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'NORMAL' AND 'CINE' SUBSTITUTION IN THIOMETHOXY-DEHALOGENATION OF HALOGENOBENZOFURAZANS

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Abstract—Halogenobenzofurazans react with sodium thiomethoxide in methanol giving, in addition to the thiomethoxy-derivative corresponding to the starting halogenobenzofurazan, the product of cine-substitution. These two products are formed by two distinct 'addition-elimination' mechanisms. The first, 'SNAr-type', gives the normal substitution product, while the latter, 'anomalous-type', affords the cine-substitution derivative.

Previously we reported the behaviour of halogenobenzofurazans (halogen = 4-F, 4-Cl, 5-Cl, 4-Br) in the methoxy-dehalogenation by sodium methoxide in methanol.[1] In all the cases the halogen could be replaced by a methoxide ion in relatively mild conditions which were justified on the basis of an appreciable activation of the system by the oxygen and two aza groups of the heterocyclic ring. The intervention of a SNAr-type mechanism has been suggested and is discussed for these reactions.

In order to further define the reactivity of benzofurazanhalogeno derivatives towards nucleophiles, we extended our investigation to thiomethoxy-dehalogenation.

RESULTS AND DISCUSSION

In the reaction between 4-halogeno- or 5-halogenobenzofurazans and MeS^- in methanol both the normal substitution (NS) and cine-substitution (CS) thiomethoxy derivatives were obtained, except in the case of 4-fluorobenzofurazan, which afforded only the NS derivative.

On the other hand, in the case of iodobenzofurazans, in addition to the thiomethoxydehalogenation products, some unsubstituted benzofurazan (VPC) was obtained and probably formed by the reducing action of free methanethiol (Experimental).

*In deuteriomethanol a lower relative amount of CS with respect to NS derivative was also obtained. *E.g.*, from 4-bromobenzofurazan at 25°, 24% of 5-thiomethoxy- and 76% of 4-thiomethoxybenzofurazan were obtained, while in MeOH at the same temperature 36% and 64% were isolated respectively. For corresponding kinetic data, see Table 2.

Table 1. Relative percentages of two products at 45°

Halogen in halogenobenzofurazan	4-Methylthiobenzofurazan %	5-Methylthiobenzofurazan %
4-F	100	—
4-Cl	74·6	25·4
4-Br	72·2	27·8
5-Cl	7·8	92·2
5-Br	11·5	88·5

The relative percentages of two thiomethoxy derivatives which could be obtained from each halogenobenzofurazan (measured by vpc) are given in Table 1.

Both the isomers, besides the unreacted starting halogeno derivatives, were the only products which could be isolated. Furthermore, each isomer, separately mixed with MeS^- in methanol under similar conditions to those employed in thiomethoxy-dehalogenation, was recovered unchanged. Therefore the possibility that the CS product formation was due to isomerization of the NS product could be excluded. Thus the CS product was considered as a true cine-substitution product, according to Bunnett's definition.[2]

Moreover, when the reactions of the 4-chloro derivative were carried out in deuteriomethanol, the CS product (*i.e.* 5-thiomethoxybenzofurazan) contained deuterium in the position 4 previously occupied by the halogen,* in proportion (*ca* 85%) corresponding to medium (MeOD + MeSH) deuteria-

Table 2. Second order kinetic constants (sec^{-1} mol^{-1} l) for the reactions between halogenobenzofurazans and sodium thiomethoxide in methanol

Halogen	25°C		35°C		45°C		E_a(kcal/mol)		$\Delta S^{\neq}$(cal $mol^{-1}K^{-1}$)	
	NS	CS	NS	CS	NS	CS	NS	CS	NS	CS
4-Fluoro*	$9{\cdot}1\times10^{-4}$	—	$2{\cdot}2\times10^{-3}$	—	$5{\cdot}2\times10^{-3}$	—	16·2	—	−20·0	—
4-Chloro	$1{\cdot}8\times10^{-5}$	$9{\cdot}5\times10^{-6}$	$5{\cdot}4\times10^{-5}$	$2{\cdot}5\times10^{-5}$	$1{\cdot}3\times10^{-4}$	$4{\cdot}4\times10^{-5}$	18·5	13·3	−20·0	−38·0
4-Bromo	$8{\cdot}5\times10^{-5}$	$4{\cdot}8\times10^{-5}$	$2{\cdot}4\times10^{-4}$	$1{\cdot}2\times10^{-4}$	$5{\cdot}0\times10^{-4}$	$1{\cdot}9\times10^{-4}$	17·2	13·5	−21·6	−35·0
5-Chloro	$4{\cdot}2\times10^{-5}$	$5{\cdot}0\times10^{-6}$	$1{\cdot}3\times10^{-4}$	$1{\cdot}3\times10^{-5}$	$3{\cdot}5\times10^{-4}$	$2{\cdot}9\times10^{-5}$	19·7	16·5	−14·6	−29·5
5-Bromo	$1{\cdot}6\times10^{-4}$	$3{\cdot}1\times10^{-5}$	$4{\cdot}6\times10^{-4}$	$7{\cdot}6\times10^{-5}$	$1{\cdot}2\times10^{-3}$	$1{\cdot}6\times10^{-4}$	18·7	15·1	−15·0	−30·6
4-Bromo†	$6{\cdot}3\times10^{-5}$	$2{\cdot}0\times10^{-5}$	—	—	—	—	—	—	—	—

NS = Normal Substitution.
CS = Cine-Substitution
*See text.
†Experiments carried out in deuteriomethanol.

tion percentage. On the other hand, the NS product in MeOD, when it was the only product of the reaction (*i.e.*, from 4-fluorobenzofurazan), or when it was obtained in addition to the CS product (*e.g.*, from 4-chlorobenzofurazan), was identical with that isolated in light methanol.

However, an 'elimination-addition' pathway for cine-substitution, as frequently suggested for this kind of reaction, is unlikely since, if this is the case, not only CS, but also NS products would contain deuterium. In addition, the very similar reactivity of chloro- and bromo-derivatives cannot be easily rationalized on the basis of an 'elimination-addition' mechanism since it is known that when this mechanism is operative, chloro and bromo-derivatives usually behave differently.[3]

Moreover, it should be also considered that, when MeS^- is utilized, an elimination reaction from a vinylic-type derivative would be unlikely, since the thiomethoxide-ion is normally considered a poor basic reagent and shows a low affinity towards hydrogen ions. In accord with this hypothesis we did not observe deuterium exchange in the unreacted materials or in the final normal substitution products.

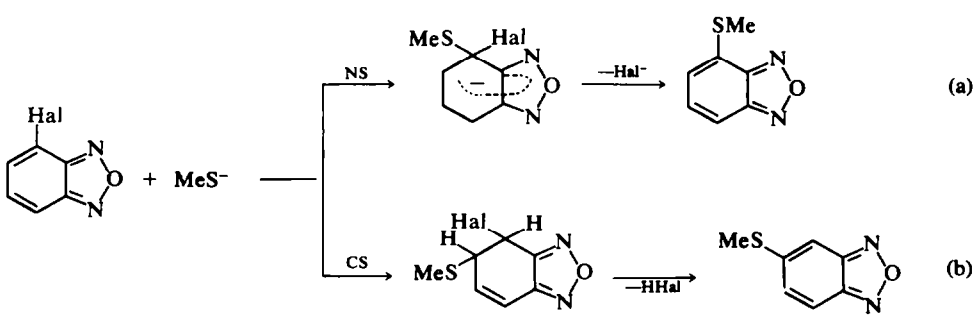
Moreover in activated ethylenic systems,[4] in which 'elimination-addition' paths are rather frequent, when the reactions are performed with thiolate ions, "direct-substitution" is usually preferred (*i.e.*, the direct nucleophilic attack on the carbon bearing halogen is observed). However, dehydrohalogenations promoted by thiolate ions are known.[5]

On the other hand, the experimental results are in a good agreement with an 'addition-elimination' SNAr-type mechanism for the normal substitution (HS) and an anomalous type 'addition-elimination' mechanism[6] for the cine-substitution (CS), as depicted in the Scheme.

In the Scheme the normal substititution proceeds through nucleophilic attack on the carbon bonded to the halogen and subsequent expulsion of halide ion; a similar nucleophilic attack on the adjacent carbon gives an intermediate adduct which by dehydrohalogenation affords the cine-substitution derivative.

The formation of an intermediate adduct is very likely for the systems investigated which can easily form addition products. In fact, some examples of adducts to the benzofurazan ring have been reported.[7] Nevertheless, in our case these adducts were not detected in spite of many attempts. It can be considered, however, that, since anionic species are present, dehydrohalogenation could be very fast, in order to regenerate the aromatic character of the benzofurazan derivative. Therefore the formation of the intermediate in a cine-substitution path would be the 'rate-determining' step.

On the other hand, the relative amounts of NS and CS products (Table 1), for a given temperature,



does not vary by changing the relative initial concentrations of the halogeno derivative and MeS^- (the last in any case is in large excess with respect to the halogeno compound), being the same for all reaction percentages. Therefore, both pathways (a and b in the Scheme) follow the same kinetic law.

Furthermore, the reaction of 4-fluorobenzofurazan, which gives only the NS product, obeys a clean second order kinetics (first order in each reactant). Thus, by assuming that this is valid also for the NS pathway for other halogenobenzofurazans, all kinetic constants for both paths were easily calculated (Table 2).

Moreover, by inspection of Table 2, further and very useful conclusions can be drawn: (1) The reactivity sequence in the NS reaction ($F \gg Br > Cl$) is in agreement with the 'Addition-Elimination' SNAr-type mechanism (class A in the Bunnett's classification)[8] suggested by us; (2) Finally, concerning the CS reaction scheme, the formation of an intermediate adduct (which apparently occurs in the 'rate-determining' step) may follow a 'synchronous'[9] rather than a 'stepwise'[10] mechanism, as suggested by the relatively high activation entropy values.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. Microanalyses were made on a Hewlett-Packard C.H.N. analyser by Mrs. R. De Leonardis, Institute of Pharmaceutical Chemistry, Bari. ^1H NMR spectra were recorded on a Varian HA-100 instrument.

Materials. MeOH and MeOD (Fluka) were purified following the standard procedures. CCl_4 for NMR measurements was a good commercial product (R. P. Carlo Erba). 4-Fluorobenzofurazan, b.p. 83° at 12 mm; 4-chlorobenzofurazan, m.p. 83–84°; 5-chlorobenzofurazan, m.p. 44°; 4-bromobenzofurazan, m.p. 107°; and 5-bromobenzofurazan, m.p. 74°, were synthesized as previously described.[1,11] Methanethiol was synthesized according to the method described by Backer and Stienstra.[12]

Reaction products. All halogeno compounds gave (except 4-fluorobenzofurazan) both 4- and 5-thiomethoxybenzofurazan, in the relative percentages reported for t = 45° in Table 1 (measured by VPC: see text). The two products were separated each from the other by chromatografy on silicagel, using hexane-ether 7:3 as eluent. Analytical data (4-thiomethoxybenzofurazan, m.p. 77–78° from EtOH. Found: C, 50·61; H, 3·60; N, 17·22; S, 19·11; 5-thiomethoxybenzofurazan, m.p. 101–102° from EtOH. Found: C, 50·88; H, 3·70; N, 16·88; S, 18·92; required for $C_7H_6N_2OS$: C, 50·60; H, 3·61; N, 16·86; S, 19·23) and NMR spectra in CCl_4 (4-thiomethoxybenzofurazan; $ABCX_3$ system; $\tau_A = 2{\cdot}76$, $\tau_B = 3{\cdot}03$, $\tau_C = 2{\cdot}47$, $\tau_X = 7{\cdot}36$; $J_{AB} = 7$ c/s, $J_{AC} = 9$ c/s, $J_{BC} = 0{\cdot}9$ c/s; 5-thiomethoxybenzofurazan: $ABCX_3$ system; $\tau_A = 2{\cdot}75$, $\tau_A = 2{\cdot}75$, $\tau_B = 2{\cdot}89$, $\tau_C = 2{\cdot}34$, $\tau_X = 7{\cdot}45$; $J_{AB} = 1{\cdot}6$ c/s, $J_{AC} = 0{\cdot}9$ c/s, $J_{BC} = 9{\cdot}4$ c/s) were all in agreement with the proposed structures.

Rate measurements. Kinetic experiments were carried out in MeOH in an appropriately thermostatted apparatus, following the appearance of halide ion (Volhard), or (in the case of 4-fluorobenzofurazan) the disappearance of base (thiomethoxide). In all cases a strong excess of thiomethoxide ion in respect to halogenobenzofurazan was employed. Further, with respect to thiomethoxide ion, a more consistent excess of methanethiol was utilized, to shift the equilibrium $(MeSH + MeO^- \rightleftarrows MeS^- + MeOH)$[13] towards the methanethiolate ion. The pseudo-first order kinetic constants, being the sum of those corresponding to each pathway (*i.e.*, $k_{1(tot)} = k_{1(a)} + k_{1(b)}$), were dissociated (using ratios between two isomers) in the single terms. From these, corresponding second order kinetic constants were calculated. All the kinetic data are average of values obtained from two or more independent experiments: the experimental error is ±3%.

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