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KINETIC STUDY OF THE REACTIONS OF 2-AMINO-5-CHLOROBENZOPHENONE WITH HCl in MeOH–H_2O

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The reaction of 2-amino-5-chlorobenzophenone (1) with 0·5–2 M HCl was studied in 1:1 (v/v) MeOH–H_2O at 60 and 80 °C. Products that were isolated were characterized as 2-(*N*-methylamino-5-chlorobenzophenone (2), 2-amino-3,5-dichlorobenzophenone (3), 2-*N*-methylamino-3,5-dichlorobenzophenone (4), 2-(*N*,*N*-dimethylamino-5-chlorobenzophenone (5), 2,4-dichloro-10-methyl-9,10-acridinone (6) and 2,4-dichloro-9,10-acridinone (7). The rates of reaction of 1 and the rates of formation of 2–5 were measured at several HCl concentrations. The methyl transfers, the chlorination and the cyclization reactions that give rise to 2–7 were unexpected under the present reaction conditions. A set of differential equations was proposed in order to calculate the rate constants for each step of this complex reaction. The proposed reaction scheme also takes into account the reaction 2→1 and permits the calculation of the rate constants for this reversible reaction. The experimental values of the rate constants for reaction of 1 were compared with those for 2 under the same reaction conditions, in order to evaluate the importance of the methyl group on the methyl transfer reactions; it was found that the methyl group is not required for the unexpected reaction to occur. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

The acid-catalysed hydrolysis of benzodiazepinones is an area of active research because of both its chemistry and its potential concern in pharmacological studies.[1] Knowledge of the structural features,[2, 3] and of the effects of solvent, pH, temperature or a combination of these parameters on the rates of degradation of the drug and the rates of formation of the different reaction products,[1, 4–6] have recently afforded useful clues regarding drug formulation and storage[1b] and analytical procedures.[5, 7, 8] Recent studies have been focused on the mechanisms by which the degradation of the drug and the formation of the reaction products occur[1, 7] as well as on structural determinations[4–6, 9] that help in understanding the drug–receptor interactions[9–11] and to improve earlier analytical procedures.[12–16]

We have recently described the kinetics of the reaction of 2-*N*-methylamino-5-chlorobenzophenone (the main product of the acid hydrolysis of diazepam)[16] with HCl: the rate of disappearance of the substrate and the rates of formation of the reaction products were determined.[7] In this paper we describe a kinetic study of the reaction of 2-amino-5-chlorobenzophenone (**1**) with HCl at several concentrations in methanol–water (50:50) at 60 and 80 °C.

This research is of interest because of the complex reactions that are taking place, shown in equation (1), as well as for its relevance for characterizing the acid hydrolysis of benzodiazepinones.[17–20]

The methyl transfers and the chlorination and cyclization reactions that give rise to products **2**–**7** (eqn 1) were not expected to occur under the conditions of the reaction and this study was undertaken with the aim of contributing to the knowledge of these unexpected reactions and analyse the relevance of the methyl group.

EXPERIMENTAL

Materials. Methanol,[19] toluene,[19] cyclohexane[20] and tetrahydrofuran (THF)[21] were purified and made anhydrous by methods described previously. Methanol–aqueous solutions were prepared using doubly distilled, deionized water. Hydrochloric acid (Aldrich) (37%, ACS reagent) was used throughout the work, and the results were confirmed by testing p.a. grade HCl from other origins. Melting points are uncorrected and were determined with an Arthur Thomas or Kofler apparatus. The gas chromatographic (GC) system was a Hewlett-Packard Model 5830 gas chromatograph

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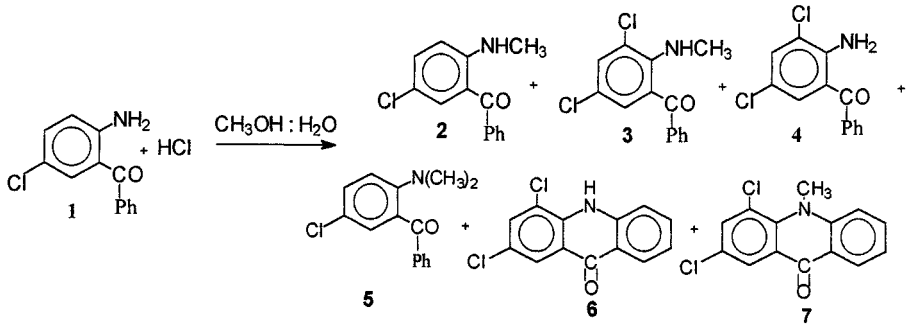
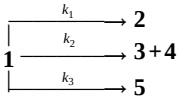


equipped with a flame ionization detector (FID), with dried nitrogen as the carrier gas. Different stationary phases [1·5% OV-101 (dimethylsilicone), 3% OV-17 (phenylmethyl–50% phenylsilicone), 8% NPGS (neopentyl glycol succinate) and SE-30 (methylsilicone)] on Chromosorb W AW were used to determine each product. Quantitative GC determinations were carried out with an 8% NPGS column. The temperature settings were oven 210, injection port 260 and FID 230 °C. The flow rate was 28 ml min^{-1}. This system does not separate the chlorinated products **3** and **4**; these products were detected using an SE-30 or OV-17 column. UV spectra were recorded with a Hewlett-Packard HP 8541 A photodiode-array spectrophotometer and a Shimadzu UV 1601 PC in the case of first- and second-derivative UV spectra. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC-200 spectrometer and referenced to internal TMS. Electron impact (EI) mass spectra were recorded at 70 eV on a Varian Mat CH-7a instrument equipped with a Mat 166 data processor and a Varian 1400 gas chromatograph.

Isolation and characterization of the reaction products. Compound **1** (35 mg) ($3{\cdot}0\times10^{-3}$ M) was allowed to react with 0·5 M HCl in 1:1 (v/v) MeOH–H_2O at 80 °C for 35 days. At this point, it was found that **1** had reacted up to 78%, as determined by analytical GC and TLC. The main reaction products were isolated and characterized as 2-*N*-methylamino-5-chlorobenzophenone (**2**), 2-amino-3,5-dichlorobenzophenone (**3**) and 2-*N*-methyl-amino-3,5-dichlorobenzophenone (**4**) ([**3**+**4**] = $1{\cdot}7\times10^{-3}$ M, (56%), [**2**] = $0{\cdot}1\times10^{-3}$ M (3%). When **1** (35 mg) was allowed to react in 1·5 M HCl under the same conditions for 8 days (50% of reaction), it was determined by analytical GC, EI-MS and TLC that the main reaction products were 2-*N*-methylamino-5-chlorobenzophenone (**2**) ([**2**] = $0{\cdot}66\times10^{-3}$ M, 20%) and 2-*N*,*N*-dimethylamino-5-chlorobenzophenone (**5**) ([**5**] = $0{\cdot}5\times10^{-3}$ M, 16%). Two other minor reaction products, namely 2,4-dichloro-9,10-acridinone (**6**) and 2,4-dichloro-10-methyl-9,10-acridinone (**7**) were also isolated and characterized. The isolation and characterization of products **2**–**7**, as well as their independent synthesis, were carried out by methods described previously.[5]

Kinetic measurements. Stock solutions ($1{\cdot}5\times10^{-2}$ M) of the substrate, **1**, were prepared in methanol and stock solutions of HCl were prepared in water. Appropriate volumes of the stock solutions were mixed and diluted as required to obtain the desired reactant concentrations in 1:1 MeOH–H_2O solvent. In the present study, aliquots of solutions of **1** in sealed ampoules were placed in the thermostat and allowed to reach constant temperature. An aliquot was taken, worked up and the concentration measured by GC; this was considered as $[\mathbf{1}]_0$. The rate of disappearance of the reactant and the rate of formation of products were monitored by GC at appropriate time intervals; typical runs are shown in Tables 1 and 2. The reactions were followed for at least three half-lifes and the final values were determined after at least ten half-lifes. Calculations of the rate constants were carried out by a computer program designed to give the best straight line in each case. The first portions of the curves behave as parallel reactions under certain reaction conditions. In that case we consider the following simplified reaction scheme:



The differential equations were derived following classical procedures;[20b, 22] a typical set is as follows:

$$k = k_1 + k_2 + k_3$$

$$-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = (k_1 + k_2 + k_3)\,[\mathbf{1}]$$

$$\ln([\mathbf{1}]/[\mathbf{1}]_0) = kt$$

$$\mathrm{d}[\mathbf{2}]/\mathrm{d}t = k_1[\mathbf{1}]$$

$$\mathrm{d}([\mathbf{3}]+[\mathbf{4}])/\mathrm{d}t = k_2\,[\mathbf{1}]$$

$$\mathrm{d}[\mathbf{5}]/\mathrm{d}t = k_3\,[\mathbf{1}]$$

The system was solved by numerical integration. The equations used to obtain the actual concentrations are shown below for the case where mainly parallel first-order reaction

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kinetics are observed:

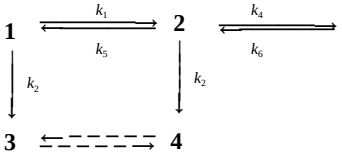
$$[\mathbf{1}] = 1\mathbf{1}]_0\, e^{-kt}$$

$$[\mathbf{2}] = (k_1[\mathbf{1}]_0/k)(1 - e^{kt})$$

$$[\mathbf{3}+\mathbf{4}] = (k_2[\mathbf{1}]_0/k)(1 - e^{kt})$$

$$[\mathbf{5}] = (k_3[\mathbf{1}]_0/k)(1 - e^{kt})$$

Nevertheless, in most cases the best fit was obtained with a whole set of differential equations corresponding, in each case, to the several parallel and/or consecutive reactions formally represented as follows:



The corresponding differential equations are

$$-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = (k_1+k_2)\,[\mathbf{1}] - k_5\,[\mathbf{2}]$$

$$\mathrm{d}([\mathbf{3}]+[\mathbf{4}])/\mathrm{d}t = k_2\,[\mathbf{1}] + k_3\,[\mathbf{2}]$$

$$\mathrm{d}[\mathbf{2}]/\mathrm{d}t = k_1\,[\mathbf{1}] - (k_3+k_4+k_5)\,[\mathbf{2}] + k_6\,[\mathbf{5}]$$

$$\mathrm{d}[\mathbf{5}]/\mathrm{d}t = k_4\,[\mathbf{2}] - k_6\,[\mathbf{5}]$$

The method of resolution of this complex system will be published elsewhere;[23] as an example, the solved system for the case of negligible k_5 and k_6 gave the following general equations to obtain the actual concentrations:

$$[\mathbf{1}] = [\mathbf{1}]_0\, e^{-(k_2+k_1)t}$$

$$[\mathbf{2}] = k_1[\mathbf{1}]_0/(k_3+k_4-k_1-k_2)[e^{-(k_1+k_2)t} - e^{-(k_5+k_4)t}]$$

$$[\mathbf{5}] = k_4k_1[\mathbf{1}]_0/(k_3+k_4-k_1-k_2)[e^{-(k_3+k_4)t}/(k_3+k_4) - e^{-(k_1+k_2)t}/(k_1+k_2)] + k_4\,k_1[\mathbf{1}]_0/(k_1+k_2)(k_3+k_4)$$

$$[\mathbf{3}]+[\mathbf{4}] = -k_1[\mathbf{1}]_0\, e^{-(k_1+k_2)t}/(k_1+k_2) + k_3k_1[\mathbf{1}]_0/(k_3+k_4-k_1-k_2)[e^{-(k_3+k_4)t}/(k_3+k_4) - e^{-(k_1+k_2)t}/(k_1+k_2)] + k_2[\mathbf{1}]_0/(k_1+k_2) - k_3k_1[\mathbf{1}]_0/[(k_3+k_4)(k_1k_2)]$$

Simulation of the system, through variation of the constraints of the values of the different partial reaction rates of $k_{\partial i}$ which produce the minimum sum of the square of the differences between the experimental and the theoretical points were obtained. Fitting of the curves was carried out by iterative procedures until a good fit between the simulated and experimental plots were obtained in every case. The experimental points and the calculated plots are shown in Figures 1–4.

Rate constants were obtained at least in duplicate and average results are presented in Tables 4 and 5. The reproducibility of the rate constants is within 3% for the reaction of **1** and around 5% for the formation of reaction products. The calculated partial reaction rates (the rate constant for each individual step) are shown in Tables 3 and 4.

RESULTS

Reaction of 2-amino-5-chlorobenzophenone (1) with HCl in MeOH–H_2O at 80 °C

The spectrophotometric technique was not appropriate to follow the kinetics because the UV spectra of the products **1**–**5** and the first- and second-order derivatives of the UV spectra are very similar. Taking into account the amounts of products observed in preliminary studies,[5,7] several GC conditions were examined for the quantitative determination of the main reaction products; the systems described in the Experimental section allowed the determination of the actual concentrations of products **1**, **2**, **3**+**4** and **5**. The acridinones **6** and **7** cannot be determined by GC and their concentrations were estimated by semi-quantitative TLC. A range of 0·5–2·0 M HCl and two temperatures, 60 and 80 °C, were selected. Because of the complexity of the reaction, most of the results will be presented in the form of figures for the sake of clarity; some typical examples are given in Tables 1–4.

Table 1 shows the molar concentrations of **1**, **2** and **3**+**4** in the reaction of **1** with 0·5 M HCl at 80 °C against time for the first 35 days. It can be observed that [**1**] decreases steadily and [**2**] and [**3**+**4**] increase steadily. At the end of

Table 1. Reaction of 2-amino-5-chlorobenzophenone (**1**) with 0·5 M HCl in 1:1 (v/v) methanol–H_2O at 80 °C[a]

Time (days)	[**1**] (10^3 M)	[**2**] (10^3 M)	[**3**+**4**] (10^3 M)	Time (days)	[**1**] (10^3 M)	[**2**] (10^3 M)	[**3**+**4**] (10^3 M)
0	3·0	0	0	15	1·9	0·15	1·0
3·0	2·9	0	0·21	21	1·7	0·17	1·2
7·0	2·7	0·02	0·28	33	0·65	0·22	2·1
11·1	2·2	0·09	0·65	34	0·66	0·20	2·0

[a] $[\mathbf{1}]_0 = 3{\cdot}07 \times 10^{-3}$ M; $t_{1/2} = 23{\cdot}7$ days.
[b] From this time on, acridinones **6** and **7** were also detected by TLC. Compound **5** was not detected. At longer reaction times some other compounds, with higher retention times than that of the benzophenones, were detected in trace amounts (yield ≤ 3%).

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Table 2. Reaction of 2-amino-5-chlorobenzophenone (**1**) with 0·5 M HCl in 1:1 (v/v) methanol–H_2O at 60 °C[a]

Time (days)	[**1**] (10^3 M)	[**2**] (10^3 M)	[**3**+**4**] (10^3 M)	Time (days)	[**1**] (10^3 M)	[**2**] (10^3 M)	[**3**+**4**] (10^3 M)
0	3·3	0	0	37	3·0	0·05	0·19
9·2	3·2	0·01	0·01	57[b]	2·5	0·04	0·34
16	3·2	0·02	0·05	82	2·4	0·03	0·74
23	3·2	0·04	0·09	87	2·0	0·03	1·0
36	3·1	0·02	0·19	125	1·8	0·04	1·1

[a] $[\mathbf{1}]_0 = 3{\cdot}33 \times 10^{-3}$ M, $t_{1/2}$ = 145 days.
[b] From this time on, acridinones **6** and **7** were also detected. Compound **5** was not detected.

the reaction, compounds **1**, **3**+**4** and **2** were detected, plus traces of other compounds with higher retention times. The chlorination compounds are the main reaction products, ($[\mathbf{3}+\mathbf{4}] = 1{\cdot}7 \times 10^{-3}$ M), as shown in Table 1. Analytical TLC showed also the presence of traces of products **6** and **7**. The linear plot of $\ln([\mathbf{1}]_0/[\mathbf{1}])$ vs time shows that the degradation of **1** follows first-order kinetics. The pseudo-first-order specific rate coefficient calculated from the regression plot is $3{\cdot}4 \times 10^{-6}\ s^{-1}$, corresponding to the half-life of 24 days. Treatment of the data up to 35 days of reaction was consistent with two parallel reactions, corresponding to the formation of **2** and **3**+**4**; the specific rate coefficients were calculated from plots of the molar concentrations of each product as a function of $1 - e^{-kt}$. The results, the average of at least duplicate runs, are shown in Table 3 for this and other reactions at different HCl concentrations. Simulation of the complex reaction kinetics at each HCl concentration gave the pseudo-first-order specific rate coefficients, which are also shown in Table 3. Fairly good agreement with the experimental rates is observed.

The results of the reaction of **1** with 0·84 M HCl at 80 °C are shown in Figure 1. It can be observed that (a) the overall degradation of **1** is faster than with 0·5 M HCl; (b) the amounts of chlorination products, **3**+**4**, up to 15 days are similar to the amounts of **2** (at 11 days, $[\mathbf{3}+\mathbf{4}] = 0{\cdot}42 \times 10^{-3}$ M and $[\mathbf{2}] = 0{\cdot}35 \times 10^{-3}$ M). After 25 days of reaction, [**3**+**4**] becomes more important than [**2**], which diminishes ($[\mathbf{3}+\mathbf{4}] = 2{\cdot}3 \times 10^{-3}$ M and $[\mathbf{2}] = 0{\cdot}55 \times 10^{-3}$ M). Treatment of the data similarly to those for the reaction with 0·5 M HCl gave the pseudo-first-order rate coefficients shown in Table 3. The half-life of the reaction of **1** is 17 days.

The reaction of **1** with 1·52 M HCl at 80 °C (Figure 2) shows that (a) the overall degradation of **1** is faster than with

Table 3. Reaction of 2-amino-5-chlorobenzophenone (**1**) with HCl in 1:1 (v/v) methanol–H_2O: pseudo-first-order rate constants

			$10^7 k_\psi$, (s^{-1})				
T (°C)	[HCl] (M)	k_{exp}	k_1	k_2	k_3	k_4	k_5
80	0·5	3·4	0·13[a]	2·7[a]			
			0·26[b]	3·3[b]	14[b]	0[b]	38[b]
	0·84	3·9	3·5[a]	1·9[a]		0[a]	
			4·0[b]	1·1[b]	8·1[b]	0·03[b]	14[b]
	1·57	10	9·5[a]	0·98[c]		16[c]	
			9·2[b]	0·23[b]	0·46[b]	17[b]	9·2[b]
	2·0	16	14[b]	0·23[b]	0·46[b]	21[b]	9·2[b]
			16[c]	0·85[c]		17[c]	
60	0·5	0·54	0·01[a]	0·48[a]			
			0·20[b]	0·3[b]	4·1[b]	0[b]	5·8[b]
		0·59		0·61[d]			
	0·86	0·74	0·02[a]	0·57[a]	0[a]	0[a]	
			0·11[b]	0·55[b]	0·87[b]	0[b]	5·2[b]
	1·5	0·61	0·37[a]	0[a]	0[a]	0·13[a]	
			0·44[c]	0[c]	0[c]	0·74[c]	
			0·58[b]	0[b]	0[b]	0·58[b]	1·2[b]
	2·0	0·97	0·52[b]	0[b]	0[b]	0·35[b]	0·31[b]

[a] Reaction rate constants calculated considering parallel reactions.
[b] Rate constants simulated with the method described in the Experimental section (see Kinetic measurements).
[c] Rate constants simulated with the Tutsim procedure.
[d] Reaction in 1:1 (v/v) THF–water.

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Table 4. Reaction of 2-amino-5-chlorobenzophenone (**1**) with HCl in 1:1 (v/v) methanol–H_2O: second-order rate constants

			$10^7 k_2$ ($M^{-1} s^{-1}$)					
T (°C)	[HCl] (M)	k_{exp}	k_1	k_2	k_3	k_4	k_5	k_5'[a]
80	0·5	6·8	0·26[b]	5·4[b]		0[b]		
			0·52[c]	6·6[c]	28[c]	0[c]	76[c]	83[c]
	0·84	4·7	1·5[b]	2·2[b]		0[b]		
			4·8[c]	1·4[c]	9·6[c]	0[c]	16[c]	19[c, f]
	1·6	6·5	5·9[b]	0·15[c]	0·29[c]	11[c]	5·9[c]	3·9[c]
			6·0[d]	0·62[d]		9·9[d]		
	2·0	7·8	6·9[b]	0·12[c]	0·23[c]	10[c]	4·6[e]	4·1[c]
			16[d]	1·8[d]		17[d]		
60	0·5	0·98	0·07[b]	0·7[b]				
			0·68[c]	0·6[c]	8·1[c]	0[c]	12[c]	11[c]
		1·2		1·2[e]				
	0·86	0·86	0·02[b]	0·66[b]	0[b]	0[b]		
			0·13[c]	0·64[c]	1·0[c]	0[c]	6·0[c]	6·1[d]
	1·6	0·41	0·24[b]	0[b]	0[b]	0·08[b]		
			0·38[c]	0[c]	0[c]	0·38[c]	0·75[c]	0·58[c]
			0·28[d]	0[d]	0[d]	0·48[d]		
	2·0	0·48						
			0·26[c]	0[c]	0[c]	0·17[c]	0·16[c]	

[a] Bimolecular rate constants for the demethylation of **2** with HCl in methanol–H_2O.[3]
[b] Partial rate constants calculated considering parallel in reactions.
[c] Rate constants simulated with the proposed method.
[d] Rate constants simulated with the Tutsim procedure.
[e] Reaction in 1:1 (v/v) THF–water.
[f] Reaction in 1·0 M HCl.

1·0 M HCl; (b) the concentration of **2** increases up to 7 days and then decreases; (c) a new product, **5**, appears after a short induction period; the concentration of **5** increases slowly up to 7 days and then decreases slightly; (d) the amounts of chlorination products (**3**+**4**) are significantly smaller than those of the other degradation products. Compounds **3** and **4** appeared after 7 days of reaction, when [**2**] and [**5**], the main reaction products, started to decrease.

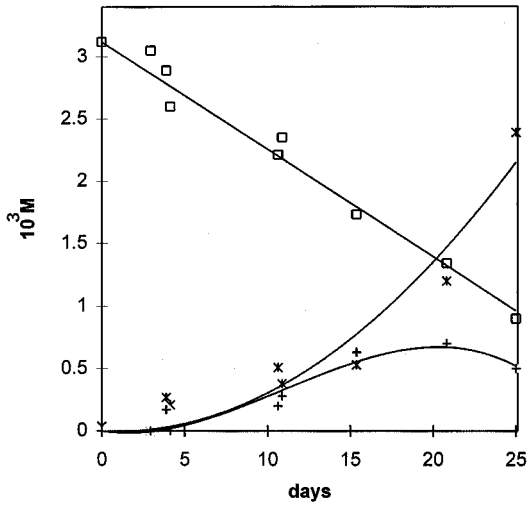

Figure 1. Reaction of 2-amino-5-chlorobenzophenone (**1**) with 0·84 M HCl in HCl in 1:1 methanol–water at 80 °C. (□) [**1**]; (+) [**2**]; (∗) [**3**+**4**]

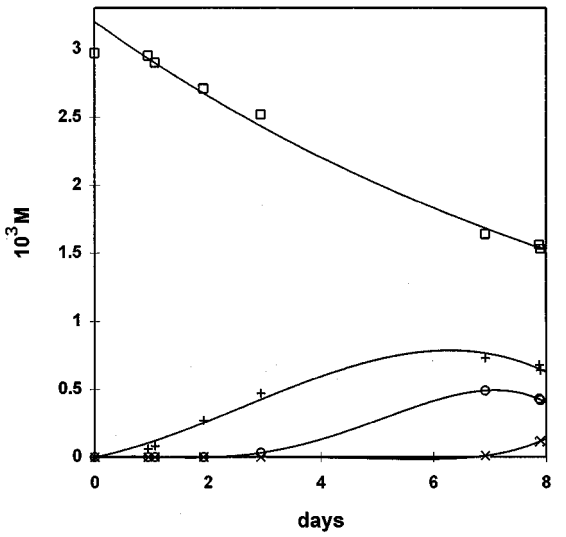

Figure 2. Reaction of 2-amino-5-chlorobenzophenone (**1**) with 1·5 M HCl in 1:1 methanol–water at 80 °C. (□) [**1**]; (+) [**2**]; (∗) [**3**+**4**]; (○) [**5**]

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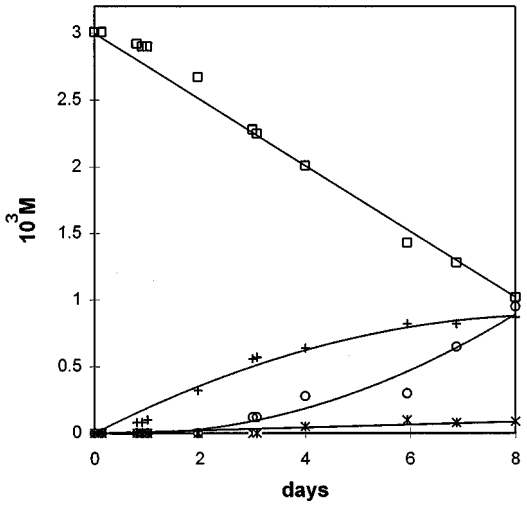

Figure 3. Reaction of 2-amino-5-chlorobenzophenone (**1**) with 2·0 M HCl in 1:1 methanol–water at 80 °C. (□) [**1**]; (+) [**2**]; (*) [**3**+**4**]; (○) [**5**]

The half-life of the reaction of **1** was 7·9 days. The main reaction products under these conditions were **2** and **5**; the actual concentrations are shown in Table 2.

The reaction with 2·0 M HCl (Figure 3) has a half-life of 6·3 days. The chlorination products (**3**+**4**) were detected only as traces; [**2**] increased up to 6 days, while [**5**] increased steadily after a short induction period. Compounds **2** and **5** were the main reaction products; at the end of the reaction, traces of other products with higher retention times were detected.

Reaction of 2-amino-5-chlorobenzophenone with HCl at 60 °C

The reaction of **1** with 0·5 M HCl at 60 °C showed behaviour similar to that at 80 °C, although some peculiarities deserve comments, as can be observed in Table 2. The half-life of the reaction was 145 days; the main reaction products were **3** and **4**, which at this time reached a total concentration of $1{\cdot}1\times10^{-3}$ M ($[\mathbf{1}]_0=3{\cdot}3\times10^{-3}$ M). An induction time of nearly 20 days was observed.

Up to 130 days of reaction the system followed a behaviour consistent with parallel reactions. The calculated pseudo-first-order specific rate coefficients for all the HCl concentrations studied are shown in Table 3. It was observed that with more concentrated HCl solutions, the overall rate of reaction increased slightly; **5** appeared for [HCl]=1·5 and 2·0 M. At 0·84 M [HCl], **3** and **4** were the main degradation products, which reached their maximum concentration in 116 days ($[\mathbf{3}]+[\mathbf{4}]=1{\cdot}5\times10^{-3}$ M; $[\mathbf{1}]_0=3{\cdot}1\times10^{-3}$ M) and then remained constant up to 133 days, while [**2**] increased steadily. Only traces of **5** were detected.

At 1·5 M HCl, in contrast to the reaction at 80 °C, formation of chlorination products was not observed; [**2**] was higher than [**5**], and both increased steadily up to 100 days. The whole reaction was very slow: after 106 days [**1**] was $1{\cdot}7\times10^{-3}$ M ($[\mathbf{1}]_0=3{\cdot}0\times10^{-3}$ M). At the end of the reaction only **2** ($0{\cdot}7\times10^{-3}$ M) and **5** ($0{\cdot}3\times10^{-3}$ M) were identified. Other components had retention times higher than that of the *o*-aminobenzophenones. These reactions had an induction time of nearly 20 days, probably needed for the build-up of the minimum concentration of the intermediates required.

At 2·0 M HCl, the formation of chlorination products was not detected; [**2**] increased up to 80 days and then decreased slightly; the concentration of **5** was very low. The overall reaction was slow ($t_{1/2}$=110 days): after 100 days of reaction [**1**] was $1{\cdot}3\times10^{-3}$ M ($[\mathbf{1}]_0=3{\cdot}0\times10^{-3}$ M). The observed induction time was nearly 30 days.

To find out the effect of the solvent on the rates and the product distribution, the reaction was also examined in 1:1 (v/v) THF–H_2O in order to compare the results with those obtained in the kinetic study of **2**. It was observed that the overall degradation of **1** follows first-order rate kinetics, and the rate was slightly faster in THF–H_2O than in MeOH–H_2O ($t_{1/2}$=136 days vs $t_{1/2}$=145 days, both in 0·5 M HCl at 60 °C). The main chlorination product was **3**. After 57 days, [**1**] decreased to $2{\cdot}7\times10^{-3}$ M ($[\mathbf{1}]_0=3{\cdot}4\times10^{-3}$ M) and [**3**] increased to $0{\cdot}88\times10^{-3}$ M. When the reaction mixture was examined by GC–MS after longer reaction periods, only unidentified products with ion fragments showing incorporation of the butyl moiety of cleaved THF were observed, apart from **3**. The isolation and characterization of these products were not considered relevant for the present study.

Table 4 shows the calculated bimolecular rate coefficients for all the reactions studied. Column 9 in Table 4 shows the experimental rate coefficients for the demethylation of **2**.[7]

DISCUSSION

The formation of the four main products, **2**–**5**, and also the other two compounds, **6** and **7**, isolated in trace amounts from the reaction of 2-amino-5-chlorobenzophenone with HCl in MeOH–H_2O (50:50), follows the complex behaviour shown in Figures 1–3. However, examination of the kinetic results, and those of the previously studied reactions of 2-(*N*-methyl)amino-5-chlorobenzophenone (**2**),[7] leads to conclusions that may clarify some of the mechanistic pathways.

Because of the large number of determinations needed, only two temperatures were examined in detail. Comparison of the data in Tables 1 and 2, and those in Tables 3 and 4, indicates that the overall reaction exhibits an important energy of activation, typical of polar reactions. A crude estimation based on the experimental rates gives an energy of activation of *ca* 90 kJ mol^{-1} for the reaction of **1**, which

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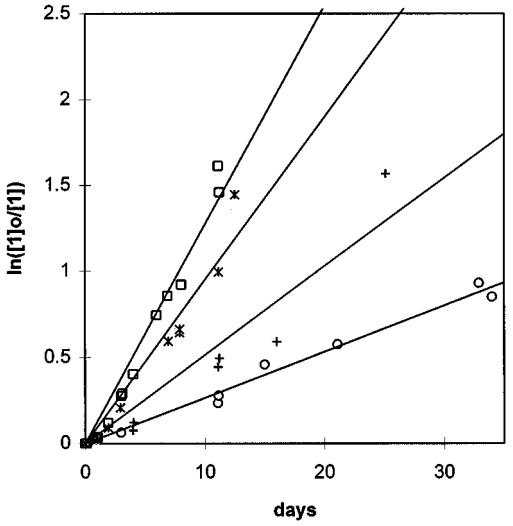


Figure 4. Reaction of 2-amino-5-chlorobenzophenone (**1**) with different concentrations of HCl in 1:1 methanol–water at 80 °C. [HCl]: (○) 0·5; (+) 0·85; (*) 1·57; (□) 2 M

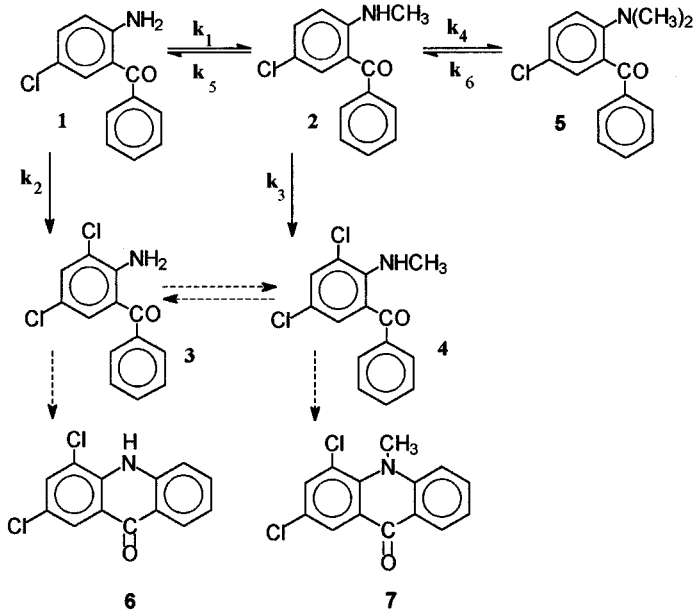
is similar to that of 83·6 kJ mol^{-1} for the reaction of **2** calculated previously from the overall rates determined in the range 35–80 °C.[7] It can also be observed that the rates of formation of the reaction products of **1** are very sensitive to temperature.

Although the trends in the results are similar at both temperatures, there are some differences. Figure 4 shows that the rate of reaction of **1** at 80 °C increases steadily with [HCl]. On the other hand, Table 3 shows that the overall rate for the reaction at 60 °C shows little change in the range 0·5–1·5 M HCl, although it is slightly higher in 2·0 M HCl. The reactions show considerable induction times, especially in 1·5–2 M HCl, and no chlorination is observed for [HCl] > 1 M.

On examining the partial rates in Table 3, it can be observed that the rate of formation of **2**, k_1 (see Scheme 1), is highly sensitive to [HCl] and it increases with increase in [HCl], while the rate of demethylation of **2** to form **1**, k_5, decreases at higher [HCl]. Figure 5 shows the formation of **2** at different [HCl]; a high rate is observed for [HCl] ≥ 1·5 M and a decrease in [**2**] after 6–7 days, which is consistent with the mechanism proposed in Scheme 1 and the reversibility of the reaction. Since the alkylation reaction is expected to occur on the unprotonated amine, the observed results could indicate that protonated methanol is the methylating agent, as shown by equation (2).

Regarding the demethylation reaction of **2**, it was found previously that the rate of the reaction **2→1** also increases with increase in [HCl],[7] hence the reversible mechanism would be operating, and protonated water would be the reactant attacking the amino nitrogen [equation (2)]. An oxidative demethylation of some substituted *N*,*N*-dimethylanilines in methanol has been reported recently.[8]

Methylation of **2** to form **5** is also favoured by high HCl concentrations and, in fact, **5** only appeared in ≥1·5 M HCl. A mechanism similar to that depicted in equation (1) could be envisaged for the methylation of **2** to form **5**. The methylation reactions require a large energy of activation; k_1



Scheme 1

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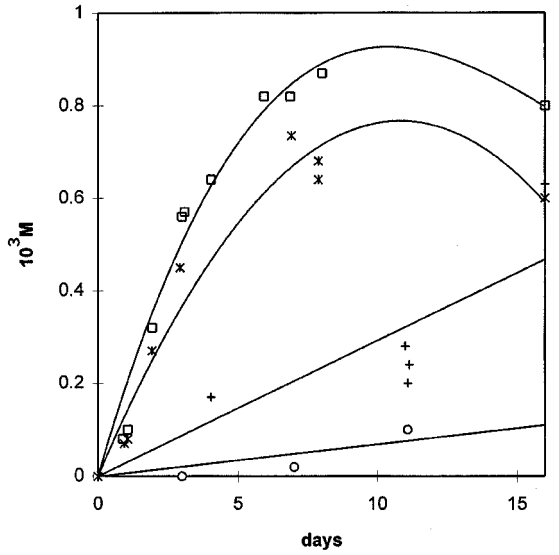


Figure 5. Formation of **2** at different [HCl] (○) 0·5; (+) 0·85; (*) 1·57; (□) 2 M

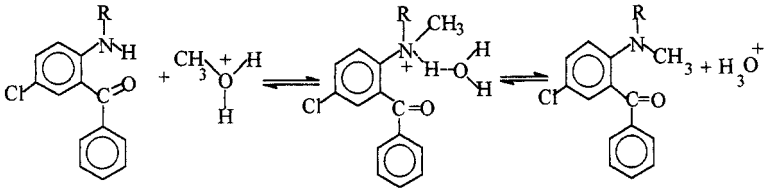
decreases from $9{\cdot}2\times10^{-7}$ M^{-1} s^{-1} at 80 °C to $0{\cdot}58\times10^{-7}$ M^{-1} s^{-1} at 60 °C (Table 4). In both cases, it was found that the rate of demethylation was higher than the rate of methylation ($k_1<k_5$). The rate of demethylation decreases slightly when [HCl] increases; this is probably related to the higher pK_a of the methylated amine, **2**, compared with **1**.

The appearance of the observed chlorination products is unusual under the present reaction conditions. Furthermore, chlorination was also observed in the reactions of **2** with HCl in the same binary solvent,[7] and the reaction rate for **2→4** was faster than that for **1→3**, as expected for electrophilic aromatic substitution. The fact that **3** was observed also in the reaction of **1**, as well as the extent of the partial rates, indicates that the methyl group on the N is probably not required for the chlorination to occur, and that formation of **3** takes place directly from **1**, and not through demethylation of **4**. Nevertheless, the equilibrium **3⇌4** (see Scheme 1) cannot be discarded on the grounds of the present studies. The formation of chlorination products at different HCl concentrations (Figure 6) indicates that chlorination should occur on unprotonated **1** (the reaction does not take place in 2·0 M HCl), and the observed straight lines are consistent with the irreversibility of the reactions (see Scheme 1).

Examination of the partial second-order rate constants in Table 4 shows that the chlorination of **1** to **3** with 0·5 M HCl is faster than the methylation ($k_2>k_1$), and close to the overall experimental rate (5·4 vs 6·8 M^{-1} s^{-1}); this indicates that the pathway from **1** to **3** actually occurs, at least at low HCl concentration. Consistently with this conclusion, when comparing the kinetics of the reaction of **1** and **2** it can be observed that k_{3+4} in the reaction of **2**[4] is faster than in the reaction of **1** (this work), which strongly confirms that the step **1→3** is important in the reaction of unprotonated **1**. Confirming the involvement of methanol in the reversible **1⇌2** reaction, when the reaction was carried out in THF–H_2O methylation, obviously was not observed, the rate of reaction was slightly higher and only chlorination of **1** to **3** was observed.

An additional agreement with the proposed reaction scheme is offered from an alternative treatment of the kinetic results considering that only one pathway of chlorination occurs. The data are shown in Table 5. It can be observed that when the chlorination of **1** is neglected ($k_2=0$), the value calculated for k_3 is very close to that obtained in the reaction of **2** (see the data in Ref. 3), which is consistent with a prevailing pathway **2→4** when starting from **2**. When the chlorination of **2** is neglected ($k_3=0$), the value calculated for k_2 is very close to that shown in Table 4, consistent with a prevailing **1→3** pathway when starting from **1**, as concluded before. Nevertheless, the best calculated values and full agreement between simulated and experimental curves [Figures 1–3 and Figures 7–10 (not shown here; for the reactions carried out at 60 °C)], are obtained when both reaction pathways are included in the differential equation set.

Which is the electrophilic chlorinating agent is not easy to establish under the present reaction conditions. Although the possibility that chlorine can be formed from reaction with traces of oxygen remaining in the sealed ampoules cannot be completely discarded, each ampoule was carefully flushed with nitrogen before sealing, and no differences in the proportion of chlorination products were observed when the ampoules were not sealed under nitrogen. Also, the possibility that traces of metal salts that could act as catalysts being dissolved in the reagent was also checked by using HCl of different brands, and discarded since similar results were obtained in all cases. The fact that the reaction was faster at low HCl concentrations also made



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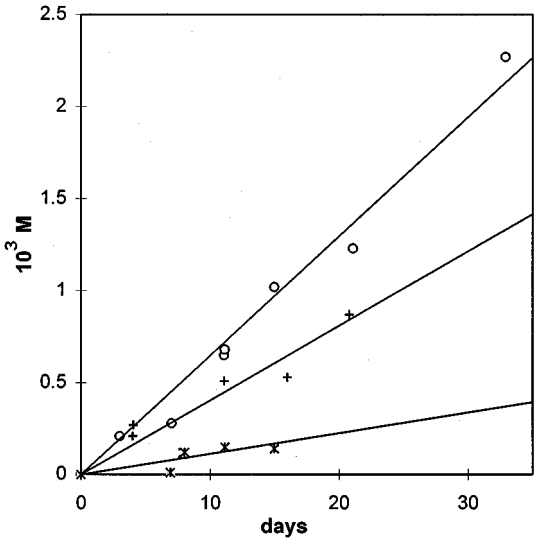

Figure 6. Formation of **3**+**4** at different [HCl]; (○ 0·5; (+) 0·85; (∗) 1·57 M

it highly improbable that the reaction could be due to trace impurities in the reagent. A speculative mechanism involving a common intermediate for the chlorination and cyclization reactions could be envisaged, but it would require further studies to confirm it.

A further analysis of the data from this work shows that the second-order rate coefficients for the demethylation of **2**, listed in the last column of Table 5, are similar to the calculated values of k_5 determined in the present work for the same reaction, but from a completely independent set of data. The good agreement between both sets of values, in spite of the complexity of the reaction scheme, gives confidence in the treatment of the kinetic results. The rate coefficients, k_4, for the methylation of **2**, determined in the present work, are of the same order of magnitude as those obtained for the reaction of **2** under similar reaction conditions.[7]

Table 5. Reaction of 2-amino-5-chlorobenzophenone (**1**) with HCl 1:1 (v/v) methanol–H_2O: alternative calculations[a]

			$10^7 k_\psi$ (s^{-1})			
T (°C)	[HCl] (M)	k_{exp}	k_1	k_2	k_3	k_4
80	0·5	3·4	3·7	0	60	0
			0·23	3·2	0·0	0
	0·84	3·9	4·0	0	19	0
			1·4	3·3	0	2·4
	1·57	10	8·6	0	3·5	15
			8·1	0·46	0	15
60	0·5	0·54	8·6	0	3·5	15
			8·1	0·46	0	15
	0·86	0·74	0·47	0	9·8	0
			0·06	0·62	0	0

[a] The partial rate constants shown were obtained by considering that chlorination occurs (i) only from **2** (first line) and (ii) only from **1** (second line), for each [HCl].

Regarding the relevance that the present findings could have on studies of the acidic hydrolysis of diazepam, the present results apply strictly to the reactions of **1** with HCl in 1:1 MeOH–H_2O. The point related to the present study is that the reported methods for the determination of benzodiazepines and their metabolites are based on a previous treatment of the sample which is heated (often at 100 °C) with HCl to effect the hydrolysis.[11–16, 24] As is demonstrated in the present work that **1** and **2** react with HCl, it is reasonable to assume that studies dealing with the metabolism of diazepam and/or of other related benzodiazepines may have overestimated the extent of metabolism of these compounds, since the standard analytical procedures include a pretreatment of the sample by heating it with HCl for 15–30 min. Although the observation of 'unexpected' products has not been reported before, 'unknown peaks' have been described in some GC and HPLC studies,[1, 25, 26] and also in thin-layer chromatography of the acid hydrolysis of some benzodiazepine derivatives[12] and in aged samples of benzodiazepines that were studied by FT-IR and NMR spectroscopy.[4]

The mechanism(s) by which cyclization occurs under the present reaction conditions is(are) not entirely clear. Compounds **6** and **7** were independently prepared by dehydrochlorination of 5-chloro-2-amino-2′-chlorobenzophenone with sodium hydride in anhydrous THF, followed by chlorination with sulphonyl chloride and further methylation with CH_3I, conditions that are different from those of the present study. Although the chlorine atom at the 3-position seems to be necessary, because monochlorinated acridinones were not detected, further research is needed to explain these odd reactions that occur to a smaller extent.

CONCLUSIONS

The present work demonstrates that unexpected chlorinations and cyclizations occur in the reactions of 2-aminobenzophenones with HCl in MeOH–H_2O. The decrease in the chlorination rates with increasing HCl concentration indicates that the reaction occurs with unprotonated **1**; this and the position at which the reactions occur are consistent with an electrophilic aromatic substitution mechanism. On the other hand, the increase in methylation and demethylation rates with increasing HCl concentration suggests the involvement of protonated reactants. A complex reaction scheme that includes parallel and consecutive reactions, some of them reversible, is confirmed by the good agreement between the experimental data and the simulated plots obtained from solving the proposed differential equation system. A simpler reaction scheme in which methylation and/or demethylation are not reversible did not give satisfactory agreement.

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