

Nucleophilic aromatic substitution reactions promoted by aryl and heteroaryl amine nitranions

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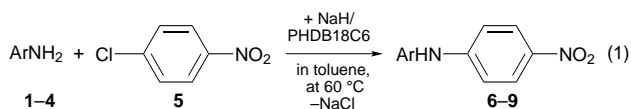
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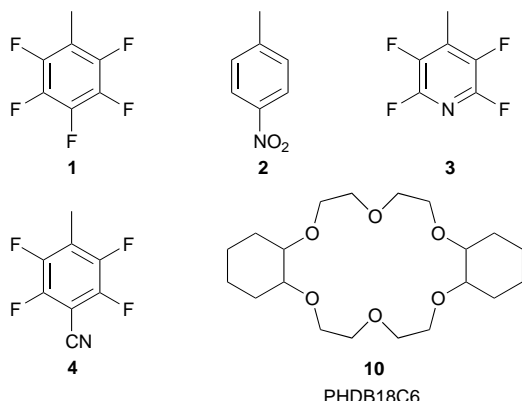
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The nucleophilic substitution reaction of chlorine in 4-chloronitrobenzene by *N*-anions from aryl and heteroarylamines **1–4**, to give the corresponding diarylamines, has been studied in solvents of different polarity (toluene and DMSO). The reactivity of these nitranions is found to be two orders of magnitude higher in DMSO. Such a difference is attributed to the different reacting species (ion pairs and free ions in toluene and DMSO, respectively). The β_{Nu} values obtained (0.31 and 0.26), very similar and relatively low, suggest a moderate extent of charge transfer from nucleophile to substrate in the transition state of both systems.

Diarylamines are very important industrial intermediates. They are used as stabilizers and antioxidants for rubber and polymers, stabilizers for explosives, polymerization and corrosion inhibitors, and in dye preparation.¹ For this reason, diarylamines are currently produced on a large scale ($>10^5$ tons per year) world-wide, principally by Monsanto, Bayer, and Uniroyal.² These compounds are prepared industrially by the condensation of an aromatic amine with phenol in the presence of a mineral acid at high temperature (325 °C), or by reaction of the appropriate aniline with activated halobenzenes, such as 4-nitro or 2,4-dinitro derivatives, in the presence of copper salts and potassium carbonate, at 200 °C.¹



Ar = C₆F₅ (**1**), 4-NO₂C₆H₄ (**2**), C₅F₄N- (**3**), 4-CNC₆F₄ (**4**)

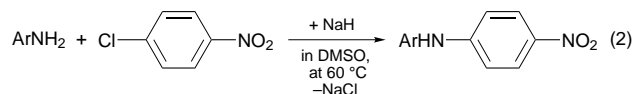


In addition, some examples of the synthesis of diarylamines under phase-transfer-catalysis (PTC) conditions have been reported in the literature. They concern the reaction of arylamides with halobenzenes catalyzed by TDA-1³ and reactions of arylamines with halonitrobenzenes in the presence of copper salts, alkali carbonate and catalytic amounts of

dibenzo-18-crown-6 or quaternary onium salts.⁴ Very recently, a convenient procedure for the synthesis of substituted diphenylamines under PTC conditions with concentrated bases was reported.⁵

The present work reports a kinetic study of the formation reaction of nitrodiarylamines **6–9** from arylamines **1–4** and 4-chloronitrobenzene **5** in toluene in the presence of perhydrodibenzo-18-crown-6 PHDB18C6 **10** and solid NaH (reaction 1).

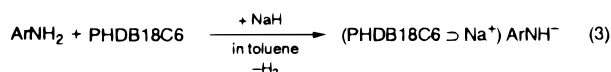
Reaction 1 has also been performed in DMSO for the sake of comparison (reaction 2).



Results and Discussion

Formation of the nitranions **1a–4a**

The aryl and heteroarylamine nitranions ArNH[–] **1a–4a** were generated by stirring, under argon atmosphere, a toluene solution of amine **1–4** and PHDB18C6 **10**, in comparable amounts, with a three-fold excess of NaH as solid phase, at 25 or 60 °C (reaction 3). The anion formation was monitored spectroscopically by UV-visible and ¹H or ¹⁹F NMR spectroscopic determinations.



As shown in Table 1, the UV/VIS absorption maxima of the nitranions of pentafluoroaniline **1a**, 4-aminotetrafluoropyridine **3a** and 4-cyanotetrafluoroaniline **4a** unfortunately overlap with those of the corresponding amines, **1**, **3** and **4**, respectively, and for this reason only the ionization of 4-nitroaniline **2** could be observed. Fig. 1 shows that the nitration of 4-nitroaniline **2** is completely generated after 20 min at 60 °C and about 10% after the same time at room temperature (see Experimental).

Since amines **3** and **4** are more acidic^{6–8} than 4-nitroaniline **2** (see Table 1), the rate of formation of their anions, **3a** and

Table 1 UV/VIS absorption maxima of arylamines **1–4** and their complexed sodium salts (PHDB18C6 \supset Na⁺)ArNH[−] in toluene at 25 °C

	Arylamine ^a	pK _a ^b	λ_{\max}/nm	
			ArNH ₂	(PHDB18C6 \supset Na ⁺)ArNH [−]
1	C ₆ F ₅ NH ₂	23.1	285 ^c	286 ^c
2	4-NO ₂ C ₆ H ₄ NH ₂	21.5	343 ^c	444 ^c
3	4-NC ₅ F ₄ NH ₂	19.2	282	289
4	4-CNC ₆ F ₄ NH ₂	17.9	285	314

^a [Arylamine] = 1.6–2.8 × 10^{−4} M. ^b Values related to 9-phenylfluorene as a standard (pK_a = 18.5). ^c Same values at 25 and 60 °C.

4a, is expected to be at least the same. For the same reason no predictions can be made for the less acidic^{6–8} pentafluoroaniline **1**.

Nitranions **1a–4a** were also generated in DMSO, using in this case a large excess (10–100 molar equivalents) of lithium and sodium hydrides or potassium dimsyl (CH₃SOCH₂[−]) as the bases. Since both DMSO and the dimsyl anion absorb in the same region as the amines **1**, **3** and **4** (250–340 nm) only the UV spectra of 4-nitroaniline **2** and its anion **2a** with different cations (Li⁺, Na⁺ and K⁺) were recorded. The λ_{\max} values are reported in Table 2 together with those of 1-amino-4-nitronaphthalene **11** whose pK_a (18.0)⁹ is in the same acidity range as the arylamines studied. As shown in Table 2, the position of the UV/VIS absorption maxima of nitranions **2a** and **11a** does not depend on the metal cation, clear evidence that in DMSO they exist mainly as free ions ArNH[−].^{10–12}

The time required for the anion generation was evaluated in both deuterated benzene and DMSO by ¹H and ¹⁹F NMR spectroscopy. The method is based on the variation of the chemical shift δ of the atoms in positions sensitive, upon molecule ionization, to the electron density redistribution, in our case the fluorine 4 atom in pentafluoroaniline **1**, the two hydrogen 2 atoms in 4-nitroaniline **2**, and the two fluorine 2 atoms in both 4-aminotetrafluoropyridine **3** and 4-cyanotetrafluoroaniline **4**. The results (see Table 3 for pentafluoroaniline **1**) evidence the different time necessary for quantitative anion formation in the two solvents. In the less polar benzene, an almost constant concentration of nitranion

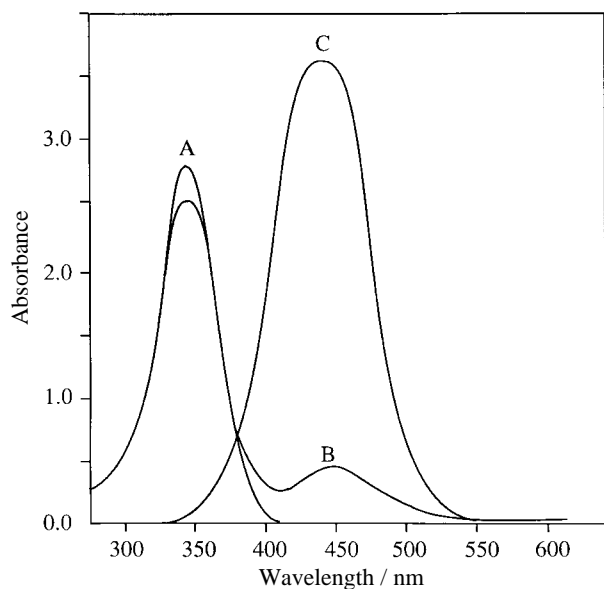


Fig. 1 UV/VIS spectra of 4-nitroaniline **2** 1.8 × 10^{−4} M in toluene in the presence of PHDB18C6 **10** at 25 °C (curve A); 20 min after the addition of NaH, at 25 °C (curve B); or 60 °C (curve C)

Table 2 UV/VIS absorption maxima of arylamines **2a** and **11b** and their alkali metal salts ArNH[−]M⁺ (M = Li, Na, K) in DMSO at 25 °C

		λ_{\max}/nm
2	4-NO ₂ C ₆ H ₄ NH ₂ 4-NO ₂ C ₆ H ₄ NH [−]	383 463 ^c
		440 445 ^c

^a [**2**] = 1.2–1.7 × 10^{−4} M. ^b [**11**] = 1.0–3.1 × 10^{−4} M. ^c Same value for Li⁺, Na⁺ and K⁺.

Table 3 ¹⁹F NMR chemical shifts of the fluorine 4 atom in pentafluoroaniline **1** and its nitranion **1a** in C₆D₆ and (CD₃)₂SO

ArNH ₂ ^a	Solvent	$\delta_{\text{ArNH}_2}^*/\text{ppm}$	$\Delta t/\text{min}$	$\delta_{\text{ArNH}^-}^*/\text{ppm}$
	C ₆ D ₆	−168.0 ^b	0	—
			2	−172.2 ^b
			20	−185.0 ^b
			30	−187.7 ^b
			40	−189.2 ^b
	(CD ₃) ₂ SO	−167.1 ^c	0	—
			2	−182.0 ^c
			12	−184.5 ^c
			20	−185.2 ^c
			30	−185.5 ^c

^a [Aniline] = 2.5–10 × 10^{−2} M. ^b At 60 °C. ^c At 25 °C.

(PHDB18C6 \supset Na⁺)ArNH[−] is achieved in 20–30 min at 60 °C with pentafluoroaniline **1**, whereas only 4 min at 25 °C are sufficient for the most acidic 4-cyanotetrafluoroaniline. By contrast, in DMSO, the nitranions ArNH[−] are generated much faster. In this solvent a constant concentration is obtained after only 2–3 min at room temperature, whatever the arylamine acidity may be.

Reactivity of the nitranions **1a–4a**

A kinetic study of the nucleophilic substitution of chlorine in 4-chloronitrobenzene (4-CNB) **5** by amines **1–4** was carried

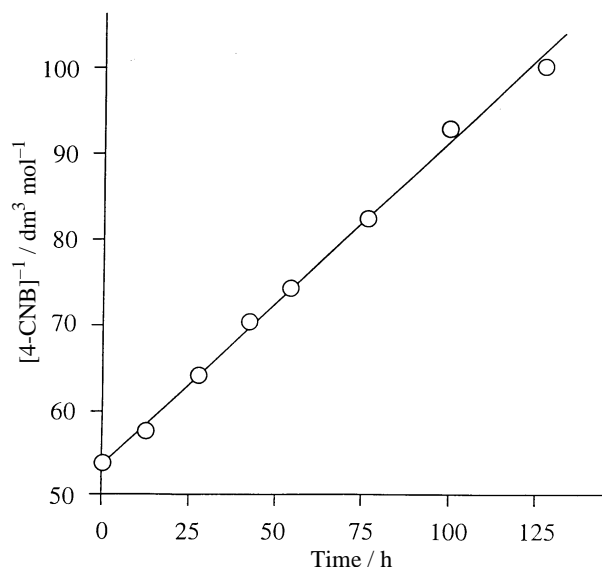


Fig. 2 Second-order plot for the reaction of 4-nitroaniline **2** (0.019 M) with comparable amounts of 4-chloronitrobenzene **5** and PHDB18C6 **10** in toluene at 60 °C

out in toluene by reacting comparable amounts of substrate **5** and the preformed (PHDB18C6 \supset Na⁺)ArNH[−] complex. Reaction rates were measured by potentiometric titration of the leaving group, in this case the chloride ion, or alternatively by measuring the disappearance of the substrate and/or the appearance of the diarylamine by GC analysis. Similar kinetics were performed in DMSO. All reactions follow regular second-order kinetics (eqn 4), as shown for a typical determination in toluene (see Fig. 2).¹³

$$\text{rate} = k[\text{Nitrane}][4\text{-CNB}] \quad (4)$$

The second-order rate constants k (M^{−1} s^{−1}) are reported in Table 4 together with those measured in DMSO. The nucleophilicity sequence found (**1** > **2** > **3** > **4**) is the same in both solvents. It reflects the increasing reactivity of the *N*-anion by increasing the amine basicity (Table 1). Comparison shows that nitrane ions **1a–4a** are 200–500-fold more reactive in DMSO than in toluene. Such behavior is most likely due to a change in the reacting species with diminishing solvent polarity. Whereas in DMSO ($E_T^N = 0.444$)¹⁴ mostly free ions ArNH[−] are found (see Table 2), in the less polar toluene ($E_T^N = 0.099$)¹⁴ ion pairs (crown \supset Na⁺) ArNH[−] are the major contributors to the overall anion reactivity.^{14–16} Since ion pairs are well known to be less reactive than the corresponding free ions, this is the main reason for the lower k values obtained in toluene.^{14–16}

Good correlations ($r = 0.993$ or better) were obtained in both solvents by plotting the corresponding $\log k$ vs. $\text{p}K_a$ in

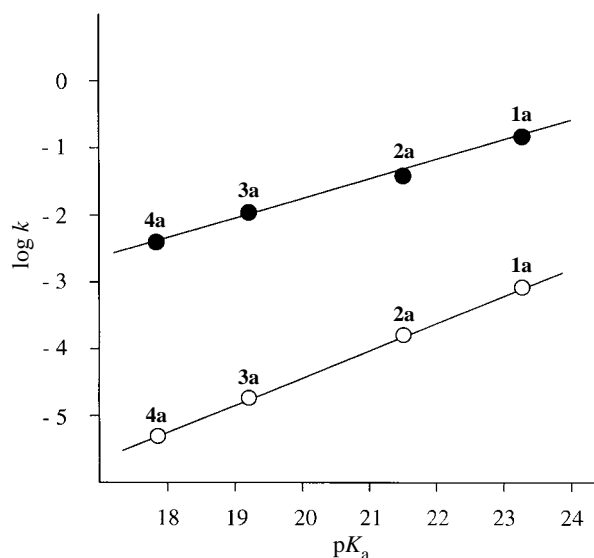


Fig. 3 Brønsted plot of the log of the rate constants k (M^{−1} s^{−1}) of nitrane ions **1a–4a** with 4-CNB **5** vs. the $\text{p}K_a$ values in DMSO of their conjugate amines **1–4** in toluene (○) and DMSO (●)

DMSO (see Fig. 3). The ‘Brønsted-like’ correlation obtained in toluene gives a β_{Nu} value (0.31) very similar to that (0.26) in DMSO (eqn 5 and 6).

$$\log k_{\text{toluene}} = 0.31\text{p}K_{\text{DMSO}} - 11.35 \quad (r = 0.993) \quad (5)$$

$$\log k_{\text{DMSO}} = 0.26\text{p}K_{\text{DMSO}} - 7.03 \quad (r = 0.996) \quad (6)$$

Even if β_{Nu} in toluene has no real significance if compared with that in DMSO, the similarity of these values seems to indicate that the sensitivity of the anions to changes in basicity is only slightly affected by the type of species (free ion or ion pair).¹⁷ In addition, these data suggest that the extent of charge transfer from the nucleophile to the substrate in the transition state of reaction 1 should be similar and not very advanced in either system.^{17,18}

Conclusion

The data as a whole highlight the considerable difference in reactivity of the *N*-anions **1a–4a**, according to the solvent polarity. Such behavior is mainly due to the different reacting species: mostly free ions in dipolar DMSO and ion pairs in the low polarity toluene. The good Brønsted correlations obtained, with very similar β_{Nu} values, suggest comparable transition states in both media. In addition, the results could suggest a possible alternative route for the synthesis of diarylamines, especially in the case of the most basic amines.

Experimental

Materials and solvents

Commercial sodium hydride (20% suspension in silicon oil) was washed twice before use with anhydrous *n*-hexane and then kept in a dry box under argon atmosphere in order to remove solvent traces. 4-Chloronitrobenzene **5**, 4-nitroaniline **2**, PHDB18C6 **10**, and dry DMSO were commercially available compounds, used without additional purification. Toluene was purified and dried using standard methods and stored over molecular sieves under nitrogen (Karl–Fischer titration showed a water content ≤ 30 ppm).¹⁹ Pentafluoroaniline **1**, 4-aminotetrafluoropyridine **3**, and 4-cyanotetrafluoroaniline **4** were prepared by known procedures.^{20–22}

Table 4 Second-order rate constants k (M^{−1} s^{−1}) of reaction 1 in toluene^a and DMSO^b at 60 °C

	ArNH [−]	10 ³ k / $\text{M}^{-1} \text{s}^{-1}$		$k_{\text{DMSO}}/k_{\text{toluene}}$
		Toluene	DMSO	
1	C ₆ F ₅ NH [−]	0.592 (74)	111.2 (26)	188
2	4-NO ₂ C ₆ H ₄ NH [−]	0.096 (12)	33.2 (8)	346
3	4-NC ₃ F ₄ NH [−]	0.023 (3)	11.2 (3)	487
4	4-CNC ₆ F ₄ NH [−]	0.008 (1)	4.25 (1)	531

^a A toluene solution (4–12 mL) of 4-chloronitrobenzene (0.02–0.2 M) and preformed nitrane (PHDB18C6 \supset Na⁺)ArNH[−] (0.02–0.2 M).

^b A DMSO solution (8–12 mL) of 4-chloronitrobenzene (0.02–0.04 M) and preformed nitrane ArNH[−] (0.02–0.04 M). ^c Average of at least two determinations. The error in these values is estimated to be 5%. ^d k_{rel} in parentheses.

General methods

The UV/VIS spectra were recorded on a Lambda-6 Perkin-Elmer spectrophotometer. ^1H and ^{19}F NMR spectra were recorded on a Bruker AC 300 spectrometer using C_6D_6 and $(\text{CD}_3)_2\text{SO}$ as solvents and C_6F_6 and tetramethylsilane as internal standards. Potentiometric titrations were carried out with a Metrohm 670 Titroprocessor by using a combined silver electrode isolated with a potassium nitrate bridge. Karl-Fischer determinations were carried out with a Metrohm 684 KF coulometer.

GLC data were obtained with an Alltech RSL-150 column ($10\text{ m} \times 0.35\text{ mm}$ polydimethylsiloxane, $0.25\text{ }\mu\text{m}$ thickness) or a Superox II column ($10\text{ m} \times 0.35\text{ mm}$ polyethylene glycol, $0.25\text{ }\mu\text{m}$ thickness).

UV/VIS spectra determinations. (a) An aliquot (3 mL) of a standardized toluene solution of amine and PHDB18C6 **10** in equal amounts (10^{-4} – 10^{-5} M) was placed in a 10 mm quartz cell and the UV spectrum was recorded. The remaining solution was added with a molar excess (about 3 molar equiv) of sodium hydride and magnetically ($800 \pm 50\text{ rpm}$) stirred. Samples (3 mL) were withdrawn at various times by stopping the stirrer for 20–40 s to allow adequate separation and then analyzed by UV spectroscopy. All measurements were carried out under argon atmosphere. In the case of 4-nitroaniline **2**, the concentration of amine present was calculated by the relation $A = \epsilon cl$, taking the absorbance value at $\lambda = 330\text{ nm}$ ($\epsilon = 13\,078\text{ M}^{-1}\text{ cm}^{-1}$) where the contribution of the nitranion is negligible.

(b) The DMSO solutions of amine and sodium hydride (10^{-4} – 10^{-5} M) in evacuated flasks were placed in an integrally soldered apparatus equipped with a flat quartz cell. The apparatus was evacuated to 10^{-4} mm Hg and then soldered off from the vacuum system. The spectra of arylamine and its anion were recorded in sequence.

NMR spectra measurements. A C_6D_6 solution (about 0.5–0.7 mL) of amine **1–4**, 4-chloronitrobenzene **5** and PHDB18C6 **10**, in equal concentrations (10^{-1} – 10^{-2} M), was placed in a NMR tube previously purged with argon. After the ^1H and ^{19}F NMR spectra had been recorded, a three-fold excess of NaH was added to the solution and the reaction mixture was heated to 60°C . NMR spectra were recorded at different times and the quantitative composition of the reaction mixture was calculated from the integral ratio.

Kinetic measurements. Kinetics were carried on in water-jacketed one-neck flasks containing toluene or DMSO solutions of preformed nitranion **1a–4a** and 4-chloronitrobenzene **5** in equal concentrations 0.02–0.04 M.

In a typical procedure, 8–10 flasks were thermostatted at $60 \pm 0.1^\circ\text{C}$, purged with argon and filled with sodium hydride (three-fold excess), and either a standardized toluene solution (4–6 mL) of the amine and crown ether **10**, or a standardized DMSO solution (4–6 mL) of amine. The solution was magnetically stirred long enough to generate the nitranion (10–30 min). After the stirring was stopped the appropriate standardized solution (4–6 mL) of 4-chloronitrobenzene **5** was added to the preformed nitranion and the timing started. At different times the reactions were quenched by adding 30–50 mL of methanol containing 1–2 mL of 32% HNO_3 and the Cl^- formed was titrated potentiometrically with 0.01 N AgNO_3 .

As an alternative, a standardized toluene solution (2 mL) of 4-chloronitrobenzene **5** (0.4 M) and *n*-tetradecane (0.2 M), as an internal standard, was added to a flask thermostatted at $60 \pm 0.1^\circ\text{C}$ containing a standardized solution (2 mL) of pre-

formed *N*-anion (0.4 M) and the timing was started. At different times aliquots were withdrawn, quenched with 0.5 mL of H_2O , dried with Na_2SO_4 , centrifuged and analyzed by GLC (see General methods).

The second-order rate constants were calculated using a least-squares computer program from the equation $1/[A] - 1/[A]_0 = kt$, where A = nitranion or 4-CNB (see Fig. 2). All rates involved at least 8–10 samplings and gave correlation coefficients of 0.993 or better.

Acknowledgements

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