Kinetics and Reactivity of Substituted Anilines with 2-Chloro-5-nitropyridine in Dimethyl Sulfoxide and Dimethyl Formamide

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ABSTRACT: The kinetics of the reaction of substituted anilines with 2-chloro-5-nitropyridine were studied in dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) at different amine concentrations and temperatures in the range 45–60°C. In both solvents the reaction was not a base-catalyzed one. A plot of $\Delta H^{\#}$ versus $\Delta S^{\#}$ for the reaction in DMSO and DMF gave good straight lines with isokinetic temperatures 128°C and 105°C, respectively. Good linear relationships were obtained from the plots of log k_1 against σ° values at all temperatures with negative ρ values (-1.63 to -1.28 in DMSO) and (-1.26 to -0.90 in DMF). © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 645–650, 2002

INTRODUCTION

Kinetic studies of nucleophilic substitution reactions of activated aromatic substrates with amines have been the subject of many excellent reviews and books [1–6]. On the other hand, several investigations have demonstrated a great increase in the reactivity of the anionic nucleophiles in dipolar aprotic solvents due to the increase of the basicity of the base [7–10].

It was found that the presence of an electronegative nitrogen atom in the aromatic ring, such as pyridine derivatives, makes nucleophilic substitution much easier than that in the presence of corresponding benzenes [8–12]. As a part of the broad program of study of N-hetero atom and the transmission of the substituent electronic effect in the nucleophile, the kinetic data of the reaction of 2-chloro-5-nitropyridine (**1**) with substituted anilines **2a–g** in dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) are reported so to identify and assess the relative importance of solvation factors. During this study the applicability of Hammett linear free energy relationship is tested and the nature of the transition state developed is discussed.

EXPERIMENTAL

The melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were (in $CDCl_3$) measured on JEOL EX-270 spectrophotometer equipped with a variable temperature accessory; all the spectra were calibrated

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against Me_4Si as internal standard. IR spectra (KBr pellets) were measured on a Perkin–Elmer Paragon 1000. Electronic spectra were measured on UV–vis Shimadzu 160-A spectrophotometer. Elemental analyses of the reaction products were carried out at the Faculty of Science, Alexandria University, Egypt.

Starting Material

The purification of DMSO [13], DMF [14], aniline, and 2-chloro-5-nitropyridine has been described previously [15]. The used 4-methylaniline, 4-methoxyaniline, 4-chloroaniline, 4-bromoaniline, 3-methylaniline, and 3-chloroaniline were commercial specimens (Aldrich products). They were purified by crystallization or vacuum distillation.

General Procedure

A mixture of 2-chloro-5-nitropyridine (**1**) (0.5 g; 3.14 mmol) and anilines **2a–g** (5 mmol) was refluxed for 1–2 h in DMSO or DMF (5 ml). The mixture was cooled and then poured into ice-cold water with vigorous stirring, the formed precipitate was filtered and recrystallized from benzene–petroleum ether mixture as colored needles. The physical properties, spectral, and elemental analyses are given in Table I.

Kinetic Measurements

The reactions of 2-chloro-5-nitropyridine (**1**) with substituted anilines **2a–g** in DMSO and DMF were followed spectrophotometrically at 45, 50, 55, and 60°C in all the studied reactions. The recorded spectra at the end of the reaction were identical to the spectra of the corresponding authentic sample of the substitution product in the same solvent. A stock solution of **1** in DMSO and DMF was prepared (5×10^{-3} M) and diluted to 5×10^{-4} M before use. Solutions of the various anilines (1 M) were prepared, just before use, by dissolving a weighed amount of **2a–g** in a known volume of DMSO and DMF. Solutions of **1** and **2a–g** were seperately allowed to attain the desired temperature ±0.5°C in a thermostat bath before being mixed. The resulted change in absorbance with time was recorded on UV–vis Shimadzu 160-A spectrophotometer at $\lambda = 390$ nm.

The first-order rate constants k_Ψ were calculated using Eq. (1), where A_0, A_t, and A are the values of the absorbance at zero time, time t, and at the end of the reaction respectively.

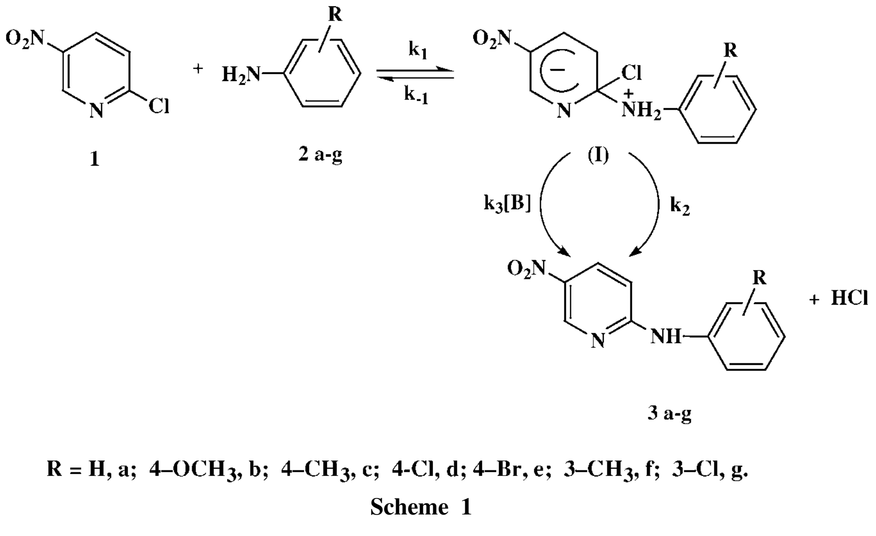
$$\ln(A - A_t) = -k_\Psi t + \ln(A - A_0) \tag{1}$$

A second-order reaction rate k_A was calculaled from the obtained straight lines passing through the origin as a result of the plots of the reaction rate constant (k_Ψ) values versus substituted aniline **2a–g** concentrations (in the range 0.1–1 M), while the concentration of compound **1** remained constant (5×10^{-4} M) [Eq. (2)].

$$k_A = k_\Psi / [\mathbf{2a\text{–}g}] \tag{2}$$

RESULTS AND DISCUSSION

The reaction of 2-chloro-5-nitropyridine **1** with meta- and para-substituted anilines **2a–g** in DMSO and DMF gave the expected corresponding substitution products **3a–g**, (Scheme 1). Elemental analyses, UV, IR, and ^{1}H NMR spectra indicated an anilino-dechlorination process (Table I).



R = H, a; 4–OCH$_3$, b; 4–CH$_3$, c; 4-Cl, d; 4–Br, e; 3–CH$_3$, f; 3–Cl, g.

Scheme 1

Table I Properties, UV, IR, and ^{1}H NMR Spectral Data of 2-Anilino-5-nitropyridines (**3a–g**)

						$\bar{\upsilon}$ (cm^{-1})			^{1}H NMR [δ (ppm)] in CDCl$_3$									Calc. (%) (Found)		
Compound	R	Yield (%)	m.p. (°C)	λ[a] (nm)	ε (l^{-1} mol^{-1} cm^{-1})	NO$_2$	C═N	NH		$H_{2',6'}$ (d, 2H)	$H_{3',5'}$ (d, 2H)	$H_{4'}$ (t, 1H)	H_3 (d, 1H)	H_4 (d, 1H)	H_6 (s, 1H)	–NH[b] (s, 1H)	Molecular Formula	C	H	N
3a	H	74	144	391	23940	1508	1535	3341		6.94	7.13	7.06	6.46	8.02	8.92	10.12	$C_{11}H_9N_3O_2$	61.39	4.18	19.35
				264	6500	1350												(61.27)	(4.09)	(18.97)
3b	4OCH$_3$[c]	72	149	401	22340	1503	1530	3329		6.85	7.18		6.52	8.12	8.88	10.98	$C_{12}H_{11}N_3O_3$	58.77	4.48	17.14
				264	11350	1351												(58.76)	(4.45)	(17.06)
3c	4CH$_3$[d]	75	139	399	21790	1501	1533	3339		6.82	7.16		6.48	8.08	8.86	10.27	$C_{12}H_{11}N_3O_2$	62.88	4.80	18.34
				266	7330	1354												(62.84)	(4.72)	(18.23)
3d	4Cl	88	184	392	18200	1510	1531	3334		6.92	7.21		6.56	8.16	8.96	10.80	$C_{11}H_8N_3O_2Cl$	52.90	3.20	16.83
				265	7800	1355												(52.83)	(3.14)	(16.53)
3e	4Br	71	153	391	24820	1511	1536	3346		6.96	7.22		6.58	8.14	8.98	10.75	$C_{11}H_8N_3O_2Br$	44.89	2.72	14.28
				286	23390	1358			H_2	H_4	H_5	H_6						(44.78)	(2.58)	(14.12)
3f	3CH$_3$[e]	89	122	394	15720	1503	1535	3336	(s, 1H)	(d, 1H)	(t, 1H)	(d, 1H)	6.50	8.10	8.86	10.25	$C_{12}H_{11}N_3O_2$	62.88	4.80	18.34
				263	7030	1352			6.90	7.12	7.18	7.00						(62.83)	(4.78)	(18.31)
3g	3Cl	83	169	386	19080	1508	1530	3332	7.16	7.38	7.22	7.13	6.54	8.12	8.92	10.82	$C_{11}H_8N_3O_2Cl$	52.90	3.20	16.83
				264	11410	1356												(52.87)	(3.16)	(16.78)

[a] In DMSO.

[b] Disappear in D$_2$O.

[c] 4OCH$_3$ appear at δ 3.58 (s, 3H).

[d] 4CH$_3$ appear at δ 2.35 (s, 3H).

[e] 3CH$_3$ appear at δ 2.34 (s, 3H).

The generally accepted mechanism of S_NAr reactions, when primary or secondary amines are used as nucleophiles, is well established [7,14,16–21], (Scheme 1).

Application of the steady-state hypothesis gives [Eq. (3)]

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \tag{3}$$

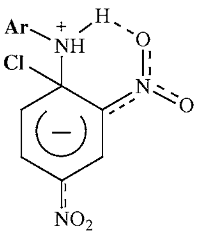
where k_A is the observed second-order rate constant and "B" can be either a second molecule of the nucleophile or an added base.

The rate-limiting step can be either the formation of the zwitterionic intermediate (I) or its decomposition giving the products. If $k_{-1} \ll (k_2 + k_3[B])$, then $k_A = k_1$ and the reaction is not base catalyzed. It has been suggested that the mechanism of the uncatalyzed path could be similar to that of the catalyzed one with a solvent molecule acting as the base [14,21–27]. It has been found that this mechanism is not tenable in hydroxylic solvents as well as when using a secondary amine as nucleophile and chlorine as leaving group [28]. The solvent-catalyzed mechanism is largerly different in rates in solvents of widely different basicity [14,17,21].

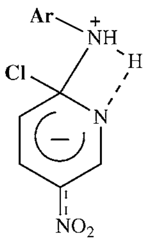
The reaction of 2-chloro-5-nitropyridine (**1**) with substituted anilines **2a–g** in DMSO and DMF is not a base catalyzed one (see Experimental section), hence $k_A = k_1$, and the formation of (I) is the rate-limiting step. The k_1 values for the previous reactions at 45, 50, 55, and 60°C are given in Tables II and III.

Examination of the data in Tables II and III shows that there is a decrease in the k_1 values from DMSO to DMF by ca. 2–6 times. This difference in the rate depends on both the nature and the position of the substituent in the aniline ring. For example the relative reactivity of **1** with aniline in DMSO and DMF is 2.6:1 similar to that obtained for the reaction of the same nucleophile with 1-chloro-2,4-dinitrobenzene [21] (3.2:1). These results are in accordance with the fact that DMSO is more basic and has a more solvating power than DMF [13,29,30].

The span of the reactivities, however, for the reaction of 1-chloro-2,4-dinitrobenzene with aniline at 30°C in DMSO ($k_2 = 4.33 \times 10^{-4}$ l mol^{-1} sec^{-1}) and in DMF ($k_2 = 1.35 \times 10^{-4}$ l mol^{-1} sec^{-1}) [21] is greater than the k_1 values (calculated theoritically and obtained by extrapolation) for the reaction of **1** with the same nucleophile in DMSO (3.59×10^{-4} l mol^{-1} sec^{-1}) and in DMF (1.053×10^{-4} l mol^{-1} sec^{-1}) under the same conditions. This is explained by the fact that the presence of an ortho-nitro group in 1-chloro-2,4-dinitrobenzene is more effective than the presence of an ortho-aza function in **1**. This may be due to the following reasons: (a) The hydrogen bond formation between the ammonium hydrogen and the ortho-nitro group (**II$_a$**) is greater than with an aza group (**II$_b$**).



II$_a$



II$_b$

Such a hydrogen bond has been shown to stabilize Meisenheimer complex of the type II, (b) the release of steric strain in the transition state derived from 1-chloro-2,4-dinitrobenzene leads to steric acceleration of the rate [19,21]; (c) The nitro group stabilizes the developed negative charge more than an aza group in the transition state [18,19]. Also by comparing the

Table II Second-Order Rate Constants k_A, Activation Parameters, and ρ for the Reaction of 2-Chloro-5-nitropyridine (**1**) with Substituted Anilines **2a–g** in DMSO

		k_1 (10^{-4} l mol^{-1} sec^{-1})					
Compound	R	45°C	50°C	55°C	60°C	$\Delta H^{\#}$ (kJ mol^{-1})	$-\Delta S^{\#}$ (J mol^{-1} K^{-1})
2a	H	17.8	25.7	36.7	51.9	60.6 (±0.5)	107.7 (±1.7)
2b	$4OCH_3$	44.9	60.2	80.2	105.8	47.9 (±0.8)	139.7 (±1.9)
2c	$4CH_3$	29.9	41.1	56.0	75.7	52.2 (±0.4)	129.8 (±1.0)
2d	4Cl	4.9	7.8	12.4	19.3	78.7 (±0.8)	61.5 (±2.3)
2e	4Br	6.9	10.6	16.1	24.2	71.2 (±0.7)	82.3 (±2.0)
2f	$3CH_3$	22.0	31.5	44.6	62.4	58.8 (±0.5)	111.5 (±1.6)
2g	3Cl	4.4	6.8	10.6	16.2	74.6 (±0.7)	75.4 (±2.3)
ρ		−1.63 (±0.01)	−1.51 (±0.01)	−1.40 (±0.01)	−1.28 (±0.02)		
r		0.99	0.99	0.99	0.99		

Table III Second-Order Rate Constants k_A, Activation Parameters, and ρ for the Reaction of 2-Chloro-5-nitropyridine (**1**) with Substituted Anilines **2a–g** in DMF

		k_1 (10^{-4} l mol^{-1} sec^{-1})				$\Delta H^{\#}$	$-\Delta S^{\#}$
Compound	R	45°C	50°C	55°C	60°C	(kJ mol^{-1})	(J mol^{-1} K^{-1})
2a	H	6.8	10.5	15.9	23.8	27.1 (±0.7)	82.5 (±2.1)
2b	4OCH3	15.1	21.3	26.6	40.8	55.8 (±0.8)	124.0 (±1.8)
2c	4CH3	10.4	15.3	22.2	31.9	63.2 (±0.8)	130.9 (±2.6)
2d	4Cl	2.6	4.4	7.2	11.7	85.6 (±1.1)	45.1 (±1.3)
2e	4Br	3.3	5.4	8.7	13.9	82.2 (±0.7)	53.9 (±2.1)
2f	3CH3	8.2	12.2	18.1	26.4	66.5 (±0.7)	95.5 (±2.1)
2g	3Cl	2.4	4.1	6.8	11.2	87.2 (±1.5)	40.7 (±4.5)
ρ		−1.26 (±0.01)	−1.14 (±0.01)	−1.02 (±0.01)	−0.90 (±0.01)		
r		0.99	0.99	0.99	0.99		

reactivity of compound **1** in DMSO at 55°C ($k_1 = 36.72 \times 10^{-4}$ l mol^{-1} sec^{-1}), Table II, with that of the reaction of the corresponding *p*-nitrochlorobenzene towards aniline ($k_2 = 6.28 \times 10^{-6}$ l mol^{-1} sec^{-1}), which is studied spectrophotometrically in DMSO at 55°C (using 5×10^{-3} of the substrate and 1 M aniline), it is found that the expected higher reactivity of the former compound is due to the presence of an aza group which stabilizes the negative charge developed in the transition state [18,19].

In both solvents, the entropy of activation values $\Delta S^{\#}$ are negative as expected for bimolecular reaction (Tables II and III). The low negative $\Delta S^{\#}$ values in DMSO than in DMF indicated that

(a) the order of the transition state is sensitive to the change in nature of the solvent;
(b) the present reaction involves a neutral nucleophile and a negatively charged leaving group Cl^-, therefore there are two different charges on the transition state and hence their solvation energies are different;
(c) the transition state is a dipolar one because there is a concomitant development of a delocalized negative charge in the hetarene ring and an sp^3 positively charged nitrogen atom, transition state (I) (Scheme 1). The solvation of (I) in DMSO and DMF presumably arises from an ion–dipole interaction suggesting that it is weaker in DMF; and
(d) the transition state is more strongly solvated by basic solvents when amines are used as nucleophiles [1–5].

Within the same series, electron-donating substituents in aniline moiety, intensify the lone pair on the nitrogen atoms, i.e. increase the nucleophilicity. This favors the formation of more ordered transition states reflecting high negative entropies of activation $\Delta S^{\#}$. In contrast, the presence of electron-withdrawing substituents in the aniline moiety reduces the ability of attachment of the lone pair on the nitrogen atom, thus reflecting low negative entropies of activation.

Tables II and III show the order of decreasing reactivity of substituted anilines towards **1** in DMSO and DMF: $4OCH_3$, $4CH_3$, $3CH_3$, H, 4Br, 4Cl, 3Cl. Consequently, the variation of the rate constants depends upon the nature and position of the substituent in the aniline moiety. It is useful to correlate the effect of meta- and para-substituents in the substrate or the nucleophile with the reactivity to investigate the properties of the activated complex. Plots of log k_1 values in DMSO and DMF at different temperatures versus the σ° constants [31] for the various substituents in the aniline moiety gave good straight lines with ρ values varying between (-1.63 ± 0.01; $r = 0.99$ to -1.28 ± 0.02; $r = 0.99$) and (-1.26 ± 0.01; $r = 0.99$ to -0.90 ± 0.01; $r = 0.99$) respectively (Tables II and III). The negative ρ values are due to the presence of substituent on the nucleophile [20] and their low values suggest a very weak development of positive charge implying a rather reactant-like TS.

A plot of $\Delta H^{\#}$ against $\Delta S^{\#}$ for the reaction in DMSO and DMF gave good straight lines of slopes 128°C and 105°C, respectively which are the values of isokinetic temperatures for these reactions (the temperature at which the substituent effect is supposed to be reversed). The previous values were far from the temperatures used during the kinetic runs. Furthermore the mechanism for the reaction series in both solvents was similar and common for all members. A significant feature of the results is that a plot of log (k/k_0) for the reaction of **1** in DMSO against log (k/k_0) in DMF exhibits a linear relationship with a slope very close to unity (gradient $= 0.99 \pm 0.04$; $r = 0.99$). This indicates that the structure of the transition state is not

Table IV Some Solvent Parameters for DMSO and DMF [28]

Solvent	ε	E	π^*
DMSO	46.45	3.2	1.00
DMF	36.71	2.6	0.88

significantly altered by the change of the substituent in the nucleophile as well as the nature of the solvent despite the difference in reactivity caused by this change.

Attempts were made to correlate some qualitatively solvent parameters to our reaction and the developed transition state. It is concluded from Tables II, III and IV that (a) the present reaction becomes faster in media of high dielectric constant $(\varepsilon)k_{\mathrm{H}}$ (DMSO)/k_{H} (DMF) = 2.45 at 50°C, (b) the rate becomes larger in solvents of high electrophilic solvation parmaters, E values, and (c) the reaction rate is enhanced with increasing the solvatochromic values of the scale parameter π^* which is an index of solvent dipolarity and measure the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect.

These informations enable us to deduce that the activated complex is a dipolar intermediate and the reaction proceeds via two-step mechanism (S_NAr) similar to the commonly accepted aromatic bimolecular process in which the formation of intermediate (I) is the rate-determining step with rapid decomposition of this intemediate leading to the products **3a–g** ($k_2 \gg k_1 > k_{-1}$) [27b, 32–34] (Scheme 1).

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