Trends in Organic Chemistry

Review

The crucial role of H-bonding in the mechanisms of reactions with diamines in aprotic solvents

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ABSTRACT

In the widely reported mechanistic studies of Aromatic Nucleophilic Substitutions (ANS) most of the discussions are centered in the nature of the halo-nitro-aromatic substrates, the basicity of the nucleophile and the polarity or dipolarity of the solvent. However, in the reactions of monofunctionalized amines with aromatic substrates bearing poor nucleofuges carried out in solvents of low permittivity, weak non-covalent interactions, such as intra- and/or inter-molecular H-bonding, play a significant role. When these special features concur in the reaction system, a mechanism, called the "*dimer nucleophile mechanism*", operates in which a third-order in amine kinetic law is obeyed. The mechanism has been properly characterized by abundant evidence, showing the influence of weak non-covalent interactions, due to the nucleophile nature, the substrates used and the reaction medium. In the present paper, we discuss new examples of that mechanism to show the crucial role of H-bonding. Several aspects were studied: the influence of the nucleophile structure (specially its capacity of developing intra- and/or intermolecular hydrogen bond interactions); the "resonance-assisted" H-bond; and the effect of aprotic hydrogen bond acceptor (HBA) co-solvent/additives. A comprehensive further treatment of kinetic results is described including reactions where the first-step or the second-step are rate determining.

KEYWORDS: hydrogen-bonding, diamines, aprotic solvents, polyamines, mixed aggregates, dimer nucleophile mechanism

1. INTRODUCTION

The elucidation of mechanisms of reactions is a main area of interest, not only because of its fundamental relevance, but also for projecting new practical routes in different fields of scientific and technical research. In this sense, an active investigation on Aromatic Nucleophilic Substitution (ANS) which includes fundamental [1, 2, 3] and applied chemistry [4, 5, 6] is being developed at present. Kinetic studies on the effects of solvent polarity and non-covalent interactions on reaction mechanisms have been recently reported [7, 8, 9, 10]. On the other hand, hydrogen bonding (H-bonding) and other non-covalent interactions have been found to play a crucial role on reactions under ultrasound irradiation applied to the synthesis of differently substituted phenylenediamines [4]; on the preparation of a corticotropin-releasing factor antagonist by ANS [5]; and the synthesis of fluorescence probe using a new fluorogenic compound derivatized from 7-aminocoumarin for oligonucleotides detection [6], to name just a few applications to modern organic synthesis.

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For *ipso*-substitution reactions (S_N^{ipso}) with amines in aromatic compounds activated by electron withdrawing groups, the classical two-step base-catalysed ANS mechanism has been extensively reviewed [11,12]. However, several ANS reactions with amines in aprotic solvents were shown to exhibit an "anomalous" upward curvature in the plot of k_A vs [B]. For these systems, if the third-order rate coefficient, k_A/ [B], is plotted vs [B], straight lines are obtained, a new kinetic law is obeyed showing a *third-order* dependence in amine concentration and a *fourth-order* kinetics. These results were interpreted as a new mechanism that involves the attack of the dimer of the amine in the first step, superimposed on the classical reaction with the monomer. The first report of the so-called *"dimer nucleophile mechanism"* was published three decades ago [13] and was fully confirmed by abundant evidence from several different approaches [1, 12].

Alternative mechanisms have been suggested, thus, Banjoko *et al.* [14] interpreted the third-order term in amine concentration in the reactions of anilines with pricryl phenyl ethers, as due to a mechanism that occurs through an eight-membered cyclic intermediate that includes two molecules of amine. Nevertheless, for the formation of that highly ordered transition state, a large negative entropy of activation would be expected, but the estimated values are within the usual ranges. A few years ago, Mancini *et al.* [15] proposed a six-membered cyclic intermediate in the reaction pathway, of the reactions of 1-fluoro-2,6-dinitrobenzene and alicyclic amines in pure ethyl acetate and in ethyl acetate-chloroform binary solvent mixtures. The authors propose that in pure ethyl acetate and in mixtures with low chloroform concentrations, the reactions proceed via the formation of a six-membered cyclic dipolar aggregate.

Taking into account the inability of apolar solvents to stabilize ionic species, and the prevalence of self-aggregation of amines through H-bonding of diverse stoichiometry, (being the dimers the predominant oligomers), Nudelman and Palleros [13] proposed that a dimer (B:B) of the nucleophile attacks the substrate, and a third molecule of amine assists the decomposition step. The intermediate reaction is highly zwitterionic; the extra amine molecule is needed to stabilize the developing charge in a solvent of very low permittivity. The proposed mechanism does not preclude attack by the monomer; nevertheless, due to the higher electron density on the hydrogen-bonded nitrogen, the H-bonded amines (forming inter- or intra-molecular homo-aggregates) are better nucleophiles than monomeric amines, as has been determined by theoretical calculations [16].

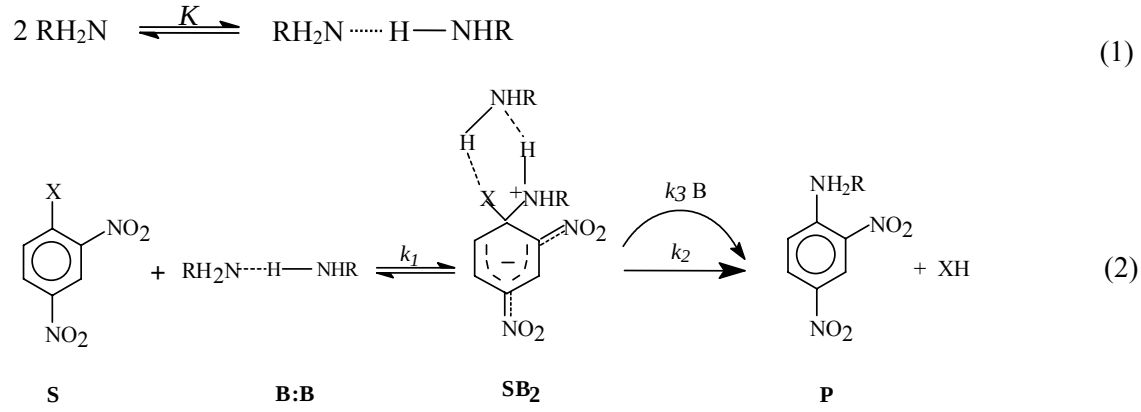
Recently, we reported kinetic data [1, 9, 17, 18] and theoretical calculations [19] on ANS reactions with mono- and polyamines, particularly chosen for their special structures as potentially able to form intra- or intermolecular H-bonds. To show the crucial role that weak covalent interactions play in defining the reaction mechanism, in this paper we discuss reactions of diamines with substrates where the first step is rate determining, such as 2,4-dinitrochlorobenzene (DNClB), and with 2,4-dinitrofluorobenzene (DNFB) in which departure of the nucleofuge is the rate-determining step, all the reactions carried out in solvents of low permittivity.

2. Inter-molecular hydrogen-bond in diamines

Intermolecular H-bonding increases the nucleophilicity of the dimer compared to the monomer, as confirmed by semi-empirical and *ab- initio* theoretical calculations [20]. There have been abundant studies in the last decade reporting the effects of varying electron withdrawing groups in the substrate [21], the importance of stereoelectronic effects in aliphatic, alicyclic and aromatic amines, [22, 23], their influence on the reactivity of ANS reactions [24], and the crucial role that pure solvents and/or binary solvent mixtures play on the reactivity and mechanisms of these reactions [25, 26, 27, 28]. However, the reactions of diamines and their potential ability to react associated through H-bonds, had not been so far addressed.

In the Nudelman's mechanism [12] it is proposed that a dimer (B:B) of the nucleophile attacks the substrate, S, forming the intermediate, SB_2. Since the reaction intermediate is highly zwitterionic, a

third molecule of amine is needed to stabilize the developing charge for the decomposition step in a solvent of very low permittivity. Abundant experimental evidence has proved the different reaction pathways that include inter- or intramolecular H-bonded homo-dimer as well as mixed dimers of the amine with other hydrogen bond acceptors (HBA) [18].



To examine the importance of H-bonding interactions in ANS with diamines carried out in aprotic solvents, the reactions of DNFB and DNClB with 1,2-diaminoethane (EDA), 3-dimethylamino-1-propylamine (DMPA) and 1-(2-aminoethyl)piperidine (2-AEPip), were studied in toluene at 25º ± 0, in the presence of variable amounts of the nucleophile. The reactions proceed straightforwardly to give the expected N-substituted-2,4-dinitroanilines, a quantitative yield of the substitution product is obtained in all reactions under study. 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. [1, 18]. The expression for k_A and k_A/ [B], considering only the attack by the dimer with poor nucleofuges can be reduced to Eqs. 1-4, where K = [B:B]/[B]^2 is the equilibrium constant for the monomer:dimer equilibrium shown in Eq. 1. The complete expression for k_A and k_A/ [B] coefficients and the different limiting situations were previously described [12].

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

$$\frac{k_A}{[B]} = \frac{k_1 k_2 K}{k_{-1}} + \frac{k_1 k_3 K[B]}{k_{-1}} \quad (4)$$

Tables 1 and 2 show the observed results for the reactions of the appointed diamines with DNFB and DNClB, respectively: the bimolecular rate coefficients k_A and the ratio k_A/[B] are given. For the reactions of DNFB with EDA, DMPA and 2-AEPip it can be observed that the second-order rate coefficients, k_A, increase rapidly with amine concentration, [B], and the plot of k_A *vs* [B], (not shown) revealed a quadratic dependence. On the other hand, if the quotient k_A/[B] is plotted *vs* [B], straight line is obtained; this result is consistent with a third-order in amine kinetic law.

The kinetic behaviour is analogous for both substrates.The reactions with DNFB can be interpreted by the mechanism shown in Eqs. 1-4. The rates with the three amines are similar, but in the plot of k_A/[B] *vs* [B] the straight line for the reaction with EDA has a no null intercept. This indicates that both, the monomer and the dimer nucleophile mechanisms are operating in the reaction with this amine [18], while the reaction with DMPA and 2-AEPip proceeds entirely through the dimer nucleophile mechanism.

As expected for a less activated substrate, the reactions of DNClB are slower than those of DNFB, though the kinetic behaviour is very similar. The second- order rate coefficients, k_A, for EDA, DMPA and 2-AEPip were found to

Table 1. Reaction of 2,4-dinitrofluorobenzene, DNFB, with 3-dimethylamino-1-propylamine (DMPA), 1,2-diaminoethane, (EDA), and 1-(2-aminoethyl) piperidine, (2-AEPip), in toluene at 25.0 ± 0.2ºC. Second- (k_A), and third- (k_A/[B]) order rate coefficients.

10^3[DMPA][a], M	4.97	6.01	6.97	8.00	8.97	
k_A, s^{-1} M^{-1}	1.19	1.54	2.12	2.78	3.64	
$10^2 k_A$/[B], s^{-1} M^{-2}	2.39	2.56	3.04	3.48	4.06	
10^3[EDA][a], M	4.94	6.00	7.00	7.94	8.99	10.0
k_A, s^{-1} M^{-1}	0.72	0.96	1.21	1.43	1.75	2.09
$10^2 k_A$/[B], s^{-1} M^{-2}	1.46	1.60	1.72	1.80	1.95	2.09
10^3[2-AEPip][b], M	5.02	5.97	6.96	7.98	8.95	9.94
k_A, s^{-1} M^{-1}	1.59	2.34	3.15	4.18	5.85	6.57
$10^2 k_A$/[B], s^{-1} M^{-2}	3.17	3.92	4.52	5.24	6.54	6.61

[a][DNFB] = 5.0 x 10^{-4} M. [b][DNFB] = 5.15 x 10^{-4} M.

Table 2. Reaction of 2,4-dinitrochlororobenzene, DNClB, with 3-dimethylamino-1-propylamine (DMPA), 1,2-diaminoethane (EDA) and 1-(2-aminoethyl)piperidine, (2-AEPip), in toluene at 25.0 ± 0.2ºC. Second- (k_A), and third- (k_A/[B]) order rate coefficients.

[DMPA][a], M	0.497	0.601	0.697	0.800	0.897	1.00	1.20	1.50	2.01	
$10^3 k_A$, s^{-1} M^{-1}	0.485	0.72	0.99	1.26	1.55	1.98	2.59	3.93	5.92	
$10^3 k_A$/[B], s^{-1} M^{-2}	0.976	1.20	1.42	1.57	1.73	1.98	2.16	2.62	2.94	
[EDA][a], M	0.494	0.60	0.704	0.794	0.899	1.00	1.20	1.50		
$10^3 k_A$, s^{-1} M^{-1}	1.69	2.25	2.84	4.11	4.52	6.21	8.39	13.50		
$10^3 k_A$/[B], s^{-1} M^{-2}	3.42	3.75	4.03	5.18	5.03	6.21	6.99	8.98		
[2-AEPip][b], M	0.496	0.597	0.791	0.999	1.20	1.51	1.73	2.01	2.31	2.54
$10^3 k_A$, s^{-1} M^{-1}	1.92	2.48	3.12	4.88	5.98	8.73	10.9	15.4	22.9	26.4
$10^3 k_A$/[B], s^{-1} M^{-2}	3.87	4.15	3.95	4.88	4.98	5.78	6.30	7.66	9.91	10.4

[a][DNClB] = 5.0 x 10^{-4}M. [b][DNClB] = 5.09 x 10^{-4}M.

increase rapidly with amine concentration, [B]; the plot of k_A *vs* [B] shows a quadratic dependence, while the quotient k_A/[B] plotted against [B] is a straight line. These results are consistent with a third-order in amine kinetic law, similarly to what was observed with DNFB, confirming the presence of dimers of DMPA, EDA and 2-AEPip acting as nucleophiles. Taking into account that for this substrate, the first step is r.d.s., the expression for k_A and k_A and k_A/ [B], involving attack by the dimer and the monomer are Eqs. 5-6. The different limiting situations were recently derived [9].

$$k_A = \frac{\left(k_3 k_4 + k_1 k_5 K_1 K_2\right)[B] + k_1 k_3 K_1 [B]^2}{K_2\left(k_{-4} + k_5\right)} \qquad (5)$$

$$\frac{k_A}{[B]} = \frac{k_3 k_4 + k_1 k_5 K_1 K_2}{K_2\left(k_{-4} + k_5\right)} + \frac{k_1 k_3 K_1 [B]}{K_2\left(k_{-4} + k_5\right)} \qquad (6)$$

For reactions of DNClB with DMPA and EDA, the intercept in the plot of k_A/[B] *vs* [B] is null,

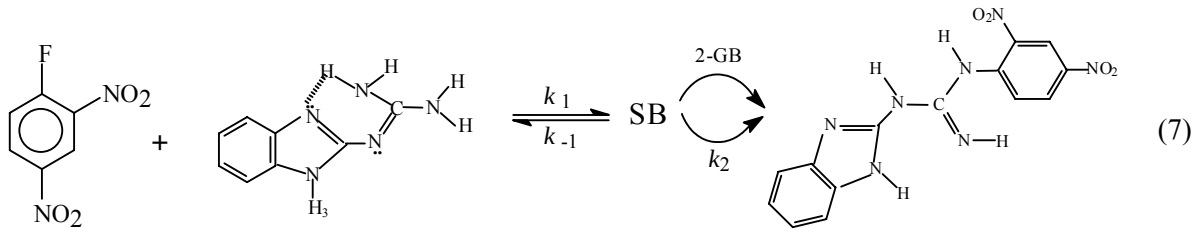
which indicates that the reactions fully proceed by the dimer nucleophile mechanism. On the contrary, the reactions with 2-AEPip has no null intercept: both, the monomer and the dimer nucleophile, mechanisms occur in the reaction with DNClB, while the reaction with DNFB proceeds entirely through the dimer mechanism.

3. Intramolecular hydrogen-bond in polyamines

When two (or more) amino groups are in an appropriate geometry, a strong intramolecular H-bonding can be easily established, and those compounds exhibit unusually high basicity [29]. Intra-molecular H-bonding in the nucleophile also causes an increase in nucleophilicity, as it was demonstrated experimentally in kinetic studies of reactions with *cis*- and *trans*-1,2-diaminocyclohexane. In fact, although due to steric hindrance the reactions with the *cis*-isomer would be expected to be slower, the favoured intramolecular H-bond between both close amine groups, increases the nucleophilicity of the *cis*-1,2-diaminocyclohexane and the reaction is faster than with the *trans*-isomer [30].

To examine the interpretation that the intermolecular H-bonds in EDA, DMPA and 2-AEPip are responsible for the observed results, the reactions of nucleophiles able to form intramolecular H-bonding were also studied. Taking into account their special structure the polyamines chosen were: histamine, N-(3-amino-1-propyl)morpholine, (3-APMo) and 2-guanidinobenzimidazole (2-GB). Histamine has a rigid structure with two basic sites: the pseudo amidino group (imidazole) and the amino group of the side chain separated by three carbon atoms, two of which belong to the alkyl chain; in 3-APMo a flexible side chain of three carbon atoms is separating the amino group of alicyclic nitrogen. 2-GB is a complex molecule with a benzimidazole ring and a guanidino group; it is a multifunctional plane molecule, with a delocalized π system. It has five nitrogen atoms that act as basic sites and presents the possibility, like histamine, of forming a six-membered ring that favors the stability of intramolecular H-bond.

Addressing the different reactivity of the amines, the kinetics of the reaction with 3-APMo were studied at 25 ± 02ºC and the reactions with histamine and 2-GB were studied at 40 ± 0.2 ºC, all in presence of variable amounts of the nucleophile, in toluene. Table 3 shows the observed k_A values for the reactions of histamine, 2-guanidinobenzimidazole (2-GB) and N-(3-amino-1-propyl)morpholine, (3-APMo) with DNFB and Table 4 the k_A values for histamine and 3-APMo reactions with DNClB. The second-order rate coefficients increase steadily with the three nucleophiles; the plot of k_A *vs* [B] is a straight line with zero intercept and a correlation coefficient, $R^2 = 0.991$ for histamine, $R^2 = 0.989$ for 2-GB and $R^2 = 0.992$ for 3-APMo [1]. For histamine and 2-GB, intramolecular hydrogen-bonds are easily established because their rigid geometries prevent the formation of intermolecular dimers: the classical mechanism of base-catalysed decomposition of the zwitterionic intermediate, SB, is obeyed. The null intercept indicates that the spontaneous decomposition of SB is negligible, as expected from the poor nucleofugacity of fluorine in aprotic solvents. The kinetic results obtained are consistent with an "atypical" base catalyzed decomposition of the zwitterionic intermediate derived from an *"intramolecular dimer"* as shown by (Eq. 7).



(7)

Table 3. Reaction of 2,4-dinitrofluorobenzene, DNFB, with histamine, N-(3-amino-1-propyl)morpholine, (3-APMo) and 2-guanidinobenzimidazol, 2-GB, in toluene at 40.0 ± 0.2ºC[c] and 25.0 ± 0.2ºC[d], respectively. Second, k_A, order rate coefficients.

10^3[Histamine][a,c], M	5.00	5.99	7.00	7.98	8.98	10.1			
$10^3\,k_A$, $s^{-1}\,M^{-1}$	5.30	6.26	7.75	8.79	9.69	10.5			
10^3[3-APMo][b,d], M	5.05	6.10	7.00	8.04	9.01	10.2	12.0		
k_A, $s^{-1}\,M^{-1}$	1.36	1.72	2.05	2.29	2.51	2.85	3.49		
10^2[2-GB][b,c], M	0.61	0.75	0.92	1.08	1.21	1.51	2.02	2.50	3.00
$10^5\,k_A$, $s^{-1}\,M^{-11}$	0.64	0.84	1.09	1.42	1.51	1.71	2.32	2.91	3.80

[a][DNFB] = 1.0 x 10^{-4} M. [b][DNFB] = 5.15 x 10^{-4} M.

Table 4. Reaction of 2.4-dinitrochlorobenzene, DNClB, with histamine and N-(3-aminopropyl)-morpholine, 3-(APMo), in toluene at 40.0 ± 0.2ºC and 25.0 ± 0.2ºC, respectively. Second (k_A), order rate coefficients.

[Histamine][a], M	0.25	0.50	0.70	0.90	1.20	1.50	1.85	2.15		
$10^5\,k_A$, $s^{-1}\,M^{-1}$	1.20	3.90	5.60	7.20	9.3	10.6	12.8	15.5		
[3-APMo][b], M	0.300	0.537	0.604	0.805	0.900	1.01	1.20	1.48	1.75	2.01
k_A, $s^{-1}\,M^{-1}$	1.53	2.54	3.44	4.02	4.54	4.94	5.59	6.89	7.97	9.25

[a][DNClB] = 1.0 x 10^{-4}M. [b][DNClB] = 5.09 x 10^{-4}M.

Though, in principle, it could be expected that the molecular structure of DMPA might be considered similar to that of 3-APMo, it is worthwhile to note that in DMPA the nitrogen is approximately planar while the sp^3 nitrogen in the chair conformation of morpholine is more basic. Thus, the nitrogen is forced to adopt a more rigid sp^3 structure that easily contributes to the formation of a H-bonded structure; 3-APMo is also too sterically hindered for another molecule to approach at the distance needed to form an intermolecular H-bonded structure. Intramolecular hydrogen bond in 3-APMo also plays an important role in stabilizing the molecule, since a pseudo-six membered ring is formed between the amino group of the lateral chain and the nitrogen of the alicyclic group. In 2-AEPip, the intramolecular H-bond involves the formation of a five-membered ring, which prevents proper conformational stabilization.

Table 4 shows the k_A values for the reactions of histamine and N-(3-amino-1-propyl)morpholine, (3-APMo) with DNClB in toluene at 40ºC and 25ºC, respectively, in the presence of variable amounts of the nucleophile. The second-order rate coefficients increase steadily with both nucleophiles; the plot of k_A *vs* [B] exhibit a linear dependence on amine concentration with a null intercept. Although in this case the first step is rate determining, the kinetic behaviour is very similar to DNFB and the same considerations apply to these systems.

These kinetic results indicate the formation of inter- and intramolecular H-bonding in bifunctional flexible structure amines with 2 and 3 methylene groups, and with histamine and 2-GB, which have rigid structures, are consistent with studies of tautomerism and gas-phase proton affinity of bidentate ligands previously reported. Raczynska and Wozniak [16] studied bifunctional ligands with rigid and flexible conformations, and could show the consequences of "internal salvation" in the gas phase for different diamines.

Recently, Babatunde [31] afforded further evidence for cyclic transition state mechanism in ANS reactions carried out in non-polar aprotic solvent. The author studied the kinetics of reactions of phenyl-2,4,6-trinitrophenyl ether with 1,2- and 1,4-diaminobenzene in benzene and observed a third order in amine in the reactions with 1,4-diaminobenzene, while the reactions with the 1,2-isomer shows second order dependence on amine concentration. Though the author rationalized the results in terms of a cyclic transition state mechanism, this is another clear-cut evidence for the dimer mechanism: in the 1,2-diaminobenzene intramolecular H-bond prevents the intra-molecular H-bonded aggregate which is formed with the 1,4-diaminobenzene, the isomer that shows a third order in amine kinetic law. We have recently reported new kinetic [1, 32] as well as theoretical [19, 33] additional evidence for the dimer nucleophile mechanism.

4. A "resonance assisted" hydrogen-bond?

It has been recently reported the formation of intramolecular H-bond in guanidines, amidines, substituted formamidines [34] and in 2-guanidinobenzimidazole (2-GB) related to the "resonance assisted" H-bonding concept [35]. The study of guanidino group has attracted increasing interest in recent years due to their chemical properties and potential applications in various fields of chemistry. The guanidino functional group has high basicity and, in some cases, low nucleofilicidad [36]; it is a stable group, has net positive charge in a wide range of pHs, and is found in biological molecules such as guanine, creatine and arginine [36b]. It has been recently used to study the mechanism of phosphodiester hydrolysis, as the recipient of anions in synthetic sensors, and as solid phase support to investigate the binding of deoxyribonucleic acid guanidine aromatic arrays and antigenic agent [37].

Conjugated systems can increase the strength of the H-bond, due to the synergism of H-bond and π delocalization. The impact of intramolecular H-bond in the electronic structure of neutral guanidino group and the aromatic portion of the molecule due to its characteristic of H-bond assisted by resonance, provides stability to the molecule due to large π electrons delocalization [38]. Empirical parameters showing the interactions between solute and solvent, or the dependence of the reactivities by changing the solvent, are good descriptors for the interactions that occur at the molecular level, in particular non-covalent interactions, and may be used to explain physical and chemical properties of solutes in solutions. The solvatochromic parameters used for that purposes have been widely reviewed [39].

Table 5. Reaction of 2.4-dinitrofluorobenzene, DNFB and 2.4-dinitrochlorobenzene, DNClB with 2-guanidinobenzimidazole (2-GB) in dimethylsulphoxide (DMSO) at 40.0 ± 0.2ºC. Pseudo first- $k\psi$, and second-order rate coefficients, k_A.

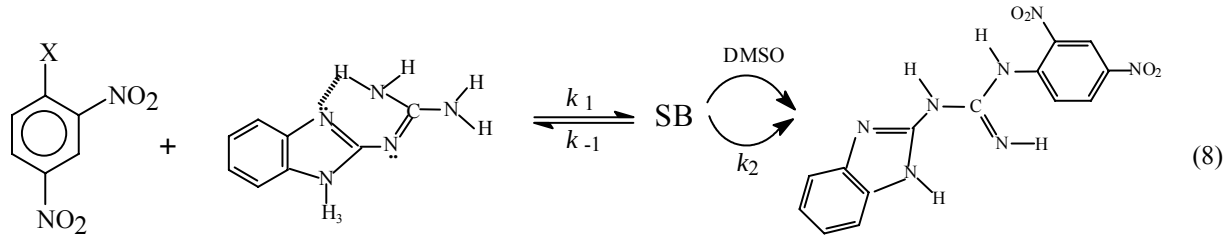
DNFB[a]			DNClB[b]		
10^2[2-GB]/M	$10^5\, k\psi$, , s^{-1}	$10^4\, k_A$, $s^{-1}M^{-1}$	10^2[2-GB]/M	$10^7\, k\psi$, s^{-1}	$10^6\, k_A$, $s^{-1}M^{-1}$
0.54	0.62	11.4	0.50	0.59	11.8
0.71	0.82	11.5	1.08	1.25	11.6
0.90	1.08	12.0	3.22	3.87	12.0
1.08	1.19	11.0	4.00	4.75	11.9
2.00	2.23	11.1	5.00	6.37	12.7
3.00	3.31	11.0	6.08	7.73	12.7
5.00	5.56	11.1	8.01	10.1	12.7

[a][DNFB] = 5.019 x 10^{-4} M. [b][DNClB] = 5.02 x 10^{-4} M.

4.1. Reactions of DNFB and DNClB with 2-GB in DMSO

To examine the effect of a dipolar aprotic HBA solvent on the H-bond formation, the kinetics of the reactions of DNFB and DNClB with 2-GB were studied at 40º ± 0.2C, at nucleophile concentration in the range 0.005-0.08 M. The product was quantitatively formed and kinetics of pseudo first order with respect to the substrate was observed [1]. Table 5 shows the pseudo first-, k_ψ, and second-, kA, order rate coefficients values for the reactions of 2-GB with DNFB and DNClB in DMSO.

Contrary to what was observed in toluene, in the reactions carried out in DMSO with both substrates, the pseudo first-order rate coefficients, k_ψ, increase uniformly with [2-GB], the plots of k_ψ vs [B] are straight-lines with zero intercept and correlation coefficients of R2 = 0.999 and R2 = 0.998, respectively. No significant dependence of the second-order rate coefficients, kA, with the amine concentration was observed in the whole concentration range studied. These results are satisfactorily explained as an amine molecule intervening in the first step, which is the rate-determining step of reaction, and DMSO assists the zwitterionic intermediate decomposition, taking into account its good hydrogen bond acceptor (HBA) characteristics (β = 0.76, ET (30) = 45.0) [39]. In spite of its greater basicity (pK 2-GB = 6.91) [40] 2-GB is less favored to assist the reaction intermediate decomposition, due to its important steric requirements (Eq. 8).



(8)

X = Cl, F

These results are consistent with the impairment produced by the dipolar aprotic solvent used in the formation of dimers of 2-GB. In fact, spectroscopic studies of proton exchange reveals that DMSO prevents the intermolecular aggregation of 2-GB [41]. The proposed "*intramolecular dimer*" has an additional stabilization due to the relocation of π electrons in the conjugated system, a factor that increases the strength of intramolecular hydrogen bonds, this is an example of the so-called "resonance assisted" hydrogen bond (RAHB) [35].

4.2. Reactions of DNFB with 2-GB in solvent mixtures

To analyse how specifically fine changes in the reaction media influences the H-bond formation and the kinetic behaviour, DMSO was added to toluene for reactions of DNFB with 2-GB. The rate behaviour is compared with that shown in the reaction of DNFB with *cis*- and *trans*-1,2-diaminocyclohexane (1,2-DACH) in methanol-toluene binary solvents [30].

Table 6 shows the observed second-order rate coefficients, k_A, for the reactions of DNFB with 2-GB in DMSO-toluene binary solvents and with *cis*- and *trans*-1,2-diaminocyclohexane (1,2-DACH) in methanol-toluene binary solvents. An important decrease in the rate of reaction with the 1,2-DACH mixture was observed on addition of small amounts of MeOH to toluene. The rate decreases up to 50% toluene-50% MeOH and then a twofold increase takes place on going to 100% MeOH. The sharp decrease in rate is interpreted as partially due to the rupture of the intramolecular H-bond of *cis*- amino groups, by competition with external H-bonding with the HBD solvent (MeOH α = 0.93) [39], decreasing

Table 6. Reaction of 2.4-dinitrofluorobenzene, (DNFB) with 2-guanidinobenzimidazole (2-GB)[a] in dimethylsulphoxide (DMSO)-toluene binary solvents at 40.0 ± 0.2ºC and with *cis*- and *trans*-1,2-diaminocyclohexane (1,2-DACH) in MeOH-toluene binary solvents. Second-order rate coefficients, k_A.

2-GB[a,b]		1,2-DACH)[c,d]	
% DMSO (v/v)	$10^4 k_A$, $s^{-1}M^{-1}$	%MeOH(v/v)	k_A, $s^{-1}M^{-1}$
2	4.21	0	0.481
5	6.70	3	0.0591
7	7.80	6	0.0355
9	8.74	10	0.0283
10	9.38	20	0.0248
20	9.45	30	0.0229
40	9.83	40	0.0226
60	9.98	50	0.0211
80	10.2	70	0.0352
100	11.0	100	0.0434

[a][2-GB] = 0.0108 M. [b][DNFB] = 5.019 x 10^{-4} M. [c][DACH] = 0.0802 M (49 % *cis*-, 51 % *trans*-). [d][DNFB] = 6.08 x 10^{-5} M.

the nucleophilicity of the amine. On the other hand, in the reactions studied in binary mixtures DMSO-toluene, starting from small additions of DMSO to toluene, evidence for preferential solvation was observed as described below. A significant increase in rate is 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 *"mixed aggregates"* nucleophile:co-solvent. The mixed aggregate increases the reaction rate since the amine now acts as a hydrogen-bond donor (HBD) with greater nucleophilicity. For 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 cibotatic zone [1]. This result is an additional evidence in favor of the importance of H-bond interactions in determining the amine nucleophylicity.

To support the interpretation of the experimental results, theoretical semi-empirical and *ab-initio* calculations were performed in vacuum, toluene and DMSO to investigate the likelihood of 2-GB H-bond formation. For 2-GB an intramolecular hydrogen bond is identified in vacuum and in both solvents. For DMSO, intermolecular H-bonds between 2-GB and the solvent were found: a mixed solute-solvent 2-GB: DMSO dimer. The intra-molecular hydrogen bond in 2-GB is slightly weakened by the action of both solvents as it is inferred from the values of the electronic densities at the critical point. Solvation energies, calculated as the difference in energy at 0 ºK for the molecule in solvent and in vacuum, reveal a stronger interaction for DMSO than toluene [19].

5. Further treatment of kinetic results

One of the most prominent feature of the *dimer nucleophile mechanism* is the forth order kinetics (third order in amine) that has been observed with many different substrate-nucleophile systems. But, this particular mechanism was confirmed by other specific features such as: observation of a negative energy of activation [12], catalysis by HBA additives [13, 42] preferential solvation in

mixed solvents [1, 12, 17], conformational unusual effects in cycloalkyldiamines [30], linear kinetic behaviour in *"inverse plots"* [12], and ^{1}H-NMR spectroscopic evidence of the homo- and mixed-aggregates [32]. Although alternative mechanisms have been suggested to explain the forth order kinetics, no one has been able to explain the above mentioned features. Initially, most of the systems in which third-order in amine kinetic law was observed were performed using poor nucleofuge substrates [e.g. 12, 30], nevertheless, in the last years we reported evidence for this atypical kinetic behavior using also a good nucleofuge [1, 17, 18, 42].

To afford additional assessment to the scope of "*dimer nucleophile*" mechanism, further treatment of the different kinetic equations was reported with the polyamines kinetic results, as well as the deduction of k_A and k_A/[B] expressions for reactions where the first step is rate-determining [9]. The reactions of 2,4-dinitrofluorobenzene, DNFB, and 2,4-dinitrochlorobenzene, DNClB with aniline, [42], 1,2-diaminoethane (EDA), 3-dimethylamino-1-propylamine (DMPA) and 1-(2-aminoethyl)piperidine (2-AEPip) in toluene exhibit appropriate kinetic behavior to apply refined treatments for the estimation of the different *k´*s involved.

5.1. Reactions of DNFB: Second step rate-determining

Inversion of Eq. 4 gives Eq. 9, which allows some estimation of the different k's involved:

$$\frac{[B]}{k_A} = \frac{1}{k_1 K} + \frac{k_{-1}}{k_1 k_2 K + k_1 k_3 K [B]} \qquad (9)$$

Taking into account that the uncatalysed decomposition of zwitterionic intermediate is slower than the base-catalyzed one, Eq. 9 can be simplified to Eq. 10:

$$\frac{[B]}{k_A} = \frac{1}{k_1 K} + \frac{k_{-1}}{k_1 k_3 K [B]} \qquad (10)$$

A plot of de [B]/k_A *vs* [B]$^{-1}$ ("inversion plots") should be linear, except where the conditions that allow the simplification to Eq. 10 are not fulfilled. The data for [B]$^{-1}$ and [B]/k_A for the reactions of DNFB with aniline, EDA, DMPA and 2-AEPip in toluene were calculated and compared with the rate coefficients calculated from Eqs. 4 and 10, finding satisfactory agreement between both sets of data, which proves the validity of the treatment applied to the kinetic data and estimate the magnitude of some constants.

These reactions exhibit useful kinetic behaviour in a range of [B] for the evaluation of the similar expressions from the plot of k_A/[B] *vs.* [B]. The inversion plots for the studies amines are linear and the values for the intercepts allow an estimation of the order of magnitude of $\frac{k_1 k_2 K}{k_{-1}}$; the slope gives $\frac{k_1 k_3 K}{k_{-1}}$; from both quotients the ratio coefficient relationship $\frac{k_3}{k_2}$ can be reckoned [9].

The values obtained for slope were similar for aniline and EDA and matching for DMPA and 2-AEPip. For aniline no significant difference are observed between the uncatalyzed and base catalyzed step, while for EDA the base catalysed step is twice more important than the uncatalyzed one. For DMPA and 2-AEPip the ratio k3 /k2 could not be calculated as intercepts of three order plots are zero.

5.2. Reactions of DNClB: First step rate-determining

The ratio coefficient relationship slope/intercept of the Eq 6. derived for the reactions where the first step is rate-determining, allows an estimation of the magnitude of the quotient [9]:

$$\frac{Slope}{Intercept} = \frac{k_1 k_3 K_1}{k_3 k_4 + k_1 k_5 K_1 K_2}$$

k5 should be smaller than k3, because the reaction with the dimer is faster, k1 should be smaller than k3 since the first step is rate-limiting, and K1 and K2 are small values (K1 ≅ 0.1 M-1) [see reference 9]. Therefore, considering the limiting situation k3 k4 >> (k1 k5) K1K2, the ratio can be simplified to:

$$\frac{Slope}{Intercept} = k_1 K_1 / k_4$$

which allows an estimation of the incidence of both mechanisms in the global reaction.

Inversion of Eq. 6 in it simplified form is Eq. 11:

$$\frac{[B]}{k_A} = \frac{K_2(k_{-4} + k_5)}{k_1 k_3 K_1 [B]} + \frac{(k_{-1} + k_3)}{k_1 k_3 K_1} \qquad (11)$$

The data for [B]-1 and [B]/kA for the reactions of DNClB with aniline, EDA, DMPA and 2-AEPip in toluene were calculated and compared with the rate coefficients calculated from Eq. 6, finding satisfactory agreement between both sets of data.

According to the the relationship slope/intercepts of the reactions with aniline, the contribution of the dimer mechanism and classical monomer mechanism are similar. This result indicates that dimer mechanism contributes significantly to the reaction rate at relatively high aniline concentrations.

For EDA and DMPA the ratio slope/intercept could not be calculated because the intercept in third-order plot is zero, indicating that the reactions with this substrate proceeds only by the dimer mechanism. However, in the reactions with 2-AEPip, the relationship slope/intercepts point out that the contribution of the dimer mechanism to the global reaction is almost twice that of the monomer. This result suggests that the dimer mechanism contributes significantly to the overall reaction rate. These results altogether constitute an additional confidence to the dimer nucleophile mechanism, even when the first step is rate determining.

CONCLUSIONS

The present kinetic studies afford abundant evidence on the crucial role of inter- and intramolecular H-bonding in defining the reaction mechanism of diamines in media of low permittivity and different HBA capacity. The kinetic results obtained in aprotic solvents show the importance of the aggregation of the nucleophile in non-polar solvents due to its ability to establish self-hydrogen bonding interactions. In HBA dipolar aprotic solvents, the microscopic aggregation with the solvent competes with the self-aggregation of the nucleophile; the results are interpreted as due to the formation of *"mixed aggregates"*. Although the rates of reaction with DNClB, as expected for a less activated substrate, are three orders of magnitude lower, they exhibit a kinetic behaviour similar to those observed with DNFB: the results obtained with di-and polyfunctionalamine shows the importance of nucleophile structure due to its ability to establish intra- or intermolecular H-bond interactions.

When the nucleophile structure, such as some diamines, allows an intramolecular H-bond formation, this significantly reduces or prevents the formation of intermolecular dimers. Therefore, a second order in amine concentration is observed in these systems, indicating that the nucleophile is a monomer under the conditions that favor the mechanism of dimer, due to the formation of an *"intramolecular dimer"*.

The nature of noncovalent weak interactions developed in aprotic media alters the properties of the nucleophile. The present results confirm that the association of amines in aprotic solvents plays an important role in defining the mechanisms and afford substantial evidence in favor of the "dimer nucleophile" mechanism observed with amines in aprotic solvents.

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