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REACTIVITY OF 4-NITRO- AND 4-NITRO-7-HALOGENO-2,1,3-BENZOTHIADIAZOLES TOWARD METHOXIDE ION

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Abstract—4-Nitro-2,1,3-benzothiadiazole reacted with sodium methoxide (0.1–1 M) in methanol yielding 2,1,3-benzothiadiazole-4,7-dione monoxime (syn + anti). Methoxy-dehalogenation of 4-nitro-7-halogeno-derivatives yielded 4-nitro-7-methoxy-2,1,3-benzothadiazole under similar conditions. In both cases transitions attributable to the formation of Meisenheimer complexes were detected.

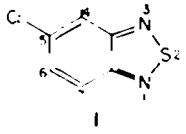
In previous papers we have reported a series of investigations on the reactivity of x - nitro - 2,1,3-benzo-oxadiazoles (benzofurazans) with methoxide ion in methanol.[1] In all cases stable Meisenheimer complexes at unsubstituted (C–H) and/or substituted (C–OMe) positions were detected. A remarkable effect of such a phenomenon on the reactivity (methoxy-dehalogenation) of halogenonitrobenzofurazans was found. In fact, as far as the reactions of 4 - nitro - 5 - halogeno and 5 - nitro - 4 - halogeno - benzofurazans are concerned,[1e] a modified second order equation[2]

$$k = [1/2t(0.5a-b)]\ln[b(0.5a-x)]/[0.5a(b-x)] \quad (1)$$

was required. This was due to the consumption of a second equivalent of methoxide in a fast stage following the methoxy-dehalogenation (Meisenheimer complex formation between the reaction product and MeO).

The methoxy-dehalogenation of 4 - nitro - 7 - halogenobenzofurazans[1e] was found to be independent of the concentration of the reagent in excess (the substrate or the methoxide ion). This was due to the fast formation of a stable Meisenheimer complex on C–H before the nucleophilic attack on C–Hal.

In the methoxy-dehalogenation of 5 - chloro - 4 - nitro - 2,1,3 - benzothiadiazole (**1**)[1] no effects attributable to the formation of similar Meisenheimer complexes were found[1e] under the conditions used (MeO and substrate *ca* 0.01M).



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In order to detect the formation of Meisenheimer complexes, the reactions of 4 - nitro - (**2**) and 4 - nitro - 7 - halogeno - 2,1,3 - benzothiadiazoles (**3**) with methoxide ion in methanol were carried out in higher concentrations of methoxide ion (0.1–1 M *ca*).

RESULTS AND DISCUSSION

A methanolic solution (pale yellow) of 4 - nitro - 2,1,3 - benzothiadiazole, when treated with sodium methoxide (*ca.* 1M), immediately became progressively darker but if the solution was acidified (aqueous HCl) after few seconds, the starting nitrobenzothiadiazole was recovered. Acidification (HCl aq) after longer periods (*ca* 1 hr or more), yielded a new product which by analysis and NMR was identified as 2,1,3 - benzothiadiazole - 4,7 - dione monoxime (syn + anti), identical with that previously synthesized by nitrosation of 4 - hydroxy - 2,1,3 - benzothiadiazole.[4] A similar behaviour has been reported for 5-nitro- and 5-nitro-6-chloro-benzofurazan,[5] which afforded benzofurazan - 4,5 - dione - 5 - monoxime and 6 - chlorobenzofurazan - 4,5 - dione - 5 - monoxime respectively.

The UV spectrum recorded at various times during the reaction indicated many transitions. The first three transitions were measured by the stopped-flow technique. The first two transitions were completed within a few seconds. Thus, in the light of the above experiments, they can be related to reversible reactions and the kinetic data treated on the basis of the equation.[6]

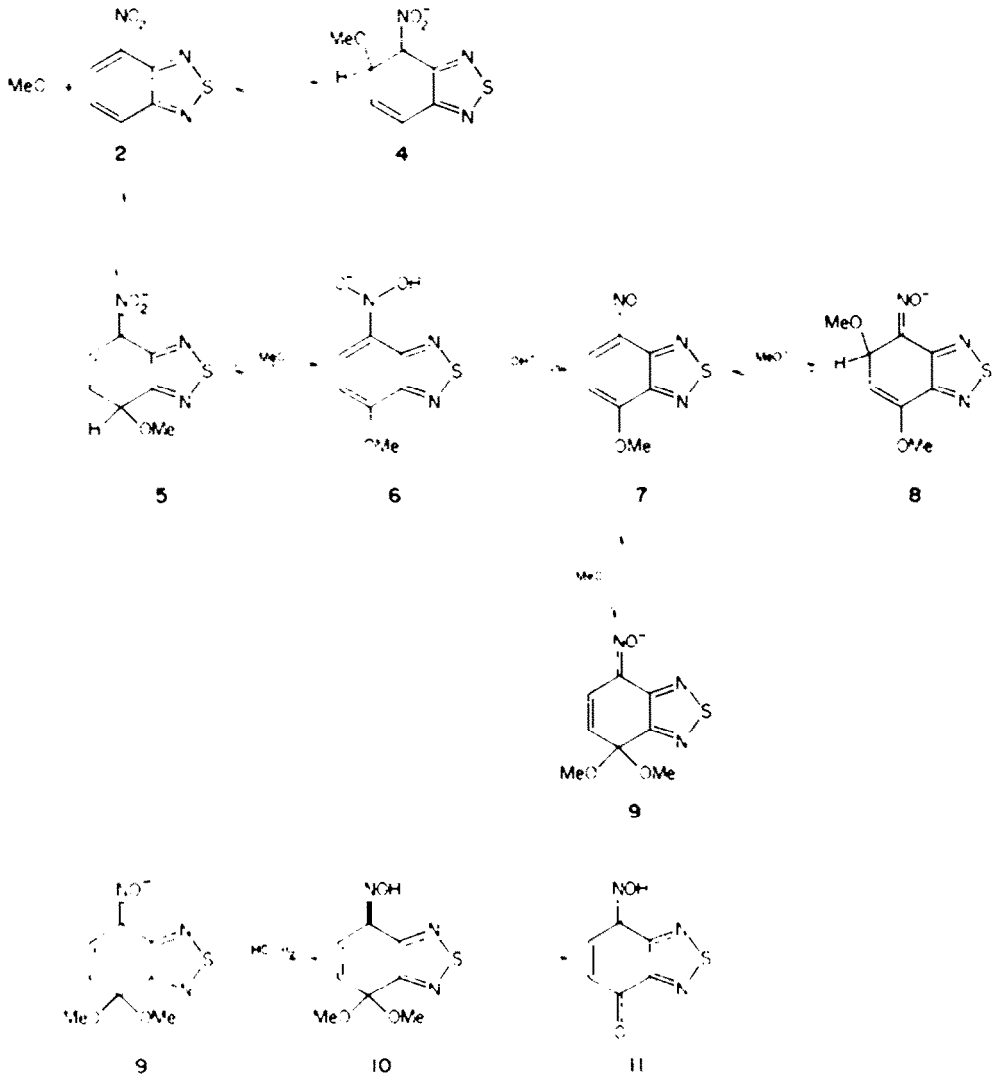
$$k_{1obs} = \bar{k}[MeO^-] + \bar{k} \quad (2)$$

The third transition is second order in methoxide ion. The corresponding third order kinetic constant at 25°C is 7.8×10^{-2} sec $^{-1}$M $^{-2}$; $\bar{k}$ values for the first and the second transition are 60 sec $^{-1}$ M $^{-1}$ and 0.6 sec $^{-1}$ M $^{-1}$ respectively ($\bar{k}$ values are not reported because of their high uncertainty: see Experimental). On the other hand some EPR experiments carried out under similar conditions did not reveal appreciable signals. The following mechanism is based on the data presented.

The first and the second transitions have been attributed to the reversible formation of the Meisenheimer complexes at C–H and C–H respectively. The complex at C–H would be formed more rapidly than that at C–H, but would be less stable; it would then react with a second equivalent of methoxide, affording the nitroso-derivative (**7**). This, in the presence of excess methoxide ion, would afford both the Meisenheimer complexes (**8** and **9**) (the nitroso group has been reported to be an even more effective activating group than the nitro-group).[7]

The complex **9**, which would be more stable than **8** by analogy with other reported cases,[1e] afforded the quinone monoxime (**11**) by treatment with aqueous HCl.

In conclusion, this mechanism which partly resembles that of the Nef reaction,[8] involves only ionic reactions. The competition of electron-transfer reactions[9] has not



Scheme 1.†

†Only one of the possible structures of each Meisenheimer complex is reported.

been considered since no EPR signals were detected (Experimental). On the other hand a similar mechanism is probably valid also for the other above-cited cases, i.e. the reactions of 5-nitro- and 5-nitro-6-chloro-benzofurazan with methoxide ion.[5]

In fact in both cases the expected more stable Meisenheimer complexes are those at C_4-H, since other activated positions capable of even more stable Meisenheimer complexes formation are lacking (the activating effect of a nitro-group in position 5 is mainly exerted on position 4 because of the quinonoid character of the benzofurazan system).[10] Thus, in these cases a high concentration of methoxide ion could act as a base and catalyse the proton transfer, in the same way as in the scheme.

The formation of similar Meisenheimer complexes from nitrobenzofurazan derivatives has been demonstrated previously by NMR.[1a] Some attempts to obtain analogous NMR evidence for the Meisenheimer complexes of 4-nitrobenzothiadiazole failed. In fact, the addition of CD_3O^- in CD_3OD in the high concentration required for NMR immediately gave a dark precipitate preventing recording of a suitable spectrum.

The actual formation of Meisenheimer complexes is suggested, however, by other evidences (e.g. UV spectrum). Moreover, a similar behaviour is expected for the other nitro- and nitro - halogeno - benzothiadiazoles, though no effects have been found previously on the methoxy-dehalogenation of 5 - chloro - 4 - nitro - 2,1,3-benzothiadiazole.[1a] In this case a normal second order equation was required, instead of that "modified" (eqn 1) used for the corresponding 5 - chloro - 4 - nitrobenzofurazan.[1a] The methoxy-dehalogenation of 7 - halogeno - 4 - nitro - 2,1,3 - benzothiadiazoles (halogen = Cl, Br) has now been investigated. Again, "normal" kinetic behaviour (i.e. overall second order and first order in each reactant) has been observed [in methanol, at 25°C, k(sec $^{-1}$ M $^{-1}$) are 2.3×10^{-2} and 1.3×10^{-2} for 7-chloro- and 7 - bromo - 4 - nitro - 2,1,3 - benzothiadiazole respectively]. In spite of this, a stopped-flow analysis revealed for both halogeno-derivatives a fast transition preceding the methoxy-dehalogenation which may be attributed to the formation of the Meisenheimer complex at C_4-H. Starting from 7 - methoxy - 4 - nitro - 2,1,3 - benzothiadiazole (i.e. the product of the methoxy-dehalogenation), the formation of two Meisenheimer complexes (at C_4-H and C-OMe) was

expected. However, only one transition has been measured and has been attributed to the formation of the presumably more stable[1b] Meisenheimer complex at C–OMe. The expected faster transition corresponding to the complex at C–H in our example has not been detected, probably because of its very low stability (see also the data reported for the corresponding benzofurazan derivative).[1c]

Table 1. Kinetic and thermodynamic constants for the reactions of 7 - halogeno - (preliminary transition) and 7 - methoxy - 4 - nitro - 2,1,3 - benzothiadiazole (one only transition) with sodium methoxide in methanol at 25°C. (In parenthesis the values of the corresponding nitrobenzofurazan[1b,c] derivatives are reported)

7-Substituent	$\vec{k}$(sec^{-1} M^{-1})	$\overleftarrow{k}$(sec^{-1})	$K_c = \vec{k}/\overleftarrow{k}$(M^{-1})
Chloro	80	~2	~40
	(5100)	(1.8)	(2800)
Bromo	78	~2	~39
	(5200)	(3.8)	(1300)
Methoxy	0.34	0.22	1.5
	(14.5)	(7.1×10^{-3})	(2050)

Kinetic data related to the above-described transitions have been treated once again on the basis of the equation (2). The values so obtained, as well as those of the corresponding benzofurazan derivatives, are reported in the table. The comparison indicates that values of $\vec{k}$ are considerably lower in benzothiadiazole than in benzofurazan derivatives. This corresponds also to a lower thermodynamic stability of the Meisenheimer complexes.

In conclusion, the Meisenheimer complexes with methoxide ion are formed not only (as previously reported) by nitrobenzofurazans, but presumably also in their sulphur analogues, the nitro - 2,1,3 - benzothiadiazoles here studied. However, according the greater aromatic character of the benzothiadiazole system and the lower electron-withdrawing power of the cyclic sulphur (with respect to the oxygen of benzofurazan ring), the latter complexes are much less stable, so that no kinetic effects are observed in the methoxy-dehalogenation of halogenonitrobenzothiadiazoles in the used concentrations i.e. [substrate] and [MeO$^-$] *ca.* 10^{-2} M.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. Microanalyses were made on a Hewlett-Packard C,H,N analyser. UV Measurements were made with a Zeiss M4QII spectrophotometer; PMR and EPR spectra were recorded with a Varian HA-100 and JEOL JES-PE-3X instrument respectively. Mass spectra were recorded on a Perkin-Elmer Model 270 spectrometer. Stopped-flow determinations were performed with a Gibson-Durrum stopped-flow apparatus.

Materials. 4-Nitro (m.p. 107°),[11] 4 - nitro - 7 - chloro- (m.p. 198–199°),[12] and 4 - nitro - 7 - bromo - 2,1,3 - benzothiadiazole (m.p. 219–220°)[12] have been synthesized as previously reported. Methanol for kinetic and EPR experiments was the commercial product (RP-ACS Carlo Erba) purified further according the standard procedures. DMSO-d_6 for PMR measurements was a good commercial product.

Reaction products. The product obtained form 4 - nitro - 2,1,3 - benzothiadiazole after acidification (aq HCl) of the methanolic solution of reaction ([MeO$^-$] *ca.* 1M and in excess with respect to the substrate; time of reaction *ca.* 1h) resulted to have analytical data and molecular weight identical to those of the starting nitro-derivative, but different m.p. (243°, dec.) and mass spectrum (not reported; that of 4 - nitro - 2,1,3 - benzothiadiazole has been reported previously).[11] On the other hand, PMR (in DMSO d_6, internal standard TMS) was identical within experimental error to that reported for 2,1,3 - benzothiadiazole - 4,7 - dione monoxime (*syn* + *anti*: 1.97 and 3.29τ, J = 10.7 c/s for *syn*; 2.38 and 3.29, J = 10.9 Hz for *anti*)[4] excepted for the signals of OH protons (reported −4.20 and 4.40 for *syn* and *anti* respectively) which in our case were not detected (very broad signals?). Even the *syn*/*anti* ratio was similar within the experimental error (*ca.* 75:25). In the light of the above results the structure of 2,1,3 - benzothiadiazole - 4,7 - dione monoxime (**11**) was assigned. The product obtained from 7 - halogeno - 4 - nitro - 2,1,3 - benzothiadiazoles (both chloro- and bromo-) was 7 - methoxy - 4 - nitro - 2,1,3 - benzothiadiazole (m.p. 206°).[14]

Kinetic experiments. In all cases an appropriately thermostated apparatus (25°) was utilized. The methoxy-dehalogenation of 7 - halogeno - 4 - nitro - derivatives has been followed titrimetrically ([Substrate] and [MeO$^-$] *ca.* 10^{-2} M) measuring the halide ion (Volhard). All the other transitions were measured by stopped flow technique ([MeO$^-$] *ca.* 0.1–1M) at the following wavelengths: 360, 360, 355, and 330 nm for 7-H, 7-Cl, 7-Br, and 7-OMe- 4 - nitro - 2,1,3 - benzothiadiazole respectively. Pseudo-first order conditions (MeO$^-$ in a large excess) were used. The obtained data in the case of reversible transitions were treated on the basis of the equation (2),[5] $k_{obs} = \vec{k}[MeO^-] + \overleftarrow{k}$, where k_{obs}, $\vec{k}$ and $\overleftarrow{k}$ are the observed pseudo-first order, the forward second order and the reverse first order kinetic constants respectively. From this equation $\vec{k}$ have been obtained as slopes plotting k_{obs} versus [MeO$^-$] while $\overleftarrow{k}$ values, because of their high uncertainty, in some cases have not been reported. The experimental error for $\vec{k}$ (methoxy-dehalogenation) as well for $\vec{k}$ values [from equation (2)] is ±5%, while in the case of $\overleftarrow{k}$ (when reported) it is much larger and variable, depending on the magnitude of the slope (=$\vec{k}$) and on $\overleftarrow{k}$ itself.

EPR *experiments.* At concentrations of methoxide ion similar to those utilized for kinetic experiments (*ca.* 0.5M), or higher, no appreciable EPR signals were detected for the reactions (in methanol) of 4 - nitro - 2,1,3 - benzothiadiazole. This was confirmed also by spin-trapping experiments carried out with tert-Butyl benzylidene nitrone.[15] In the latter experiments appreciable EPR signals were detected; these, however, resulted identical to those detected in a blank experiment (i.e., using only the Benzylidene nitrone and methoxide ion in similar conditions).

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