Research Article

Journal of Physical Organic Chemistry

Received: 26 January 2010, Revised: 19 February 2010, Accepted: 22 February 2010, Published online in Wiley Online Library: 21 July 2010

(wileyonlinelibrary.com) DOI 10.1002/poc.1712

Hydrogen-bonded nucleophile effects in ANS: the reactions of 1-chloro and 1-fluoro-2,4-dinitrobenzene with 2-guanidinobenzimidazole, 1-(2-aminoethyl)piperidine and *N*-(3-aminopropyl)morpholine in aprotic solvents

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The kinetics of the reactions of 2,4-dinitrofluorobenzene (DNFB) and 2,4-dinitrochlorobenzene (DNClB) with 2-guanidinobenzimidazole (2-GB) at 40 ± 0.2 °C in dimethylsulphoxide (DMSO), toluene, and in toluene–DMSO mixtures, and with 1-(2-aminoethyl)piperidine (2-AEPip) and *N*-(3-aminopropyl)morpholine (3-APMo) in toluene at 25 ± 0.2 °C were studied under pseudo first-order conditions. For the reactions of 2-GB carried out in pure DMSO, the second-order rate coefficients were independent of the amine concentration. In contrast, the reactions of 2-GB with DNFB in toluene, showed a kinetic behaviour consistent with a base-catalysed decomposition of the zwitterionic intermediate. These results suggest an intramolecular H-bonding of 2-GB in toluene, which is not present in DMSO. To confirm this interpretation the reactions were studied in DMSO–toluene mixtures. Small amounts of DMSO produce significant increase in rate that is not expected on the basis of the classical effect of a dipolar aprotic medium; the effect is consistent with the formation of a nucleophile/co-solvent *mixed aggregate*. For the reactions of 3-APMo with both substrates in toluene, the second-order rate coefficients, k_A, show a linear dependence on the [amine]. 3-APMo is able to form a six-membered ring by an intramolecular H-bond which prevents the formation of self-aggregates. In contrast, a third order was observed in the reactions with 2-AEPip: these results can be interpreted as a H-bonded homo-aggregate of the amine acting as a better nucleophile than the monomer. Most of these results can be well explained within the frame of the '*dimer nucleophile*' mechanism. Copyright © 2010 John Wiley & Sons, Ltd.

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

INTRODUCTION

There has been an active research in the last two decades to elucidate how the aggregation state of reactants can influence the mechanisms of organic reactions.[1,2] Aromatic nucleophilic substitutions (ANS) have been extensively studied because of their importance in fundamental Organic Chemistry; in the syntheses of pharmaceuticals and other bioactive agents, the interest stems from the fact that they can proceed in a great variety of ways.[3–5] Lately, Crampton and colleagues. have reported additional data about ring substitution[6] and leaving-group[7] effects in ANS of substituted nitrobenzenes with aliphatic amines, as well of electronic and steric effects in reactions with aniline[8,9] and with substituted anilines,[8,10] all of them realised in dipolar aprotic solvents. ANS of a 2,4-dinitrophenyl substituted pyrazole with primary amines leads to the substitution of the pyrazolo substituent; thus the 5-amino-1*H*-4-pyrazolecarbonitrile has been recognised as a new leaving group.[11]

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On the other hand, ANS by amines has been recognised to be extremely affected by the solvent.[1,2,12] Their study is currently receiving increased interest since they constitute a suitable model that contributes 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 can occur involving the solvent molecules.[13–20] A specific solvent effect has been recently demonstrated in the solvent-controlled leaving group selectivity in ANS carried out on a highly functionalised substituted xanthone, giving rise to a useful synthesis for the xanthone core of a new antibiotic.[21] Similarly, experimental and theoretical exploration of acid-catalysed multi-step ANS showed that the mechanisms in polar and non-polar solvents (i.e. toluene) are different.[22] When the reactions are carried out in solution, noncovalent-binding interactions of different types are established that can be involved in the general concept of 'solvent effects', of which hydrogen bonding is one of the most important specific microscopic interactions.[1,2,13–15]

The inter- and intramolecular hydrogen bonding are one of the principal types of weak non-covalent interactions that play a role in defining the physical properties and reactivity of a large variety of structures in chemical and biological systems.[23,24] This subject is currently receiving increased interest and a growing number of studies in gas phase as well as theoretical calculations are being undertaken to understand the influence of the internal (structural) and external (solvent) effects on the hydrogen bonded configurations. Raczynska and co-workers reported the features of hydrogen bonding in the gas phase of polyfunctional compounds such as cyclic and acyclic substituted diamines, vinamidines and guanidines,[25] substituted formamidines and amidinazines,[26] all of which can develop intramolecular hydrogen bonding called *'internal solvation'*. The observed enhancement of gas-phase basicity of these compounds was interpreted as due to the intramolecular hydrogen bonding cyclisation.[25] Intramolecular hydrogen bonding also plays an important role in biological molecules involving polyfunctional groups. It was found that a six-membered ring cyclic structure is formed in the protonated histamine[27] and N^{α}, N^{α}-dimethylhistamine.[28] Within this context, it is worth mentioning that part of the high basicity of the arginine is due to the '*internal solvation*' of the guanidinium cation moiety as shown by a careful *ab initio* study,[29] which confirmed earlier conjectures.[25]

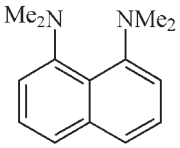
We recently published atypical findings in ANS carried out in aprotic solvents using diamines that were purposefully selected due to their special structures able to form intra- or intermolecular hydrogen bonds such as ethylendiamine; 3-dimethylamino-1-propylamine and histamine.[30] The results obtained were well explained within the frame of the '*dimer nucleophile*' mechanism. In a thorough examination of nucleophile structure effect regarding its self-aggregation states, the present paper describes a kinetic and spectroscopic study of the reactions between 2,4-dinitrofluorobenzene (DNFB) and 2,4-dinitrochlorobenzene (DNClB) with 2-guanidinobenzimidazole (2-GB) in dimethylsulphoxide (DMSO), in toluene and in binary toluene–DMSO mixtures. Likewise, the reactions of the same substrates with diamines having an alicyclic amino group near the nucleophilic nitrogen in the lateral chain having two or three methylene groups, such as 1-(2-aminoethyl)piperidine (2-AEPip) and *N*-(3-aminopropyl)morpholine (3-APMo), were studied in toluene. The observed results afford evidence concerning the critical role that hydrogen-bond interactions and formation of '*mixed aggregates*' play in the kinetics of these reactions.

RESULTS AND DISCUSSION

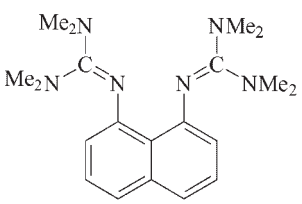
There is at present considerable interest in the experimental and theoretical studies of hydrogen bonding effects on the conformation and stability of organic molecules.[31–37]

Intramolecular hydrogen bonds are involved in the control of the conformation of many biological molecules and they contribute to the interactions needed for efficient molecular recognition.[38,39] It has been shown[1,2,19,20] that for ANS reactions of nitro-activated substrates and amines in non-polar aprotic solvents, auto-association of amines is very important because of the low permittivity of the media. Self-association of amines to form mainly dimers by hydrogen bonding interactions increases its nucleophilicity; consequently the dimer is a better nucleophile, as it was confirmed by semi-empirical[1] and *ab initio* calculations.[40] On the other hand, when two amino groups are in an appropriate geometry, like in 2-guanidinobenzimidazole (2-GB), intramolecular H-bonding is easily established, and those compounds exhibit unusually high basicity.[41]

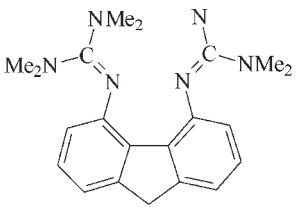
2-GB has important biological properties,[42–45] it is a polyfunctional planar molecule with a delocalised π electronic system, in which the formation of an intramolecular hydrogen bond was determined in solid state by X-ray diffraction.[46,47] Due to the intramolecular H-bonds, guanidine systems have strong basicity; some of them constitute the new 'proton sponges'. Thus, 1,8-bis(tetramethylguanidino)naphthalene (TMGN)[48] and 4,5-bis(tetramethylguanidino)-fluorene (TMGF)[49] are stronger bases than the 1,8-bis(dimethylamino)naphthalene (DMAN), due to the more favourable intramolecular H-bond effect.



DMAN



TMGN



TMGF

To examine the importance of hydrogen bonding interactions in ANS with amines, the reactions of DNFB and DNClB with a polifunctionalised amine, 2-GB, in DMSO, toluene, and DMSO–toluene binary solvents and with diamines as 1-(2-aminoethyl)piperidine (2-AEPip) and *N*-(3-aminopropyl)morpholine (3-APMo) in toluene were studied. The selected amines were chosen for their potential ability to form inter- and/or intramolecular H-bonds. The reactions proceed straightforwardly to give the expected N-substituted 2,4-dinitroaniline, in almost quantitative yield. The determinations were carried out under pseudo-first order conditions; the rate dependence with amine concentration was studied and good kinetic behaviour was observed throughout the work.

Reactions of DNFB and DNClB with 2-GB in DMSO

The kinetics of the reactions of DNFB and of DNClB, with 2-GB in DMSO, were studied at $40 \pm 0.2\,^{\circ}C$ in the presence of variable amounts of the nucleophile. Table 1 presents the pseudo-first, k_ψ, and the bimolecular rate coefficients k_A for the reactions with DNFB. It can be observed that the pseudo-first order rate coefficients, k_ψ, increase linearly with amine concentration, [B], in the whole range studied. On the other hand, no dependence of the bimolecular rate coefficients, k_A, on [B] was observed.

Table 2 shows the corresponding k_ψ and k_A values for the reactions of 2-GB with DNClB in DMSO at $40 \pm 0.2\,^{\circ}C$ in the presence of variable amounts of the nucleophile. As expected for a less-activated substrate, the reactions of DNClB are slower than those of DNFB; the kinetic behaviour is very similar. With both substrates, the plot (not shown) of k_ψ *versus* [2-GB] is a straight line with null intercept; the correlation coefficients being $R^2 = 0.999$ for DNFB and $R^2 = 0.998$ for DNClB, respectively. These results are consistent with a mechanism in which a molecule of amine attacks the substrate in the first step, and this becomes the rds. This is likely due to an increase in k_{-1} coupled to the inability of 2-GB to assist proton transfer from the zwitterionic intermediate. Thus, decomposition of the zwitterionic intermediate by DMSO (a well known hydrogen-bond acceptor (HBA), β value = 0.76, $E_T(30) = 45.0$)[5], becomes thermodynamically more favorable than a potential base-catalysed decomposition. The 2-GB steric hindrance attempts to catalyze.

Table 1. Reaction of 2,4-dinitrofluorobenzene, DNFB,[a] with 2-guanidinobenzimidazole (2-GB) in dimethylsulphoxide (DMSO) at $40.0 \pm 0.2\,^{\circ}C$. Pseudo first-, k_ψ, and second-order rate coefficients, k_A

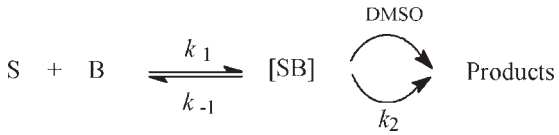
10^2[2-GB]/M	$10^5\ k_\psi\ (s^{-1})$	$10^4\ k_A\ (s^{-1}M^{-1})$
0.54	0.62	11.4
0.71	0.82	11.5
0.90	1.08	12.0
1.08	1.19	11.0
2.00	2.23	11.1
3.00	3.31	11.0
5.00	5.56	11.1

[a] $[DNFB] = 5.019 \times 10^{-4}$ M.

Table 2. Reaction of 2,4-dinitrochlororobenzene, DNClB,[a] with 2-guanidinobenzimidazole (2-GB) in dimethylsulphoxide (DMSO) at $40.0 \pm 0.2\,^{\circ}C$. Pseudo first-, k_ψ, and second-order rate coefficients, k_A

10^2[2-GB]/M	$10^7\ k_\psi\ (s^{-1})$	$10^6\ k_A\ (s^{-1}M^{-1})$
0.50	0.59	11.8
1.08	1.25	11.6
3.22	3.87	12.0
4.00	4.75	11.9
5.00	6.37	12.7
6.08	7.73	12.7
8.01	10.1	12.7

[a] $[DNClB] = 5.02 \times 10^{-4}$ M.



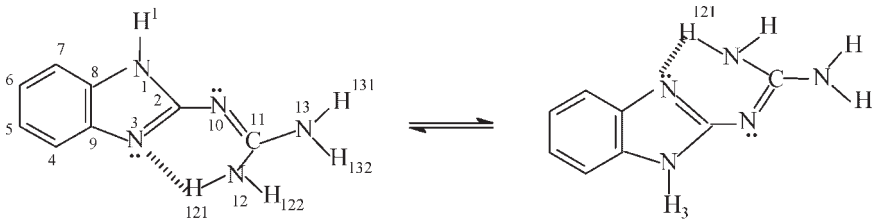
Though from the present results is not possible to infer that the intramolecular hydrogen bond is present in 2-GB, they are in agreement with ^1H, ^{13}C and ^{15}N NMR spectroscopy studies carried out in DMSO-d6 solutions.[50] The authors proposed that 2-GB exhibits an open structure in DMSO solution, where all NH moieties form H-bonds with the solvent. The kinetic results also agree with the studies of proton exchange of $^{15}N12/^{15}N13$ of $^{15}N1/^{15}N3$ of 2-GB (refer Scheme 1) in solution with protic and dipolar aprotic solvents.[51] It was shown that the equivalent conformers 1 and 2 are the principal contributors[52] (Scheme 1). These conformers are in equilibrium and may be stabilised by intramolecular hydrogen bonding. The impact that this intramolecular H-bond has on the bond order of the neutral guanidine group and on the dynamic conformations was related to the concept of '*resonance-assisted hydrogen bond*' (RAHB).[53,54]

The results indicate that the $^{15}N12/^{15}N13$ exchange is rapid and accelerated by protic solvents. The exchange of $^{15}N1/^{15}N3$ in 2-GB at the imidazole ring correlates with proton exchange, but it is not mechanistically related to guanidino $^{15}N12/^{15}N13$ exchange. In 2-GB dissolved in CD_3OD, both processes are fast on the NMR time scale; however, DMSO-d6 inhibits the $^{15}N1/^{15}N3$ exchange and allows $^{15}N12/^{15}N13$ exchange. This behaviour indicates that proton exchange is a bimolecular process in the absence of protic polar species, while in DMSO-d6 the intramolecular homo-aggregation of 2-GB is inhibited.

Reactions of DNFB with 2-GB in toluene

To examine the effects of an apolar aprotic solvent on the kinetics behaviour, the reactions of 2-GB with DNFB were studied in toluene. Table 3 shows that the bimolecular rate coefficients, k_A, increase steadily with [B]; and the plot of k_A *versus* [B] is a straight line with a null intercept with a correlation coefficient of $R^2 = 0.988$ (Fig. 1).

Contrary to the observations in DMSO, the reactions with DNFB in toluene showed a kinetic behaviour consistent with a



Scheme 1. Principal conformers of 2-GB

base-catalysed decomposition of the zwitterionic intermediate. These results suggest the formation of a strong intramolecular hydrogen bond in 2-GB that prevails over the formation of intermolecular 2-GB dimers, and an '*atypical*' base-catalysed decomposition of the zwitterionic intermediate SB due to an '*intramolecular dimer*' is obeyed. The null intercept indicates that the spontaneous decomposition of SB is negligible, as expected from the poor nucleofugacity of fluorine in an aprotic solvent.

Reactions of DNFB and DNClB with 2-GB in solvent mixtures

To analyse how specifically changes in the reaction media influence the kinetic behaviour, an HBA co-solvent was added to toluene, a non-hydrogen bonding aromatic solvent (NHBA). The reactions were studied in DMSO–toluene binary mixtures; starting from small additions of DMSO to toluene, evidence for preferential solvation was observed as described below. Table 4 shows the observed second-order rate coefficients, k_A, for the reactions of DNFB with 2-GB in DMSO–toluene binary solvents. Figure 2 shows the significant increase in rate observed with small additions of DMSO to toluene up to 15%; then the increase diminishes. The dramatic effect caused by small additions of DMSO to toluene suggests that a specific effect must be involved. This effect is consistent with the formation of nucleophile/co-solvent *mixed aggregates* that prevents the self-aggregation of the nucleophile. The mixed aggregate increases the reaction rate since the amine now acts as a hydrogen-bond donor (HBD) and therefore increases its nucleophilicity. The observed results afford new evidence to the '*dimer nucleophile*' mechanism. In that mechanism, the homo- or mixed dimer of the amine (a hydrogen-bonded molecular complex) acts as the true nucleophile forming an intermediate-complex, and a third molecule of amine assists the decomposition step, Eqn (2). For a

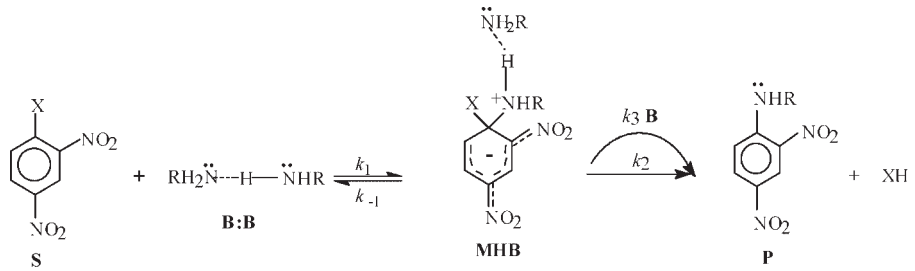


Table 3. Reaction of 2,4-dinitrofluorobenzene, DNFB,[a] with 2-guanidinobenzimidazole (2-GB) in toluene at 40.0 ± 0.2 °C. Second-order rate coefficients, k_A

10^2[2-GB]/M	10^5 k_A ($s^{-1}M^{-1}$)
0.61	0.64
0.75	0.84
0.92	1.09
1.08	1.42
1.21	1.51
1.51	1.71
2.02	2.32
2.50	2.91
3.00	3.80

[a] [DNFB] = 5.15×10^{-4} M.

HBA co-solvent > 20% the reactions show the kinetic behaviour found in pure DMSO; it is likely that a preferential solvation by DMSO molecules occurs in the 2–3 solvent shells around the cibotactic zone.

Although the specific effect of the aggregation of the nucleophile with DMSO could also operate in the second step, the above interpretation is preferred since it also explains the early reported '*anomalous*' effect of small additions of DMSO observed when the first step is rate determining.[55] Similar rate accelerations due to the addition of small amounts of a HBA co-solvent were found in the reactions of 1,2-dinitrobenzene with butylamine in benzene. While the reaction is almost insensitive to other additives, the accelerations observed upon the addition of DMSO to benzene exceed expectations based only on considerations of the polarity of the medium,[56] in line with the present finding for the reactions studied in toluene/DMSO binary solvents. To support this interpretation of the experimental results, theoretical semi-empirical and *ab initio* calculations were performed to investigate the likelihood of 2-GB: DMSO hydrogen bond formation. It was found that 2-GB exhibits intra- and

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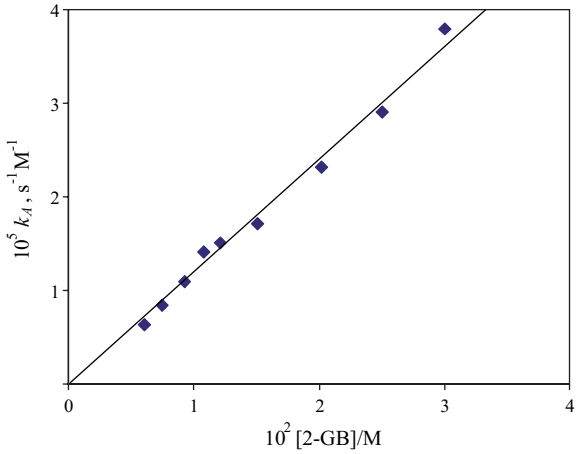

Figure 1. Second-order rate coefficients, k_A, for the reaction of dinitrofluorobenzene (DNFB) with 2-guanidinobenzimidazole (2-GB) in toluene at 40.0 ± 0.2 °C as a function of [2-GB]

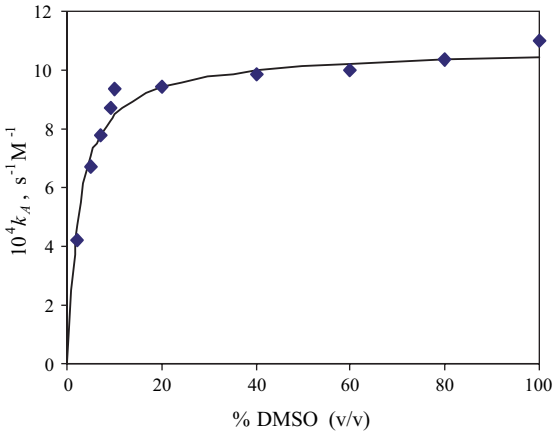

Figure 2. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrofluorobenzene (DNFB) with 2-guanidinobenzimidazole (2-GB) in dimethylsulphoxide (DMSO)–toluene binary solvents as a function of percentage of DMSO in the binary solvent at 40.0 ± 0.2 °C

intermolecular hydrogen bond formation leading to homo 2-GB and mixed solute–solvent dimers.[57]

Reactions of DNFB and DNClB with 2-(AEPip) and 3-(APMo) in toluene

The kinetics of the reactions of DNFB and DNClB, both with 2-(AEPip) and 3-(APMo), in toluene, were studied at 25 ± 0.2 °C in the presence of variable amounts of the nucleophile. Table 5 shows the observed results for the reactions of 2,4-dinitrofluorobenzene, DNFB, with 1-(2-aminoethyl)piperidine, 2-(AEPip), and *N*-(3-aminopropylmorpholine, 3-(APMo): the bimolecular rate coefficients, k_A, are given. Table 6 shows the corresponding values for the reactions of both amines with 2,4-dinitrochlorobenzene, DNClB, in toluene. It can be observed that the second-order rate coefficients, k_A, for the reactions with 2-(AEPip) increase rapidly [B], and the plots of k_A *versus* [B] (refer Figs 3 and 4) show a quadratic dependence (for Fig. 4 different scales for the k_A values should be used in the plot due to the reactivity difference of the two amines in DNClB). On the other hand, the corresponding third-order rate coefficient values for the reactions of 2-(AEPip) with DNCIB and DNFB in toluene at 25.0 ± 0.2 shown in Table 7 and plotted as Figs 5 and 6, 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[1,2,13–15,58,59] and can be interpreted by the mechanism shown in Eqns (3)–(5) where the dimer (B:B) of the nucleophile attacks the substrate, *S*, forming the intermediate, SB_2; then a third molecule of amine assists the decomposition step. The intermediate in Eqn (4) is highly zwitterionic; the extra amine molecule is needed to stabilise the developing charge in this solvent of very low permitivity. The kinetic law is given by Eqn (5), where $K = [B:B]/[B]^2$ stands for the amine self-association constant.

$$2BB : B \tag{3}$$

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

$$k_A = \frac{k_1 k_2 K[B] + k_1 k_3 K[B]^2}{k_{-1} + k_2 + k_3[B]} \tag{5}$$

Table 4. Reaction of 2,4-dinitrofluorobenzene, (DNFB, 5.019×10^{-4} M) with 2-guanidinobenzimidazole (2-GB)[a] in dimethylsulphoxide (DMSO)-toluene binary solvents at 40.0 ± 0.2°C. Second-order rate coefficients, k_A

% DMSO (*v/v*)	$10^4 k_A$ ($s^{-1}M^{-1}$)
2	4.21
5	6.70
7	7.80
9	8.74
10	9.38
20	9.45
40	9.83
60	9.98
80	10.2
100	11.0

[a] [2-GB] = 0.0108 M.

Table 5. Reaction of 2,4-dinitrofluorobenzene, DNFB, with 1-(2-aminoethyl)piperidine 2-(AEPip) and *N*-(3-aminopropylmorpholine, 3-(APMo), in toluene at 25.0 ± 0.2 °C. Second-order rate coefficients, k_A

3-APMo		2-AEPip	
$10^3[B]$ (M)	k_A ($s^{-1}M^{-1}$)	$10^3[B]$ (M)	k_A ($s^{-1}M^{-1}$)
5.05	1.36	5.02	1.59
6.10	1.72	5.97	2.34
7.00	2.05	6.96	3.15
8.04	2.29	7.98	4.18
9.01	2.51	8.95	5.85
10.2	2.85	9.94	6.57
12.0	3.49		

[DNFB] = 5.15×10^{-4} M.

Table 6. Reaction of 2,4-dinitrochlorobenzene, DNClB[a] with 1-(2-aminoethyl)piperidine, 2-(AEPip), and *N*-(3-aminopropylmorpholine, 3-(APMo), in toluene at 25.0 ± 0.2 °C. Second-order rate coefficients, k_A

3-APMo		2-AEPip	
[*B*] (M)	$10^3 k_A$ ($s^{-1}M^{-1}$)	[*B*] (M)	$10^3 k_A$ ($s^{-1}M^{-1}$)
0.300	1.53	0.496	1.92
0.537	2.54	0.597	2.48
0.604	3.44	0.791	3.12
0.805	4.02	0.999	4.88
0.900	4.54	1.20	5.98
1.01	4.94	1.51	8.73
1.20	5.59	1.73	10.9
1.48	6.89	2.01	15.4
1.75	7.97	2.31	22.9
2.01	9.25	2.54	26.4

[a] [DNClB] = 5.09×10^{-4} M.

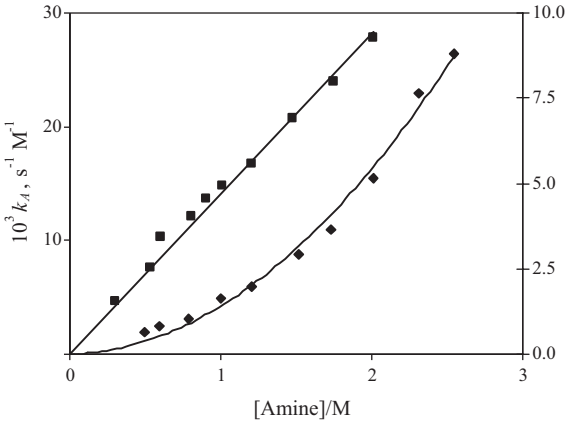

Figure 4. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrochlorobenzene (DNClB) with ◆ 1-(2-aminoethyl)piperidine, 2-(AEPip) (10^3 left *Y*-axis scale) and ■ *N*-(3-aminopropylmorpholine 3-(APMo) (10^3 right *Y*-axis scale) at 25.0 ± 0.2 °C as a function of [amine]

On the other hand, for the reactions of 3-APMo with both substrates in toluene, the second-order rate coefficients, k_A, exhibit a linear dependence on amine concentration as expected for a classical mechanism of base-catalysed decomposition of the zwitterionic intermediate; the plot of k_A *versus* [B] is a straight line with a null intercept and a correlation coefficient of $R^2 = 0.992$ for the reactions with DNFB (Fig. 3) and $R^2 = 0.991$ for the reactions with DNClB (Fig. 4). Because of the ability of 3-APMo to form a six-membered ring, an intramolecular hydrogen bond is established which prevents the formation of self-aggregates. It can be observed in Fig. 6 that the straight line for the reaction of 2-(AEPip) with DNClB has a no null intercept. This indicates that both the monomer and the dimer nucleophile mechanisms occur in the reaction with this substrate, while the reaction with DNFB proceeds entirely through the 'dimer nucleophile mechanism'.

The magnitudes of the rates of both amines with the same substrate are similar; in all the reactions studied in the present work, DNFB reacts faster than DNClB. These results are consistent with those reported in the literature.[20]

The present kinetics results that indicate inter- and intramolecular hydrogen bonds in flexible structure bifunctionalised amines with two and three methylene groups are in agreement with studies of gas phase basicity of bidentate ligands reported. Raczynska and Wozniak[60] studied the gas phase basicity of rigid and flexible conformation bidentate ligands and concluded that intramolecular hydrogen bonding called '*internal solvation*' is responsible for an enhancement of gas phase basicities. The thermodynamic parameters and proton affinities for compounds of general formula $Y(CH_2)_nX$ (X,Y = OR, NR_2; R = H or alkyl; $n = 2$) have been determined; the results suggest that when $n = 2$, the intramolecular H-bond is partial or does not exist.[61]

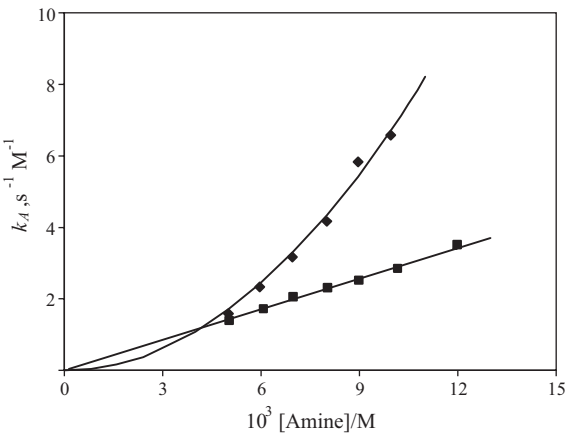

Figure 3. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrofluorobenzene (DNFB) with ◆ 1-(2-aminoethyl)piperidine, 2-(AEPip) and ■ *N*-(3-aminopropylmorpholine, 3-(APMo) at 25.0 ± 0.2 °C as a function of [amine]

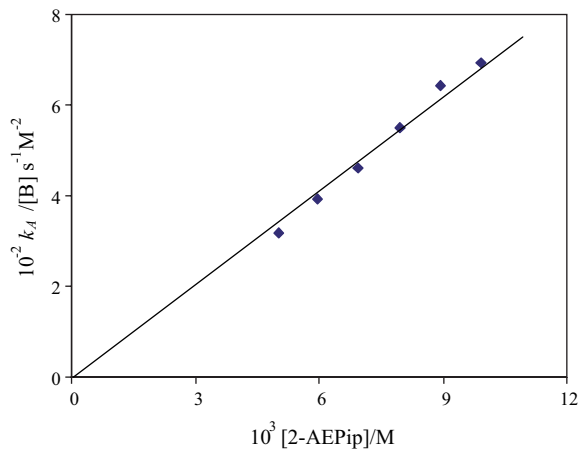

Figure 5. Third-order rate coefficient, $k_A/[B]$, for the reactions of 2,4-dinitrofluorobenzene (DNFB) with 1-(2-aminoethyl)piperidine, 2-(AEPip), in toluene at 25.0 ± 0.2 °C as a function of [amine]

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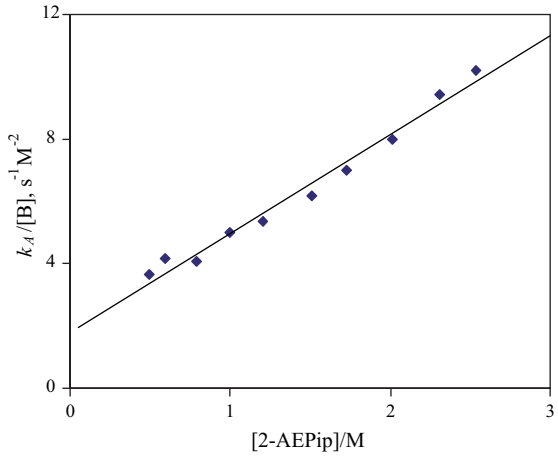
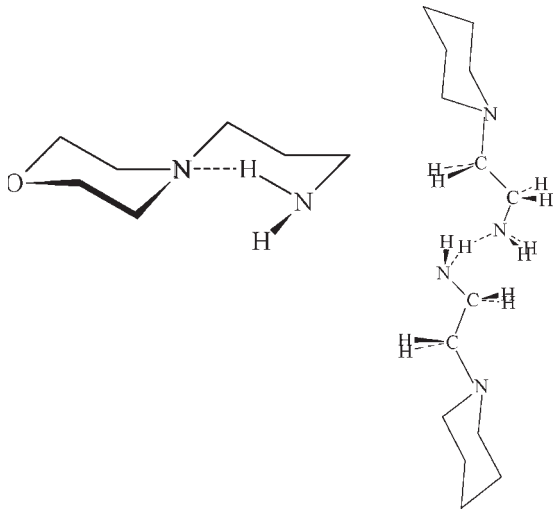


Figure 6. Third-order rate coefficient, $k_A/[B]$, for the reactions of 2,4-dinitrochlorobenzene (DNClB) with 1-(2-aminoethyl)piperidine, 2-(AEPip) in toluene at 25.0 ± 0.2 °C as a function of [2-AEPip]



The proposed structures for the intramolecular H-bonded 3-APMo and the intermolecular dimer 2-AEPip that should act as the respective nucleophiles in the present ANS reactions are shown above.

CONCLUSIONS

The present results show that for ANS reactions of nitro-activated substrates and polyamines in aprotic solvents, homo-(or hetero-) association of amines is very important because of the low permitivity of the media and the strong involvement 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 intramolecular homo-aggregate, as well as mixed (hetero-) aggregates with other hydrogen-bond acceptor present in the reaction media, are faster than with the non-hydrogen-bonded nucleophile. The hydrogen bonded nucleophile structure is crucial: bi- and polyamines for which internal hydrogen bond is expected are prone to react in the monomeric state, while those in which no intramolecular hydrogen bonds are possible can react by the '*dimer nucleophile*' mechanism. In HBA solvents, such as DMSO, the role of *mixed aggregates* is clearly demonstrated.

Table 7. Reactions of 2,4-dinitrofluorobenzene, DNFB, and 2,4-dinitrochlorobenzene, DNClB, with 1-(2-aminoethyl)piperidine, 2-(AEPip), in toluene at 25.0 ± 0.2 °C. Third-order rate coefficient, $k_A/[B]$

DNFB[a]		DNClB[b]	
$10^3[B]$/M	10^{-2} $k_A/[B]$ ($s^{-1}M^{-2}$)	[B]/M	10^3 $k_A/[B]$ ($s^{-1}M^{-2}$)
5.02	3.17	0.496	3.87
5.97	3.92	0.597	4.15
6.96	4.52	0.791	3.95
7.98	5.24	0.999	4.88
8.95	6.54	1.20	4.98
9.94	6.61	1.51	5.78
		1.73	6.30
		2.01	7.66
		2.31	9.91
		2.54	10.4

[a] [DNFB] = 5.15×10^{-4} M.
[b] [DNClB] = 5.09×10^{-4} M.

EXPERIMENTAL

The general procedures for spectroscopic determinations and for the purification of reagents and solvents are given as Supplementary Materials.

2-guanidinobenzimidazole, (2-GB, Aldrich) was crystallised twice from ethyl acetate. To assure fully removal of the solvent, the crystals were dissolved in chloroform and vacuum was applied until a dried residue was obtained; it was reduced to powder in a mortar and the procedure was repeated until no impurities were detected by thin-layer chromatography. Finally, it was kept in a desiccator protected from light under dry nitrogen atmosphere (mp 242–244 °C, lit,[50] 242.8–244.5 °C). IR. ν cm^{-1}: 3448, 3210 (N—H), 1648 (C═N), 1600, 1542 (C═C), 1392, 1274 (C—N).

1-(2-aminoethyl)piperidine, (2-AEPip, Aldrich): the commercial product was kept over sodium strings during several days, distilled by reduced pressure fractional distillation over zinc powder and then twice over sodium strings under reduced pressure. The fraction 78–80 °C at 20 mmHg was collected. It was kept in a desiccator under dry nitrogen atmosphere, protected from light, and it was re-distilled before using

N-(3-aminopropyl)morpholine, (3-APMo, Aldrich): the commercial product was kept over sodium strings during several days, distilled by reduced pressure fractional distillation over zinc powder and then twice over sodium strings under reduced pressure. The fraction 96–97 °C at 20 mmHg was collected. It was kept in a desiccator under dry nitrogen atmosphere, protected from light, was re-distilled before using 2,4-dinitrochlorobenzene (DNClB, Sigma), and was crystallised twice from absolute ethanol (mp 52–53 °C, lit.[62] 52–53 °C).

2,4-dinitrofluorobenzene, (DNFB, Merck), was distilled at reduced pressure under nitrogen (b.p. 122–123 °C at 5 mmHg, lit,[62] 119 °C at 2 mmHg) and was kept in a desiccator protected from light under dry nitrogen atmosphere.

1-*N*-(2-benzimidazol)-3-*N*-(2,4-dinitrophenyl)guanidine, *N*-(2,4-dinitrophenyl)-1-(2-aminoethyl)piperidine and *N*-(2,4-dinitropheny)-*N*-(3-aminopropyl)morpholine were prepared from 2,4-dinitrochlorobenzene and 2-guanidinobenzimidazole, *N*-(3-aminopropyl)morpholine and 1-(2-aminoethyl)piperidine, respectively, following the general procedure reported for *N*-(2,4-dinitrophenyl)-2-methoxyaniline.[63] In all cases, the compounds were obtained in almost quantitative yields as dark orange, the former, and yellow crystals the other two products, respectively. [1-*N*-(2-benzimidazol)-3-*N*-(2,4-dinitrophenyl)guanidine (mp 218–220 °C), ^{1}H NMR (DMSO-d6): δ 11.12 (s, 1*H*), 9.03 (s, 1*H*), 8.25 (d, 1*H*), 7.20 (m, 2*H*), 7.10 (d, 1*H*), 6.92 (m, 2*H*), 2.30 (s, 1*H*), 2.10 (s, 2*H*). ^{13}C NMR (DMSO-d6): δ 160.00, 152.00, 149.90, 148.48, 147.80, 140.80, 128.87, 125.80, 123.70, 121.30, 120.30, 119.34, 114.34, 110.20. IR (KBr) ν cm^{-1}: 3439 and 3196 (N—H),. 1640 (N—H) and (NH_2), 1626 (C═N), 1510, (NO_2), 1340, (NO_2), 780 (NH_2)]. [*N*-(2,4-dinitrophenyl)-1-(2-aminoethyl)piperidine (mp 122–123 °C), ^{1}H NMR ($CDCl_3$): δ 9.04 (s, 1*H*), 8.15 (d, 1*H*), 6.81 (d, 1*H*), 3.36 (t, 2*H*), 2.63 (t, 2*H*), 2.40 (t, 4*H*), 1.49 (m, 6*H*), 1.02 (s, 1*H*)• ^{13}C RMN ($CDCl_3$) δ 150.91, 148.50, 147.15, 131.52, 120.77, 115.34, 49.70, 47.90, 43.80, 27.80, 25.90. IR (KBr) ν cm^{-1}: 3480 (N—H), 1530 (N—H), 1540 and 1380, (NO_2)]. [*N*-(2,4-dinitrophenyl)-*N*-(3-aminopropyl)morpholine (mp 145–146 °C) ^{1}H NMR ($CDCl_3$): δ 9.02 (s, 1*H*), 8.30 (d, 1*H*), 7.20 (d, 1*H*), 3.61 (t, 4*H*), 3.07 (t, 2*H*), 2.85 (t, 2*H*), 2.21 (t, 4*H*), 2.00 (s, 1*H*), 1.80 (m, 2*H*).^{13}C NMR ($CDCl_3$): δ 150.91, 148.50, 147.15, 131.52, 120.77, 115.34, 68.10, 51.40, 46.70, 39.90. IR (KBr) ν cm^{-1}: 3520 (N—H), 1635 (N—H), 1510 and 1340 (NO_2), 1110 (C—O—C)].

Ancillary spectrophotometric measurements

UV-VIS spectra of the substrates, the product, and different mixtures of both compounds with the amine in toluene and dimethylsulphoxide at several concentrations were recorded in a Shimadzu UV-VIS 240 graphic printer PR-1 spectrophotometer. The extinction coefficients of the products were determined at λ_{max} and at $\lambda = 460$ and 400 nm; at the three wavelengths the reagents are transparent under these conditions. All the solutions were found to obey Beer's law.

[1-*N*-(2-benzimidazol)-3-*N*-(2,4-dinitrophenyl)guanidine: Toluene: $\lambda_{max} = 340$ nm, $\varepsilon_{340} = 1.413 \times 10^4$ cm^{-1} M^{-1}, $\varepsilon_{460} = 2.39 \times 10^3$ cm^{-1} M^{-1}; DMSO: $\lambda_{max} = 375$ y 425 nm, $\varepsilon_{375} = 1.392 \times 10^4$ cm^{-1} M^{-1}, $\varepsilon_{425} = 1.3 \times 10^4$ cm^{-1} M^{-1}, $\varepsilon_{460} = 4.5 \times 10^3$ cm^{-1} M^{-1}]; [*N*-(2,4-dinitrophenyl)-*N*-(3-aminopropyl)morpholine: Toluene: $\lambda_{max} = 346$ nm, $\varepsilon_{346} = 1.04 \times 10^4$ cm^{-1} M^{-1}, $\varepsilon_{400} = 3.5 \times 10^3$ cm^{-1} M^{-1}]; [*N*-(2,4-dinitrophenyl)-1-(2-aminoethyl)piperidine: Toluene: $\lambda_{max} = 348$ nm, $\varepsilon_{348} = 1.29 \times 10^4$cm^{-1} M^{-1}, $\varepsilon_{400} = 4.31 \times 10^3$ cm^{-1} M^{-1}].

Kinetic procedures

Kinetic runs were performed by the methods previously reported,[64] following the appearance of the reaction product at $\lambda = 460$ or 400 nm. The reactions of 2-GB were carried out in sealed ampoules (under nitrogen) at 40 ± 0.2 °C and the reactions of 2-AEPip and 3-APMo were followed directly in the thermostated cell of the spectrophotometer at 25 ± 0.2 °C. The absorption spectrum of the reaction mixture at 'infinite time' corresponded within ±2% with the 'theoretical' value calculated from the application of Beer's law to solutions of the product independently prepared in the desired solvent. In all cases, pseudo-first-order kinetics were observed. Pseudo-first-order coefficients, k_Ψ, were obtained by the least-squared 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 ± 2%. No corrections for expansion coefficients were applied to the concentration values.

Acknowledgements

The authors gratefully acknowledged financial support from the Universidad Nacional del Comahue (grant no. I123-UNCo) and from the National Research Council (CONICET) from Argentina (grant no. PIP 6019).

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