Role of Addition Compounds in the Halogenation of Benzofurans and Benzothiophens

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The bromination of benzofuran and its 2-methyl, 3-methyl, and 2,3-dimethyl derivatives and the chlorination of 2,3-dimethylbenzothiophen were investigated in CS_2 at −40 and −50° by n.m.r. spectroscopy. In all cases the formation of an adduct between the halogen and the heteroaromatic derivative is observed. Decomposition of the adduct leads to ring halogenated products with benzofuran and the monomethylbenzofurans, and to side-chain halogenated compounds with the 2,3-dimethyl derivatives. These results are discussed in terms of mechanism of both conventional and non-conventional electrophilic aromatic substitution.

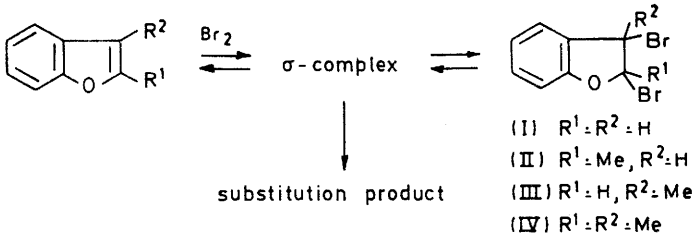
NON-CONVENTIONAL electrophilic aromatic reactions of alkylaromatic compounds are the object of continuing interest.[1,2] Our research is presently directed to the study of the side-chain electrophilic halogenation of alkyl derivatives of heteroaromatic compounds.[3,4] In particular we are interested in defining the possible role of addition compounds in the reaction mechanism.

In a study of the side-chain chlorination of 2,3-di-

[1] S. R. Hartshorn, *Chem. Soc. Rev.*, 1974, **3**, 167.
[2] A. Fisher and J. N. Ramsay, *Canad. J. Chem.*, 1974, **52**, 3960.
[3] E. Baciocchi and L. Mandolini, *J. Chem. Soc.* (*B*), 1968, 397.
[4] E. Baciocchi, S. Clementi, and G. V. Sebastiani, *J.C.S. Perkin II*, 1974, 1882.

methylbenzothiophen [3] kinetic evidence clearly indicated a fast reaction between chlorine and the aromatic compound leading to the formation of a stable adduct, the most probable structure of which was considered to be that of an addition compound at the 2,3-double bond. It was suggested that this adduct could be a reaction intermediate *en route* to the side-chain substitution products.

However, subsequent results on the side-chain halogenation of 2,3-dimethylbenzofuran [4] indicated that this reaction substantially takes place without the intermediacy of an addition compound of the halogen at the 2,3-double bond. This conclusion appeared surprising since it is well known that benzofuran should form addition products much more easily than benzothiophen. In order to clarify the apparent contrast between the results of these two halogenation reactions we have undertaken a low temperature n.m.r. study on the molecular bromination of benzofuran and its 2-methyl, 3-methyl, and 2,3-dimethyl derivatives. The reaction of chlorine with 2,3-dimethylbenzothiophen has also been investigated. The aim of this work was to observe whether addition compounds were formed and to study their conversion into the final products. The study could also provide interesting information on the general mechanism of halogenation of five-membered heteroaromatic substrates.



SCHEME 1

RESULTS AND DISCUSSION

The reaction of benzofuran with Br_2 to give the addition compound (I) is well known.[5] When the reactants were mixed in CS_2 in an n.m.r. tube placed in the probe at −40°, the appearance of the peaks characteristic of (I) was immediately observed. This adduct was recently shown to have a *trans*-structure.[6] The stability of (I) in solution and in the solid state is very high. No modification of the n.m.r. spectrum occurs on standing at room temperature for 72 h. At room temperature the adduct is insoluble in MeOH, but at *ca.* 40° the solid begins to dissolve and the MeOH solution turns yellow. The n.m.r. spectrum of this solution shows the simultaneous presence of benzofuran and (I). By cooling the solution the colour disappears and (I) again separates from the liquid. This result clearly indicates the existence of an equilibrium between (I) and benzofuran. The same equilibrium is also observed in AcOH at *ca.* 80°. In this solvent at 120° an irreversible reaction leading to 2-bromobenzofuran is observed.

The equilibrium between benzofuran and (I) presumably involves a σ-complex from which the substitution product may be formed by the irreversible loss of 2-H. The halogenation of benzofuran can therefore be described by Scheme 1, where (I) is formed in a side-equilibrium, without being involved in the direct pathway from the reagents to the final products. Direct elimination of HBr from the addition compound is unlikely since it would produce 3-bromobenzofuran because of the higher acidity of 3-H. Accordingly, 3-bromobenzofuran is known to be formed from (I) only in the presence of strong bases.[5]

The fact that, depending on temperature, we separately observe the exclusive formation of (I), the presence of the equilibrium between (I) and benzofuran, and the irreversible formation of the substitution product is related to the differences in activation energy of the three reactions which Br^- undergoes on the σ-complex: (i) attack at C-3 to give (I); (ii) attack at the Br atom to produce the starting materials; (iii) attack at 2-H to give the substitution product. Reaction (i) greatly predominates at room temperature. As the temperature increases reaction (ii) becomes competitive with (i) and the equilibrium between (I) and benzofuran is established. A further increase of temperature (AcOH, *ca.* 120°) makes process (iii) important, and since this process is irreversible the complete conversion of benzofuran and (I) into the substitution product is observed.

Scheme 1 also applies to the bromination, under the same conditions, of 2-methyl- and 3-methyl-benzofuran. At first the formation of the addition products (II) and (III) is observed, since the n.m.r. spectrum shows the heteroaromatic ring protons adsorbing at higher fields, whereas the signals of methyl protons fall at slightly lower field than in the substrate, as expected for an addition compound. Both (II) and (III) should have a *trans*-structure in agreement with the *trans*-structure of the adduct (I). The chemical shifts are listed in Table 1, and the variation in the n.m.r. spectrum of 2-methylbenzofuran is shown in Figure 1.

In the bromination of 3-methylbenzofuran peaks attributable (absence of 2-H) to the substitution product, 2-bromo-3-methylbenzofuran, are observed together with those of (III). This indicates a very fast conversion: after 15 min at −40° most of (III) is converted

[5] R. Stoermer and B. Kahlert, *Ber.*, 1902, **35**, 1633.
[6] T. Okuyama, K. Kunugiza, and T. Fueno, *Bull. Chem. Soc. Japan*, 1974, **47**, 1267.

into the substitution product. Decomposition of (II) into the corresponding substitution product, 2-methyl-3-bromobenzofuran, is much slower: after 1 h at −30° (II)

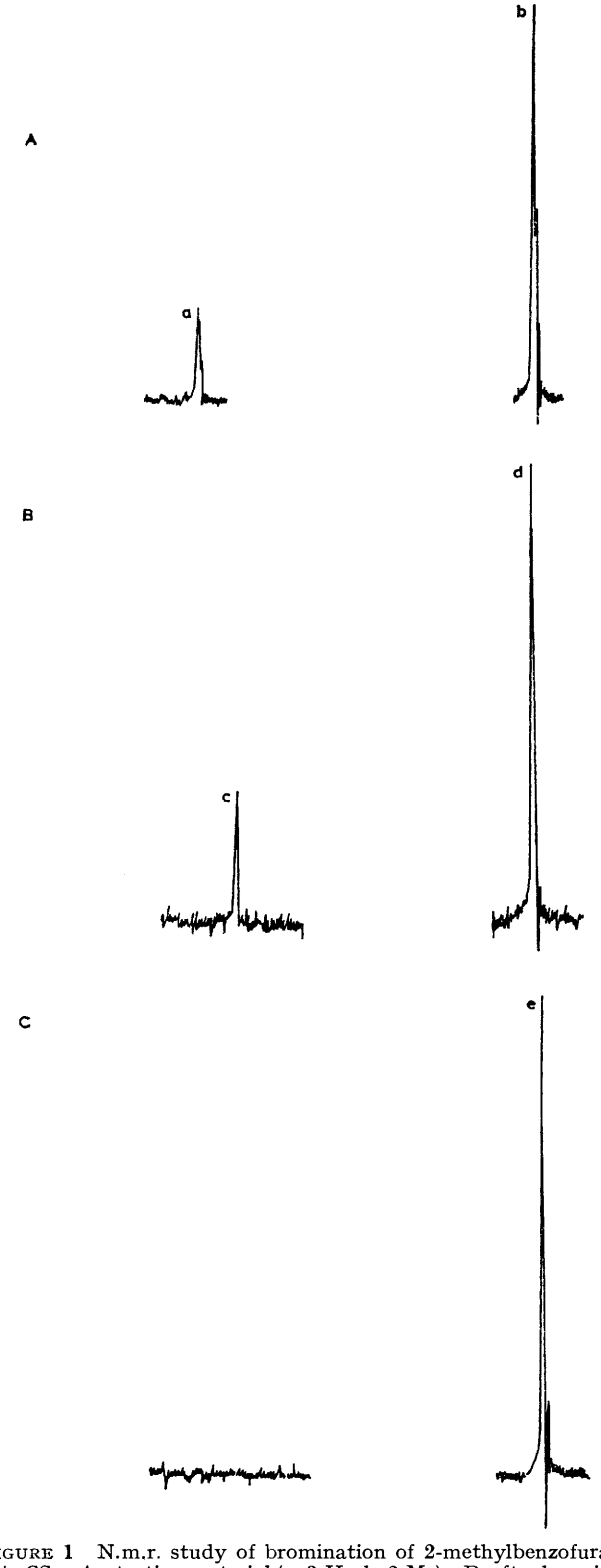


FIGURE 1 N.m.r. study of bromination of 2-methylbenzofuran in CS_2: A, starting material (a, 3-H; b, 2-Me); B, after bromine addition at −40° [c, 3-H and d, 2-Me of (II)]; C, after 1.5 h at room temperature (e, 2-Me of 2-methyl-3-bromobenzofuran)

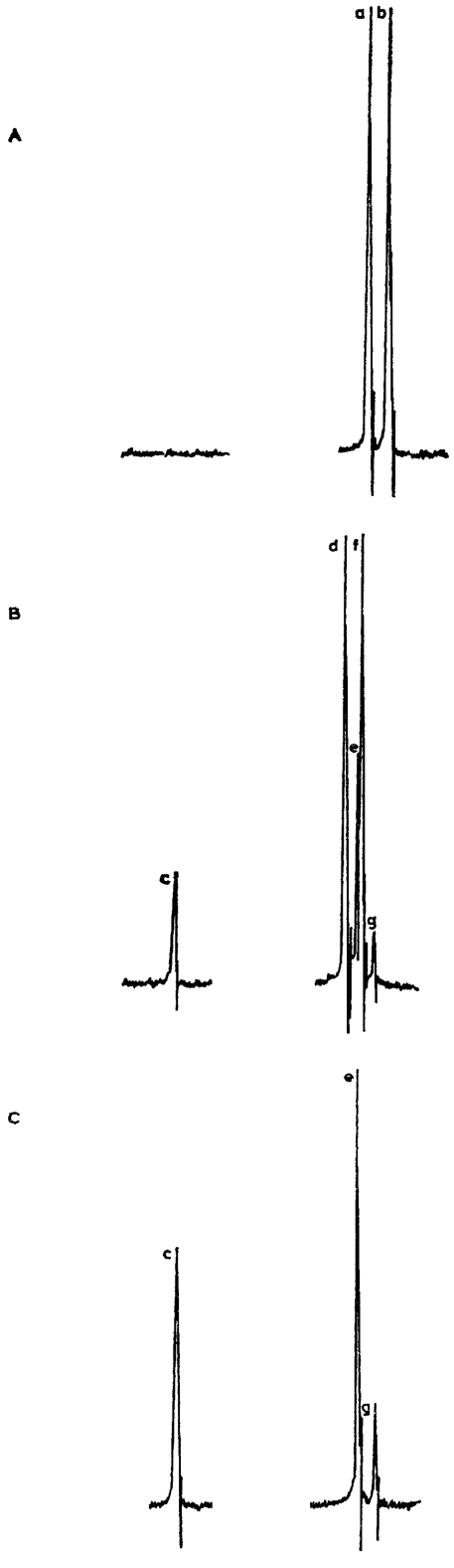


FIGURE 2 N.m.r. study of bromination of 2,3-dimethylbenzofuran in CS_2: A, starting material (a, 2-Me; b, 3-Me); B, after bromine addition at −40° [c, 2-CH_2Br of (V) and 3-CH_2Br of (VI); d, 2-Me of (IV); e, 2-Me of (VI); f, 3-Me of (IV); g, 3-Me of (V)]; C, after 45 min at −40°; letters identify signals as in B

is still the only species present in solution, whereas at 25° a rapid conversion takes place. Moreover the decomposition of both (II) and (III) can be estimated to be very much faster than that of (I).

Scheme 1 can qualitatively rationalize these observations when the relative stabilities of the σ-complexes and of the addition products are compared. The rate of conversion of the addition product into the substitution product increases as the stability of the σ-complex increases and as the stability of the addition compound decreases. Clearly, on the basis of the electrophilic reactivity of benzofurans,[7] the stability of the σ-complexes should increase in the order benzofuran ≃ 2-methylbenzofuran < 3-methylbenzofuran, whereas that of the adducts increases in the order 3-methylbenzofuran ≃ 2-methylbenzofuran < benzofuran, because of steric interactions. Actually, combination of these stability orders leads to the observed reactivity order (III) > (II) > (I).

In the reaction of 2,3-dimethylbenzofuran with Br_2 at −40° in CS_2 the addition product (IV) is immediately formed (Figure 2): the methyl protons resonate at lower field than in the starting material, as in (II) and (III) (see Table 1). The addition product (IV), for which a *trans*-structure is also supposed, undergoes extremely fast decomposition, and after 45 min at −40° the n.m.r. signals of (IV) are replaced by peaks which can be attributed to a 1 : 3.5 mixture of 2-bromomethyl-3-methylbenzofuran (V) and 3-bromomethyl-2-methylbenzofuran (VI). This result was confirmed by repeating the reaction under the same experimental conditions outside the n.m.r. tube and hydrolysing the crude mixture, as previously described,[4] to the corresponding hydroxymethyl derivatives.

TABLE 1

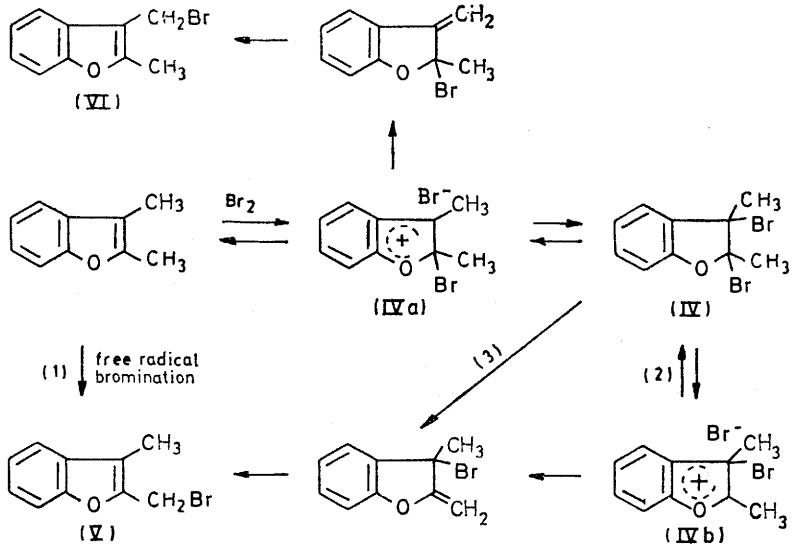
Bromination of heteroaromatic substrates in CS_2. N.m.r. chemical shifts (δ) for 2- and 3-substituents in the starting materials, adducts, and final products

	Starting compound	Addition compound	Final product
Benzofuran	7.40 (2-H), 6.56 (3-H) 7.62 (2-H), 6.75 (3-H) [a]	6.75 (2-H), 5.60 (3-H) 7.03 (2-H), 5.85 (3-H) [a]	6.54 (3-H) 6.70 (3-H) [a]
2-Methylbenzofuran	2.39 (2-Me), 6.25 (3-H)	2.46 (2-Me), 5.84 (3-H)	2.42 (2-Me)
3-Methylbenzofuran	7.29 (2-H), 2.20 (3-Me)	7.06 (2-H), 2.32 (3-Me)	2.16 (3-Me)
2,3-Dimethylbenzofuran	2.30 (2-Me), 2.09 (3-Me)	2.53 (2-Me), 2.35 (3-Me)	2.40 (2-Me), 4.50 (3-CH_2Br) 4.50 (2-CH_2Br), 2.20 (3-Me)
2,3-Dimethylbenzothiophen	2.42 (2-Me), 2.22 (3-Me)	2.15 (2-Me), 2.05 (3-Me)	4.65 (2-CH_2Cl), 2.32 (3-Me)

[a] In AcOH. [b] Chlorination.

These were analysed by g.l.c. obtaining a ratio of alcohols in agreement with that of the bromides derived from the n.m.r. study. Thus, there is no doubt that also the bromination of this substrate involves, in some way, the formation of an addition product to the 2,3-double bond.

Nevertheless, this conclusion is not inconsistent with the previous study,[4] where, on the basis of the prevailing formation of (VI), the addition compound (IV) was suggested not to be a reaction intermediate. A general picture for the bromination of 2,3-dimethylbenzofuran is shown in Scheme 2. The addition compound (IV) is formed in a side-equilibrium, and therefore is not an intermediate *en route* to the main product (VI).



SCHEME 2

The rate of decomposition of (IV) is very high and comparable with that of (III). This is qualitatively justified since (IV) is expected to be less stable than (III)

[7] S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc.* (*B*), 1971, 79.

because of one more eclipsing interaction between Me and Br, whilst the stability of the σ-complexes should be similar for 3-methyl- and 2,3-dimethylbenzofuran.

Scheme 2 indicates three possible routes for explaining the presence of a significant amount (*ca.* 30%) of (V) in the products. In the previous study [4] the direct free radical reaction on 2,3-dimethylbenzofuran, route (1), which competes with the prevailing electrophilic reaction, was indicated as the most probable. Further data supporting this conclusion have been obtained and are collected in Table 2. Attack at the 2-methyl group in

TABLE 2

Variation of the product distribution with the experimental conditions in the bromination of 2,3-dimethylbenzofuran

Solvent	T/°C	$[Br_2]$/M	(VI) : (V) [a]	Ref.
CS_2	20	0.06	0.03	*b*
CS_2	20	0.6	3.0	*b*
CS_2	−40	0.6	3.5	*b*
AcOH (dark)	20	0.06	3.2	4
AcOH	20	0.06	2.2	*b*
AcOH, 90%	20	0.06	200	*b*

[a] For explanation of symbols see text. [b] This work.

CS_2 is strongly favoured by dilution as expected for a reaction occurring by a free radical mechanism.[8] The (VI) : (V) product ratio is also influenced by the light since bromination in acetic acid gives a smaller (VI) : (V) ratio when carried out in daylight than in the dark. Finally, in aqueous acetic acid, where the ionic reaction is expected to be largely accelerated, nearly exclusive bromination at the 3-methyl group was observed.

Although no experimental evidence can be claimed to support a mechanism different from the free radical one, route (2) involving the formation of the σ-complex (IVb), from which (V) may be formed according to Scheme 2, cannot be excluded. This possibility was never taken into account in our previous discussion [4] since the α-position of benzofuran is usually much more reactive towards electrophiles than the β-position,[7] thus indicating a large energy difference between the transition states leading to (IVa and b). However, our present results now clearly indicate that addition compounds are involved in the bromination and these adducts, albeit formed in a side-equilibrium, can influence both kinetics and product distribution. In particular the difference in the activation energies for the formation of (IVa and b) from the decomposition of the adduct could be less than that for the reaction between bromine and substrate. Besides, the proton loss in the last step is favoured for (IVb) because of the higher acidity of protons of the 2-methyl group, thus compensating for the difference in the formation rate.

Route (3) seems to be the less probable in view of the results with unsubstituted benzofuran discussed above and of the experimental conditions which are not suitable for *E*2 reaction.

We also attempted an n.m.r. investigation of the reaction between chlorine and 2,3-dimethylbenzothiophen in CS_2 at −50°. After mixing the reactants the signals for the two methyl groups show an upfield shift (see Table 1). As the reaction mixture is warmed to room temperature these peaks are slowly replaced by peaks at δ 4.65 (CH_2) and 2.32 (CH_3) of 2-chloromethyl-3-methylbenzothiophen.

These findings indicate that the reaction between chlorine and 2,3-dimethylbenzothiophen involves the fast formation of an adduct between Cl_2 and substrate and are therefore in agreement with the results obtained in the kinetic study.[3]

The adduct is probably an addition product to the 2,3-double bond, since two shifted methyl groups are still present. The upfield shift is in agreement with that observed in the addition products formed between chlorine and 1-methylnaphthalene.[9,*] Therefore, it seems reasonable to suggest that the side-chain chlorination of 2,3-dimethylbenzothiophen occurs *via* a mechanism similar to that leading from 2,3-dimethylbenzofuran to (VI).

EXPERIMENTAL

Materials.—Benzofuran (Fluka; b.p. 173—175°) was a commercial sample distilled at atmospheric pressure. 2-Methylbenzofuran,[4] b.p. 188—190°, 2,3-dimethylbenzofuran,[4] b.p. 103—105° at 17 mmHg, and 2,3-dimethylbenzothiophen,[3] b.p. 123—124° at 10 mmHg, were available from previously related studies. 3-Methylbenzofuran,[11] b.p. 195—197°, 2-bromobenzofuran,[5] b.p. 221—223°, and 2,3-dibromo-2,3-dihydrobenzofuran,[5,6] m.p. 86—87° were prepared according to literature procedures. The n.m.r. spectrum of the latter compound was in agreement with previous data.[6] The side-chain-substituted bromomethyl derivatives of 2,3-dimethylbenzofuran are unstable and syntheses were unsuccessful. The corresponding hydroxymethyl derivatives, obtained by hydrolysis, were identified by comparison with authentic specimens.[4] The n.m.r. spectrum in CS_2 of 2-hydroxymethyl-3-methylbenzofuran showed peaks at δ 2.10 (3 H, s, 3-Me) and 4.45 (2 H, s, 2-CH_2OH), that of 3-hydroxymethyl-2-methylbenzofuran had δ 2.28 (3 H, s, 2-Me) and 4.45 (2 H, s, 3-CH_2OH).

Reactions reported in Table 2 were carried out as described in ref. 4. Solvents were purified as usual. Commercial halogens (Fluka) were used without further purification.

N.m.r. Studies.—N.m.r. spectra were determined on a JEOL C-60HL spectrometer with tetramethylsilane as internal standard. In general, a solution of the aromatic substrate in CS_2 (0.3 ml; *ca.* 1M) was put into an n.m.r.

* The downfield shift of the methyl signals in the addition products involving bromine can be explained by a negative magnetic anisotropy effect of the bromine atom of the proton chemical shift [10] The anisotropic contribution is known to decrease on passing from bromine to chlorine.[10]

[8] M. S. Kharasch, P. C. White, and F. R. Mayo, *J. Org. Chem.*, 1938, **3**, 33.
[9] G. Cum and P. B. D. de la Mare, *J. Chem. Soc.* (*C*), 1967, 1590.
[10] H. Spisecke and W. G. Schneider, *J. Chem. Phys.*, 1961, **35**, 722.
[11] C. C. Price, ' Organic Syntheses,' Wiley, New York, 1953, **33**, 43.

tube and placed in the probe of the spectrometer at −40°. An equivalent amount of molecular halogen in CS_2 at the same temperature (0.2 ml; *ca.* 1.4M) was added to the cold tube and the spectrum taken several times at intervals of *ca.* 5 min. The temperature of the probe was then raised in 10° increments and the spectrum again taken at each temperature. Chemical shifts are accurate to within 0.03 p.p.m.

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