JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18**: 880–885
Published online 6 June 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.957

Role of hydrogen-bonded nucleophiles in aromatic nucleophilic substitutions in aprotic solvents. Reactions of halonitrobenzenes with ethylenediamine, 3-dimethylamino-1-propylamine and histamine in toluene†

Cecilia E. Silvana Alvaro[1] and Norma Sbarbati Nudelman[2]*

[1]Departamento de Química, Facultad de Ingeniería, Universidad Nacional del Comahue, Buenos Aires 1400, 8300 Neuquén, Argentina
[2]Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P 3 Ciudad Universitaria (1428), Buenos Aires, Argentina

Received 20 January 2005; revised 23 March 2005; accepted 5 April 2005

ABSTRACT: The kinetics of the reactions between 1-halogeno-2,4-dinitrobenzene (halogen = F, Cl) and the amines ethylenediamine (EDA) and 3-dimethylamino-1-propylamine (DMPA) were studied in toluene at 25 ° ± 0.2C under pseudo-first-order conditions using varying amounts of amine. Even with Cl as the nucleofugue (where usually the first step is rate-determining), a third-order-in-amine kinetic law was observed: these results can be interpreted within the 'dimer nucleophile' mechanism where the amine homo-aggregates are better nucleophiles than the amine monomers. To confirm this interpretation, the reaction of 2,4-dinitrofluorobenzene with histamine was studied in the same solvent. Because of the rigid geometry, an intramolecular hydrogen bond is easily established, which prevents the formation of self-aggregates. Consequently, the plot of k_A vs. [histamine] is a straight line, as expected for a classical mechanism of base-catalysed decomposition of the zwitterionic intermediate. All these results are well explained in the frame of the 'dimer nucleophile' mechanism. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen bond; aromatic nucleophilic substitution; aprotic solvents; hydrogen-bonded nucleophiles; mixed aggregates; dimer nucleophile mechanism

INTRODUCTION

The role that inter- or intramolecular hydrogen bonding plays in defining the physical properties and reactivity of a large variety of structures is now widely recognized in chemical and biological systems.[1,2] On the other hand, other types of weak non-covalent interactions in determining chemical reactivity are also current subjects of increasing interest.[3,4] When the reactions are carried out in solution, intermolecular forces of different types are established that can be involved in the general concept of 'solvent effects', of which hydrogen bonding could be one of the more important specific microscopic interactions. Several scales of quantitative measures of solvent polarity have been proposed and reviewed recently.[5] The most successful solvent scales are those that involve several parameters, each one related to a specific solvent property.[6–8] Regarding the particular interaction of hydrogen bonding, the α and β parameters have been defined to be good descriptors of the ability of a solvent to be a hydrogen-bond donor or acceptor, respectively.[1,9]

Nevertheless, for the case of aprotic non-polar solvents, solute–solvent hydrogen bonding almost does not occur and properties measured in the gas phase or solid state can afford useful information. Fine measures of amine basicities in the gas phase have been reported recently,[10] as well as theoretical calculations, mainly performed by Zou and co-workers, at the HF/6–31G* level for different data sets of solvents.[11,12] The authors established linear correlations between empirical parameters and theoretical descriptors,[13] and Katritzky and co-workers[14] reported an extensive attempt to relate solvent scales to the theoretical descriptors. On the other hand, Spange and co-workers[15] estimated the empirical donor–acceptor and polarity parameters of several solids and they concluded that empirical polarity parameters are recommended as useful characteristics for describing the surface properties of several solids.

**Correspondence to:* N. S. Nudelman, Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P 3 Ciudad Universitaria (1428), Buenos Aires, Argentina.
E-mail: nudelman@qo.fcen.uba.ar
Contract/grant sponsor: University of Buenos Aires; *Contract/grant number:* EX213-UBA.
Contract/grant sponsor: Universidad Nacional del Comahue; *Contract/grant number:* I094-UNCo.
†Selected paper presented for a special issue dedicated to Professor Otto Exner on the occasion of his 80th birthday.

Aromatic nucleophilic substitution (S_NAr) by amines has been recognized to be extremely affected by the solvent.[16,17] Such study is currently receiving increased interest because S_NAr by amines is a suitable model to contribute to the understanding of the microscopic properties of solvent in reactions due to the complex interactions between the amine, the substrate and/or the intermediate that occur involving the solvent molecules.[18–20] The mechanisms of reactions in protic solvents are well established but S_NAr in aprotic solvents exhibits peculiar features for studying specific and non-specific solvent effects.[17] Evidence for nucleophile aggregation,[21] substrate–nucleophile electron-donor acceptor (EDA) complexes[22] and other types of complexes[23,24] has been reported by different authors when reactions were carried out in aprotic solvents.

In the present work, we describe the study of S_NAr using diamines that were purposefully selected for their special structures, because potentially they would be able to form intra- or intermolecular hydrogen bonds in aprotic solvents. The substrates are 2,4-dinitrochlorobenzene and 2,4-dinitrofluorobenzene: S_NAr of chlorine by amines is known to occur in the first rate-determining step but S_NAr of fluorine by amines is susceptible to base catalysis because the decomposition of the zwitterionic intermediate is very often rate-determining.[16,17]

RESULTS AND DISCUSSION

Self-association of amines to form mainly dimers by hydrogen-bonding interactions is a long-known phenomenon[25] and it has been shown that the dimers are responsible for the 'dimer nucleophile' mechanism when amines are used as nucleophilic reagents in S_NAr carried out in aprotic solvents.[21] Intermolecular hydrogen bonding increases the nucleophilicity of the dimer compared with the monomer, as confirmed by semi-empirical[17] and *ab initio* calculations.[26] On the other hand, when two amino groups are in a rigid appropriate geometry, strong intramolecular hydrogen bonding is easily established and such compounds exhibit unusually high basicity.[27]

To examine the importance of hydrogen-bonding interactions in S_NAr with amines carried out in aprotic solvents, the reactions of 2,4-dinitrofluorobenzene (DNFB) and 2,4-dinitrochlorobenzene (DNClB) with diamines in toluene were studied. The selected amines were ethylenediamine (EDA), 3-dimethylamino-1-propylamine (DMPA) and histamine, specially chosen for their potential ability to form inter- and/or intramolecular hydrogen bonding.

The reactions proceed in a straightforward manner to give the expected N-substituted-2,4-dinitroaniline, and a quantitative yield of the substitution product was obtained in all reactions under study. The determinations were carried out under pseudo-first-order conditions; the rate dependence on the amine concentration was studied and good kinetic behaviour was observed throughout the work.

Reactions of DNFB and DNClB with EDA and DMPA in toluene

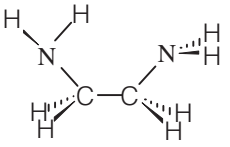
The kinetics of the reactions of DNFB and DNClB, both with DMPA and EDA, in toluene were studied at $25 \pm 0.2\,^{\circ}C$ in the presence of variable amounts of the nucleophile. Table 1 shows the observed results for the reactions with DNFB: the bimolecular rate coefficient k_A and the ratio k_A/[B] are given. Table 2 shows the corresponding values for the reactions of EDA and DMPA with DNClB in toluene. It can be observed that the second-order rate coefficient k_A increases rapidly with amine concentration [B] and the plot of k_A vs. [B] (see Fig. 1), shows a quadratic dependence. On the other hand, the plot of k_A/[B] vs. [B] (Fig. 2) shows a straight line; this result is consistent with a third-order-in-amine term in the kinetic law. This kinetic behaviour has been observed previously in other systems,[17,28] and can be interpreted by the mechanism shown in Eqns (1)–(3), where the dimer (B:B) of the nucleophile attacks the substrate S to form the intermediate SB_2; then a third molecule of amine assists in the decomposition step. The intermediate in Eqn (2) is zwitterionic; the extra amine molecule is needed to stabilize the developing charge in this solvent of very low permitivity. The kinetic law is given by Eqn (3), where $K = [B{:}B]/[B]^2$ is the amine self-association constant.

$$2B \overset{K}{\rightleftharpoons} B{:}B \tag{1}$$

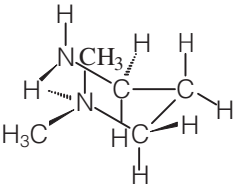
$$S + B{:}B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB_2] \overset{k_3[B]}{\underset{k_2}{\circlearrowright}} \text{Products} \tag{2}$$

$$k_A = \frac{k_1 k_2 K[B] + k_1 k_3 K[B]^2}{k_{-1} + k_2 + k_3[B]} \tag{3}$$

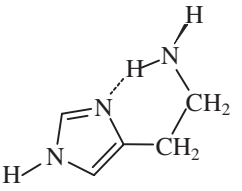
The magnitudes of the rates with both amines are similar but it can be observed in Fig. 2 that the straight line for the reaction with EDA has a no-null intercept. This indicates that both the monomer and the dimer



EDA



DMPA



Histamine

Table 1. Reaction of 2,4-dinitrofluorobenzene (DNFB, 5×10^{-4} M) with 3-dimethylamino-1-propylamine (DMPA) and ethylenediamine (EDA) (B) in toluene at 25.0 ± 0.2 °C (second- and third-order rate coefficients are k_A and k_A/[B], respectively)

DMPA			EDA		
10^3[B] (M)	k_A ($s^{-1}M^{-1}$)	$10^{-2}k_A$/[B] ($s^{-1}M^{-2}$)	10^3[B] (M)	k_A ($s^{-1}M^{-1}$)	$10^{-2}k_A$/[B] ($s^{-1}M^{-2}$)
4.97	1.19	2.39	4.94	0.72	1.46
6.01	1.54	2.56	6.00	0.96	1.60
6.97	2.12	3.04	7.00	1.21	1.72
8.00	2.78	3.48	7.94	1.43	1.80
8.97	3.64	4.06	8.99	1.75	1.95
			10.0	2.09	2.09

Table 2. Reaction of 2,4-dinitrochlororobenzene (DNClB, 5×10^{-4} M) with 3-dimethylamino-1-propylamine (DMPA) and ethylenediamine (EDA) (B) in toluene at 25.0 ± 0.2 °C (second- and third-order rate coefficients are k_A and k_A/[B], respectively)

DMPA			EDA		
[B](M)	$k_A \times 10^3$ ($s^{-1}M^{-1}$)	k_A/[B] $\times 10^3$ ($s^{-1}M^{-2}$)	[B] (M)	$k_A \times 10^3$ ($s^{-1}M^{-1}$)	k_A/[B] $\times 10^3$ ($s^{-1}M^{-2}$)
0.497	0.485	0.976	0.494	1.69	3.42
0.601	0.72	1.20	0.60	2.25	3.75
0.697	0.99	1.42	0.704	2.84	4.03
0.800	1.26	1.57	0.794	4.11	5.18
0.897	1.55	1.73	0.899	4.52	5.03
1.00	1.98	1.98	1.00	6.21	6.21
1.20	2.59	2.16	1.20	8.39	6.99
1.50	3.93	2.62	1.50	13.50	8.98
2.01	5.92	2.94			

nucleophile mechanisms are operating in the reaction with this amine, whereas the reaction with DMPA proceeds entirely through the dimer nucleophile and is slightly faster than with EDA.

Table 2 shows the k_A and k_A/[B] values for the reactions of DNClB with DMPA and EDA in toluene at 25 °C in the presence of variable amounts of the nucleophile. Although, as expected for a less-activated substrate, the reactions of DNClB are slower than those of DNFB, the kinetic behaviour is very similar. The second-order rate coefficient k_A was found to increase rapidly with amine concentration [B]; the plot of k_A vs. [B] (Fig. 3) shows a quadratic dependence whereas the plot of k_A/[B] vs. [B] is a straight line as shown in Fig. 4. These results

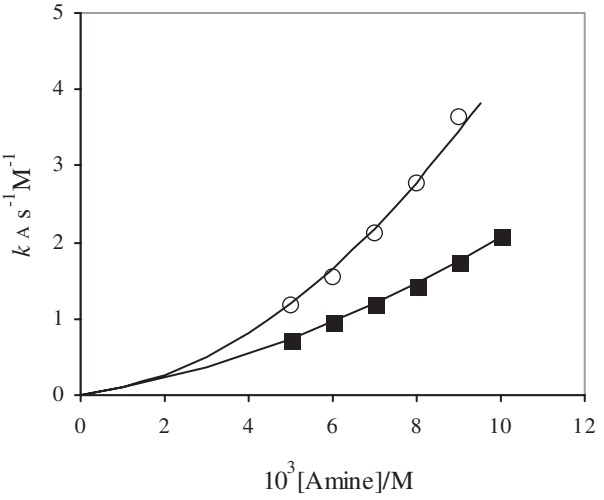


Figure 1. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrofluorobenzene (DNFB) with (○) 3-dimethylamino-1-propylamine (DMPA) and (■) ethylenediamine (EDA) in toluene at 25.0 ± 0.2 °C as a function of amine concentration

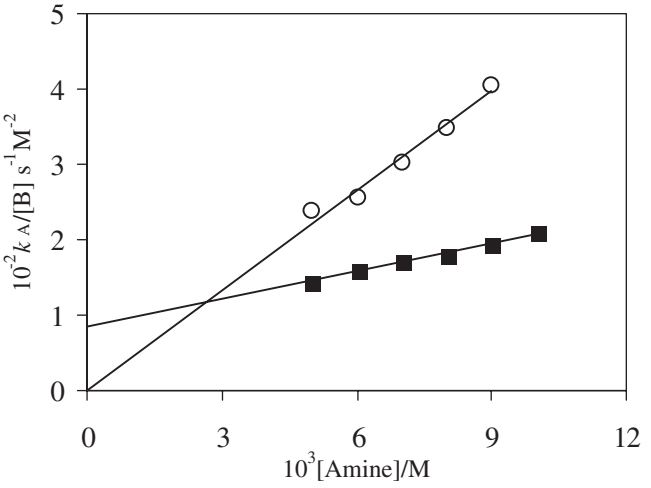


Figure 2. Third-order rate coefficients, k_A/[B], for the reactions of 2,4-dinitrofluorobenzene (DNFB) with (○) 3-dimethylamino-1-propylamine (DMPA) and (■) ethylenediamine (EDA) in toluene at 25.0 ± 0.2 °C as a function of amine concentration

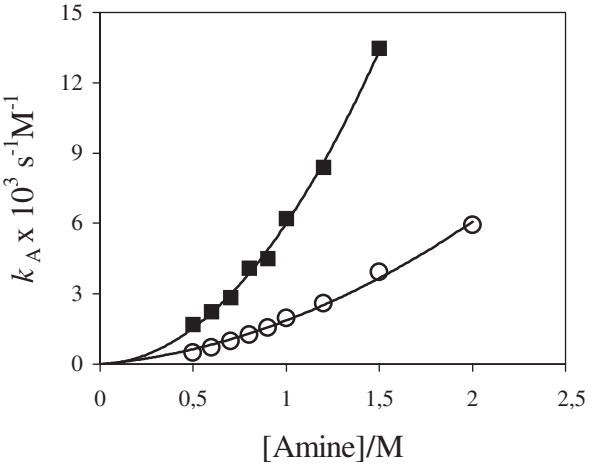


Figure 3. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrochlorobenzene (DNClB) with (○) 3-dimethylamino-1-propylamine (DMPA) and (■) ethylenediamine (EDA) in toluene at 25.0 ± 0.2 °C as a function of amine concentration

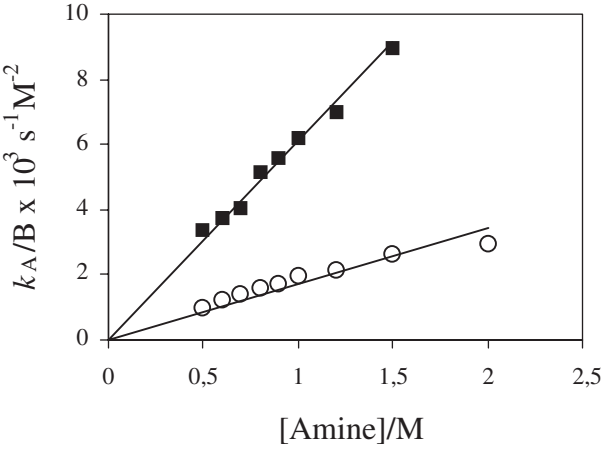
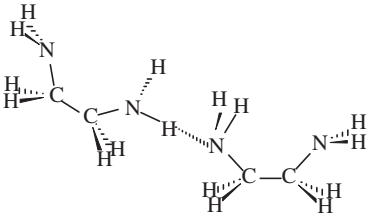
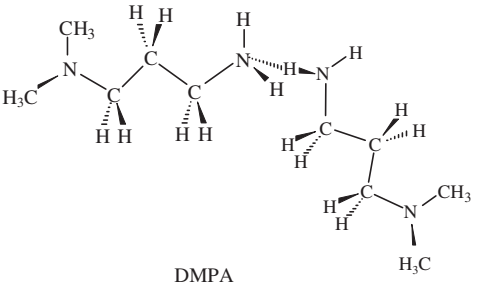


Figure 4. Third-order rate coefficients, k_A/[B], for the reactions of 2,4-dinitrochlorobenzene (DNClB) with (○) 3-dimethylamino-1-propylamine (DMPA) and (■) ethylenediamine (EDA) in toluene at 25.0 ± 0.2 °C as a function of amine concentration

are consistent with a third-order-in-amine term in the kinetic law, similar to what was observed with DNFB, confirming the presence of dimers of DMPA and EDA acting as nucleophiles following the mechanism shown by Eqns (1)–(3). For both amines the intercept in Fig. 4 is null, indicating that the reactions proceed fully by the 'dimer nucleophile' mechanism. It can be observed that in this case the reaction with EDA is faster than with DMPA, reflecting the steric effects of the more hindered amine in attacking the substrate S and forming the intermediate SB_2, where the nucleofugue is now a rather bulky atom. Molecular structures of the open-chain dimers of EDA and DMPA are shown below.



EDA



DMPA

Reactions of DNFB with histamine in toluene

To confirm the overall interpretation that the intermolecular hydrogen bondings in EDA and DMPA are responsible for the observed results, the reactions of a nucleophile able to form intramolecular hydrogen bonding were studied. Table 3 shows the k_A values for the reaction of histamine with DNFB in toluene at 40 °C in the presence of variable amounts of the nucleophile. The second-order rate coefficient increases steadily with [B]; the plot of k_A vs. [B] is a straight line with a null intercept and a correlation coefficient of $R^2 = 0.991$ (Fig. 5). For histamine the intramolecular hydrogen bonding prevents the formation of intermolecular dimers and the classical mechanism of base-catalysed decomposition of the zwitterionic intermediate SB is obeyed.[16] The null intercept indicates that the spontaneous decomposition of SB is negligible, as expected from the poor nucleofugacity of fluorine in an aprotic solvent.

The present results show that for S_NAr reactions of nitro-activated substrates and amines in non-polar aprotic solvents auto-association of amines is very important

Table 3. Reaction of 2,4-dinitrofluorobenzene (DNFB, 1×10^{-4}M) with histamine in toluene at 40.0 ± 0.2 °C (k_A is second-order rate coefficient)

10^3[Histamine] (M)	$k_A \times 10^3$ ($s^{-1}\,M^{-1}$)
5.00	5.30
5.99	6.26
7.00	7.75
7.98	8.79
8.98	9.69
10.1	10.5

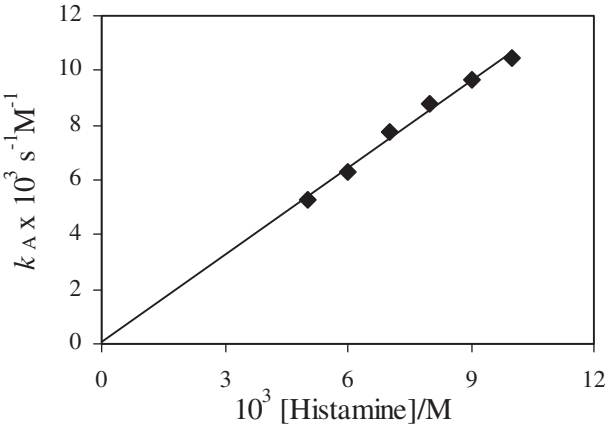


Figure 5. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrofluorobenzene (DNFB) with histamine in toluene at 40.0 ± 0.2 °C as a function of histamine concentration

because of the low permittivity of the media and the importance of hydrogen-bonding interactions. Because of the higher electron density on the hydrogen-bond donor nitrogen, hydrogen-bonded amines are better nucleophiles than those in which no hydrogen-bonding interactions are possible. So, the reactions with inter- or intramolecular homo-aggregate, as well as mixed (hetero-) aggregates with other hydrogen-bond acceptors present in the reaction media, are faster than with the non-hydrogen-bonded nucleophile. The intervention of the amine on the leaving group departure from the zwitterionic intermediate is the more usual explanation of the autocatalytic behaviour.

Some other proposals have been given for the third-order-in-amine kinetic law observed in some special systems.[23,24,29] In particular, the formation of the *homo-(or hetero-) conjugated acid* BH^+B by proton transfer from the intermediate, proposed by Hirst,[29] and the electrophilically catalysed departure of the nucleofugue due to this aggregate are common to the 'dimer nucleophile' mechanism and both can be formulated as essentially the same and as reflecting parts of a spectrum of methods for the formation of the second intermediate. Nevertheless, only the 'dimer nucleophile' mechanism explains other experimental findings such as the 'inversion' plots and the conformational effects observed in reactions with *cis*- and *trans*- 1,2-diaminocyclohexane. As observed in the present case with histamine, the intramolecular hydrogen-bonding interaction in the *cis*-isomer makes this amine more nucleophilic in spite of the stronger steric effects.[30]

EXPERIMENTAL

General procedures

The UV–Vis spectra were recorded in a Shimadzu UV-VIS 240 spectrophotometer and the ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. The *J* values are given in hertz. The NMR spectra were determined in $CDCl_3$ as solvent and thin-layer chromatography was performed on Merck Kiesegel 60 F_{254}. Melting points were determined in a Kofler hot stage and are uncorrected.

Reagents and solvents

All solvents and reagents were analytical reagent grade. Toluene was kept over sodium wire for several days and distilled twice over sodium as described previously.[31] Solvent was stored in a special vessel protected from light that allows delivery without air contamination.

Ethylenediamine (EDA, Fluka) was kept overnight over potassium hydroxide, distilled over zinc powder and then over sodium; both distillations were carried out at normal pressure and retrieve the fraction b.p. 116–118 °C (lit. 116.5 °C).[32] It was kept in a desiccator protected from light. 4(5)-2′-Aminoethylimidazole (histamine base) (Fluka) was used without any purification and was kept in a desiccator protected from light.

2,4-Dinitrochlorobenzene (DNClB, Sigma) was crystallized twice from absolute ethanol (m.p. 52–53 °C, lit.[18a] 52–53 °C). 2,4-Dinitrofluorobenzene (DNFB, Merck) was distilled at reduced pressure under nitrogen (b.p. 122–123 °C at 5 mmHg, lit. 119 °C at 2 mmHg)[30] and was kept in a desiccator protected from light under a nitrogen atmosphere.

2-Amino-1-(*N*-2,4-dinitrophenyl)ethylamine, 4(5)-2′-(*N*-2,4-dinitrophenyl)aminoethyl imidazole and 3-dimethylamino-1-(*N*-2,4-dinitrophenyl)propylamine were prepared from DNClB and the corresponding amine following the procedure reported for *N*-(2,4-dinitrophenyl)-2-methoxyaniline.[33] In all cases, the compounds were obtained in almost quantitative yields as yellow crystals. [2-Amino-1-(*N*-2,4-dinitrophenyl)ethylamine (m.p. 108–110 °C); ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 1H), 8.93 (d, 1H), 6.87 (d, 1H), 8.12 (m, 1H), 3.28 (t, 2H), 3.00 (t, 2H), 1,40 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 40.90, 48.31, 121.51, 121.87, 132.55, 148.10, 148.50, 149.90. 4(5)-2'-(*N*-2,4-Dinitrophenyl)aminoethylimidazole (m.p. 158–160 °C), ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 1H), 9.03 (d, 1H), 7.10 (d, 1H), 8.25 (m, 1H), 3.24 (t, 2H), 3.05 (t, 2H), 7.59 (s, 1H), 8.08 (s, 1H), 12.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.19, 38.79, 118.85, 120.56, 123.12, 130.01, 141.88, 147.80, 148.50, 149.00. 3-Dimethylamino-1-(*N*-2,4-dinitrophenyl)propylamine (m.p. 100–102 °C); ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 1H), 9.30 (d, 1H), 7.40 (d, 1H), 8.48 (m, 1H), 3.70 (t, 2H), 2.01(t, 2H), 2.65 (t, 2H), 2.31 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 27.65, 44.48, 45.40, 58.01, 119.34, 122.35, 128.87, 147.80, 148.48, 149.90.]

3-Dimethylamino-1-propylamine (DMPA) was prepared from dimethylamine and acrylonitrile following a known technique.[34] After 2 days, the excess of dimethylamine was distilled under reduce pressure at 75–77 °C/

11 mmHg). The *N*,*N*-dimethylpropanenitrile obtained was reduced with Na/EtOH. Distillation of the resulting product gave DMPA as a liquid, which was stored under a nitrogen atmosphere at 5 °C. [^{1}H NMR ($CDCl_3$): δ 1.30 (s, 2H, -NH_2), 1.71 (m, 2H, -CH_2-), 2.32 (s, 6H, CH_3), 2.41 (t, 2H, -CH_2-), 2.84 (t, 2H, -CH_2-).]

Ancillary spectrophotometric measurements

The UV–Vis spectra of the substrates, products and different mixtures of both compounds with the amines in toluene at several concentrations were recorded in a Shimadzu UV-VIS 240 spectrophotometer. The extinction coefficients of the products were determined at λ_{max} and at $\lambda = 400$ and 450 nm; at these wavelengths the reagents are transparent under these conditions. All the solutions were found to obey Beer's law.

[2-Amino-1-*N*-(2,4-dinitrophenyl)ethylamine: $\lambda_{max} = 348$ nm, $\varepsilon_{348} = 1.08\ 10^4\ cm^{-1}\ M^{-1}$; 4(5)-2'-(*N*-2,4-dinitrophenyl)aminoethyl imidazole: $\lambda_{max} = 349$ nm, $\varepsilon_{349} = 9.55\ 10^3\ cm^{-1}\ M^{-1}$; 3-dimethylamino-1-*N*-(2,4-dinitrophenyl)propylamine**:** $\lambda_{max} = 351$ nm, $\varepsilon_{349} = 1.66 \times 10^4\ cm^{-1}\ M^{-1}$, $\varepsilon_{450} = 1.60 \times 10^3\ cm^{-1}\ M^{-1}$.]

Kinetic procedures

Kinetic runs were performed by the methods reported previously,[35] following the appearance of the reaction product at $\lambda = 450$ or 400 nm. The reactions of DNClB and DNFB with DMPA and EDA were carried out at 25 ± 0.2 °C and the reactions of DNFB with histamine were carried out at 40 ± 0.2 °C. The reactions were followed directly in the thermostated cell of the spectrophotometer at the indicated temperature. The absorption spectrum of the reaction mixture at 'infinite time' corresponded within $\pm 2\%$ with the 'theoretical' value calculated from application of Beer's law to solutions of the product prepared independently in the desired solvent. In all cases pseudo-first-order kinetics were observed. Pseudo-first-order coefficients, k_Ψ, were obtained by the least-square method as the slope of the correlation ln $(A_\infty - A_t)/A_\infty$ against time, where A_∞ is the optical density of the reaction mixture measured at 'infinity' (more than ten half-lives); the second-order rate coefficients, k_A, were obtained by dividing k_Ψ by the amine concentrations. Rate coefficients were reproducible to $\pm 2\%$. No corrections for expansion coefficients were applied to the concentration values.

Acknowledgements

Financial help from the University of Buenos Aires (grant no. EX213-UBA) and the Universidad Nacional del Comahue (grant no. I094-UNCo) is gratefully acknowledged.

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