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A Comprehensive Mechanism for Aromatic Nucleophilic Substitution in Aprotic Solvents: Derivation of the Whole Reaction Scheme for Third Order in Amine Kinetic Law

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Abstract When aromatic nucleophilic substitutions (ANS) with amines are carried out in solvents of low permittivity, a third order in amine kinetic law is often determined. Initially considered an "atypical" behavior, this and *other peculiar findings* could be consistently accommodated in a new mechanism for ANS that we called the *"dimer nucleophile"* mechanism. At present, there are abundant studies in the current literature where the "dimer" mechanism has been observed. Though most of the reported 4th order ANS occurred with poor nucleophiles, we recently designed special systems that allowed the "dimer" mechanism be observed also with substrates where the first step is rate determining. In the present paper, the kinetic behavior and reactivity for ANS reactions performed with halonitrobenzenes and several bi- and poly-functionalized amines in toluene is reported. Special systems implying nucleophiles of flexible structure and appropriate rigid molecular geometry, regarding their hydrogen bond self-aggregation states were designed; the presence of non-nucleophilic hydrogen bond acceptor additives was also studied. It is shown that the nature of non-covalent weak interactions developed in aprotic media alter the properties of the nucleophile. Our results confirm that the association of amines in aprotic solvents plays an important role in defining the ANS mechanisms. An overall reaction Scheme is presented herewith, including determination of the partial *k's* of the individual steps in the complex reaction.

Keywords Aromatic Nucleophilic Substitution, Aprotic Solvents, Aggregation Effects, Overall Kinetic Treatments, "Dimer" Nucleophile Mechanism

1. Introduction

The elucidation of mechanisms of reaction is a main area of interest, not only because of its fundamental relevance, but also for projecting new practical routes in other fields of scientific and technological research. In this sense, an active investigation on Aromatic Nucleophilic Substitution (ANS) which includes fundamental[1-6] and applied[7-11] research is being developed at present. The interest stems from the fact that ANS can proceed through a variety of pathways[12, 13] and the many-sided nature of the catalysed ANS mechanisms[4]. Synthesis of polymeric materials[7], dyes[8], pharmaceuticals[9, 10] and other bioactive agents[11] based on ANS have been recently reported, including a patented treatment of halohydrocarbons and polychlorinated biphenyls for the decontamination of groundwater[14].

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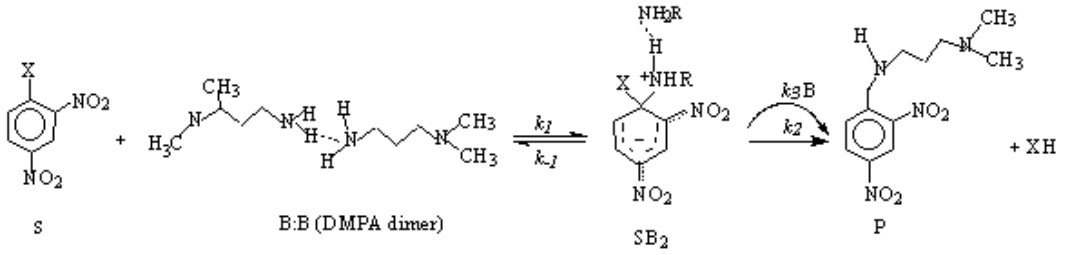
Though ANS by amines has been recognised to be extremely affected by the solvent[12, 15], only few attempts have been made to study the effects of solvent in a systematic way[16-20]. If ANS with amines and substrates activated by electron withdrawing groups are carried out in solvents of low permittivity weak non-covalent interactions, play a significant role[21-23]. H-bonding and other non-covalent interactions have been also found on ANS under ultrasound irradiation applied to the synthesis of substituted phenylenediamines[24], on the preparation of a corticotropin-releasing factor antagonist[10], and in the synthesis of a new fluorescence probe[11], to mention just a few applications in modern organic synthesis.

Nudelman and Palleros [25, 26] proposed three decades ago, that the observed kinetic behaviour of third order dependence on amine (B), is consistent with a new mechanism involving attack of the dimer of the nucleophile (B:B) Eqn. 1, where S and P stand for substrate and products, respectively, and B is shown as DMPA (one of the studied diamines in the present paper).



(1)

Though the most notorious feature is the forth order kinetic law, the "dimer nucleophile mechanism" was subsequently confirmed by additional evidence such as: observation of a negative energy of activation; catalysis by HBA agents; homo- and hetero-aggregates; preferential solvation in mixed solvents; conformational specific effects; and linear "inverse plots"[12]. These atypical findings cannot be accommodated by any other alternative mechanism. The "dimer" mechanism has been properly characterized by abundant evidence, even by other authors, and it is also described in Organic Chemistry textbooks[27]. In a new approach, we recently reported ANS using mono-, di- and polyamines, that were purposefully designed because their special structures allowed forming intra- or intermolecular homo-dimers, the effects of hydrogen bond acceptors (HBA), and of co-solvent/additives leading to mixed hetero-dimers were also determined[14-16, 19].

A recent concern was why the "dimer nucleophile" has been only observed in ANS carried out with poor nucleofugue substrates? In an attempt to answer this question we undertook kinetic determinations of ANS with substrates where the first step is known to be rate determining, we designed special substrate-nucleophile systems that allowed kinetic determinations in toluene at relatively low and high[B]. The reactions studied exhibit appropriate kinetic behaviour to apply refined treatments for the estimation of the partial k´s involved. An overall reaction Scheme consistent with the present and previous results was developed, a comprehensive kinetic treatment was derived that comprises a large variety of systems as it is discussed below.

2. Material and Methods

2.1. General Procedures

UV-VIS spectra were recorded in a Shimadzu UV-VIS 240 graphic printer PR-1 spectrophotometer. 1H and 13C NMR spectra were recorded in a Bruker ARX-300 spectrometer instrument. J values are given in Hz. NMR spectra were determined in CDCl3 as solvent. The IR spectra were recorded in a KBr disc using a Nicolet Nexus FT-IR spectrometer. Thin-layer chromatography was performed on Merck Kiesegel 60 F254. Melting points were determined in a Kofler hot stage and are uncorrected.

2.2. Reagents and Solvents

Reagents and solvents were purified using previously reported procedures [1].

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 78-80ºC at 20 mmHg was collected. It was kept in 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 desiccator under dry nitrogen atmosphere, protected from light, and was re-distilled before using

Ethylendiamine (ETDA, 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. 116-118ºC (lit. 116.5ºC) [22]. 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

3-dimethylamino-1-propylamine (DMPA) was prepared from dimethylamine and acrylonitrile, [28]. After two days, the excess of dimethylamine was distilled under reduce pressure 75-77ºC/11 mmHg). The N,N-dimethylpropanenit rile obtained was reduce with Na/EtOH. Distillation of the resulting product gave 3-dimethylamino-1-propylamine as a liquid, which was stored under nitrogen atmosphere at 5ºC. 1H NMR (CDCl3): 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-).

Aminoethylimidazole (histamine base, Fluka) was used without further purification and was kept in a desiccator protected from light.

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 ºC, lit.[29] 242.8–244.5ºC). IR ν cm_1: 3448, 3210 (N—H), 1648 (C—N), 1600, 1542

(C—C), 1392, 1274(C—N).

2,4-dinitrochlorobenzene (DNClB, Sigma), was crystallized twice from absolute ethanol (mp 52-53°C, lit. [1] 52-53°C).

2,4-dinitrofluorobenzene, (DNFB, Merck), was distilled at reduced pressure under nitrogen (b.p. 122–123 8C at 5mm Hg, lit.[22] 119ºC at 2 mmHg) and was kept in a desiccator protected from light under dry nitrogen atmosphere.

The substitution products were prepared from 2,4-dinitrochlorobenzene and the corresponding amine. In all cases, the compounds were obtained in almost quantitative yields, as yellow crystals. The substitution compounds were characterized as follows:

[N-(2,4-dinitrophenyl)-1-(2-aminoethyl)piperidine (mp 122-123 °C), ^{1}H NMR ($CDCl_3$): δ 9.04 (s, 1H), 8.15 (d, 1H), 6.81 (d, 1H), 3.36 (t, 2H), 2.63 (t, 2H), 2.40 (t, 4H), 1.49 (m, 6H), 1.02 (s, 1H). ^{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, (NO2)].

[N-(2,4-dinitrophenyl)-N-(3-aminopropyl)morpholine (mp 145-146ºC) 1H NMR (CDCl3): δ 9.02 (s, 1H), 8.30 (d, 1H), 7.20 (d, 1H), 3.61 (t, 4H), 3.07 (t, 2H), 2.85 (t, 2H), 2.21 (t, 4H), 2.00 (s, 1H), 1.80 (m, 2H).13C 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)]. [N-(2,4-dinitrophenyl)ethylenediamine (mp 108-110°C), 1H 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), 13C NMR (CDCl3): δ 40.90, 48.31, 121.51, 121.87, 132.55, 148.10, 148.50, 149.90]. IR (KBr) ν cm-1: 3320 (-N-H); 2850 (C-H, -CH_2); 1640 (–NH_2); 1590 (C-C); 1510 (–NO_2); 1470 (C-H –CH_2); 1340 (–NO_2); 1120 (-C-N); 890 (C-H); 780 (two bands, –NH_2); 710 (C-H)].

[N-(2,4-dinitrophenyl)histamine (mp 158-160°C), 1H NMR ($CDCl_3$): δ 12.60 (s, 1H), 9.03 (s, 1H), 8.25 (d, 1H, 3JHH = 9.5 Hz), 8.08 (s, 1H), 7.59 (s, 1H), 7.10 (d, 1H, 3JHH = 9.5 Hz), 3.20 (t, 2H), 3.05 (t, 2H), 2.30 (s, 1H), 13C NMR ($CDCl_3$)ppm: δ 150.91, 148.50, 147.15 ,136.20, 131.52, 122.40, 121.30, 120.77, 115.34, 38.79, 23.19. IR (KBr) ν cm^{-1}: 3450 (N-H); 2750 (C-H, -CH_2); 1640 (N-H); 1590 (C-C); 1510 (C-C); 1500 (–NO_2); 1455 (C-H, -CH_2); 1340 (–NO_2); 880 (C-H); 770 (δC-H).

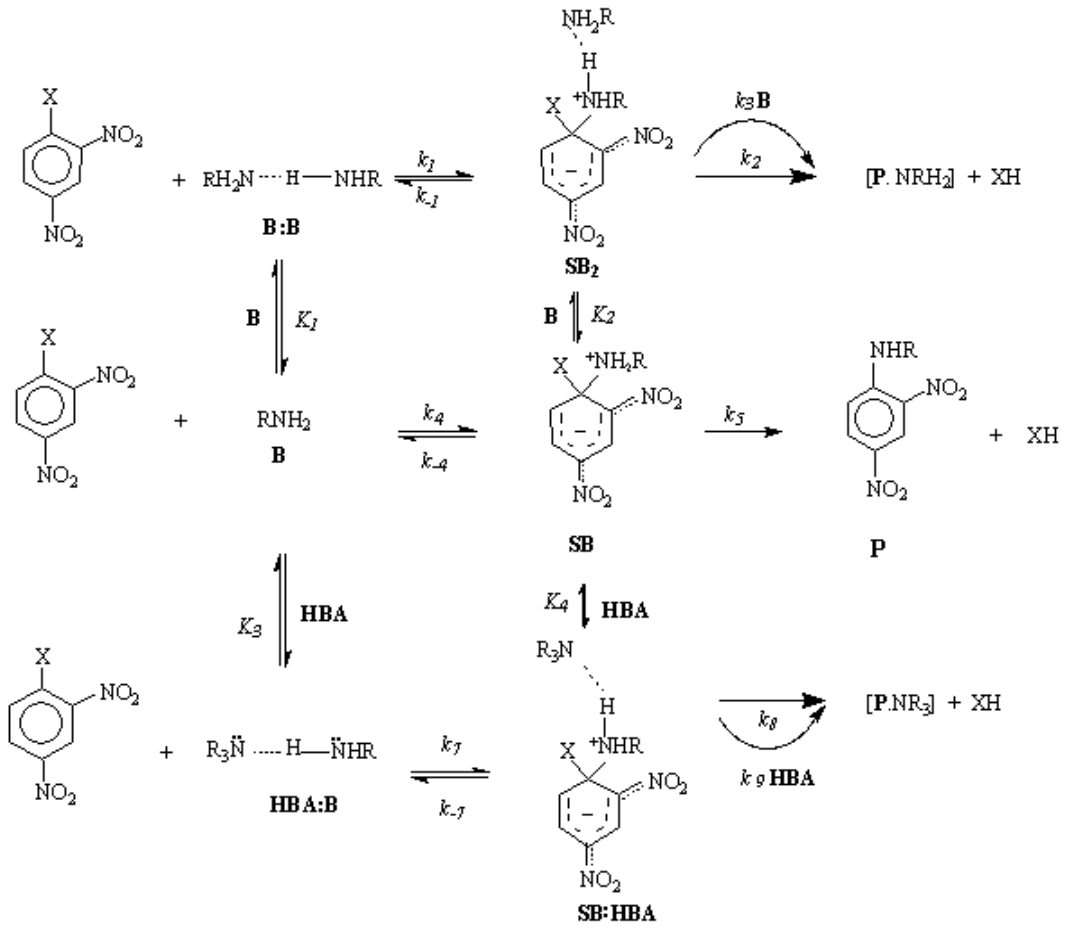
[3-dimethylamino-1-N-(2,4-dinitrophenyl)propylamine (mp 100-102ºC), 1H NMR ($CDCl_3$): δ 2.10 (s, 1H), 9.30 (d, 1H), 7.40 (d, 1H), 8.48 (m, 1H), 3.70 (t, 2H), 2.01(t, 2H), 2.65 (t, 2H), 2.31 (s, 6H), ^{13}C NMR (CDCl3): δ 27.65, 44.48, 45.40, 58.01, 119.34, 122.35, 128.87, 147.80, 148.48, 149.90]. IR (KBr) cm-1: 3320 (N-H); 2850 (C-H, -CH_2); 1658 (-N-H); 1500 (–NO_2); 1470 (-C-H, -CH_2); 1340 (–NO_2); 1380 (C-H, –CH_3); 1120 (C-N); 860 (-C-H); 740 (C-H).[1-N-(2-benzimidazol)-3-N-(2,4-dinitrophenyl)guanidine (mp 218–220 °C), 1H NMR (DMSO-d6): d 11.12 (s, 1H), 9.03 (s, 1H), 8.25 (d,1H), 7.20 (m, 2H), 7.10 (d, 1H), 6.92 (m, 2H), 2.30 (s, 1H), 2.10 (s, 2H). 13C NMR (DMSO-d6): d 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)].

2.3. Kinetic Procedures and Ancillar Spectrophotometric Measurements

UV-VIS spectra of the substrates, the products, and different mixtures of both compounds with the amine in toluene 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 λ = 450 and 400 nm; at that wavelengths the reagents are transparent under these conditions. All the solutions were found to obey Beer's law. Kinetic runs were performed by the methods previously reported [22], following the appearance of the reaction product at λ = 450 or 400 nm. The reactions of DNClB and DNFB with ethylendiamine, 3-dimethylamino- 1-propylamine, 1-(2-aminoethyl)piperidine and N-(3-aminopropyl) morpholine were recorded directly in the thermostated cell of the spectrophotometer at 25 ± 0.2°C. The reactions of the same substrate with histamine and 2-guanidinobenzimidazole were carried out in sealed ampoules (under nitrogen) at 40 ± 0.2°C. In all cases pseudo-first-order rate kinetics were observed. The absorption spectrum of the reaction mixture at "infinite time" corresponded within ±2 % with the "theoretical" value calculated from application of Beer's law to solutions of the product independently prepared in the desired solvent. Pseudo-first-order coefficients, kΨ, were obtained by the least-squared method as the slope of the correlation ln (A∞ - At)/ A∞ against time, where A∞ is the optical density of the reaction mixture measured at "infinity" (more than ten half-lives).

3. Results and Discussion

One of the easily determined feature of the "dimer nucleophile" mechanism is the forth order kinetics (third order in amine); this has been mostly observed in substrate nucleophile systems, where departure of the nucleofuge is the rate determining step. In Nudelman's mechanism, the intermediate SB_2 is highly zwiterionic and the extra amine molecule stabilizes the developing charges in non-polar aprotic solvents. The proposed mechanism does not preclude attack by the monomer, as shown in the three step pathway depicted below in Scheme 1. Nevertheless, due to the electron density on the hydrogen-bonded nitrogen, the H-bonded amines (forming inter- or intramolecular homo-aggregates) are better nucleophiles than monomeric amines[12]. This arouse the concern why "dimer nucleophiles" are not observed when the first step is rate determining?.



X = F, Cl

B = R(Ph) NH_2, NHR_2, NH R(Ph)$_2$, NH_2 R(Ph) NH_2

HBA = R_3N, R_2CO, R_2O

Scheme 1. Overall reaction diagram including equilibrium between the intermediates SB, SB_2 and HBA:B

Regarding amine self-aggregation and other non-covalent interactions, the nucleophile structure is very important in ANS carry out in aprotic solvents. The following discussion includes ANS with good and poor leaving groups substrates, using di- and polyamines The determinations were carried out under pseudo-first order conditions; the rate dependence with amine concentration was determined and good kinetic behaviour was observed throughout the work. The derivation of kinetic laws for all reaction steps including monomer, homo- and hetero-dimer nucleophiles that could be formed, is discussed.

3.1. Reactions of Di- and Polyamines with DNFB in Toluene (Second Step Rate Determining)

The kinetics of the reactions of DNFB with: 1-(2-aminoethyl)piperidine, 2-(AEPip)[1], N-(3-aminopropyl)morpholine,[1] 3-(APMo), ethylendiamine (ETDA)[15], 3-dimethylamino-1-propylamine (DMPA)[22], histamine[22] and 2-guanidinobenzimidazole (2-GB), were studied in the presence of variable amounts of the nucleophile. Tables 1 and 2 shows the observed results for the reactions with DNFB: the bimolecular rate coefficient kA and the ratio kA/[B] are given. For 2-(AEPip), ETDA and DMPA the second-order rate coefficients, kA, were found to increase rapidly with amine concentration,[B]; the plot of kA vs[B], (not shown), illustrates a quadratic dependence, while the quotient kA/[B] plotted against[B] is a straight line. This result is consistent with a third-order-in-amine term in the kinetic law, which has been observed previously in other systems,[12, 16, 25-26] and can be interpreted by the mechanism shown in Eqn. (2), where the dimer (B:B) of the nucleophile attacks the substrate S to form the intermediate SB2; then a third molecule of amine assists the intermediate in the decomposition step. The simplified form of kinetic law is given by Eqn (3), where K =[B:B]/[B] stands the amine self-association constant.

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

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

Table 1. Reaction of 2,4-dinitrofluorobenzene, DNFB, with Histamine, 2-GB at 40.0 ± 0.2ºC and 3-APMo and 2-GB in Toluene at 25.0 ± 0.2ºC. Second- kA, Order Rate Coefficients

Histaminea		3-APMob		2-GBb	
103[B]/ M	103 kA s-1M-1	103[B] M	kA, s-1M-1	102[B]/M	105 kA, s-1M-1
5.00	5.30	5.05	1.36	0.61	0.64
5.99	6.26	6.10	1.72	0.75	0.84
7.00	7.75	7.00	2.05	0.92	1.09
7.98	8.79	8.04	2.29	1.08	1.42
8.98	9.69	9.01	2.51	1.21	1.51
10.1	10.5	10.2	2.85	1.51	1.71
---	---	12.0	3.49	2.02	2.32
---	---	---	---	2.50	2.91
---	---	---	---	3.00	3.80

a[DNFB] = 1.00 x 10-4 M, b[DNFB] = 5.15 x 10-4 M

The order of magnitude of the rates with 2-(AEPip)[1], 3-(APMo)[1], ethylendiamine (ETDA)[22] and (DMPA)[22] are similar, but the produced plots for third order coefficient shows that the straight line for the reaction with ETDA has a no null intercept. This indicates that both, the monomer and the dimer nucleophile mechanisms are operating in the reaction with this amine, while the reaction with DMPA proceeds entirely through the dimer nucleophile and it is slightly faster than with ETDA.

For histamine, 3-APMo and 2-GB the second-order rate coefficient increases steadily with[B], the plots of kA vs.[B] are straight lines with a null intercept, R2 = 0.992 (not shown). In the three cyclic amines, intramolecular H-bonding is easily established due to the rigid molecular geometry that prevents the formation of intermolecular dimers. The strong intramolecular hydrogen bond prevails over the formation of intermolecular amine dimers, and an 'atypical' base-catalysed decomposition of the zwitterionic intermediate SB due to an 'intramolecular dimer' is obeyed.

We recently published variable-concentration 1H-RMN studies of the cited amines. The results have shown that 3-APMo, histamine and 2-GB are able to form a six-membered ring by intramolecular hydrogen bonding, while ETDA, DMPA, and 2-AEPip form dimers by intermolecular hydrogen bonds[30].

3.2. Reactions of Diamines with DNClB in Toluene (First Step Rate Determining)

The kinetics of the reactions of DNClB with the 2-(AEPip), 3-(APMo), ETDA, DMPA, and histamine were studied in the presence of variable amounts of the nucleophile. Tables 3 and 4 shows the observed results for the reactions with DNClB: the bimolecular rate coefficient kA and the ratio kA/[B] are given.

Table 2. Reaction of 2,4-dinitrofluorobenzene, DNFBa, with 3-Dimethylamino-1-propylamine (DMPA), 1-(2-aminoethyl)piperidine, 2-(AEPip) and Ethylenediamine (ETDA), B, in Toluene at 25.0 ± 0.2ºC. Second- (kA), and Third- (kA/[B]) Order Rate Coefficients

DMPAa			ETDAa			2-(AEPip)b		
103[B]/ M	kAs-1 M-1	102kA/ [B] s-1M-2	103 [B]/M	kAs-1M-1	10-2kA/ [B] s-1M-2	103[B] M	kA, s-1M-1	10-2 kA/[B], s-1M-2
4.97	1.19	2.39	4.94	0.72	1.46	5.02	1.59	3.17
6.01	1.54	2.56	6.00	0.96	1.60	5.97	2.34	3.92
6.97	2.12	3.04	7.00	1.21	1.72	6.96	3.15	4.52
8.00	2.78	3.48	7.94	1.43	1.80	7.98	4.18	5.24
8.97	3.64	4.06	8.99	1.75	1.95	8.95	5.85	6.54
---	---	---	10.0	2.09	2.09	9.94	6.57	6.61

a[DNFB] = 5.00 x 10-4 M, b[DNFB] = 5.15 x 10-4 M

Table 3. Reaction of 2,4-dinitrochlororobenzene, DNClB[a], with 3-Dimethylamino-1-propylamine (DMPA), 1-(2-aminoethyl)piperidine, 2-(AEPip) and Ethylenediamine (ETDA), B, in Toluene at 25.0 ± 0.2ºC. Second- (k_A), and Third- (k_A/[B]) Order Rate Coefficients

DMPAa			ETDAa			2-(AEPip)b		
[B]/M	103 kA s-1M-1	103 kA/[B]s-1M-2	[B]/M	103 kA s-1M-1	103 kA/[B] s-1M-2	[B] /M	103 kA, s-1M-1	103kA/[B] s-1M-2
0.497	0.485	0.976	0.494	1.69	3.42	0.496	1.92	3.87
0.601	0.72	1.20	0.60	2.25	3.75	0.597	2.48	4.15
0.697	0.99	1.42	0.704	2.84	4.03	0.791	3.12	3.95
0.800	1.26	1.57	0.794	4.11	5.18	0.999	4.88	4.88
0.897	1.55	1.73	0.899	4.52	5.03	1.20	5.98	4.98
1.00	1.98	1.98	1.00	6.21	6.21	1.51	8.73	5.78
1.20	2.59	2.16	1.20	8.39	6.99	1.73	10.9	6.30
1.50	3.93	2.62	1.50	13.50	8.98	2.01	15.4	7.66
2.01	5.92	2.94	---	---	---	2.31	22.9	9.91
---	---	---	---	---	---	2.54	26.4	10.4

a[DNClB] = 5.0 x 10-4M, b[DNClB] = 5.09 x 10-4M

Table 4. Reaction of 2,4-dinitrochlororobenzene, DNClB, with N-(3-aminopropyl)morpholine (3-APMo) and Histamine, in Toluene a 25.0 ± 0.2ºC. Second-Order Rate Coefficients, kA, s-1M-1

3-(APMo)a		Histamineb	
[B]/M	103 kA, s-1M-1	[B]/M	105 kA, s-1M-1
0.300	1.53	0.25	1.2
0.537	2.54	0.50	3.9
0.604	3.44	0.70	5.6
0.805	4.02	0.90	7.2
0.900	4.54	1.20	9.3
1.01	4.94	1.50	10.6
1.20	5.59	1.85	12.8
1.48	6.89	2.10	15.5
1.75	7.97	---	---
2.01	9.25	---	---

a[DNClB] = 5.09 x 10-4M, b[DNClB] = 5.12 x 10-4

Although, as expected for a less activated substrate, the reactions of DNClB are slower than those of DNFB, the kinetic behaviour is very similar for all the studied amines. For ETDA, DMPA and 2-(AEPip) the second-order rate coefficients, kA, were found to increase rapidly with amine concentration,[B]; the plot of kA vs[B], shows a quadratic dependence, while the quotient kA/[B] plotted against[B] is a straight line. These results are consistent with a third-order in amine and overall fourth order kinetics. By contrary, and similarly to the results obtained with poor leaving group substrate, histamine and 3-(APMo), kA exhibit a linear dependence with amine concentration.

In the above reactions with polyamines, it is observed that the more reactive nucleophiles are those with flexible structures. Polyamines with conjugated systems nearby the nucleophilic nitrogen have less reactivity. The observed reactivity of these new nucleophiles is fully consistent with the "dimer nucleophile" mechanism.

3.3. Derivation of the Whole Kinetic Law for Third Order in Amine when First Step is Rate Determining

The whole kinetic expression for the second order coefficient, kA, when the second step is rate-determining, as well as the simplification that can be applied to limiting situations were previously discussed. The expression for kA considering only the attack by the dimer can be reduced to equations 2, 3 where K is the equilibrium constant for the monomer:dimer equilibrium.

ANS reactions carried out in aprotic solvents using mono-[16, 21] and polyfunctionalized amines[1, 22] able to form intra- or intermolecular hydrogen bond with good leaving groups substrates also leads to atypical finding, and the "dimer nucleophile" mechanism is very well established in these systems. Initially, most of the systems in which third-order in amine kinetic law was observed were performed using poor nucleofuge substrates[25, 26]; in the last years we reported evidences for this atypical kinetic behavior observed also with a good nucleofuge substrate[1, 21-23].

It is very well accepted that in ANS reactions of amines with good nucleofuges substrates, such as DNClB, the first step is the rate limiting. To analyze this situation, involving attack by the dimer and the monomer, it should be considered that: (a) the first step is slower than the second one and (b) that the dimer is better nucleophile than the monomer. Application of the steady-state treatment to the whole mechanism for the dimer and monomer leads to Eqn. 4, that involves the specific rate constants for each step, the association equilibrium for the nucleophile, K1, and the constant for the equilibrium between the intermediates SB and SB_2, K_2 (Scheme 1).

$$k_A = \frac{k_4k_5 + \left(\frac{k_3}{K_2}k_4 + k_1k_5K_1\right)[B] + k_1\frac{k_3}{K_2}K_1[B]^2}{k_{-4} + k_5 + \left(\frac{k_{-1}}{K_2} + \frac{k_3}{K_2}\right)[B]} \quad (4)$$

the kinetic expression for the third-order rate coefficient is given by Eqn. 5:

$$\frac{k_A}{[B]} = \frac{\left(\frac{k_3}{K_2}k_4 + k_1k_5K_1\right) + k_1\frac{k_3}{K_2}K_1[B]}{k_{-4} + k_5 + \left(\frac{k_{-1}}{K_2} + \frac{k_3}{K_2}\right)[B]} \quad (5)$$

Taking into account that in the reactions carried out with DNClB[1, 21-23]:

a) in the plots of kA vs[B] the intercept = 0, which indicates that at least one of these two factors, k_4k_5, are negligible.

b) the plots of kA/[B] vs[B] are linear in the whole range of[B] studied, what implies that k-4 + k5 >> (k-1 + k3)[B] / K2. This inequality is clear at low concentrations of[B] because the intermediate from the monomer, SB, is more acidic than the dimer one, SB2, and it should revert quickly to reagents (k-4 >> k-1.)

c) since the plots of kA/[B] vs[B] are linear with null intercepts, the values k3k4 and k1K1k5 are negligible (≅ 0), which implies that k4 and k5 are also negligible. Therefore, the mechanism involving the monomer if it exists, should be negligible, and the mathematical expression for kA can be simplified to Eqn. 6:

$$k_A = \frac{(k_3k_4 + k_1k_5K_1K_2)[B] + k_1k_3K_1[B]^2}{K_2(k_{-4} + k_5)} \quad (6)$$

The third order rate coefficient is given by Eqn 7:

$$\frac{k_A}{[B]} = \frac{k_3k_4 + k_1k_5K_1K_2}{K_2(k_{-4} + k_5)} + \frac{k_1k_3K_1[B]}{K_2(k_{-4} + k_5)} \quad (7)$$

d) If it is assumed that amine aggregation is not relevant (K1 is negligible), the third order rate coefficient would be independent of[B] and the slope of plot of kA/[B] vs[B] should be null, according to Eqn. 8. This situation has not been observed.

$$\frac{k_A}{[B]} = \frac{k_3k_4}{K_2(k_{-4} + k_5)} \quad (8)$$

Even when the first step is rate determining, our results show a linear dependence of kA/[B] vs[B], what affords a further empirical support to "dimer nucleophile" mechanism, as shown by the fulfillment of Eqn. 7 observed for the reactions with DNClB[1, 21-23].

The ratio slope/intercept of the Eqn. 6, derived for the reactions where the first step is rate-determining, allows an estimation of the magnitude of the quotient:

$$\frac{\text{slope}}{\text{intercept}} = \frac{k_1k_3K_1}{k_3k_4 + k_1k_5K_1K_2} \quad (9)$$

k_5 should be smaller than k_3, because the reaction with the dimer is faster, k_1 should be smaller than k_3 since the first step is rate-limiting, and K_1 *and* K_2 are small values ($K_1 \cong 0.1$ M^{-1})[12]. Therefore, considering the limiting situation $k_3 k_4 >> (k_1k_5) K_1K_2$, the ratio can be simplified to the equation below:

$$\frac{\text{slope}}{\text{intercept}} = \frac{k_1k_3K_1}{k_3k_4 + k_1k_5K_1K_2} \quad (10)$$

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

3.4. Catalysis by Hydrogen-Bond Acceptor (HBA) Additives in ANS Reactions Carry Out in Aprotic Solvents

Overwhelming evidence of the participation of mixed aggregates between the amine nucleophile and HBA additives[12, 21, 31], HBA co-solvents[1, 12, 16, 19, 20, 32] on the rates of ANS has been accumulated in the literature. When the reactions are run in presence of HBA additive, such as tertiary non nucleophilic amines[21, 31] or in the presence of small amounts of HBA solvent[1, 12, 16], a new mixed associated nucleophile, B:HBA, is present in the system as depicted in Scheme 1. Three competing nucleophile reactions can occur: attack by the dimer (measured by k_1), by the monomer (determined by k_4), and by the B:HBA aggregate (measured by k_7). An equilibrium between the three possible tetrahedral intermediated SB, SB_2 and SB:HBA is established (measured by the equilibrium constants K_2,, K_3 and K_4, respectively) as depicted in Scheme 1.

Defining the partial rate constants as:

$$k_{-1} = \frac{k'_{-1}}{K_2}$$

$$k_{-7} = \frac{k'_{-7}}{K_4}$$

$$k_8 = \frac{k'_8}{K_4}$$

where:

$$K_2 = \frac{[SB][B]}{[SB_2]}$$

and

$$K_4 = \frac{[SB][HBA]}{[SB{:}HBA]}$$

By application of the steady-state hypothesis for intermediates SB, SB2 and SB2:HBA, the following kinetic expression is obtained, Eqn 11:

$$k_A = \frac{k_4k_5 + (k_3k_4 + k_1k_5K_1)[B] + k_1k_2K_1[B]^2 + (k_1k_8K_1 + k_3k_7K_3)[B][HBA]}{(k_{-1} + k_3)[B] + (k_{-7} + k_8)[HBA] + k_{-4} + k_5} + \frac{(k_5k_7K_3 + k_4k_8)[HBA] + k_7k_8K_3[HBA]^2}{(k_{-1} + k_3)[B] + (k_{-7} + k_8)[HBA] + k_{-4} + k_5} \quad (11)$$

It can be observed that Eqn. 11 contains terms of first and second order in the concentration of each of the species, B, B:B and the HBA-additive, and also a mixed term which depends on both.

When[HBA] = 0, Eqn. 11 becomes the Eqn. 6 that only considers the attack by dimer, B:B, and the free amine, B when the first step is rate limiting.

Considering all possible pathways due to the attack of the monomer, dimer and mixed dimer as well as the simplification that can be applied in limiting situations, the general expression for kA can be written in the condensed form of Eqn 12:

$$kA = k\alpha[B] + k\beta[B]2 + k\gamma[B][HBA] + k\delta[HBA] \quad (12)$$

which agrees with the experimental results found in previous works[21, 31]. In that works, several experiments were carried out to test Eqn. 12 by the complete study of the combined influence of homo-dimer of the amine and a heterodimer with an HBA additive; the four rate constants were estimated. It was concluded that catalysis by a nucleophile:HBA complex is more important than by the nucleophile itself, as expected on the basis of the "dimer nucleophile mechanism".

4. Conclusions

The ANS reactions with amines in aprotic solvents pose various difficulties, related to the inability of those solvents to stabilize ionic species. Overwhelming evidence on the rol of homo- and heteroaggregates of the nucleophile in solvents of low permittivity, has been afforded, and the "dimer mechanism" is currently well settled for ANS carried out with poor nucleofugues substrates.

The present paper affords kinetic evidence and derivation of the whole kinetic expressions for ANS that allow to conclude these reactions can be considered well settled in aprotic solvent. Rationalizations of the involved mechanisms are based on the strong H-bond interactions between the it-self nucleophile and nucleophile:HBA additive or

nucleophile: HBA co-solvent operating as an entity, consistent with the experimental evidence.

Due to 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 intermolecular homo- or HBA: nucleophile aggregates are faster than with the non hydrogen-bonded nucleophile. The intramolecular hydrogen bond formation in the nucleophile significantly reduces or prevents the formation of intermolecular dimers, thus, the hydrogen bonded nucleophile structure is crucial. Polyamines where internal hydrogen bond is expected are prone to react in the monomeric state under conditions that favor the dimer mechanism, which is interpreted by the formation of an "intramolecular dimer"; while those in which no intramolecular hydrogen bond is possible, react by an intermolecular homo- or heterodimer.

These new findings can contribute to show alternative pathways and/or more efficient routes to industrial chemical processes using ANS, as it is demonstrated by the current extensive literature

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