cine-Substitution in Methoxydehalogenation of Some Halogenobenzofurazans

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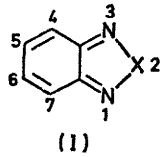
Through investigation of the reaction of 4- and 5-iodobenzofurazan with sodium methoxide in methanol a new mechanism is proposed, in addition to the S_NAr-type pathway previously reported, for the methoxydehalogenation of halogenobenzofurazans. This novel pathway, which is responsible for the '*cine*-substitution,' seems to be an 'elimination–addition' rather than an 'addition–elimination' anomalous-type mechanism (AE_a). However, some competition by the AE_a mechanism is not excluded.

2,1,3-BENZOHETERADIAZOLES (I; X = O, S, or Se) are interesting compounds, since they are on the borderline between 'aromatic' and 'ethylenic' systems; and the C(4)–C(5) and C(6)–C(7) double bonds and the C(5)–C(6) single bond have been found to be partially fixed.[1] We have previously described work on the reactivity of some halogeno- and halogenonitro-benzofurazans (I; X = O) towards sodium methoxide in



(I)

methanol.[2] For these derivatives we have suggested an 'addition–elimination' S_NAr-type mechanism (AE) (class A in Bunnett's classification) [3] on the basis of the observed second order kinetics (first order in each reactant) and the very high reactivity of the fluoro-derivative with respect to the other halogeno-derivatives.

More recently we have investigated the reaction of halogenobenzofurazans with methanethiolate ion in methanol, and have observed, together with an S_NAr-type mechanism [which affords normal substitution (NS) products], an addition–elimination 'anomalous-type' mechanism (AE_a) by which *cine*-substitution (CS) products are formed.[4] Moreover, some of us have recently detected both NS and CS products in the reactions of dihalogenobenzofurazans with methoxide ion in methanol: this prompted us to re-investigate the reactions of halogenobenzofurazans with methoxide ion and we have extended the analysis to 4- and 5-iodobenzofurazan. The results are described in this paper.

RESULTS AND DISCUSSION

Halogenobenzofurazans, when treated with MeO^- in MeOH, give 4- and 5-methoxybenzofurazan in the relative amount reported in Table 1.

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[2] D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *J. Chem. Soc.* (*B*), 1971, 2209.
[3] J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020; J. F. Bunnett and R. H. Garst, *ibid.*, 1965, **87**, 3879.
[4] L. Di Nunno, S. Florio, and P. E. Todesco, *Tetrahedron*, 1974, **30**, 863.

The overall second order rate constants measured (under pseudo-first order conditions; see Experimental section) at various temperatures are in Table 2.

If a similar mechanism to that suggested for methylthiodehalogenation (*i.e.*, S_NAr-type for the normal that observed in methylthiodehalogenation. For instance, if we consider the rate constants corresponding to *cine*-substitution at a given temperature (*e.g.*, 100°), we observe for 4-chloro-, 4-bromo-, and 4-iodo-benzofurazan k_{CS}, $\leqslant 3.3 \times 10^{-6}$, 7.5×10^{-5}, and 1.3×10^{-4},

TABLE 1

Ratios * (4-methoxy- : 5-methoxy-benzofurazan products) from the reactions of 4- or 5-halogeno-derivatives and sodium methoxide in methanol

Temperature (°C)	4-Fluoro	4-Chloro	4-Bromo	4-Iodo	5-Chloro	5-Bromo	5-Iodo
80			1·0	0·3			0·3
100	‡	†	1·4	0·3	‡	†	0·3
115			1·8	0·3			0·3

* These ratios were determined by n.m.r. spectroscopy and the error is 5%. This error is obviously reflected in the k values reported in Tables 3 and 4. † Only traces ($\leqslant 3$ and *ca.* 5% for 4-chloro and 5-bromo respectively) of the *cine*-substitution product were detected in these cases. The small values observed and the experimental error do not permit us to detect sensible differences by varying the temperature. ‡ No CS product was obtained.

TABLE 2

Overall second order rate constants for the reactions between halogenobenzofurazans and sodium methoxide in methanol

	10_3k/l mol^{-1} s^{-1}						
Temperature (°C)	4-F [a]	4-Cl [a]	4-Br [a]	4-I	5-Cl [a]	5-Br	5-I
25	0·019 [b]	0·000020 [b]			0·000089 [b]		
35	0·060						
50	0·34						
60	1·1						
78		0·014			0·050		
78·8			0·024				
80				0·033			0·051
90							0·13
100	40 [b]	0·11	0·18	0·17	0·40	0·66	0·36
115			0·62	0·58		1·9	
125						4·3	
130		1·5			5·1		
100 [c]		0·19	0·26	0·24			0·93

[a] Data from ref. 2. [b] Extrapolated from other temperatures by an Arrhenius plot. [c] Data in MeOD.

TABLE 3

Second order rate constants for the reaction between halogenobenzofurazans and sodium methoxide in methanol: hypothesized mechanism = AE_n (NS) + AE_a (CS)

	10^3k/l mol^{-1} s^{-1}									
	4-F	4-Cl	4-Br		4-I		5-Cl	5-Br	5-I	
Temperature (°C)	k_{NS}	$k_{total}(\simeq k_{NS})$	k_{NS}	k_{CS}	k_{NS}	k_{CS}	k_{NS}	$k_{total}(\simeq k_{NS})$	k_{NS}	k_{CS}
25	0·019 [a]	0·000020 [a]					0·000089 [a]			
35	0·060									
50	0·34									
60	1·1									
78		0·014					0·050			
78·8			0·012	0·012						
80					0·0076	0·025			0·039	0·012
90									0·10	0·030
100	40 [a]	0·11 [b]	0·10	0·075	0·039	0·13	0·40	0·66	0·28	0·083
115			0·39	0·22	0·13	0·45		1·9		
125								4·3		
130		1·5					5·1			
100 [c]		0·19	0·20	0·060	0·098	0·14			0·80	0·13
E_A/kcal mol^{-1}	23·3	25·6	26·1	21·3	22·0	22·4	24·9	(21·9)	25·8	25·3
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	−4·4	−10·4	−9·3	−21·3	−22·0	−18·6	−9·6	(−16·7)	−8·2	−11·9

[a] Extrapolated data. [b] The estimated k_{CS} at this temperature would be $\leqslant 3.3 \times 10^{-6}$. [c] Data in MeOD: for the relative amounts of 4- and 5-methoxybenzofurazan, see Table 5.

substitution and addition–elimination anomalous-type for the *cine*-substitution)[4] is again hypothesized, dissection of the overall kinetic constants into those corresponding to each pathway gives the data in Table 3.

However, inspection of these new data indicated apparently appreciably different behaviour with respect to respectively, which do not correlate linearly (logarithmic scale) in a satisfactory manner with those values measured (*e.g.*, at 45°) for the methylthiodehalogenation of the same derivatives (*i.e.*, k_{CS} 4.4×10^{-5}, 1.9×10^{-4}, and 4.2×10^{-4}).[4] In addition, when the reactions were carried out in deuteriomethanol, not only the CS products

(as in the methylthiodehalogenation), but also NS products and unchanged halogenobenzofurazans contained deuterium; *e.g.*, when 4-bromobenzofurazan (0·15 mol) was allowed to react at 100° with MeO^- (0·87 mol) in MeOD for 2·25 h (reaction stopped with DCl), the CS product (5-methoxybenzofurazan) was completely deuteriated at position 4 (previously occupied by the halogen) and *ca.* 50% deuteriated at position 7, while in position 6 no deuterium had been incorporated. Moreover the unchanged 4-bromobenzofurazan was deuteriated in positions 5 and 7 (60 and 35% respectively with reference to position 6 which was assumed to be non-deuteriated), and a similar deuteriation was also observed in the NS product (4-methoxybenzofurazan). On the other hand in the reactions in MeOD (at the same temperature) of 5-bromobenzofurazan (0·13 mol) with MeO^- (0·24 mol), both the unchanged material and NS product (recovered after 1·5 h) contained deuterium (100, 0, and 30% in positions 4, 6, and 7 respectively), while only traces of CS product were obtained. Moreover, an analogous H–D exchange to that observed in the unchanged 4- and 5-bromobenzofurazan (but correspondingly smaller) was also detected when non-deuteriated 4- and 5-methoxybenzofurazan are treated under similar conditions. In fact, when 4-methoxybenzofurazan (0·096 mol) reacted with MeO^- (1·34 mol) in MeOD at 100° for 2 h, only a little deuterium incorporation (*ca.* 5%) was detected. By stopping the reaction of 5-methoxybenzofurazan (0·095 mol) with MeO^- (1·24 mol) in MeOD at the same temperature after 2·25 h, 88, 0, and *ca.* 50% deuterium incorporation was detected in positions 4, 6, and 7 respectively.

From the foregoing experiments it can be argued that: (*a*) deuterium which is contained in both NS and CS methoxy-derivatives when they are formed from halogenobenzofurazans in MeOD has been incorporated almost completely before (*i.e.*, directly on the starting halogeno-derivative by H–D exchange), or during the methoxydehalogenation.

(*b*) The mechanism of ' direct ' H–D exchange involves the abstraction of protons by MeO^- (*i.e.*, phenyl anion formation) rather than the addition of MeOD and subsequent elimination of MeOH, since, in this way, deuterium incorporation at position 5 of 4-bromobenzofurazan could be not possible. Moreover, if an addition–elimination mechanism were responsible for H–D exchange, in the methylthiodehalogenations carried out in deuteriomethanol the recovered halogenobenzofurazans (and NS methylthio-derivatives) should contain deuterium, and this was not observed.

(*c*) Finally, in accord with exchange *via* a phenyl anion, the exchange sequence of the various protons seems to indicate a greater acidity of H-4 and H-7 with respect to H-5 and H-6, which is as expected on the basis of a marked inductive effect [5] of the aza-groups of the condensed heterocyclic ring [the reported δ values of benzofurazan are also in agreement: δ (CCl_4) H-4, H-7, 7·78, H-5, H-6 7·36]; [1] further, as expected, dependence on the inductive effects of other linked groups also seems to be involved.

The *cine*-substitution pathway becomes more important with respect to normal substitution on going from the fluoro- to the iodo-derivative; in the case of 4-iodobenzofurazan, *cine*-substitution is even more important than normal substitution, since the ratio of 4-methoxy- : 5-methoxy-benzofurazan is 0·3. In addition, this value is identical with that observed for the methoxydehalogenation of 5-iodobenzofurazan, and does not change with temperature.

On the basis of all these results it seems to be not unreasonable that an ' elimination–addition ' [6] rather than an ' addition–elimination ' anomalous-type [6b,7] mechanism is responsible for the *cine*-substitution in methoxydehalogenation of halogenobenzofurazans. In fact, since phenyl anions with a negative charge *ortho* to C-Hal are effectively formed under the reaction conditions as discussed above, it is likely that they can behave as ' aryne ' precursors. From such intermediates both CS and NS products are then formed, as described in the Scheme.

In the light of this Scheme, the observed relative amounts of NS and CS products for the various halogeno-derivatives can then be explained by assuming that fluoro-(and chloro-)derivatives react only by pathway *a*, while in the case of bromo-derivatives, mechanisms *a* and *b* are competitive; in the case of iodo-derivatives, since both 4- and 5-iodobenzofurazan give the same ratio 4-methoxy- : 5-methoxy-benzofurazan, it seems likely that only elimination–addition mechanism *b* is operative (which is clearly not in disagreement with the relatively easier C–I bond dissociation).

If the overall rate constants in Table 2 are dissected on the basis of these new considerations, the data in Table 4 are obtained.

Examination of the kinetic data allows further considerations to be made, in agreement with the overall scheme reported above: (*a*) the sequence of reactivity on changing the halogen in pathway *a* ($F \gg Cl > Br$) confirms the S_NAr-type mechanism previously suggested by us.

(*b*) Similarly, as expected for an elimination–addition pathway, iodo-derivatives are more reactive than the corresponding bromo-derivatives towards *cine*-substitution [$(k_b)_I > (k_b)_{Br}$].

(*c*) The smaller reactivity of 4-iodobenzofurazan with respect to 5-iodobenzofurazan despite the equivalence of the ratio 4-methoxy- : 5-methoxy- (Table 1) indicates that in the ' elimination–addition ' mechanism *b*, dehydrohalogenation is the rate-determining step.

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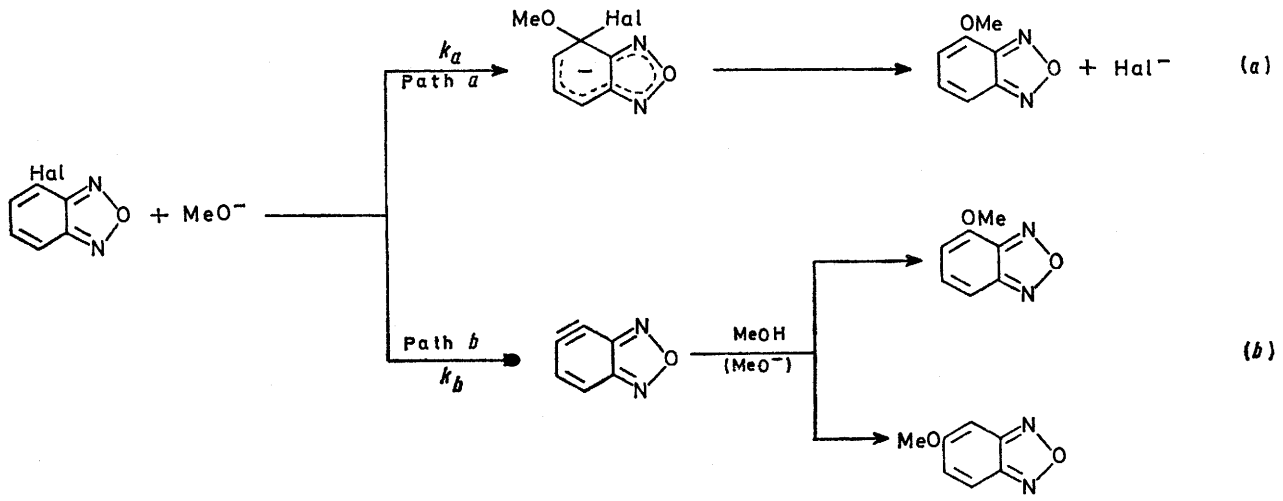
[6] (*a*) T. Kauffmann and R. Wirthwein, *Angew. Chem. International Edn.*, 1971, **10**, 20; (*b*) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273; F. Pietra, *Quart. Rev.*, 1969, **23**, 504.

[7] T. Kauffmann, R. Nürnberg, and K. Udluft, *Chem. Ber.*, 1969, **102**, 1177.

However, when the reactions are carried out in deuteriomethanol, an increase of NS with respect to the CS derivative is observed (Table 5), which also modifies the ratio of the two products in the case of iodo-derivatives (which in non-deuteriated methanol give the same ratio, 0·3).

seems to be connected to a greater extent with a favourable kinetic solvent isotope effect in pathway *a*.

In conclusion, on the basis of the foregoing experimental results, an 'elimination–addition' mechanism seems to be involved in the formation of CS products in methoxydehalogenation of halogenobenzofurazans.



SCHEME
(*a*) Fluoro-(and chloro-)derivatives; (*a*) + (*b*) bromo-derivatives; (*b*) iodo-derivatives.

TABLE 4

Second order rate constants for the reactions between halogenobenzofurazans and sodium methoxide in methanol (mechanism in the Scheme; $AE_n + EA$)

	10^3k/l mol^{-1} s^{-1}									
			4-Br		4-I				5-I	
Temperature (°C)	4-F	4-Cl					5-Cl	5-Br		
	k_a	$k_{total}(\simeq k_a)$	k_a	k_b	k_a	k_b	k_a	$k_{total}(\simeq k_a)$	k_a	k_b
25	0·019 *	0·000020 *					0·000089 *			
35	0·060									
50	0·34									
60	1·1									
78		0·014					0·050			
78·8			0·0084	0·016						
80						0·033				0·051
90										0·13
100	40 *	0·11	0·082	0·098		0·17	0·40	0·66		0·36
115			0·33	0·29		0·58		1·9		
125								4·3		
130		1·5					5·1			
100 †		0·19	0·18	0·08	0·056	0·18			0·36	0·57
E_A/kcal mol^{-1}	23·3	25·6	27·6	21·8		22·2	24·9	(21·9)		25·6
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	−4·4	−10·4	−5·8	−21·0		−18·5	−9·6	(−16·7)		−8·3

* Extrapolated data. † Data in MeOD calculated on the basis of the relative amounts of 4- and 5-methoxybenzofurazan in Table 5, and by supposing that the ratios 4-OMe : 5-OMe from pathway *b* in MeOH and MeOD are identical [0·3 (Table 1)].

From kinetic measurements of the reactions with MeO^- in MeOD at 100°, the enhancement of NS product

TABLE 5

Relative percentages * of 4- and 5-methoxybenzofurazan from 4- or 5-halogeno-derivatives and sodium methoxide in deuteriomethanol at 100°

	4-Chloro	4-Bromo	4-Iodo	5-Iodo
4-Methoxy	100	76·5	41	14
5-Methoxy		23·5	59	86

* These values were determined by n.m.r. spectroscopy and the estimated error is *ca.* 5%.

Nevertheless, some competition of an 'addition–elimination' anomalous-type mechanism as in the methylthiodehalogenation cannot be rigorously excluded.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were recorded on JEOL MINIMAR JNM-MH-60 II and Varian HA-100 instruments.

Materials.—Methanol for kinetic experiments was purified by described procedures. Methan[^{2}H]ol for hydrogen–

deuterium exchanges and kinetic experiments was partly the Fluka commercial product and partly synthesized according the method of Streitwieser; [8] carbon tetrachloride for n.m.r. measurements was a good commercial product (R.P. Carlo Erba). 4-Chloro-, m.p. 83—84°; [2,9] 4-bromo-, m.p. 107°; [2,9] 5-bromo-, m.p. 74°; [10] 4-iodo-, m.p. 94·5—95·5°; [11] and 5-iodo-benzofurazan, m.p. 93·5—94·5°,[11] were synthesized as previously reported.

Reaction Products.—These were separated by chromatography on a silica gel column, by using hexane–ether 7 : 3 as eluant. 4-Methoxy- (m.p. 89—90°) and 5-methoxybenzofurazan (m.p. 98°) so obtained were identical with authentic specimens [12] (mixed m.p.s undepressed). The relative percentages of the two isomers were measured by n.m.r. spectroscopy, from the intensity of the signals corresponding to the methoxy-protons (τ 5·97 and 6·11 in CCl_4 for 4- and 5-methoxybenzofurazan respectively).

Hydrogen–Deuterium Exchange.—The experiments were carried out in methan[^{2}H]ol at 100° on the substrates and at the concentrations reported in the text. DCl was utilized in all cases for stopping the reactions. The n.m.r. spectra of the recovered products (purified directly or after separation by chromatography as reported above) were then recorded and compared with those of non-deuteriated derivatives. The deuteriation percentages in the single positions were assigned with reference to methoxy-protons in methoxy-derivatives and to H-6 in 4- and 5-bromobenzofurazan.

Rate Measurements.—Kinetic experiments were performed by using a large excess of methoxide ion with respect to the halogenobenzofurazan (pseudo-first order conditions). They were carried out in sealed ampoules, since the reaction temperatures were all above the b.p. of the solvent. The appearance of halide ion (Volhard) was followed and the appropriate kinetic equations were utilized, the solvent expansion from 25° (the mixing temperature) to the temperatures of reaction being taken into account.[13] Data in Table 3 were calculated by dissection of the overall rate constants into those corresponding to pathways AE_n and AE_a on the basis of the relative amounts of the two products in Tables 1 and 5.

In Table 4 it was assumed that the overall rate constants of 4- and 5-iodobenzofurazan in MeOH relate exclusively to pathway *b*, while in the case of 4-bromo- in MeOH and 4-bromo-, 4-iodo-, and 5-iodo-benzofurazan in MeOD, rate coefficients k_{total} were once again dissected into the portions corresponding to each pathway (*a* and *b*). In this case the relative percentages of the two pathways were established from the yields of the 'normal' and '*cine*' substitution products (Tables 1 and 5), taking into account the share of normal substitution derivative resulting from 'elimination–addition' *b*. This in turn was calculated by using the 4-methoxy : 5-methoxy ratios (0·3) observed in the reactions of iodobenzofurazans in MeOH.

From the pseudo-first order, the second order rate constants were obtained. The experimental error, when $k_{total} = k_a$ or k_b was $\pm 3\%$, while in the other cases it was $\pm 5\%$, since these values are subject to the experimental error of the n.m.r. measurements. The probable errors for E_a and $\Delta S^{\ddagger}$ are $\pm 0{\cdot}5$ kcal mol^{-1} and $\pm 1{\cdot}5$ cal mol^{-1} K^{-1} respectively.

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