Nucleophilic Reactivity of Methoxide Ion at C-5 of 4-Nitro-7-X-benzofurazans: a Kinetic and Thermodynamic Investigation of Meisenheimer Complexes

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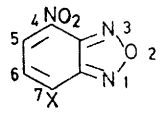
A kinetic and thermodynamic investigation of the Meisenheimer complexes formed at C-5 of 4-nitro-7-X-benzofurazans has been carried out. The results indicate some influence of resonance stabilization in the ground state due to cross-conjugation between X and the nitro- and (aza-) groups, the observed maximum rate lowering factor being *ca.* 5 for X = OMe. However the importance of repulsive interactions in the transition state between the linked group and the nucleophile is recognized. The conclusions are compared with some suggestions previously made for analogous complexes in trinitrobenzene.

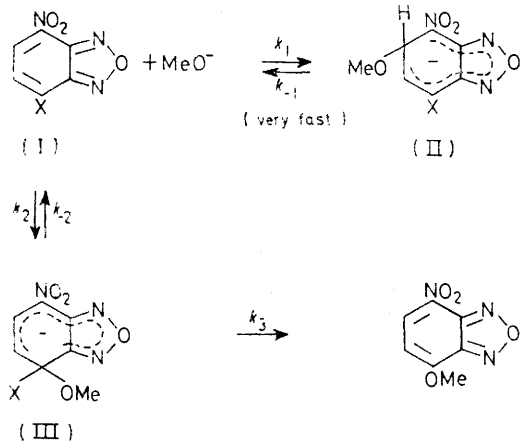
In a previous communication [1] we reported results on the reactivity of 4-nitro-7-halogenobenzofurazans (I) with MeO^- in MeOH. In all cases the reaction afforded the



X = F, Cl or Br

(I)

expected substitution derivative, 4-nitro-7-methoxybenzofurazan, apparently through a direct nucleophilic attack on C–Hal, the proposed mechanism being S_NAr-like, class A in Bunnett's classification.[2] However, this attack has been shown to be preceded by an anologous attack on C–H adjacent to $C-NO_2$ which affords a stable σ-anionic complex (see Scheme).



SCHEME

Faster nucleophilic reaction on C–H than on a substituted carbon is not new. For instance, in the reaction of 2,4,6-trinitroanisole with MeO^- in MeOH at 25°,[3] the rate constants for attack on C–H and on C–OMe (both affording Meisenheimer complexes analogous to the postulated intermediates of activated nucleophilic aromatic substitutions) are 950 and 17.3 l mol^{-1} s^{-1} respectively; this has been tentatively interpreted by Bernasconi as mainly due to the different loss of resonance stabilization (connected with conjugation between the methoxy- and nitro-groups) going from the ground to the transition state of each Meisenheimer complex. The importance of this conjugation has also been recognized by Illuminati [4] for nucleophilic substitution in 4-halogeno-2-X- and 2-halogeno-4-X-quinolines.

In the case of the benzofurazan system the available kinetic data for the nucleophilic reactions with methoxide ion suggest (see Discussion section) that the factor mainly responsible for the lower nucleophilic reactivity of C–X than C–H is presumably the higher repulsive interaction between X and the nucleophile in the transition state rather than the loss of resonance stabilization. However some decrease of reactivity connected with greater stabilization of the ground state in the case of C–X (X being capable of conjugation with the nitro- and aza-groups) cannot in principle be excluded. In order to attempt an approximate evaluation of its importance, kinetic data related to the formation of Meisenheimer complexes on C-5 of a large number of 4-nitro-7-X-benzofurazans would be helpful. We have therefore extended the investigations to 4-nitro-7-methoxy- and to a number of other 4-nitro-7-X-benzofurazans.

RESULTS

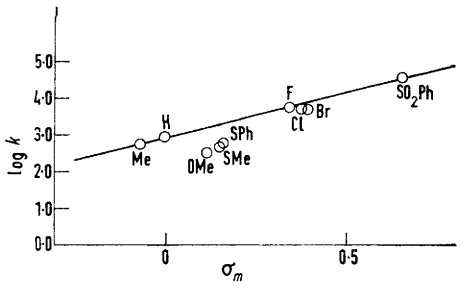
The rate constants of the preliminary reversible transition of unsubstituted, 7-methoxy-, 7-methylthio-, 7-phenylthio-, 7-methyl-, and 7-phenylsulphonyl-4-nitrobenzofurazan with MeO^- in MeOH at 25° have been measured (stopped-flow apparatus) under pseudo-first-order conditions (MeO^- in large excess over the benzofurazan) and by using the kinetic equation (1) [5] where $k_{1\,obs}$, k_1, and k_{-1} are the observed

$$k_{1\,obs} = k_1[MeO^-] + k_{-1} \qquad (1)$$

pseudo-first-order, the forward second-order, and the reverse first-order kinetic constants, respectively. The first transition has been shown previously [1] to correspond to the formation of the Meisenheimer complex on the carbon adjacent to $C-NO_2$ in the case of 4-nitro-7-chlorobenzofurazan; this has now been confirmed for 4-nitro-7-methylbenzofurazan. Further, such a complex has been postulated by Mallory

[1] D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *Chimica e Industria*, 1971, **53**, 940.
[2] J. F. Bunnett, *Ann. Rev. Phys. Chem.*, 1963, **14**, 217; J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968; F. Pietra, *Quart. Rev.*, 1969, **23**, 504.
[3] C. F. Bernasconi, *J. Amer. Chem. Soc.*, 1971, **93**, 6975.
[4] G. Illuminati, *Adv. Heterocyclic Chem.*, 1964, **3**, 285.
[5] V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1964, 1687; see also ref. 3.

and Varimbi [6] to account for the formation of the 4-chloro-5-methoxybenzofurazan when 4-nitrobenzofurazan is treated



log k–σ_m Relationship for variation of X in addition of methoxide ion to 4-nitro-7-X-benzofurazans

with sodium hypochlorite in MeOH. Analogous behaviour is expected in the other cases. In Table 2 the kinetic data corresponding to methoxydehalogenation (or to Meisenheimer complex formation) of 4-nitro-5-X-benzofurazans with MeO^- in MeOH at 25° are reported.[7]

pectively. Similarly, for the 4-nitro-7-X-benzofurazans, for X = OMe, F, Cl, and Br, k at 25° is 14.5, 3 500, 7.7, and 2.0 l mol^{-1} s^{-1} respectively. In both series the sequence of reactivity seems to be opposite to that expected on the basis of a loss of resonance stabilization. In fact, fluoro- and methoxy-derivatives are more reactive than the corresponding chloro- and bromo-derivatives, while they are presumably more stabilized by resonance in the ground state because of their higher conjugation ability.[8]

The observed sequence seems mainly connected with the extent of repulsive interactions between X and the nucleophile in the transition state, since the reactivity decreases when the size of the group increases (for instance, for the halogeno-derivatives, F ≫ Cl > Br). This differing reactivity of the halogeno-derivatives cannot be attributed, as is common, to differing positive character of the carbon site of reaction due to the electronegativities

TABLE 1

Kinetic and thermodynamic constants for the reactions of 4-nitro-7-X-benzofurazans with MeO^- in MeOH at 25°

X	k_1/ l mol^{-1} s^{-1}	k_{-1}/s^{-1}	$K_{e'}$ ($=k_1/k_{-1}$)/ l mol^{-1}	k_2/ l mol^{-1} s^{-1}	k_{-2}/s^{-1}	$K_{e''}$ ($=k_2/k_{-2}$)/ l mol^{-1}	σ_m	λ/nm
H	900	10	90				0	330
Me	580	36	16.1				−0.069	335
OMe	350	16	22	14.5 *	7.1 × 10^{-3} *	2 050 *	+0.115	337
SMe	490	10	49				+0.15	415
SPh	520	9.6	54				(+0.15)	410
F *	5 800	2.5	2 300	3 500			+0.337	330
Cl *	5 100	1.8	2 800	7.7			+0.373	340
Br *	5 200	3.8	1 300	2.0			+0.391	342
SO_2Ph †	43 000	≃3	≃14 300				(+0.60)	345

* Data from ref. 1. † k_2 Value is not reported since the product corresponding to the substitution of the nitro-group has been isolated in this case.

TABLE 2

Kinetic and thermodynamic constants * for the reactions of 4-nitro-5-X-benzofurazan with MeO^- in MeOH at 25°

X	k_1/l mol^{-1} s^{-1}	k_{-1}/s^{-1}	K_e ($=k_1/k_{-1}$)/ l mol^{-1}
OMe	147	116 × 10^{-3}	1 300
Cl	69		
Br	40		

* Data from ref. 7.

DISCUSSION

Kinetic constants corresponding to 5,5- and 7,7-dimethoxy Meisenheimer complexes from 4-nitro-5-methoxy- and 4-nitro-7-methoxy-benzofurazan respectively with MeO^- in MeOH can be compared with those for methoxydehalogenation, in the same solvent, of 4-nitro-5-halogeno- and 4-nitro-7-halogeno-benzofurazans, since the rate-determining step in the latter has been reported to be the formation of Meisenheimer-like intermediates. This comparison indicates that the reactivity sequence is not dependent on the loss of resonance stabilization (involving the halogens or methoxy-group and nitro- and aza-groups) going from the ground to the transition state. For the 4-nitro-5-X-benzofurazans at 25° we observe k 147, 69, and 40 l mol^{-1} s^{-1} for X = OMe, Cl, and Br respectively. If this had been the case, a similar variation in reactivity would be expected for each halogenobenzofurazan when C–Hal is not directly involved (*e.g.*, for nucleophilic reactions on the carbon adjacent to $C-NO_2$ affording the Meisenheimer complexes); this has not been observed.

Further confirmation can be drawn by the comparison of the kinetic constant corresponding to C-5 Meisenheimer complex formation from 4-nitrobenzofurazan with those for methoxydehalogenation of 5-chloro- and 5-bromo-4-nitrobenzofurazan.

In fact, the observed rate constants (at 25° k 900, 69, and 40 l mol^{-1} s^{-1} for H, Cl, and Br respectively) indicate that the reactivity on C–H is much higher than on both C–Cl and C–Br, while the positive character of the carbon in the case of C–H is certainly less marked than for C–Cl and C–Br.

On the other hand the lower nucleophilic reactivity of C–X than of C–H could be due also to loss of resonance stabilization in the case of C–X. However, this is difficult to assess by considering the rate constants directly related to C–X as the site of reaction, since in this case the repulsive interactions and the eventual resonance stabilization factor would be superimposed.

In the case of 4-nitro-7-X-benzofurazans, comparison

[6] F. B. Mallory and S. P. Varimbi, *J. Org. Chem.*, 1963, **28**, 1656.

[7] D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio, and P. E. Todesco, *J. Chem. Soc.* (*B*), 1971, 2209.

[8] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 1969.

of the nucleophilic reactivity of C-5 of a series of X-derivatives seemed a useful alternative approach. In fact for all the X-derivatives considered the site of reaction is invariably at C–H (*i.e.*, the repulsive interactions with the nucleophile are not changing), while the loss of resonance stabilization involving X on going from the ground to the transition state would presumably be similar to that expected for direct attack on C–X, at least because of the quinonoid character of the benzofurazan system.[9]

The examination of rate constants (k_1 in Table 1) allows the following considerations. (1) As expected, electron-withdrawing groups increase, while electron-donating groups (*e.g.* Me) decrease the reactivity with respect to the unsubstituted compound. (2) Some derivatives (namely OMe, SMe, and SPh) are appreciably less reactive than 4-nitrobenzofurazan while they would be expected to react faster on consideration of the relative position of X with respect to the site of reaction (*i.e.*, *meta*; the reported σ_m values [10] for the same groups are positive). The functions in which no cross-conjugation with nitro- and aza-groups is possible (*i.e.*, X = H, Me, and SO_2Ph) are satisfactorily correlated by means of the usual σ_m values * of X.[10] If the anomalous behaviour of OMe, SMe, and SPh is assumed to be connected with greater stabilization of the ground state, the deviation of the observed reactivity can reasonably be considered a measure of the effective importance of cross-conjugation in each case. The calculated deviation reaches a maximum in the case of the methoxy-derivative (rate lowering *ca.* 5), while for SMe and SPh it is appreciably smaller. Finally, in the case of halogeno-derivatives, no deviation is observed.

This confirms that the lower reactivity of C–Cl and C–Br relative to C–H can almost completely be attributed to the repulsive factor. On the other hand, both the repulsive interactions and the loss of resonance stabilization are responsible for the lower nucleophilic reactivity of C–OMe than C–H, as shown by the relative reactivities of C-5 in 4-nitro-5-methoxy- and 4-nitro-7-methoxy-benzofurazan. Similar considerations would also be valid for 2,4,6-trinitroanisole.[3] The observed ratio $[k(\text{C–H})/k(\text{C–OMe})]_{25} = 55$ for trinitroanisole would presumably be due both to resonance stabilization and repulsive interaction factors.

This hypothesis is also suggested by the fact that the loss of resonance stabilization is not very different for both attack on C–OMe and on C–H, since the negative charge introduced by the nucleophile would considerably reduce cross-conjugation in any case. Further support is finally given by the appreciably lower value of the ratio $k_{1,3,5\text{-trinitrobenzene}}/k_{(\text{OH})\text{ trinitroanisole}}$ (= 7.4 at 25°), where a different loss of resonance stabilization is clearly involved, but the size of the group linked to the site of reaction (and hence the repulsive interaction with the nucleophile) is unchanged (both attacks occurr on C–H).

On the other hand, no conclusions can be made on the reverse kinetic constants of the C-5 Meisenheimer complexes (from 4-nitro-7-X-benzofurazans) (k_{-1} in Table 1). In fact k_{-1} values (and hence $K_{c'} = k_1/k_{-1}$) are not sufficiently accurate to allow detailed discussion (see Experimental section). However, the observed trend for k_{-1} seems to be opposite to that of the k_1 values, which is obviously in agreement with the fact that σ-anionic complexes are stabilized by electron-withdrawing groups.

EXPERIMENTAL

M.p.s were determined on a Kofler apparatus and are uncorrected. Microanalyses were made an a Hewlett–Packard C, H, N analyser by Mrs. R. De Leonardis, Institute of Pharmaceutical Chemistry, Bari. ^{1}H N.m.r. spectra were recorded on Varian HA-100 and JEOL minimar JNM–MH–60 II instruments.

Materials.—Methanol (RP–ACS; Carlo Erba) for kinetic experiments was purified following the standard procedures. [$^2H_4$]Methanol, $(CD_3)_2CO$, C_6D_6, and CCl_4 for n.m.r. measurements were good commercial products. 4-Nitro-, m.p. 97—98° (lit.,[11] 93,[12] 98°), -7-methoxy-, m.p. 115—116°,[13] -7-phenylthio-, m.p. 157°,[11] -7-fluoro-, m.p. 52.5—53.5°,[14] and -7-chloro-benzofurazan, m.p. 96.5—97°,[11,15] were synthesized as previously described. *7-Bromo-4-nitrobenzofurazan*, m.p. 96—97°, was prepared following the procedure for 7-chloro-4-nitrobenzofurazan, starting from 4-bromobenzofurazan [7] (Found: C, 29.35; H, 0.7; N, 16.8; Br, 32.55. $C_6H_2BrN_3O_3$ requires C, 29.55; H, 0.85; N, 17.2; Br, 32.75%). *4-Nitro-7-phenylsulphonylbenzofurazan*, m.p. 204—205°, was synthesized by oxidation of 4-nitro-7-phenylthiobenzofurazan with peracetic acid (Found: C, 46.6; H, 2.65; N, 13.55; S, 10.3. $C_{12}H_7N_3O_5S$ requires C, 47.2; H, 2.3; N, 13.75; S, 10.5%), τ $(CD_3)_2CO$ 1.7—2.5 (5 H, ArH) and 1.16 and 1.38 (2 H, AB, J_{AB} 8 Hz). *7-Methylthio-4-nitrobenzofurazan*, m.p. 122—123°, was synthesized by method H of Ghosh [11] (methanol instead of ethanol in our case), τ (C_6D_6) 2.4, 4.2, and 8.3 (AMX_3, J_{AM} 8 Hz) (Found: S, 15.1. $C_7H_5N_3O_3S$ requires S, 15.2%).

N.m.r. Detection of Meisenheimer Complexes.—The Meisenheimer complex at C-5 of 4-nitro-7-chlorobenzofurazan has been previously [1] detected as a transient species. The n.m.r. spectrum, τ (CD_3OD) 1.42 and 2.18 (AB, J_{AB} 8 Hz), was recorded and $^-OCD_3$–CD_3OD (1 equiv.) was added giving τ 3.39 and 4.39 (AX, J_{AX} 6 Hz). The spectrum progressively changed to τ 2.70 and 4.47 (AX, J_{AX} 10 Hz), corresponding to the 7,7-dimethoxy-complex (III; X = OMe), and finally to τ 1.35 and 3.05 (AX, J_{AX} 8 Hz), corresponding to (I; X = OMe). Similar experiments were carried out on 7-chloro-5-deuterio-4-nitrobenzofurazan synthesized from 2,6-dichloro-4-deuterioaniline which was obtained by hydrolysis of 3,5-dichlorosulphanilamide by treatment with

* The unknown σ_m for SO_2Ph and SPh have been assumed to be not very different from the corresponding values for SO_2Me and SMe respectively.

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[14] L. Di Nunno, S. Florio, and P. E. Todesco, *J. Chem. Soc.* (*C*), 1970, 1433.

[15] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1966, 1004.

D_2O–D_2SO_4. The spectrum of 7-chloro-5-deuterio-4-nitrobenzofurazan in [$^2H_4$]methanol [τ 2.18 (t, J_{HD} *ca.* 1 Hz)] after CD_3O^- is added is shifted upfield (τ 3.40) and subsequently changes in a manner corresponding to that described above (first τ 4.49, then τ 3.05). From the experiments structure (II) was assigned to the first transient species by considering both the larger upfield shift of 5-H with respect to 6-H (due to the carbon sp_2—sp_3 hybridization change) and the lowering of $J_{5,6}$ (due to the subsequent dihedral angle change). An analogous $J_{5,6}$ lowering is observed in the first species detected when $^-OCD_3$ is added to 4-nitro-7-methylbenzofurazan and can be interpreted similarly. After *ca.* 15 min. a new spectrum is recorded, corresponding to hydrogen abstraction from the methyl group.

Rate Measurements.—Kinetic experiments were carried out in methanol at 25° using a thermostatted Gibson–Durrum stopped-flow apparatus and at the wavelengths indicated in Table 1. The experimental error for k_1 values [from equation (1)] is $\pm 5\%$, while in the case of k_{-1} it is much larger and variable, depending on the magnitude of the slope ($=k_1$) and on k_{-1} itself.

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