hydrogen atoms in the alkyl group undergo elimination to an alkene and a carboxylic acid, this takes place most readily if the hydrogen atom and acyloxy group are *cis* to each other:¹

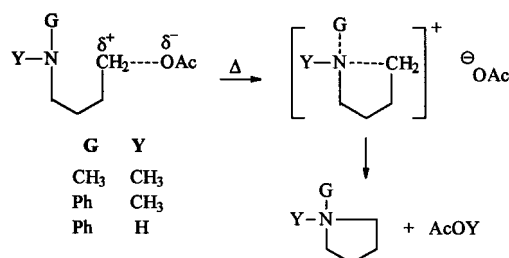


The cyclic nature of reaction (1), first proposed by Hurd and Blunck,² is now recognized as a symmetry-allowed 1,5-hydrogen shift, of which many examples are known. This mechanism was shown to be consistent with the *cis* character of the elimination reaction, which has been demonstrated by a number of experiments. The most elegant of these is the pyrolysis of *threo*- and *erythro*-2-deutero-1,2-diphenylethyl acetate.³

An unusual homogeneous, unimolecular *trans* elimination of an ester in the gas phase has been described in the pyrolytic kinetics of 4-(*N,N*-dimethylamino)-1-butyl

acetate, which was found to give *N*-methylpyrrolidine and methyl acetate.⁴ This result suggested an anchimeric assistance provided by the (CH₃)₂N group and the mechanism was explained in terms of a modest intimate ion-pair type of intermediate, where the acetoxy leaving group proceeds by intramolecular solvation to take up a CH₃ group from (CH₃)₂N to give the products.

This was followed by our recent work⁵ which examined the extent to which the presence of a phenyl group at the nitrogen atom may affect the participation of the amino group in the gas-phase elimination of 4-(*N*-methyl-*N*-phenylamino)-1-butyl acetate and 4-(*N*-phenylamino)-1-butyl acetate [Ph(CH₃)N(CH₂)₄OAc and PhNH(CH₂)₄OAc, respectively]. Also, the comparative influence of the N-atom on neighboring group participation was made clear from the kinetic results, which suggested that the lower the nucleophilicity of the amino substituent the less is its anchimeric assistance in the stabilization of the polarized C—O bond in the five-membered transition state (Scheme 1).

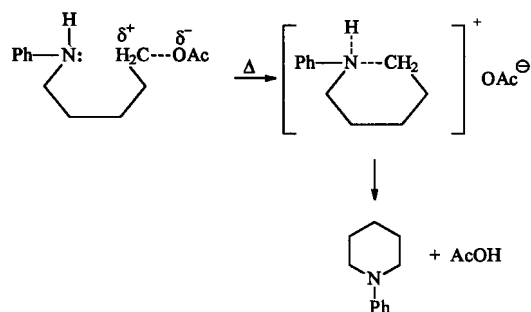


Scheme 1

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The above is in agreement with our recent findings on the gas-phase pyrolysis of 5-(*N*-phenylamino)-1-pentyl acetate, which took place via a six-membered transition state to produce *N*-phenylpiperidine (Scheme 2).



Scheme 2

In order to learn more about this interesting neighboring group participation in the gas-phase pyrolysis of amino acetates, the effects of different substituents on the reaction rate were evaluated. We therefore prepared the following substrates and measured their rates of gas-phase pyrolysis: $\text{ArNH}(\text{CH}_2)_4\text{OAc}$ and $\text{ArNH}(\text{CH}_2)_5\text{OAc}$, where $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, $4\text{-MeC}_6\text{H}_4$ and $4\text{-ClC}_6\text{H}_4$.

RESULTS AND DISCUSSION

The kinetic data and Arrhenius $\log A$ and E_a values for the present series of compounds are given in Table 1. Each of the substrates gave excellent and reproducible first-order kinetics. The homogeneity of the reaction was tested by carrying out several runs in a reaction tube with a surface-to-volume ratio of 6.0 relative to that of the normal reaction tube. The results show that the change in the rate constant was within experimental error. Hence an increase in the surface area of more than 50% caused a negligible increase in the reaction rate constant. The pyrolysis reaction of butyl and pentyl esters proceeds according to the previously suggested pathways (Scheme 1) to produce *N*-arylpiperidine and *N*-arylpiperidine, respectively, which were perfectly characterized by gas chromatography–mass spectrometry (GC–MS) and NMR spectroscopy.

The present and reported kinetic data in Table 1 together with the relative rate constants in Table 2 are discussed on the basis of the elimination pathway represented in Scheme 1. The kinetic data and product analysis reveal the following features of this pyrolysis reaction.

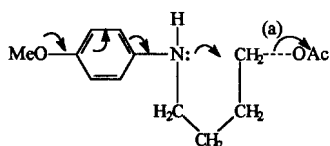
Table 1. Kinetic data for the gas-phase pyrolysis of $\text{ArNH}(\text{CH}_2)_n\text{OAc}$

<i>n</i>	Ar	<i>T</i> (K)	$10^4 k(\text{s}^{-1})$	$\log [A(\text{s}^{-1})]$	E_a (kJ mol ^{−1})
5	4-MeOC ₆ H ₄	558.6	1.74	11.95 ± 0.05	167.95 ± 0.58
		574.6	4.82		
		583.7	8.41		
		588.8	11.10		
		602.8	24.90		
5	4-MeC ₆ H ₄	580.9	1.84	10.82 ± 0.05	161.90 ± 2.54
		589.7	2.92		
		605.3	6.75		
		611.4	9.91		
		625.0	19.30		
5	4-ClC ₆ H ₄	571.4	0.66	12.69 ± 0.17	184.51 ± 1.90
		586.3	1.80		
		599.8	4.19		
		614.0	9.30		
		628.2	22.70		
4	4-MeOC ₆ H ₄	537.2	2.38	13.05 ± 0.07	171.43 ± 0.75
		543.4	3.73		
		549.1	5.52		
		558.9	10.80		
		573.0	26.30		
4	4-MeC ₆ H ₄	536.1	2.69	10.15 ± 0.16	140.78 ± 0.18
		540.1	3.43		
		546.4	5.16		
		567.7	15.40		
		572.3	20.70		
4	4-ClC ₆ H ₄	578.5	27.40	11.08 ± 0.23	159.47 ± 2.61
		568.1	2.54		
		585.7	7.32		
		588.8	8.57		
		592.6	10.60		
		606.0	20.90		

Table 2. Rate constants at 600 K and relative rates of thermal gas-phase elimination reactions of $\text{XC}_6\text{H}_4(\text{CH}_2)_n\text{OAc}$

X	<i>n</i> = 4		<i>n</i> = 5	
	$10^4 k \text{ (s}^{-1}\text{)}$	k_{rel}	$10^4 k \text{ (s}^{-1}\text{)}$	k_{rel}
4-MeO	133.4	460.0	21.3	280.3
4-Me	78.9	272.1	5.25	69.1
4-Cl	15.6	53.8	4.22	55.5
H	0.29	1.0	0.08	1.0

1. The overall reactivities are the result of (i) the electronic synergism involving the availability of the lone pair of electrons on the nitrogen atom (Scheme 2), which in turn effects the polarity of bond (a) (see Scheme 3) and (ii) the stabilizing influences associated with the product formation.
2. The rate constants of the thermal gas-phase elimination reactions (Table 2) reveal large differences in the relative reactivities with the pentyl esters, which are less reactive than their butyl equivalents, e.g. 5-[*N*-(4-methylphenylamino)]-1-pentyl acetate is 15 times less reactive than its butyl counterpart. This rate enhancement of butyl over pentyl esters is attributed to the fact that the five-membered structure is more favored than the six-membered structure in the neighboring group participation.⁶
3. Reactivity is increased by the mesomerically electron-donating 4-methoxy substituent. This is because the methoxy substituent will enhance the nucleophilicity of the nitrogen atom, which will lead to a large anchimeric assistance in the stabilization of the polarized $\text{C}_\alpha\text{—O}$ bond in the transition state (Scheme 3). This argument is well justified when the methoxy group is replaced by a chloro substituent.

**Scheme 3.** Effective participation of the lone pair of electrons in the gas-phase pyrolysis of 4-[*N*-(4-methoxyphenylamino)]-1-butyl acetate

4. The most reactive compound in this series is 4-MeOC₆H₄NH(CH₂)₄OAc. This is to be expected as a consequence of the electronic effect of the methoxy group on the availability of the lone pair of electrons on the nitrogen atom and accordingly on intramolecular solvation of the acetoxyl leaving group, together with the effective participation of the neighboring group in the formation of a five-membered structure (*N*-*p*-methoxyphenylpyrrolidine) over a six-membered structure (*N*-*p*-methoxyphenylpiperidine).

EXPERIMENTAL

Synthesis. A solution of 4-bromobutyl acetate or 5-bromopentyl acetate (0.05 mol) and the substituted aniline (0.05 mol) in 20 ml of toluene was refluxed for 9–12 h. The reaction mixture was acidified with 10% hydrochloric acid. The toluene layer was separated and the aqueous layer was basified by slow addition of solid sodium hydrogencarbonate. It was then repeatedly extracted with diethyl ether, dried over sodium sulfate and concentrated *in vacuo*, followed by distillation under reduced pressure to give the following compounds.

4-Amino-*N*-(*p*-methoxyphenyl)butyl acetate, solidified after solvent evaporation and crystallized from benzene–light petroleum in 55% yield, m.p. 66°C. Anal. Calcd for C₁₃H₁₉NO₃ (237): C, 65.82; H, 8.01; N, 5.91. Found: C, 66.15, H, 7.96; N, 6.01%. ¹H NMR (CDCl₃): δ 1.76–1.82 (s, 4H, 2CH₂), 2.04 (s, 3H, CH₃), 2.92–3.22 (t, 2H, CH₂), 3.74 (s, 3H, CH₃), 3.94–4.21 (t, 2H, CH₂); 6.54–6.82 (dd, 4H, ArH). MS: *m/z* 237 (M⁺), 176 (M – CH₃CO₂H), 136 [100%, (CH₃OC₆H₄NHCH₂)⁺], 123 (CH₃OC₆H₄NH₂).

4-Amino-*N*-(*p*-methylphenyl)butyl acetate, solidified after solvent evaporation and crystallized from diethyl ether–light petroleum in 60% yield, m.p. 69–70°C. Anal. Calcd for C₁₃H₁₉NO₂ (221): C, 70.58; H, 8.59; N, 6.33. Found: C, 70.46, H, 8.45; N, 6.23%. ¹H NMR (DMSO): δ 1.48–1.75 (m, 4H, 2CH₂), 2.01 (s, 3H, CH₃), 2.88–3.11 (t, 2H, CH₂), 3.65 (s, 3H, Ar-CH₃), 3.91–4.16 (t, 2H, CH₂), 6.43–6.80 (q, 4H, ArH). MS: *m/z* 221 (M⁺), 160 (M – CH₃CO₂H), 120 [100%, (CH₃C₆H₄NHCH₂)⁺], 106 [(CH₃C₆H₄NH)⁺].

4-Amino-*N*-(*p*-chlorophenyl)butyl acetate, b.p. 168–170°C (1 mbar), solidifies while distilling to a pale yellow semi-solid in 62% yield, m.p. 59–60°C. Anal. Calcd for C₁₂H₁₆ClNO₂ (241.5): C, 59.62; H, 6.63; N, 5.79. Found: C, 59.47, H, 6.79; N, 5.79%. ¹H NMR (DMSO): δ 1.45–1.76 (m, 4H, 2CH₂), 1.99 (s, 3H, CH₃), 2.90–3.08 (t, 2H, CH₂), 3.95–4.11 (t, 2H, CH₂), 5.66 (br s, 1H, NH), 6.49–6.60 (dd, 2H, ArH), 7.01–7.12 (dd, 2H, ArH). MS: *m/z* 241.1, 243 (M⁺), 207 [(M – Cl) + 1], 180, 182 (M – CH₃CO₂H), 140, 142 [100% (ClC₆H₄NHCH₂)⁺], 127, 129 (ClC₆H₄NH₂).

5-Amino-*N*-(*p*-methoxyphenyl)pentyl acetate, distilled at b.p. 198°C (1.3 mbar) in 50% yield. Anal. Calcd for C₁₄H₂₁NO₃ (251): C, 66.93; H, 8.36; N, 5.57. Found: C, 66.80, H, 8.30, N, 5.62%. ¹H NMR (CDCl₃): δ 1.4–1.6 (m, 6H, 3CH₂), 2.04 (s, 3H, CH₃), 2.85 (s, 1H, NH, exchanges with D₂O), 3.10–3.20 (t, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.98–4.09 (t, 2H, CH₂), 6.48–6.84 (m, 4H, ArH). MS: *m/z* 251 (M⁺), 192 (M – OCOCH₃), 176 [(M – CH₃CO₂H) – CH₃], 136 [100%, (CH₃OC₆H₄NHCH₂)⁺].

5-Amino-*N*-(*p*-methylphenyl)pentyl acetate, distilled at 180°C (1.5 mbar) in 51% yield. Anal. Calcd for C₁₄H₂₁NO₂ (235): C, 71.48; H, 8.93; N, 5.95. Found: C, 71.21, H, 8.72, N, 6.26%. ¹H NMR (CDCl₃): δ 1.22–1.78

(m, 6H, 3CH₂), 2.03 (s, 3H, CH₃), 2.90–3.07 (t, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.96–4.09 (t, 2H, CH₂), 4.64 (s, 1H, NH, exchanges with D₂O), 6.48–6.88 (m, 4H, ArH). MS: *m/z* 235 (M⁺), 174 (M – CH₃CO₂H₂), 120 [100%, (CH₃C₆H₄NHCH₂)⁺], 106 [(CH₃C₆H₄NH)⁺].

5-Amino-*N*-(*p*-chlorophenyl)pentyl acetate, distilled at 210 °C (0.5 mbar) in 55% yield. Anal. Calcd for C₁₃H₁₈NO₂Cl (255.5): C, 61.05; H, 7.05; N, 5.48. Found: C, 61.09, H, 6.80, N, 5.66%. ¹H NMR (DMSO): δ 1.42–1.78 (m, 6H, 3CH₂), 2.02 (s, 3H, CH₃), 2.85–3.37 (t, 2H, CH₂), 3.85–4.06 (t, 2H, CH₂), 6.51–6.62 (d, 2H, ArH), 7.04–7.15 (d, 2H, ArH). MS: *m/z* 255, 257 (M⁺), 194, 196 [(M – CH₃CO₂H₂)], 140, 142 [100%, (ClC₆H₄NHCH₂)⁺], 127, 129 (ClC₆H₄NH₂).

Instrumentation. The pyrolyzer was a CDS custom-made unit. It consisted of an insulated aluminum block to ensure a low temperature gradient and resistance to high temperature, a Pyrex reaction vessel to fit in a groove along the cylindrical axis of the block, a platinum resistance thermometer and a thermocouple connected to a microprocessor. The temperature of the block was controlled by means of a Eurotherm 093 precision temperature regulator. The temperature setting was achieved with a digital switch which allowed temperature read-out accurate to ±0.5 °C. The actual temperature of the reactor groove was measured by means of a Comark microprocessor thermometer. Comparative quantitative analyses of reaction mixtures were carried out using a high-performance liquid chromatographic (HPLC) system equipped with a UV-visible detector (Bio-Rad, Shimadzu SPD-10AV). The HPLC accessories included an LC-8 column (25 cm × 4.6 mm i.d.). Samples were injected with a Supelco 5 µm precision syringe.

Characterization of the substrates and the constituent fragments of the pyrolysates included elemental analysis, GC-MS, Fourier transform (FT) IR and ¹H NMR spectroscopic analysis. The GC-MS instrument included a Finigan MAT INCOS XL quadrupole mass spectrometer. FT-IR spectra were measured with a Perkin-Elmer Model 2000 spectrometer and ¹H NMR spectra with a Bruker AC-80 spectrometer. The elemental analyzer was a LECO CHNS-932 unit.

Kinetic runs and data analysis. Dilute (ppm) standard solutions of the substrates in a suitable solvent (e.g. acetonitrile) were prepared and an internal standard (e.g. chlorobenzene) was added to each solution. Care was taken to ensure that both the solvents and the internal standards were not pyrolyzable under the conditions of the reaction. Further, the standard solutions used in the kinetic runs always comprised a mixture in which the substrate gave a peak one third higher than that of the internal standard in the analytical HPLC trace. Preparation of a standard solution allowed several kinetic runs to be performed on the same reaction mixture.

A sample (0.2 ml) of the standard solution was placed in the reaction tube (9 ml) and the contents were sealed under vacuum. The tube was placed swiftly in the pyrolyzer which had been preheated to a threshold temperature that together with a convenient length of reaction time would allow only 10–20% pyrolysis. The contents of the reaction tube were then analyzed using HPLC. For each substrate, the rate coefficient represents an average from triplicate runs with a rate agreement to within ±2%. Rates were measured at regular intervals of 1–10 °C over a 46–50 °C temperature range and up to ≥95% reaction.

Rates were reproduced using tubes packed with glass helices in order to increase the reactor surface up to about ninefold. This precaution was to test for reactor surface effects. In addition, rates were measured in the presence and absence of free-radical scavengers (e.g. cyclohexene) to confirm the non-involvement of free radical pathways.

The rate coefficients were calculated using the expression $kt = \ln(a_0/a)$ for first-order reactions. The Arrhenius parameters were obtained from a plot of $\log k$ vs $1/T$ (K). The elimination rate constant at T is given by

$$\log k = \log[A(s^{-1})] - E_a(\text{kJ mol}^{-1})/4.574T(\text{K})$$

Product analysis. The products analyzed were for pyrolyses conducted at temperatures commensurate with those of the kinetic measurements. No secondary decomposition was observed for any of the compounds under study. In both the kinetic runs and product analysis, the initial conversion of 10–20% and reaction extent of ≥95% pyrolysis were maintained.

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