Kinetic and Mechanistic Studies of the Reactions between 2-Nitrothiazole, 2-Nitrobenzothiazole and some Nucleophiles

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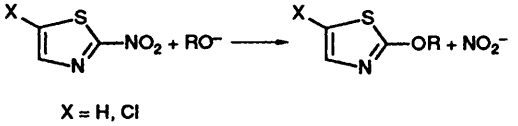
Kinetic data for the reactions between some 2-nitrothiazoles and nucleophiles (alkoxide and piperidine) are reported. The kinetic behaviour of the nitro group parallels that of the more usual leaving groups and a two-step mechanism involving nucleophilic aromatic substitution may be suggested to be in operation. A change of counter ion (Li^+, Na^+, K^+) of the anionic nucleophile indicates that the presence of the ion pairs partially favours reactivity, probably by interaction with the nitro group. The autocatalytic behaviour of the reactions between 2-nitrothiazole and piperidine is explained by the presence of an interaction between the substrate and the nucleophile in an equilibrium preceding the substitution process. Comparison of the nucleofugicity of nitro and chloro groups (as leaving groups) indicates that the presence of hydrogen bonds between the leaving group and the solvent (or the nucleophile) produces considerable variations in the observed reactivities.

Much kinetic data has been reported in the literature on nucleophilic aromatic substutution reactions, when the leaving groups are halogens.[1] Less attention has been given to the nucleophilic displacement of other leaving groups and, in particular, to the displacement of the nitro group, which is usually considered to be a good leaving group in S_NAr reactions.[2,3] The usual two-step mechanism is generally in operation in the nitro group displacement, although in some cases the cine-substitution process[4] is a complication of the reaction.

Information on the quantitative aspects of the reactivity of nitro aromatic substrates toward nucleophiles, and on the reactivity of the thiazole derivatives,[5] is described by some kinetic measurements on reactions of 2-nitrothiazole, 5-chloro-2-nitrothiazole and 2-nitrobenzothiazole with alkoxide ions and with piperidine.

Results and Discussion

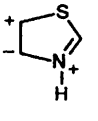
2-Nitrothiazole (TZ) and 2-nitrobenzothiazole (BTZ) react with alkoxide ions (methoxide and *tert*-butoxide) and with piperidine to produce the usual 2-alkoxythiazole[6,7] (2-*N*-piperidylthiazole[6]) and benzothiazole in almost quantitative yields. Kinetic data are reported in Tables 1 and 2.



X = H, Cl

Scheme 1

The reaction between 5-chloro-2-nitrothiazole (CTZ) and sodium methoxide deserves comment, because CTZ may be expected to react at C-5 to yield 5-methoxy-2-nitrothiazole. On the contrary, in CTZ the substitution reaction occurs at C-2 by replacing the nitro group; during methoxydenitration (Scheme 1, X = Cl) no halide ions are formed. This behaviour parallels that observed for the reactions between 2,5-dichlorothiazole and sodium benzenethiolate[8] or sodium methoxide;[9] the faster process is the halogen displacement at C-2. The reaction at C-5 of the thiazole ring is expected on the basis of previous reports on the relative reactivities of C-2 and C-5 of the thiazole ring; 5-chlorothiazole is more reactive than 2-chlorothiazole towards sodium methoxide.[10] The C-2 position of the isomer of CTZ is strongly activated[9] towards sodium methoxide by the presence of the nitro group at C-5. The reactivity enhancement of the methoxydenitration reactions by chlorine at C-5 towards C-2 reported here is very close (k_{CTZ}/k_{TZ} = 78) to the reactivity enhancement previously reported for methoxydehalogenation reactions: $k_{2,5\text{-dichlorothiazole}}/k_{2\text{-chlorothiazole}}$ = 75.3.[9] As previously reported,[10] the reactivity of C-5 toward nucleophiles (which is an apparently anomalous reactivity) is strongly dependent on the heterocyclic nitrogen basicity and on the proton-releasing ability of the solvent (or of the nucleophiles),[10,11] by a particular activation which is indicated in structure **A**. When a strongly electron-withdrawing group such as the nitro group is present on the thiazole ring, the basicity of the heterocyclic nitrogen is lowered and C-5 becomes an unactivated '*meta*-like' position with respect to the endocyclic



A

Table 1 Reactions between 2-nitrothiazole (TZ), 5-chloro-2-nitrothiazole (CTZ) and 2-nitrobenzothiazole (BTZ) and RO^-M^+ in ROH at 25 °C (unless otherwise indicated)

Substrate	R	M	k/dm^3 mol^{-1} s^{-1}
TZ	CH_3	Li	3.42×10^{-3}
TZ[a]	CH_3	Na	4.31×10^{-3} (1.04×10^{-2};[b] 3.92×10^{-2};[c])
TZ	CH_3	K	4.21×10^{-3}
TZ	$(CH_3)_3C$	Na	4.00×10^{-2}
TZ	$(CH_3)_3C$	K	2.80×10^{-2}
CTZ[d]	CH_3	Na	3.37×10^{-1} (5.73×10^{-1};[b] 1.08[c])
BTZ	CH_3	Li	4.0
BTZ	CH_3	Na	8.5
BTZ	CH_3	K	5.6
BTZ	$(CH_3)_3C$	Na	113
BTZ	$(CH_3)_3C$	K	23.0

[a] ΔH = 68.4 kJ mol^{-1}; ΔS = −61 J mol^{-1}. [b] 35 C. [c] 50 °C. [d] ΔH = 34.5 kJ mol^{-1}; ΔS = −138 J mol^{-1}.

Table 2 Reactions between 2-nitrothiazole (TZ), 2-nitrobenzothiazole (BTZ) and piperidine at 25 °C

Substrate	$[Substrate]_0/10^{-5}$ mol dm^{-3}	Solvent	$[Piperidine]_0$/mol dm^{-3}	k/dm^3 mol^{-1} s^{-1}
BTZ	8.65	EtOH	0.0249	1.98
BTZ	8.65	EtOH	0.0366	2.05
BTZ	8.65	EtOH	0.124	2.08
BTZ	8.65	EtOH	0.622	1.97
BTZ	4.05	DMSO[a]	0.185	0.369
BTZ	4.05	DMSO	0.924	0.372
BTZ	4.05	DMSO	4.62	0.359
TZ	9.00	EtOH	0.192	0.981
TZ	9.00	EtOH	0.622	0.969
TZ	9.00	EtOH	1.05	1.00
TZ	6.50	PhH	0.301	0.272
TZ	6.50	PhH	0.411	0.360
TZ	6.50	PhH	0.542	0.481
TZ	6.50	PhH	0.910	0.730
TZ	6.50	PhH	1.06	0.823
TZ	6.50	PhH	1.42	1.18

[a] Dimethyl sulphoxide.

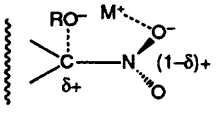
nitrogen. The pK_a value of 2-nitrothiazole is 7.5 pK_a units lower than the pK_a value of the unsubstituted thiazole.[12]

Data in Table 1 clearly indicate that the reactivity of the 2-nitrothiazole is considerably enhanced by the presence of the fused aromatic ring, *cf.* ratios k_{BTZ}/k_{TZ} = 2.0 × 10^3, 2.8 × 10^3 and 2.1 × 10^2 for sodium methoxide, sodium *tert*-butoxide and piperidine (in ethanol), respectively. The benzocondensation produces an important reactivity enhancement, as expected in S_NAr reactions (with the usual two-step mechanism), by stabilization of intermediates.[2,13] The activation parameters (ΔH and ΔS, Table 1) also comply with the parameters usually calculated for S_NAr reactions.[2,13–15]

The change of the counter ion of the alkoxide (Table 1) offers some details worthy of consideration. When Li^+, Na^+ or K^+ are the counter ions in methoxydehalogenation reactions of 2,4-dinitrochlorobenzene,[16] the relative ratios $k_{Li}:k_{Na}:k_K$ are 1:1.08 1.16. Similar ratios were observed for 2-chlorothiazole, 1:1.12:1.49, and for 4-chlorothiazole, 1:1.30:2.39. For methoxy substitution of 2-nitrothiazole the ratio is $k_{Li}:k_{Na}:k_K$ = 1:1.26:1.23 and for the same reaction of BTZ it is 1:2.1:1.4. For *tert*-butoxy-substitution of TZ, $k_{Na}:k_K$ = 1.4 and for BTZ the same ratio is 4.9. For the *tert*-butoxy-substitution reaction on 2-chlorothiazole $k_{Na}:k_K$ = 0.72 and for 4-chlorothiazole it was 0.30.

The order of the formation of ion pairs is the inverse order of reactivity of the halogeno-derivatives. The behaviour of the nitro-substitution reactions differs from the behaviour of the chloro-substitution reactions. The reactivity of the chloro derivatives was reduced by the presence of the ion pairs (RO^-/M^+). In all cases, nitro-substitution with sodium alkoxides is faster than the same reaction of the potassium alkoxides. This behaviour is more evident for the *tert*-butoxide–*tert*-butyl alcohol system than for the methoxide–methanol system. It is known that *tert*-butyl alcohol associates better than methanol.[17] The reported reactivity orders probably arise from several overlapping effects related to the presence of the ion pairs. The presence of the ion pairs is generally reported to mask the anionic nucleophile, and so to reduce the reactivity toward electrophilic centres. This effect probably prevails when chlorine is the leaving group and this general effect also depends on the associating power of the solvent. On the contrary, data in Table 1 indicates that the presence of the ion pairs partially favours the reactivity of the alkoxide ions, probably acting on the nitro group, with the counter ion **B**; the ion pair is found to be more reactive than the 'free' alkoxide.

Values of k_{obs} for the reactions between 2-nitrothiazole and piperidine increase when the initial concentration values of

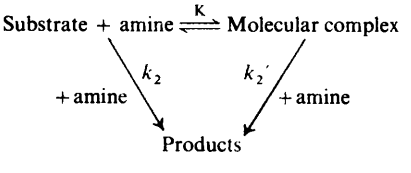


B

the piperidine are increased (Table 2). In more polar solvents (ethanol and dimethyl sulphoxide) the k_{obs} values are independent of the initial values of the concentration of the amine, as expected for simple aromatic substitution reactions. The enhancement of k_{obs} values by increasing the initial concentration value of the amine was also reported for nitro heterocyclic,[18] and homocyclic[19] aromatic derivatives in weakly polar solvents.

The behaviour of the nitro group as a leaving group parallels the behaviour usually reported for fluorine (and chlorine) as leaving groups, under the same experimental conditions. Previous data were explained[18] by the presence of the generally accepted base-catalysed pathway on the departure of HL (L is the leaving group) from the zwitterionic intermediate.[20] Since 1982, a reaction mechanism other than the usually accepted one has been suggested[21] to explain the enhancement of the reaction rates under such experimental conditions.

The increase of the k_{obs} values (for several substrate–amine systems) may be explained by the presence of a molecular complex[21] between the substrate and the nucleophile, providing a more reactive intermediate than the 'free' substrate which is only complexed by the apolar solvent. Scheme 2 is a



Scheme 2

model of the proposed reaction mechanism. Eqn. (1) may be

$$\frac{1}{k_{obs} - k_2} = \frac{1}{k_2' - k_2} + \frac{1}{(k_2' - k_2)K[\text{Piperidine}]} \quad (1)$$

obtained from Scheme 2 in order to evaluate the K and k_2' values. An approximate value of k_2 may be calculated by extrapolating the k_{obs} value at the value of the initial concentration of piperidine, k_2 = 3.5 × 10^{-7} dm^3 mol^{-1} s^{-1}.

Table 3 Reactivity ratios, k_{NO_2}/k_{Cl}, for the reactions between 2-Y-thiazoles (YTZ), 5-chloro-2-Y-thiazoles (YCTZ), 2-Y-benzothiazoles (YBTZ) (Y = NO_2, Cl) and some nucleophiles

Substrate	Nucleophile	Solvent	T/°C	k_{NO_2}/k_{Cl}
YTZ	$CH_3O^-Na^+$	Methanol	50	4.8×10^3
YCTZ	$CH_3O^-Na^+$	Methanol	50	1.8×10^3
YBTZ	$CH_3O^-Na^+$	Methanol	25	1.6×10^4
YBTZ	$(CH_3)_3CO^-Na^+$	*tert*-Butyl alcohol	25	1.9×10^5
YBTZ	Piperidine	DMSO[a]	25	1.0×10^2
YBTZ	Piperidine	Ethanol	25	1.1×10^2
YBTZ	Piperidine	Benzene	25	2.1×10^b

[a] Dimethyl sulphoxide. [b] Ratio of the second-order rate constant values for the uncatalysed process.[19]

The k_2 value of the same reaction of the 2-nitrobenzothiazole[18] was 1.5×10^{-1} dm^3 mol^{-1} s^{-1}. K, a measure of the apparent stability of the molecular complex, is 0.29 and 0.19 mol^{-1} for BTZ and TZ, respectively. Rate constant k_2' is an evaluation of the reactivity of the molecular complex toward the amine (catalysed pathway): $k_2' = 6.5 \times 10^{-2}$ and 4.1×10^{-4} dm^3 mol^{-1} s^{-1} for BTZ and for TZ, respectively.

The relative nucleofugicity of the nitro group was reported to exceed that of the chlorine atom and, in some cases, that of the fluorine atom.[15,22] Our data enable us to compare the relative nucleofugicity of the nitro group and of the chlorine atom. The k_{NO_2}/k_{Cl} ratios are collected in Table 3. In all the cases reported here, the nitro group is a better leaving group than the chlorine atom. The high nucleofugicity of the nitro group has also been explained by the presence of hydrogen bonds[23,24] (with the solvent or with the reacting nucleophile) which increase the rate of the nitro group departure in comparison with the rate of the departure of the other groups.

A kind of hydrogen bond may occur between the solvent (or the nucleophile) and the leaving group. This interaction is probably responsible (when the nucleophile is the piperidine) for the lower NO_2/Cl ratio in benzene than in ethanol. Although the ability of the leaving group is a balance of several parameters (especially basicity and the polarizability) of both entering and leaving groups,[3] the presence of hydrogen bonds may produce considerable variations in the ratios reported in Table 3 for both anionic (RO^-) and neutral (piperidine) nucleophiles. However, the major driving force of the reactivity of the nitro group with respect to the reactivity of the other leaving groups is the inductive electron-withdrawing ability of the nitro group with respect to the other leaving groups.[23] The inductive effect of the nitro group (as expressed by the σ_I value, 0.70)[25] is very high. Other leaving groups (especially the halogens) have less relevant σ_I values and are electron releasing by a mesomeric mechanism ($\sigma_R = -0.35$ and -0.20 for F and Cl, respectively). On the other hand, the nitro group has a full inductive electron-withdrawing effect: σ_R for the nitro group is zero[25] and, as a consequence, the bond order of aryl-Cl is higher than aryl-NO_2.

Experimental

Materials.—Starting materials were prepared and purified by the usual methods.[5,26] Solvents (R. P. E. Carlo Erba) were purified by the usual procedures.[27]

Analyses.—The information of the reaction products was verified in preparatory tests. The expected derivatives were taken from the reaction mixtures in high yields (>90%) and were found to be identical to the reaction products obtained from 2-halogeno derivatives.[5,6,8,18b] When X = Cl (Scheme 1), during methoxy-denitration, there were no halide ions in the reaction mixtures, as shown by Volhard analyses.

Kinetics.—Kinetic runs were performed by following the disappearance of the nitro derivatives by a UV/VIS spectrophotometric method (using a Perkin-Elmer Lambda 5 spectrophotometer). $[Ar\text{-}NO_2]_0 = 1 \times 10^{-4}$ mol dm^{-3}; $[RO^-M^+]_0 = 1 \times 10^{-3}$–$5 \times 10^{-2}$ mol dm^{-3}. The reproducibility of k_{obs} was ±4%. For the reaction between 2-nitrothiazole and piperidine in benzene the intercept and slope values, calculated by a least-squares method from eqn. (1) are as follows (errors are standard deviations): $(k_{obs} - k_2)^{-1} = [2.4 \times 10^3 \pm 5 \times 10^3] + [1.25 \times 10^5 \pm 3 \times 10^3] \cdot [\text{piperidine}]^{-1}$; correlation coefficient, 0.9989.

No evidence of the presence of σ anionic (or zwitterionic) complexes was observed for the reactions of 2-nitrothiazoles at various times of conversion, even when the initial concentration of the alkoxide ion is very high. Meisenheimer adducts were observed in the reactions of 5-nitrothiazole derivatives. This confirms the low activation (towards nucleophiles) of C-5 of the thiazole ring by electron-withdrawing groups at C-2.

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