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Kinetics and mechanism of thermal gas-phase elimination of α- and β- (*N*-arylamino)propanoic acid: experimental and theoretical analysis

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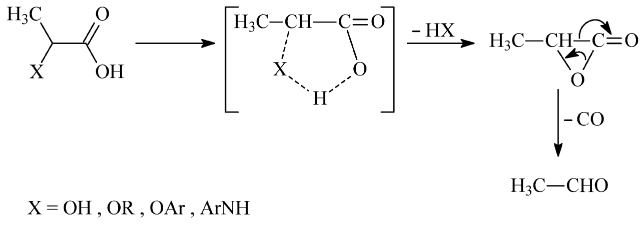
Abstract—2-(*N*-Phenylamino)propanoic acid **1a** and 3-(*N*-phenylamino)-propanoic acid **2a** together with four of their aryl analogues were pyrolysed in the gas-phase. The reactions were homogeneous and free from catalytic and radical pathways. Analysis of the pyrolysate of **1** showed the elimination products to be carbon monoxide, acetaldehyde and aniline, while the pyrolysate of **2** reveals the formation of acrylic acid in addition to aniline. Theoretical study of the pyrolysis of **2** using an ab initio SCF method lend support to a reaction pathway involving a 4-membered cyclic transition state.

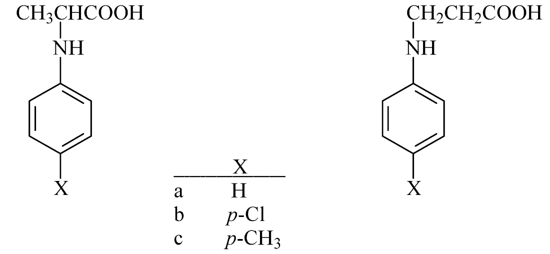
1. Introduction

We have recently reported on the kinetics and mechanism of thermal gas-phase elimination of α-substituted carboxylic acids, namely 2-phenoxypropanoic acid together with five of its aryl derivatives; phenylthio and *N*-phenylamino analogues were also investigated.[1] The reaction pathway is considered to involve a cyclic five-membered transition state associated with elimination of HX and formation of an α-lactone intermediate (Scheme 1). The effect of the α-substituent (X) is related to the basicity of X.



Scheme 1.

In this study, we look at the pyrolysis reaction of 2-(*N*-arylamino)propanoic acid **1a–c** and 3-(*N*-arylamino)propanoic acid **2a–c**; the two systems are α- and β-derivatives of propanoic acid. Substituents which make up the aryl moiety for **1a** and **2a**, phenyl group; for **1b** and **2b**, *p*-chlorophenyl for **1c** and **2c** *p*-methylphenyl group.



	X
a	H
b	*p*-Cl
c	*p*-CH_3

2. Results and discussion

2.1. Kinetics

Percent (10–20%) pyrolysis at the reaction temperature is used to evaluate the rate constant of reaction on the basis of HPLC retention data. Each recorded rate constant represents an average from at least three kinetic runs, which are in agreement to within ±2%. Rate coefficients were determined at different temperatures of 5–10 °C intervals for ≥95% reaction. The kinetic measurements of each substrate were followed over a temperature range of >50 K, an experimental requirement in thermal gas-phase elimination studies. The homogeneity of the reaction was tested by comparing the kinetic rate using an empty carbonized tube with that of similar vessel packed with glass helices. The results show that no pyrolysis occurred due to activation at the reactor surface. Since six-fold change in the amount of substrate used per kinetic run gave no significant change in rate coefficient, these reactions were deemed to be of first order. The presence or absence of a radical mechanism was

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Keywords: α- and β- (*N*-Arylamino)propanoic acid; Thermal gas-phase elimination; Theoretical analysis.

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Table 1. Rate coefficients and Arrhenius parameters for pyrolysis of **1a**–**c** and **2a**–**c**

Compound	T (K)	10^4 k (s^{-1})	Log A (s^{-1})	*E*a (kJ mol^{-1})	10^3 $k_{600\ K}$ (s^{-1})
1a	550.50	2.320	12.13±0.50	166.18±6.12	3.68
	560.85	4.640			
	570.75	9.070			
	572.05	9.810			
	591.65	30.03			
	602.15	53.38			
1b	548.50	2.320	10.04±0.15	143.58±1.64	6.63
	552.55	2.890			
	570.65	7.930			
	589.05	20.75			
	606.75	46.72			
1c	475.55	0.900	4.86±0.09	81.21±1.01	5.47
	516.15	4.210			
	537.05	8.990			
	556.35	18.29			
	576.55	31.40			
	596.85	57.54			
2a	547.50	3.260	8.53±0.34	125.96±3.63	4.64
	558.65	5.720			
	568.55	9.080			
	578.55	13.88			
	589.05	23.46			
	605.50	46.10			
2b	540.50	4.320	8.68±0.61	124.77±6.70	3.46
	543.65	5.010			
	557.35	10.34			
	567.75	14.15			
	581.95	31.90			
	590.50	44.33			
2c	506.25	4.060	3.93±0.41	71.17±5.47	6.21
	519.45	6.080			
	532.05	9.130			
	544.45	11.55			
	569.95	28.54			

also tested by adding a radical trap, the presence of cyclohexene which was used in this test had no effect on the rate.[2,3] Arrhenius plots of log *k* vs 1/*T* (K) showed strict linearity up to >90% reaction. Kinetic data, Arrhenius parameters, and rate coefficients of reaction at 600 K are summarized in Table 1. The rates at 600 K are calculated using the kinetic equation for first order reactions:

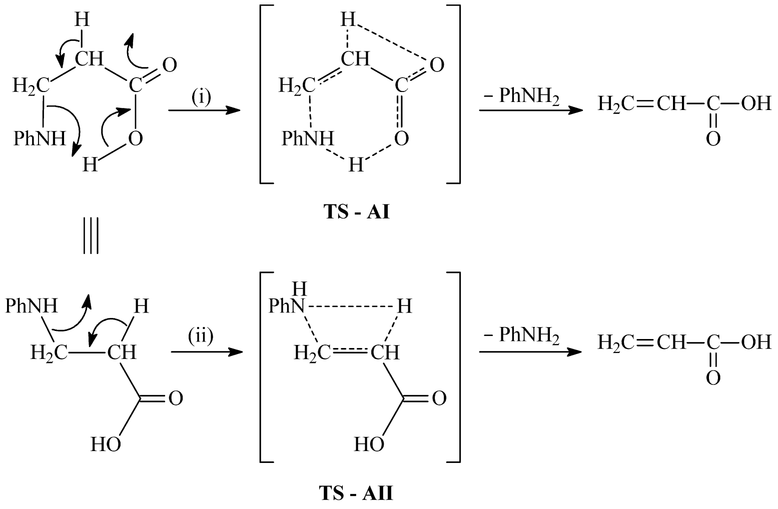
$$\log k = \log A - E_a/4.575\ T$$

The noteworthy observation in this kinetic study is that in the earlier paper[1] we reported reactivity correlations for α-substituents in propanoic acid in which the order of reactivity of the aryl groups was: –NHPh >–OPh>–SPh. On the basis of re-evaluation of the rate constant of 2-(*N*-phenylamino)propanoic acid, the order now is: –OPh >–SPh>–NHPh. This order corresponds more closely to the trend expected from the nature of the incipient phenol, thiophene and aniline fragments. It is of interest to note that there seems to be no opposing substituent effect from the *p*-position of the aryl moiety of the amino group consistent with the electron-donating character of the methyl and the electron-withdrawing character of the chloro substituent. The pyrolysates from the complete gas-phase pyrolysis of α-substituted carboxylic acids [2-(*N*-arylamino)propanoic acid **1a**–**c**] and β-substituted carboxylic acids [3-(*N*-arylamino)propanoic acid **2a**–**c**] were analysed and their constituents fully characterized using LC retention data, MS and NMR techniques.

The pyrolysates from substrates **1a**–**c** were ascertained to be $ArNH_2$, CH_3CHO and CO. The reaction pathway shown in Scheme 1 is compatible with the products of pyrolysis from **1a**–**c** and follows earlier findings by us and others.[4–7]

The pyrolysates from the pyrolytic reaction of substrates **2a**–**c** were identified as $ArNH_2$ and acrylic acid. A plausible mechanism is outlined in Scheme 2 to account for the formation of acrylic acid and substituted anilines from the pyrolysis of **2a**–**c**. This proposed pathway proceeds either through a six-membered transition state (route i) or through a four-membered transition state (route ii). Elimination of aniline in route (i) involves the acidic proton of the carboxylic group, while in route (ii) it involves the less acidic proton of the α-carbon atom.

Examining and characterizing in detail both routes (Scheme 2) in the suggested mechanism was carried out



Scheme 2.

by theoretical calculation of the thermal elimination of aniline and acrylic acid from substrate **2a** using ab initio SCF method.

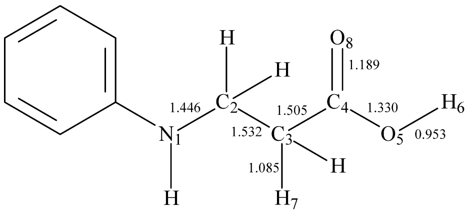


Figure 1. Schematic representation of optimized structure of **2a** to show main distances (Å), obtained by HF/6-31G* basis set.

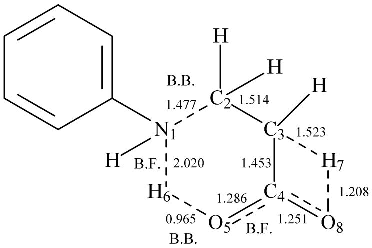


Figure 2. Schematic representation of the optimized structure of TS-AI to show main distances (Å) obtained by HF/6-31G*.

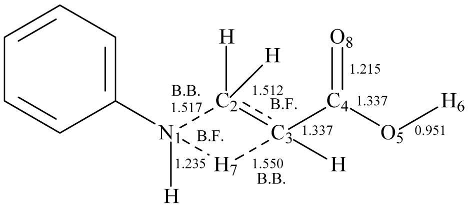


Figure 3. Schematic representation of the optimized structure of TS-AII, to show main distances (Å), obtained by HF/6-31G* basis set.

Table 2. Main distances (Å) in the substrate **2a** and transition states (AI, AII), calculated at the HF/6-31G* level

Distance, Å	**2a**	TS-AI	TS-AII
N_1-C_2	1.446	1.477	1.517
C_2-C_3	1.532	1.514	1.512
C_3-C_4	1.505	1.453	1.438
C_3-H_7	1.085	1.523	1.550
C_4-O_8	1.189	1.251	1.215
C_4-O_5	1.330	1.286	1.337
O_5-H_6	0.953	0.965	0.951
N_1-H_7	2.770	3.916	1.235
N_1-H_6	5.631	2.020	4.638
O_8-H_7	3.102	1.208	2.705

2.2. Computational studies

Theoretical studies on the thermolysis of β-substituted carboxylic acids in the gas phase were carried out using an ab initio SCF method. Calculations were carried out to explore the nature of the reaction mechanism of the unimolecular decomposition of molecule **2a**. Two competitive reaction pathways for the decomposition process have been studied. All the calculations have been performed with the TITAN computational package.[8]

The geometric parameters of the substrate **2a**, the transition states A and B, were fully optimized at the HF/6-31G* level to obtain the energy profile corresponding to the studied reaction. Each stationary structure characterized by frequency calculations was a minimum or saddle point of first-order. A scaling factor of 0.9135 for the zero-point vibrational energies has been used.[9] The structures obtained from the optimization calculations are represented in Figures 1–3.

Table 2 shows the main distances in each optimized structure. During the thermolysis process, when **2a** is being transformed into TS-AII, the N_1-C_2 and C_3-C_4 distances are increasing, whereas the C_2-C_3 and N_1-H_7 distances are decreasing.

Electronic energies, zero-point vibrational energies, enthalpies and entropies were evaluated at the HF/6-31G* level of theory for the substrate **2a**, TS-AI and TS-AII, and the products involved in the two pathways of the studied reaction are collected in Table 3.

The free energy profile for the decomposition process of the studied reaction is re-presented in Figure 4, obtained at the HF/6-31G* level.

Examination of the free energy of the two suggested transiting states shows that TS-AII has a lower free energy barrier than TS-AI (Fig. 4). The calculated activation free energies are 89.59 and 66.41 kJ mol^{-1} for the reaction via the transition states TS-AI and TS-AII, respectively. The overall process is exergonic; with reaction free energy equal to −92.89 kJ mol^{-1}.

From the results obtained, it appears that the single cyclic 4-membered ring transition state, TS-AII, is more favored than the cyclic 4- and 6-membered ring transition state, TS-AI.

Table 3. Total energy zero-point vibrational energy (ZPE) and thermal correction to enthalpy and entropy at HF/6-31G* and 573 K for **2a**, transition states and products

Species	Total energy (Hartrees)	ZPE (kcal mol^{-1})	Enthalpy (kcal mol^{-1})	Entropy (cal mol^{-1} K^{-1})
2a	−551.410335	127.988	134.533	104.899
TS-AI	−551.266869	124.854	130.937	99.273
TS-AII	−551.301672	125.137	131.305	100.440
$PhNH_2$	−285.730756	78.870	82.269	74.352
$H_2C{=}CHCOOH$	−265.653665	45.866	48.866	70.635

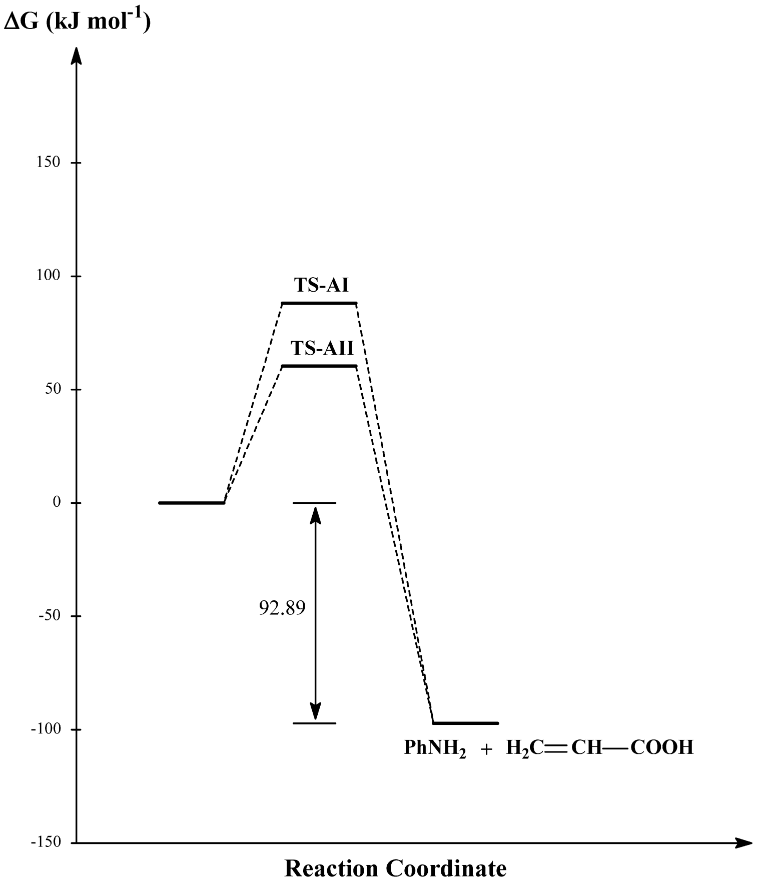


Figure 4. Free energy profile evaluated at the HF/6-31G* level for **2a** decomposition process.

3. Experimental

3.1. Synthesis

3.1.1. Ethyl 2-arylaminopropionate. A mixture of ethyl 2-bromopropionate (0.10 mol), aniline or its *p*-substituted analogues (0.10 mol) and sodium acetate (0.20 mol) was refluxed at 125 °C for 12 h. The reaction mixture was cooled, filtered free of the salt and repeatedly washed with ether. The ether was removed in vacuo and the remaining product was distilled to afford the title compounds.[10]

3.1.2. 2-Arylaminopropanoic acid, 1a–c. Ethyl 2-arylaminopropionate was hydrolysed by heating under reflux with 10% aqueous sodium hydroxide solution (100 ml) for 4–5 h. After cooling, the product was acidified by dropwise addition of diluted hydrochloric acid, the crystals of the products were filtered and recrystallized from ethyl acetate and petroleum ether to afford the title compounds in 55–75% yield. The following compounds were thus synthesized.

2-Phenylaminopropanoic acid, **1a**. Light brown crystals, mp 165.5 °C. ^{1}H NMR (acetone-d^6): δ 1.47 (d, J=7.2 Hz, 3H, CH_3), 4.12 (q, J=7.2 Hz, 1H, CH), 6.62–6.68 (m, 3H, ArH), 7.12 (t, J=7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.3, 52.9, 115.6, 119.6, 129.8, 146.5, 177.6. Anal. calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.66; N, 8.48. Found: C, 64.95; H, 6.61; N, 8.6%. MS: *m/z* 165 (M$^+$). IR (cm^{-1}): 3420 (NH), 1570 (CO).

2-(4-Chlorophenylamino)propanoic acid, **1b** White crystals, mp 143 °C. ^{1}H NMR (acetone-d^6): δ 1.47 (d, J=6.9 Hz, 3H, CH$_{-3}$), 4.1 (q, J=6.9 Hz, 1H, CH), 6.67 (d, J=8.6 Hz, 2H, ArH), 7.11 (d, J=8.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.2, 52.6, 115.1, 124.1, 129.7, 145.2, 177.9. Anal. calcd for $C_9H_{10}NO_2Cl$:, 54.13; H, 5.01; N, 7.02. Found: C, 54.0; H, 5.16; N, 7.03%. MS: *m/z* 199 (M$^+$). IR (cm^{-1}): 3400 (NH), 1592 (CO).

2-(p-Methylphenylamino)propanoic acid, **1c**. Light brown crystals, mp 142 °C. ^{1}H NMR (acetone-d^6): δ 1.45 (d, J=6.9 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.07 (q, J=6.9 Hz, 1H, CH), 6.58 (d, J=8.2 Hz, 2H, ArH), 6.93, (d, J=8.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.0, 21.0, 54.4, 115.3, 129.6, 130.4, 143.6, 179.3. Anal. Calcd. For $C_{10}H_{13}NO_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 67.39; H, 7.26; N, 8.06%. MS: *m/z* 179.1 (M$^+$). IR (cm^{-1}): 3436 (NH), 1579 (CO).

3.1.3. Preparation of 3-arylaminopropanoic acid, 2a–c. To a 10% aqueous solution of NaOH (60 ml) was added 5 g of 3-aminoaryl propionitrile[11] and the mixture was heated under reflux for 6 h. The reaction was then cooled and acidified cautiously by dropwise addition of glacial acetic acid. The acidified solution was then extracted with ethyl acetate; the extract was dried and concentrated under vacuum to afford scales of product which were crystallized from petroleum ether-ether to afford.

3-Phenylaminopropanoic acid, **2a**. Greenish crystals, mp 70.5 °C. ^{1}H NMR (acetone-d^6): δ 2.62 (t, J=6.8 Hz, 2H,

CH_2–CO), 3.43 (t, J=6.8 Hz, 2H, CH_2–NH), 6.61 (d, J=7.6 Hz, 2H, ArH), 6.67 (t, J=7.6 Hz, 1H, ArH), 7.12 (t, J=7.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 34.0, 39.8, 113.8, 118.6, 129.8, 147.6, 177.8. Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.45; H, 6.6; N, 8.48. Found: C, 65.09; H, 6.55; N 8.6%. MS: *m*/*z* 165 (M^+). IR (cm^{-1}) 3407 (NH), 1682 (CO).

3-(p-Chloroanilino)propanoic acid, **2b**. Light brown crystals, mp 125 °C, ^{1}H NMR (acetone-d^6): δ 2.62 (t, J=6.8 Hz, 2H, CH_2), 3.41 (t, J=6.8 Hz, 2H, CH_2), 6.67 (d, J=6.8 Hz, 2H, Ar H), 7.11 (d, J=6.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 34.1, 40.0, 114.9, 123.3, 129.8, 146.4, 177.8. Anal. Calcd. for $C_9H_{10}NO_2$: C, 54.13; H, 5.01; N, 7.01. Found: C, 54.5; H, 5.07; N, 7.07%. MS: *m*/*z*=199 (M^+), IR (cm^{-1}): 3424 (NH), 1708 (CO).

3-(p-Methylphenylmino)propanoic acid, **2c**. Brown crystals, mp 85.5 °C, ^{1}H NMR (acetone-d^6): 2.18 (s, 3H, CH_3), 2.59 (t, J=6.8 Hz, 2H, CH_2), 3.38 (t, J=6.8 Hz, 2H, CH_2), 6.57 (d, J=8.4 Hz, 2H, Ar H), 6.93 (d, J=8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 21.0, 34.1, 40.5, 114.4, 128.4, 130.4, 145.3, 177.8. Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 66.75; H, 7.24; N, 7.99%. MS: *m*/*z* 179.1 (M^+). IR (cm^{-1}): 3364 (NH), 1684 (CO).

3.2. Kinetic runs and data analysis

Stock solution (7 ml) is prepared by dissolving 6–10 mg of the substrate in acetonitrile as solvent to give a concentration of 1000–2000 ppm. Internal standard is then added, the amount of which is adjusted to give the desired peak area ratio of substrate to standard (2.5:1). The solvent (acetonitrile) and the internal standard (chlorobenzene) were selected because both are stable under the conditions of pyrolysis, and because they do not react with either substrate or product. Each reaction mixture is filtered to ensure that a homogeneous solution is obtained.

The weight ratio of the substrate with respect to the internal standard is calculated from the ratio of the substrate peak area to the peak area of the internal standard. The kinetic rate was obtained by tracing the rate of disappearance of the substrate with respect to the internal standard as follows.

An aliquot (0.2 ml) of each solution containing the substrate and the internal standard was pipetted into the reaction tube which was then placed in the pyrolyzer for 6 min under non-thermal conditions. A sample was then analyzed using the HPLC probe with the UV detector at wavelength of 256 nm, and the standardization value (A_0) was calculated. Several HPLC measurements were obtained with an accuracy of $\geq$2%. The temperature of the pyrolysis block was then raised until approximately 10% pyrolysis was deemed to occur over 900 s. This process was repeated after each 10–15 °C rise in the temperature of the pyrolyzer until $\geq$90% pyrolysis occurred. The relative ratios of the integration values of the sample and the internal standard (A) at the pyrolysis temperature was then calculated. A minimum of three kinetic runs were carried out at each 10–15 °C rise in the temperature of the pyrolyzer to ensure reproducible values of (A). Treatment of the kinetic data has been detailed elsewhere.[12–14]

3.3. General procedure for product analysis

The apparatus used for this purpose was the same pyrolysis unit used for kinetic studies. Each of the substraters (0.2 g) was introduced in the reaction tube, cooled in liquid nitrogen, sealed under vacuum and placed in the pyrolyzer for 900 s at a temperature comparable to that used for complete pyrolysis in the kinetic studies. The contents of the tube were then analysed by NMR and LC/MS and the yield was determined by HPLC with reference sample (Table 4). The spectral data of the pyrolysates were compared with their reference spectra.

Table 4. Product analysis of compounds **1a**–**c** and **2a**–**c**

Cpd	T (K)	Pyrolysates and yields (%)	
1a	630	Aniline (52%)	Acetaldehyde (42%)
1b	620	*p*-Chloroaniline (33.7%)	Acetaldehyde (38.3%)
1c	600	*p*-Tolylaniline (26.4%)	Acetaldehyde (12%)
2a	630	Aniline (18.6%)	Acrylic acid (25.9%)
2b	620	*p*-Chloroaniline (49.9%)	Acrylic acid (30.6%)
2c	600	*p*-Tolylaniline (33.6%)	Acrylic acid (35.6%)

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