σ-Complexes as Biochemical Probes. Part 1. σ-Complex Formation by 7-Methoxy-4-nitrobenzofurazan 1-Oxide

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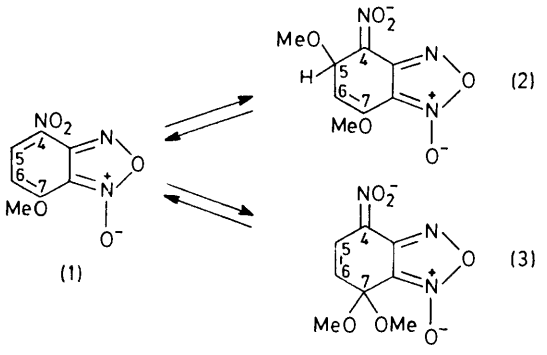
The reaction of 7-methoxy-4-nitrobenzofurazan 1-oxide with methoxide ion in dimethyl sulphoxide–methanol (or in dimethyl sulphoxide–methanol–chloroform) gives rise to a kinetically controlled C-5 adduct and a thermodynamically controlled C-7 adduct. Some unusual features in the n.m.r. spectra are discussed.

THE proposal [1-3] that the antileukaemic activity of cetain benzofurazan derivatives may be related to their tendency to form σ-complexes of the Meisenheimer type has made it pertinent that such complexes be adequately characterized. We have therefore extended our studies [4-10] of the σ-complexes formed from the interaction of aromatic nitro-compounds with bases to the benzofurazan series. Related studies have been reported from other laboratories.[11-14] We report here the interaction of 7-methoxy-4-nitrobenzofurazan 1-oxide (1)



with methoxide ion; evidence is given for the formation of the σ-complex (2), which is kinetically preferred but unstable, and the σ-complex (3), which is the thermodynamically preferred product. This appears to be the first case of a σ-complex formed from a benzofurazan *N*-oxide derivative which is isolable and thus available for further study.†

The reaction of compound (1) with sodium methoxide in dimethyl sulphoxide–methanol, at room temperature, was found by ^{1}H n.m.r. spectroscopy to yield only the 7,7-dimethoxy-adduct (3). Thus, the spectrum of a solution of (1) (0.30M) and sodium methoxide (0.34M) in $(CD_3)_2SO$–MeOD (80 : 20 v/v), taken some minutes after mixing, showed the absence of signals characteristic of (1) and new signals ascribable to (3) [δ 7.35 (1 H, d, *J* 11 Hz, H-5), 5.12 (1 H, d, *J* 11 Hz, H-6), and 3.12 (6 H, s, 2 OMe)]. The σ-complex (3) was prepared and isolated by a modified method (Experimental section) and was fully characterized.

Evidence for formation of the σ-complex (2) was obtained when the experiment was performed at lower temperature. A solution of the substrate (1) (0.2 mmol) in $(CD_3)_2SO$–MeOD (70 : 30 v/v; 0.4 ml) in an n.m.r. tube was placed inside the cooled (−15 °C) probe of the n.m.r. instrument, and a cooled solution (0.2 ml) of sodium methoxide (1.0M) in $(CD_3)_2SO$–MeOD (70 : 30 v/v) was added. The spectrum showed a peak at δ 5.48 in addition to the signals at δ 7.35 and 5.12 previously ascribed to (3). On continued scanning the δ 5.48 signal

† The σ-complexes formed in the interaction of 4-nitrobenzofurazan 1-oxide with methoxide ion in dimethyl sulphoxide–methanol are unstable.[13,15]

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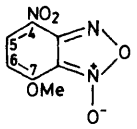
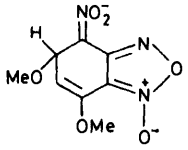
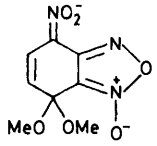
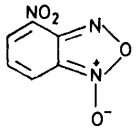
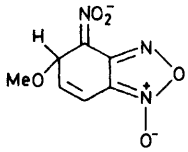
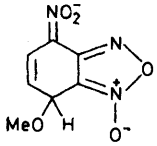
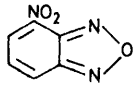
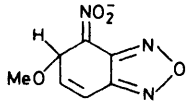
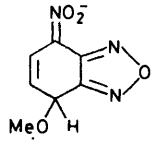
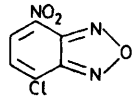
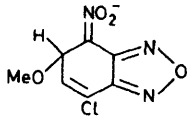
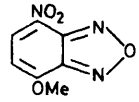
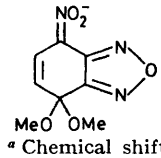
N.m.r. parameters of σ-complexes in the benzofuroxan and benzofurazan series

	MeO	H-5	H-6	Δ(H-5) [a]	Δ(H-6) [a]	$J_{5,6}$/Hz	Solvent	Ref.
	4.13	8.61	6.81			8	$(CD_3)_2SO$	This work
	4.15	8.42	6.43			8	$CDCl_3$	
	3.68 [b]	5.48	5.48	3.13	1.33		$(CD_3)_2SO$–CD_3OD	
	3.78 [b]	5.12	5.45	3.30	0.98	5	$CDCl_3$–$(CD_3)_2SO$–CD_3OD	
	3.12	7.35	5.12	1.26	1.71	11	$(CD_3)_2SO$–CH_3OD (or CD_3OD)	
	3.23 [b]	7.33	5.28	1.29	1.15	11	$CDCl_3$–$(CD_3)_2SO$–CD_3OD	
		8.62	7.55			7	$(CD_3)_2SO$	13
	[c]	5.47	6.38	3.15	1.20	5	$(CD_3)_2SO$–CH_3OD	13
	[c]	7.14	5.34	1.48	2.21	10	$(CD_3)_2SO$–CH_3OD	13
		8.70	7.88			7	$(CD_3)_2SO$	13
		5.50	6.53	3.20	1.35	5	$(CD_3)_2SO$–CH_3OD	13
		7.16	5.13	1.54	2.75	10	$(CD_3)_2SO$–CH_3OD	13
		8.58	7.82			8	CD_3OD	12
	[b]	5.60	6.60	2.98	1.22	6	CD_3OD	12
	4.22	8.73	7.07			8	$(CD_3)_2SO$	12
	3.28	7.32	5.32	1.42	1.75	11	$(CD_3)_2SO$–CH_3OD	12

[a] Chemical shift differences between parent substrate and complex. [b] Complex prepared by using CD_3ONa–CD_3OD, *i.e.* coordinating methoxy-group is deuteriated. [c] Experiments performed in 70 : 30 (v/v) $(CD_3)_2SO$–CH_3OD (obscuring the region of the methoxy-peak).

decreased in intensity and eventually disappeared completely, leaving only the peaks due to the complex (3). In this medium, the region where the methoxy-protons of the complex appear was obscured by the methanol peak (the increase in CH_3OD content over that in the previous experiment was necessary to avoid freezing of the solution at the lower temperature). Therefore the next series of experiments was performed with CD_3OD.

The reaction of compound (1) with CD_3ONa in $(CD_3)_2SO$–CD_3OD (70 : 30 v/v) was performed at −15 °C. The initial spectrum, recorded within 1 min of mixing, exhibited a sharp peak at δ 3.68 as well as the previously observed peak at δ 5.48, with an integral ratio of *ca.* 3 : 2. A second spectrum taken 5 min after mixing showed, in addition to the above mentioned signals, new signals at δ 3.12, 5.12, and 7.35 characteristic of the complex (3). The signals due to (2) began to decrease 25 min after mixing and this process became accelerated when the temperature was allowed to rise to −10 °C (10 min). On increasing the temperature to 0 °C (10 min) the signals due to (2) disappeared completely and only the signals due to (3) remained. The δ 3.68 peak can reasonably be assigned to the 7-methoxy-group in the adduct (2), and the δ 5.48 peak to the adventitiously equivalent H-5 and H-6 (see later).*

Our identification of the complex (2) was confirmed when it was noted that in $CDCl_3$ as solvent the H-5 and H-6 signals of (1) experience appreciable shifts relative to solutions in dimethyl sulphoxide–methanol. This solvent effect was utilized in the following experiment. To a solution of compound (1) (0.14 mmol) in $CDCl_3$ (0.6 ml) at −15 °C, in the n.m.r. tube situated in the probe of the spectrometer, was added a solution (0.14 ml) of CD_3ONa (1M) in $(CD_3)_2SO$–CD_3OD (70 : 30 v/v). The spectrum taken after 4 min exhibited a doublet centered at δ 5.12 (*J* 5 Hz), another centred at 5.45 (*J* 5 Hz), and a singlet at 3.78. These correspond to structure (2), with the two doublets assignable to H-5 and H-6, whereas the δ 3.78 signal corresponds to the methoxy-group at C-7. The spectrum was relatively stable for *ca.* 30 min at −15 °C, but on gradually raising the temperature to 0 °C the signals characteristic of adduct (3) began to appear until at 10 °C (25 min) only the adduct (3) was present.

For comparison with related systems, we summarize in the Table the n.m.r. parameters of a number of complexes in the benzofurazan 1-oxide and benzofurazan series. The data represent all the complexes reported to date in which addition of OMe at C-5 has been found to give a metastable adduct; the thermodynamically preferred complex is the C-7 methoxy-adduct for which the n.m.r. parameters are included. The data show that in formation of the C-5 adduct the H-5 signal experiences an upfield shift of 3.1—3.3 p.p.m., whereas that of H-6 experiences an upfield shift of 1.0—1.3 p.p.m. This accounts for the coincidence of the H-5 and H-6 signals in the spectrum of the complex (2) in dimethyl sulphoxide–methanol. In the chloroform-containing medium the solvent effect on the chemical shifts enabled the H-5 and H-6 signals to be resolved. Thus the formation of a kinetically and a thermodynamically controlled complex [16–18] from 7-methoxy-4-nitrobenzofurazan 1-oxide has been confirmed.

The stability of the 7-methoxy-adduct from 7-methoxy-4-nitrobenzofurazan 1-oxide contrasts with the case of the parent 4-nitrobenzofurazan 1-oxide, the 7-methoxy-adduct of which undergoes subsequent decomposition.[13,15] Relative to a hydrogen atom, the methoxy-substituent has been found to increase the equilibrium constant in σ-complex formation [19,20] (*e.g.* for methoxide addition to 2,4,6-trinitroanisole *vs.* 1,3,5-trinitrobenzene, in methanol at 25 °C, the K_{eq} ratio is *ca.* 100 : 1). However, in addition to the thermodynamic factor, it appears that in the present case the contrast in chemical reactivity is related to structural factors; these will be further investigated.

EXPERIMENTAL

The deuteriated solvents [$(CD_3)_2SO$, CH_3OD, and CD_3OD] were dried over molecular sieves. The sodium methoxide solutions were prepared from freshly cut sodium metal and CH_3OD (CD_3OD), and standardized before use. 7-Methoxy-4-nitrobenzofurazan 1-oxide, m.p. 163°, was prepared by nitration of 5-methoxybenzofurazan 1-oxide with acetic anhydride–nitric acid (*cf.* ref. 21) followed by the Boulton–Katritzky rearrangement [22,23] of the 5-methoxy-4-nitrobenzofurazan 1-oxide produced. A Bruker 60 MHz HFX-60 instrument was used for the n.m.r. measurements, with tetramethylsilane as internal standard.

7-Methoxy-adduct (3) *of 7-Methoxy-4-nitrobenzofurazan 1-Oxide* (1).—To a solution of the furazan (1) (506 mg, 2.40 mmol) in acetonitrile (5.3 ml) was added, with stirring, methanolic sodium methoxide (3.2M; 0.75 ml). After the reaction the solvent was evaporated off and the solid residue was washed repeatedly with acetonitrile and then dried *in vacuo*. The complex showed $\lambda_{max.}$ 363 nm (ε 24 400 l mol^{-1} cm^{-1}) in Me_2SO–MeOH (80 : 20 v/v), in agreement with the values obtained when the complex was prepared *in situ* from equimolar solutions of the substrate and sodium methoxide over a range of concentrations; $\nu_{max.}$ 1 470 (asym. NO_2 str.) and 1 250 cm^{-1} (sym. NO_2 str.), shifted from 1 545 and 1 300 cm^{-1} in the substrate; δ[$(CD_3)_2SO$] 7.30 (d, *J* 11 Hz, H-5), 5.00 (d, *J* 11 Hz, H-6), and at 3.10 (OMe). Acidification resulted in quantitative regeneration of starting material (1).

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* Attempts to separate the H-5 and H-6 resonances by use of shift reagents were unsuccessful in this solvent system.

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