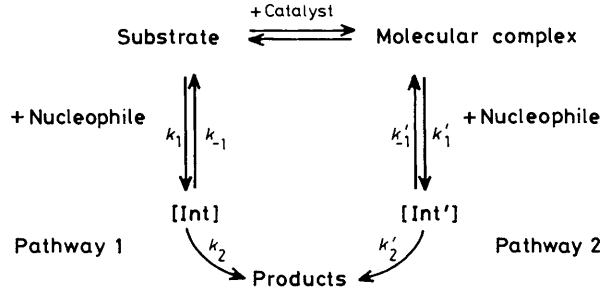
Catalytic Effects in Aromatic Nucleophilic Substitution Reactions. Reactions between 1-Fluoro-2,4-dinitrobenzene and 2-Aminothiazole Derivatives

Luciano Forlani * **and Marina Sintoni**
Istituto di Chimica Organica, viale Risorgimento 4, 40136, Bologna, Italy

The title reactions follow a second-order kinetic law in benzene and autocatalysis phenomena are not observed. The reactions are catalysed by 1,4-diaza[2.2.2]bicyclo-octane, α-pyridone, and δ-valerolactam. The kinetic data are consistent with the presence of an interaction between the substrate and the catalyst in the catalysed-reaction pathway.

In previous papers[1,2] we evaluated the possibility that some kinetic behaviour in aromatic nucleophilic substitution reactions in aprotic and scarcely polar solvents, with neutral nucleophiles (amines), may be explained by the presence of a rapidly established equilibrium between the substrate and the nucleophile or the catalyst. The formation of the molecular complex precedes the substitution reaction and Scheme 1 illustrates the main possibilities.



Scheme 1.

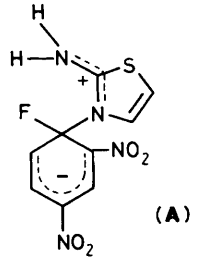
[Int] is the zwitterionic intermediate. The catalyst may also be the reacting nucleophile. At present it is difficult to state the importance of the presence of the molecular complex in the reaction pathway. The usual base-catalysis step is not indicated in Scheme 1. In both reaction pathways (1) and (2) the base catalysis may be either present or absent. In the latter case, Scheme 1 represents an alternative model to the generally accepted mechanism of the interaction of the catalyst with the zwitterionic intermediate to promote the departure of the proton and the leaving group.

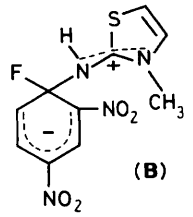
With the purpose of collecting further information about the mechanism of the catalysis, we report the kinetic results of the reactions of 1-fluoro-2,4-dinitrobenzene (FDNB) and some neutral nucleophiles in the presence of variable initial amounts of catalysts such as 1,4-diaza[2.2.2]bicyclo-octane (DABCO), 2-pyridone (P), and δ-valerolactam (Va).

Results

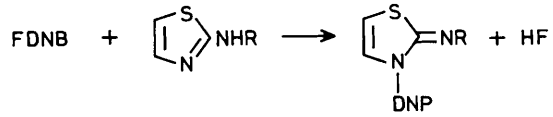
Nucleophiles were chosen such that there were large differences of basicity and nucleophilic power and also with the aim of investigating the importance of the differences in the geometry of the zwitterionic intermediate.

We have previously[3] reported that the reactions between FDNB and 2-aminothiazole (in dimethyl sulphoxide) occurs with the 'aza' endocyclic nitrogen, while the same reaction with 2-imino-3-methylthiazoline occurs at the exocyclic nitrogen. The two possible intermediates proposed were the following:

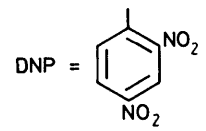


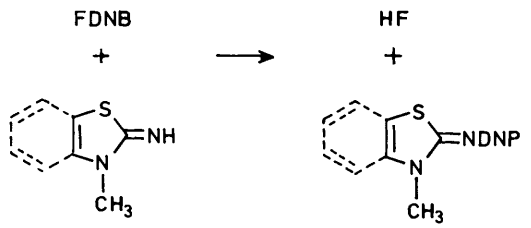


The nucleophiles investigated here in benzene were 2-aminothiazole (**1**), 2-(*N*-s-butylamino)thiazole (**2**), 2-(*N*-phenylamino)thiazole (**3**), 2-imino-3-methylthiazoline (**4**), and 2-imino-3-methylbenzothiazoline (**5**). The stoicheiometry of the reactions is as follows:



(**1**) R = H
(**2**) R = Bu^s
(**3**) R = Ph





(**4**) [(**5**)]

The reaction products[3] were obtained (in benzene) in high yields (≥95%) and the u.v.–visible absorbances of the reaction mixtures at t_∞ coincide with values of the isolated reaction products (see Experimental section). The reactions are first order in both reactants. The kinetic results are reported in Table 1 and they parallel those obtained in dimethyl sulphoxide.[4] In particular the poor reactivity of 2-(*N*-phenylamino)thiazole (**3**), with respect to 2-aminothiazole (**1**), indicates that also in apolar solvent the active species of the two possible tautomers of the 2-aminothiazole is the aromatic amine with the endocyclic nitrogen. Moreover, in benzene the intermediates may also be represented by (**A**) and (**B**).

The u.v.–visible spectrophotometric analysis of the reaction

Table 1. $k_{obs.}$ Values of the reactions between FDNB (0.5×10^{-4}—8×10^{-4} mol l^{-1}) and 2-aminothiazole derivatives in benzene at 30 °C

Concentration/mol l^{-1}					$10^5 k_{obs.}$/l mol^{-1} s^{-1}				
$[(1)]_0$[a]	$[(2)]_0$	$[(3)]_0$[b]	$[(4)]_0$[c]	$[(5)]_0$[d]	(1)	(2)	(3)	(4)	(5)
0.0591	0.0137	0.0331	0.008 29	0.0543	9.20	21.4	1.50	510	27.7
0.123	0.0275	0.1184	0.0165	0.0543	9.50	22.3	1.60	510	27.1
0.192	0.0550		0.0290	0.109	9.23	22.4		529	28.3
0.192	0.0733		0.0518	0.109	9.33	20.3		515	28.5
	0.110			0.166		19.6			27.9

pK_a Values[14,17]: [a] 5.32. [b] 4.33. [c] 9.50. [d] 7.96.

Table 2. Values of $k_{obs.}$ for reactions between 1-fluoro-2,4-dinitrobenzene $[FDNB]_0 = 6 \times 10^{-5}$ mol l^{-1} and some 2-aminothiazole derivatives in the presence of DABCO

[DABCO]/mol l^{-1}	$10^3 k_{obs.}$(4)[a]/l mol^{-1} s^{-1}	$10^4 k_{obs.}$(1)[b]/l mol s^{-1}
0.0456	5.65	1.87
0.0625	5.86	2.19
0.0675		2.28
0.114	6.32	3.18
0.141	6.60	3.74

[a] $[(4)]_0 = 7 \times 10^{-3}$ mol l^{-1}. [b] $[(1)]_0 = 5 \times 10^{-2}$ mol l^{-1}.

Table 3. $k_{obs.}$ Values for reactions between FDNB and nucleophiles in the presence of 2-pyridone and δ-valerolactam

$[FDNB]_0 = 5 \times 10^{-4}$ mol l^{-1}; $[I]_0 = 3.4 \times 10^{-2}$ mol l^{-1}

[P]/mol l^{-1}	$k_{obs.}$/l mol^{-1} s^{-1}	$[Va]_0$/mol l^{-1}	$k_{obs.}$/l mol^{-1} s^{-1}
0.0317	1.52×10^{-4}	0.0262	1.65×10^{-4}
0.0576	1.91×10^{-4}	0.0756	2.90×10^{-4}
0.0923	2.43×10^{-4}	0.126	4.05×10^{-4}
0.123	2.95×10^{-4}	0.170	5.20×10^{-4}
		0.339	8.10×10^{-4}

$[FDNB]_0 = 5 \times 10^{-5}$ mol l^{-1}; $[(4)]_0 = 2.0 \times 10^{-2}$ mol l^{-1}

0.0318	5.85×10^{-3}	0.0262	6.34×10^{-3}
0.0576	6.25×10^{-3}	0.0756	7.90×10^{-3}
0.0923	6.90×10^{-3}	0.126	9.70×10^{-3}
0.123	7.27×10^{-3}	0.170	1.10×10^{-2}

$[FDNB]_0 = 3 \times 10^{-4}$ mol l^{-1}; $[p\text{-toluidine}]_0 = 3 \times 10^{-2}$ mol l^{-1}

0.0317	2.56×10^{-4}	0.0262	1.10×10^{-3}
0.0576	4.87×10^{-4}	0.0566	2.40×10^{-3}
0.0821	7.21×10^{-4}	0.0756	3.60×10^{-3}
0.123	1.03×10^{-3}	0.126	5.54×10^{-3}

mixtures at t_0 did not show any absorbance thus indicating the absence of molecular substrate–nucleophile complexes at least in the range of concentrations investigated. The existence of molecular complexes has been reported in previous papers[1,2,5,6] when different aromatic and aliphatic amines were allowed to react with FDNB.

Tables 2 and 3 give some kinetic results of the substitution reactions performed in the presence of some of the usual catalysts DABCO, P, and Va. The $k_{obs.}$ values are enhanced by the presence of the catalysts for all the nucleophiles considered and in all cases the dependence of $k_{obs.}$ on the stoicheiometric concentration of the catalyst is linear. Table 3 also reports the data obtained by using *p*-toluidine as the nucleophile and P or Va as the catalyst. The kinetic behaviour of *p*-toluidine parallels that of the thiazole derivatives. The reactions carried out in the presence of 2-pyridone and δ-valerolactam show unusual kinetic features.

In the reactions between aliphatic amines and FDNB and in the presence of P, Va, or of other catalysts containing the amido group,[7-9] the plots of $k_{obs.}$ (in l mol^{-1} s^{-1}) values *vs.* the [catalyst] show downward curvature. Such a curvature was explained by considering the self-association of the catalyst which is in a predominant dimeric structure.[10] As a consequence, the plots of $k_{obs.}$ *vs.* [catalyst], calculated as monomeric, are linear. In our case, the plots of $k_{obs.}$ *vs.* [catalyst] (stoicheiometric) are linear. This feature cannot be ascribed to some peculiarity of the thiazole derivatives because *p*-toluidine parallels the behaviour of the thiazole derivatives.

Amines are known to depolymerize 2-pyridone, probably *via* hydrogen-bond formation.[11] Consequently, the difference between the present kinetic features and those observed using aliphatic amines may be explained by the change in position of the dimerization equilibrium of the catalyst on changing the reactive amine. However, two main points refute this hypothesis: (*a*) 2-imino-3-methylthiazoline shows a pK_a value which is in the range of the aliphatic amines showing downward curvature. Consequently, differences in the power of nucleophiles to depolymerize the catalyst is a poor explanation of the difference in the kinetic behaviour, since similar concentrations of the catalyst (and of the amine) were used for both aliphatic and aromatic (or thiazolic) amines; (*b*) both δ-valerolactam and 2-pyridone show the same kinetic behaviour, in spite of the fact that the latter is much more self-associated than the former.[10,12]

Although the considerations reported above imply a number of assumptions and simplifications, the self-association of the catalyst appears scarcely to be relevant in the present reactions. 2-Aminothiazole is also reported[13] to be largely self-associated, but the data of Table 1 do not evidence any effects of self-association on the rate constant.

Discussion

The reactivity of the 2-iminothiazoline (**4**) is higher than that of 2-aminothiazole (**1**). This trend may be easily explained by two main factors: both the basicity[14] and the steric requirements of the exocyclic nitrogen in the fixed imino derivative favour the nucleophilicity of the imino exocyclic nitrogen with respect to the nucleophilicity of the 'aza' endocyclic nitrogen. Table 1 gives the pK_a values of the nucleophiles used.

The increase in the $k_{obs.}$ values (in l mol^{-1} s^{-1}) with increasing initial concentration of the amine is generally[15] explained by a model in which the proton and the leaving group are abstracted from the zwitterionic intermediate by a second molecule of the amine, since the spontaneous departure of the leaving group [k_2 in pathway (1) of Scheme 1] would be prevented by the presence of the positive charge on the nitrogen atom.

The thiazole derivatives considered here do not show kinetic evidence for the presence of self-catalysed processes. The absence of self-catalysis in the reactions between FDNB and 2-

Table 4.

	k_2^*/l mol^{-1} s^{-1}		K/l mol^{-1}	
	P	Va	P	Va
(**1**)	1.0×10^{-3}	2.9×10^{-3}	2.2	1.1
(**4**)	1.2×10^{-2}	2.2×10^{-2}	3.3	3.0

aminothiazole is not expected considering that, in (**A**), the positive charge is remote from the reaction centre, therefore the leaving group departure can occur without catalysis. On the other hand structure (**B**) is geometrically favourable to proton abstraction in a rate-limiting equilibrium. In addition, the pK_a values[14] and the nucleophilicities[4] of (**4**) and (**5**) are close to the pK_a values and to the reactivities of amines known to exhibit self-catalysis. Consequently, the absence of self-catalysis in the reactions between FDNB and 2-iminothiazole derivatives (**4**) and (**5**) is surprising if the generally accepted mechanism of the nucleophilic aromatic substitution in apolar aprotic solvents is assumed to be operative. For all the thiazole derivatives considered here the absence of self-catalysis is supported by the absence of detectable amounts of molecular complexes between FDNB and thiazole derivatives.

When a tertiary amine (DABCO) [which is less basic (pK_a = 8.19)[16] than 2-iminothiazole (**4**) but more basic than 2-aminothiazole[17]] is initially added to the reaction mixtures, catalytic behaviour is observed for both kinds of thiazole derivatives. We reported that DABCO (which is generally used to observe enhancement of reactivity) interacts with FDNB, in a step preceding the substitution process. In contrast with the mechanism usually reported in the literature, the enhancement of the rate of the reaction between FDNB and aromatic or aliphatic amines was rationalized by the formation of a molecular complex FDNB–DABCO. The K value (0.21 l mol^{-1}) of the formation of the molecular complex FDNB–DABCO, under the present experimental conditions, agrees with the values reported in a previous paper.[5]

The equation

$$1/(k_{obs.} - k_2^0) = 1/(k_2^* - k_2^0) + 1/(k_2^* - k_2^0)2K[\text{DABCO}] \quad (1)$$

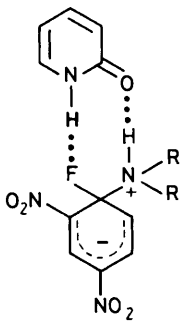
is derived from Scheme 1 and allows the calculation of k_2^* [a measure of the reactivity of the complex FDNB–DABCO, equal to $(k'_1/k'_{-1})k'_2$] and K, from the plot of $1/(k_{obs.} - k_2^0)$ *vs.* 1/[DABCO]; k_2^0 [the uncatalysed process = $(k_1/k_{-1})k_2$] is known independently from Table 1.

From the data of 2-aminothiazole (**1**) $k_2^* = 4.2 \times 10^{-3}$ (l mol^{-1} s^{-1}) and K = 0.25 l mol^{-1}; for 2-imino-3-methylthiazoline (**4**) $k_2^* = 2.2 \times 10^{-2}$ (l mol^{-1} s^{-1}) and K = 0.33 l mol^{-1}. Also in the present case, K values calculated from the kinetic data agree with the K values obtained independently from spectrophotometric analysis.[5]

Even if the statistical errors (calculated as standard deviations, see the Experimental section) are very high, the so-called catalysed process (as expressed by k_2^*) is clearly dependent on the nucleophilicity of the amine, as required by Scheme 1.

In conclusion, the kinetic behaviour of DABCO reported here agrees well with the mechanism previously reported by us.[2] The interaction between FDNB and DABCO causes an enhancement of the rate of the substitution reaction.

The catalytic power of 2-pyridone is usually explained as bifunctional catalysis in the HF elimination step. The transition state of this step may be illustrated as shown:



(**C**)

The very rigid geometry of this transition state is required for the contemporaneous elimination of HF. It can be reasonably expected that 2-aminothiazole is a poor uncatalysed nucleophile because the proton must be abstracted from the exocyclic nitrogen which is remote from the fluorine atom. In contrast, 2-imino-3-methylthiazoline affords an intermediate with the usual geometry, close to that depicted in (**B**). Both these thiazole derivatives show the same kinetic behaviour, indicating that the geometry of the zwitterionic intermediate does not seem to be important, refuting the possibility of the bifunctional catalysis (**C**). Better agreement with the experimental data is obtained if the catalytic behaviour of 2-pyridone and of the δ-valerolactam is related to their ability to interact with the nitro derivative.

Inspection (in [^{2}H]benzene) of the ^{1}H n.m.r. spectra of the FDNB–δ-valerolactam mixtures shows that the FDNB proton signals are shifted toward lower field by the addition of δ-valerolactam. Unfortunately the experimental conditions do not allow a full investigation of this molecular interaction. The nitro group is usually considered a proton-acceptor group and the deshielding of the FDNB protons is an indication that the molecular complex (substrate–catalyst) is more prone to attack by the nucleophile than the substrate, 'free' or associated with the solvent. In this way the catalytic phenomenon of 2-pyridone and of δ-valerolactam are consistent with Scheme 1.

Even if the statistical errors are high (see the Experimental section), equation (1) allows the calculation of k_2^* and K values for both thiazole derivatives: see Table 4.

For the reactions of *p*-toluidine, the uncatalysed process is unimportant with respect to the catalysed process (k_2^0 is very small[6]). The slope of the plots of $1/k_{obs.}$ *vs.* 1/[catalyst] are quite high and the intercept is close to zero. The k_2^* values can be obtained from the K values calculated for the reactions of the thiazole derivatives from the slope of the plots $1/k_{obs.}$ *vs.* 1/[catalyst]: k_2^* (l^2 mol^{-2} s^{-1}) = 1.5×10^{-2}, 3.9×10^{-3} for P and Va, respectively.

In all cases the ratios k_2^* (**4**)/k_2^* (**1**) = 5, 12, and 7 for the process catalysed by DABCO, P, and Va, respectively, and favour the imino derivative. This fact supports the occurrence of the nucleophilic attack of the amine in a rate-determining step of the catalysed pathway. Certainly, the molecular complex FDNB–DABCO[5] involves an interaction different from that of the molecular complex FDNB–P (or FDNB–Va). The formation of the molecular complex by a rapidly established equilibrium preceding the substitution process (as indicated in Scheme 1), affords a species more prone towards nucleophilic attack than the uncomplexed substrate. In fact, the values of the reported ratios are very close, in spite of the differences in structure. δ-Valerolactam is slightly more able to activate the substrate than 2-pyridone, as tested by the ratios $k_{2(Va)}^*/k_{2(P)}^*$ = 1.8, 2.9, and 3.9 for (**4**), (**1**), and *p*-toluidine, respectively. These ratios are largely unaffected by the changes of proton affinity (pK_a) of the nucleophiles. This fact is an indication that the

possible interactions between the nucleophile and the catalyst are of little importance in the catalytic pathway.

In conclusion, the kinetic data reported here are consistent with the proposed scheme. Scheme (1) does not exclude the presence of the generally accepted mechanism of catalysis, but it represents a reasonable alternative explanation of some kinetic features in aromatic nucleophilic substitution reactions.

Experimental

Materials.—Benzene was purified by distillation from sodium.[18] Thiazole derivatives were prepared and purified using described procedures.[14,17] DABCO, 2-pyridone, and δ-valerolactam were commercial products purified by usual procedures.

Kinetics.—Kinetic runs were performed by the usual methods[4,8] with a Lambda 5 (Perkin-Elmer) u.v.–visible spectrophotometer. The absorption at t_∞ was identical with that of the derivatives isolated in preparative runs. Visible spectrophotometric absorbances (used in the kinetic measurements) of the reaction products[3,4] are reported.

3-(2,4-Dinitrophenyl)-2-(s-butylimino)thiazoline, λ = 435 nm, log ε = 3.52; 3-(2,4-dinitrophenyl)-2-iminothiazoline, λ = 416 nm, log ε = 3.40; 2-(2,4-dinitrophenylimino)-3-methylthiazoline, λ 434 nm, log ε = 4.25; 3-(2,4-dinitrophenyl)-2-phenyliminothiazoline, λ = 420 nm, log ε = 3.39; 2-(2,4-dinitrophenylimino)-3-methylbenzothiazoline, λ = 400 nm, log ε = 4.14.

The intercept and slope values, calculated by least-squares method, from equation (1) are as follows: [r = correlation coefficient; $y = 1/(k_{obs.} - k_2^0)$; errors are standard deviations]. Nucleophile = (**1**): y = 241 (±100) + 477.7 (±84)/[DABCO], r = 0.9997; y = 1 100 (±327) + 505 (±310)[P], r = 0.9989; y = 357.7 (±56) + 354.7 (±86)/[Va], r = 0.9999. Nucleophile = (**4**): y = 59.4 (±58) + 89.1 (±47)/[DABCO], r = 0.9980; y = 139.9 (±40) + 42.1 (±37)/[P], r = 0.9876; y = 61.4 (±15) + 20.7 (±19)/[Va], r = 0.9987. Nucleophile = *p*-toluidine: y = −24.3 (±18) + 24.4 (±18) [P], r = 0.9979; y = −119 (±64) + 127.1 (±58)/[Va], r = 0.9993. The ^{1}H n.m.r. spectra were recorded with a JEOL 60 MHz instrument. The K value for the formation of the molecular complex FDNB–DABCO was obtained by described procedure.[5]

Acknowledgements

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