Gas-Phase Pyrolytic Reactions of N-Ethyl, N-Isopropyl, and N-*t*-Butyl Substituted 2-Aminopyrazine and 2-Aminopyrimidine

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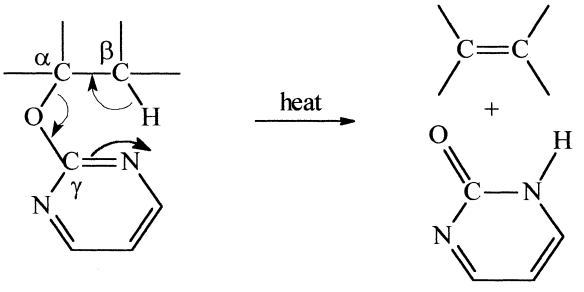
ABSTRACT: The rates of gas-phase elimination of N-ethyl (1), N-isopropyl (2), N-*t*-butyl (3) substituted 2-aminopyrazine and N-ethyl (4), N-isopropyl (5), and N-*t*-butyl (6) substituted 2-aminopyrimidine have been measured. The compounds undergo unimolecular first-order pyrolytic reactions. The relative rates of the primary : secondary : tertiary alkyl homologues at 600 K are 1 : 14.4 : 38.0 for the pyrazines and 1 : 20.8 : 162.5 for the pyrimidines, respectively. The reactivities of these compounds have been compared with those of the alkoxy analogues and with each other. Product analyses, together with the kinetic data, were used to outline a feasible pathway for the elimination reaction of the compounds under study. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 32: 403–407, 2000

INTRODUCTION

In an earlier study, one of the authors showed that both 2-alkoxypyrimidines and 2-alkoxypyrazines react by a unimolecular first-order thermal elimination process to give the alkenes and 2(1*H*)-pyrimidinone and 2(1*H*)-pyrazinone, respectively, according to the mechanism shown in Scheme I [1].



Scheme I Cyclic transition state formulation of elimination pathway of 2-alkoxypyrimidine.

The importance of the nucleophilicity of the nitrogen moiety in the alkoxy-heterocycles and its suscep-

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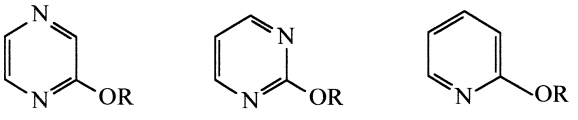
tibility to modification by ring structure has been assessed in part from consideration of the dual pathway available for transmission of the effect of replacement substituents in the heteroaromatic ring:



R = Et , iPr or Bu^t

Further, the spread of rates for the pyrolysis of both the pyrazines and pyrimidines is found to be wider than for the pyridines [2]. This suggested that the transition state for elimination in the former two systems has more carbocationic character, with the two N replacement substituents augmenting charge development. Examples of gas-phase reactivity of heteroatoms as replacement substituents in heteroaromatic compounds have been reported [3], and the electron-deficient character of the aza and diazabenzenes has for sometime been recognized [4]. To provide further insight as to the nature of the transition state of the reaction, we have in the present study sought to compare the effect of replacing the oxygen atom of the alkoxy heterocycles by the NH moiety of the amino analogues on the rates of pyrolysis of these heteroaromatic compounds. Accordingly, we prepared the ethyl, isopropyl and *t*-butylpyrazines and pyrimidines (1–6) and measured their rates of thermal gas-phase elimination in what is believed to be the first study of the structural

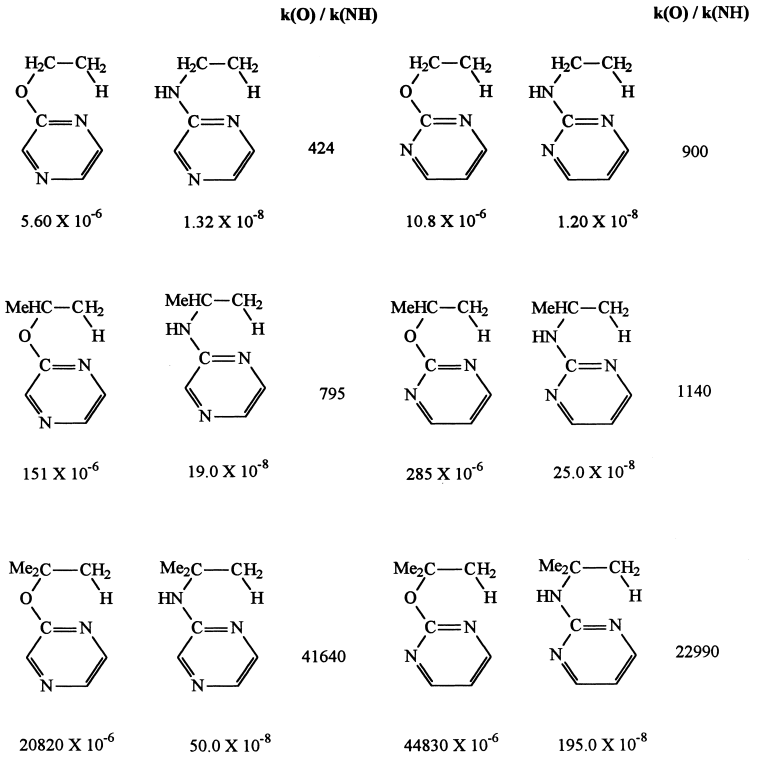
Table I Kinetic Data and Arrhenius Parameters for Pyrolysis of Compounds (1–6)

Cpd.	*T*(K)	10^4 *k*(s^{-1})	log *A*(s^{-1})	E_a(kJ mol^{-1})
(1)	714.4	0.25	12.63 ± 0.05	235.68 ± 0.78
	732.8	0.68		
	750.5	1.68		
	768.8	4.15		
	782.4	7.86		
	786.4	9.45		
(2)	685.5	0.045	12.28 ± 0.01	218.20 ± 0.14
	703.1	1.17		
	721.6	3.04		
	736.9	6.51		
	751.7	13.14		
	764.9	24.01		
(3)	644.8	0.08	11.34 ± 0.01	202.62 ± 0.15
	661.6	0.22		
	678.3	0.54		
	693.5	1.19		
	706.8	2.33		
	719.2	4.22		
	729.4	6.78		
	739.6	10.76		
(4)	755.0	1.62	12.21 ± 0.00	231.20 ± 0.04
	761.9	2.26		
	772.1	3.66		
	786.6	7.12		
	796.7	11.14		
	810.0	19.76		
(5)	726.0	5.16	12.49 ± 0.00	219.39 ± 0.03
	739.6	10.06		
	755.9	21.71		
	771.4	43.79		
	785.7	81.75		
(6)	645.1	0.36	12.39 ± 0.00	207.92 ± 0.06
	666.6	1.25		
	679.7	2.58		
	695.5	5.96		
	708.4	11.47		
	720.2	20.46		

and electronic effects arising from the replacement of O (alkoxy group) by NH (amino group) in this type of compound.

RESULTS AND DISCUSSION

The kinetic data and Arrhenius log A/s^{-1} and E_a/kJ mol^{-1} for the present series of compounds (1–6) are given in Table I. The values of log A/s^{-1} lie within a narrow range of 12.41 ± 0.21, whereas the values of the energy of activation vary between 203–236 kJ mol^{-1}. Each of the substrates gave excellent and reproducible first-order kinetics, with strict linearity up to >95% reaction over a temperature range of 67 ± 12 K. The homogeneity of the reaction was tested by comparing the kinetic rate using an empty reaction tube with that of a similar vessel packed with glass helices. The results show that the change in the rate of reaction was within experimental error. Thus, an increase in surface area of more than 50% caused a negligible change in reaction rate. It is noteworthy that the values obtained for the Arrhenius parameters are typical of polar homogeneous pyrolytic gas-phase reactions [5]. Rates of reaction at 600 K are recorded in Scheme II.



Scheme II. Relative Reactivities at 600 K of
2-alkoxypyrazines / 2-N-alkylaminopyrazine & 2-alkoxypyrimidines / 2-N-alkylaminopyrimidines

The rate constants at this temperature allow direct comparison with earlier results for related compounds and are calculated using the equation: $\log k = \log A - Ea/19.148 \times 600$.

The kinetic data together with the results of analysis of the products of reaction reveal the following:

1. The gas-phase elimination reaction of the 2-*N*-alkylamino and 2-alkoxypyrazines and their pyrimidine analogues involve a cyclic 6-membered transition state (Scheme I).
2. In both the pyrazine and the pyrimidine series, the alkylamino compounds are consistently less reactive than their alkoxy counterparts, involving rate factors of ca $4.2 \times 10^2 - 4.2 \times 10^4$. This is explained in terms of the greater contribution to reactivity provided by the more polar C_α—O bond in the alkoxy moiety compared with the less polar C_α—NH bond of the alkylamino group. The effect of bond polarity on relative reactivity has been observed to follow the trend: C_α—O > C_α—N > C_α—C [6]. Further,

the polarity of the transition state, as indicated by the rate ratio of $1^0:2^0:3^0$ *N*-alkylaminopyrazines (ca 1 : 14 : 38) being smaller than that of *N*-alkylaminopyrimidines (ca 1 : 21 : 163), is lower for the former group of compounds. This result is to be expected, since electron withdrawal by the two *ortho*-N replacement substituents of the electron-deficient pyrimidine nucleus is greater than for the ortho- and meta-nitrogens of the pyrazine isomer. The electronic effect is both inductive and mesomeric in origin, and both modes act in favor of the pyrimidine compounds. The polarity of the transition state should, therefore, be greater for the pyrimidines, as appears to be the case. The results for the considerably more polar transition state of the corresponding 2-alkoxy analogues indicate larger magnitudes of relative rates, but closer ranges of rate ratios: $1:27:3.7 \times 10^3$ for the alkoxypyrazines, and $1:26:4.2 \times 10^3$ for the alkoxypyrimidines. Apparently, bond polarity and the concomitant transition state carbocation character are advanced well enough in the alkoxy moiety in both the pyrazine and pyrimidine compounds for the electron-withdrawing effect of the N replacement substituents to make much difference to relative reactivity of analogues.

3. The rate factors (Scheme II) of the alkoxy/alkylamino analogues (k(O)/k(NH)) steadily increases with branching in the alkyl group: 424, 795, 41 640 for the pyrazine series, and 900, 1140, 22 990 for the pyrimidine series. This trend parallels the relative stabilizing influence of the alkyl groups on the carbocationic transition state and reflects the difference in polarity between the C_α—O and C_α—NH bonds. The dramatic drop in the rate factor between the *t*-butyl compounds and their ethyl homologues further confirms the effect of bond polarity and highlights the much greater stability of the incipient *t*-butyl carbocation. Similar reactivity patterns have been reported for compounds of comparable structure in the alkyl group [6].

EXPERIMENTAL

Kinetic Studies

Reaction Set-up. Preliminary kinetic results were obtained on a system featuring a Eurotherm 093 pyrolysis unit coupled to a Perkin Elmer Sigma 115 gas chromatograph. The kinetic data reported are from a reactor set-up including: (i) HPLC (Bio-rad Model 2700) fitted with a UV/VIS detector (Bio-rad Model 1740); HPLC: Column LC-8, 25 cm, 4.6 mm, 5 μm (Supelco); and CDS custom-made pyrolysis unit for the thermolysis reactions. The pyrolysis tube is jacketed by an insulating aluminum block fitted with a platinum resistance thermometer and a thermocouple connected to a Comark microprocessor thermometer.

Kinetic Runs and Data Analysis. Aliquot parts (0.2 ml) of very dilute solutions (ppm) of neat substrates in acetonitrile as solvent and chlorobenzene as internal standard were pipetted into the reaction tube, which was then sealed under vacuum (0.28 mbar) and the tube then placed inside the pyrolyzer for 600 s at a temperature where 10–20% pyrolysis is deemed to occur. The contents of the tube were analyzed using the HPLC probe.

At least three kinetic runs were repeated for each 5–10°C rise in temperature of the pyrolyzer and for the same time interval until 90–95% pyrolysis was achieved. The rates were followed over a temperature range exceeding 55 K, and the rate coefficients were calculated using the expression for a first-order reaction: $kt = \ln a_0/a$. The Arrhenius parameters were obtained from a plot of log k vs. $1/T$(K).

Product Analysis

Flow Technique. Solutions of substrates in chlorobenzene were passed down a 1 m reactor column packed with helices [7]. The column was heated to temperatures comparable to those used in the kinetic investigations. The products of pyrolysis were swept through the column using a stream of nitrogen gas, and the effluents were trapped in a glass coil surrounded by a jacket of dry ice. The material collected on the walls of the trap (glass coil) was crystallized and analyzed by NMR spectroscopy.

Synthesis

2-(N-Ethylamino)pyrazine (1). Reaction of 2-chloropyrazine in absolute ethanol with a threefold excess of 2 molar solution of ethylamine in methanol at 110°C for 72 h gave after *in vacuo* concentration, the amine hydrochloride salt, which was taken up in ether, filtered, and washed repeatedly with ether. 2-(N-ethylamino)pyrazine (45%) was obtained after concentration of the ether layer, *in vacuo*, b.p. 62°C at 0.16 mbar. δ_H ($CDCl_3$) 1.1 (3H, t, CH_3), 3.3 (2H, q, CH_2), 7.0 (1H, s, NH), 7.6–7.9 (3H, m, pyrazine). (Found: C, 58.6; H, 7.5; N, 33.9. Calc. for $C_6H_9N_3$: C, 58.5; H, 7.3; N, 34.1%).

2-(*N*-Isopropylamino)pyrazine (2). Reaction of 2-chloropyrazine in absolute ethanol with isopropylamine at 110°C for 72 h. gave after *in vacuo* concentration, the amine hydrochloride salt, which was taken up in ether, filtered, and washed repeatedly with ether. 2-(*N*-isopropylamino)pyrazine (40%) was obtained after concentration of the ether layer, *in vacuo*, m.p. 53°C. δ_H ($CDCl_3$); 1.2 (6H, d, 2Me), 4.0(1H, m, $HCMe_2$); 6.8 (1H, s, NH), 7.6–7.9 (3H, m, pyrazine). (Found: C, 61.2; H, 8.2; N, 30.9. Calc. for $C_7H_{11}N_3$: C, 61.3; H, 8.0; N, 30.7%).

2-(N-t-Butylamino)pyrazine (3). Reaction of 2-chloropyrazine in absolute ethanol with *t*-butylamine at 110°C for 15 h in a sealed tube gave after *in vacuo* concentration, the amine hydrochloride salt, which was taken up in ether, filtered, and washed repeatedly with ether. 2-(N-*t*-butylamino)pyrazine (36%) was obtained after concentration of the ether layer, *in vacuo*, m.p. 86°C. δ_H ($CDCl_3$), 1.4 (9H, s, 3Me), 6.7 (1H, s, NH), 7.6–7.9 (3H, m, pyrazine). (Found: C, 63.9; H, 8.4; N, 27.9. Calc. for $C_8H_{13}N_3$: C, 63.7; H, 8.4; N, 27.8%).

2-(N-Ethylamino)pyrimidine (4). Reaction of 2-chloropyrimidine in absolute ethanol with ethylamine in methanol at 110°C for 5 h gave after normal work-up 2-(*N*-ethylamino)pyrimidine (90%) m.p. 49–50°C., lit. m.p. 50–51°C [8].

2-(N-Isopropylamino)pyrimidine (5). Reaction of 2-chloropyrimidine with isopropylamine in absolute ethanol at 110°C for 18 h gave after *in vacuo* concentration, the amine hydrochloride salt, which was taken up in ether, filtered, and washed repeatedly with ether. 2-(*N*-isopropylamino)pyrimidine (80%) was obtained after *in vacuo* concentration of the ether layer and recrystallization from petroleum ether, m.p. 29–30°C, $\delta(CDCl_3)$, 1.2 (6H, d, 2Me), 4.1 (1H, m, $HCMe_2$), 6.5 (1H, t, C_5-pyrimidine), 6.9 (1H, s, NH), 8.3 (2H, d, C_4- and C_6-pyrimidine). (Found: C, 61.5; H, 8.1; N, 30.6. Calc. for $C_7H_{11}N_3$: C, 61.3; H, 8.0; N, 30.7%).

2-(N-t-Butylamino)pyrimidine (6). Reaction of 2-chloropyrimidine with *t*-butylamine in absolute ethanol at 110°C for 24 h gave after normal work-up 2-(N-*t*-butylamino)pyrimidine (80%) m.p. 69–70°C, lit. m.p. 71°C [9].

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