Substituent Effects in the Benzofuran System. II.[1] Electrophilic Bromination

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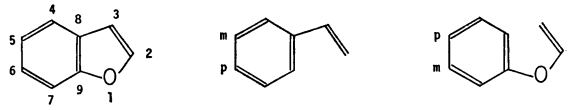
(Received August 7, 1973)

Bromination of benzofuran (BF) and its derivatives (5-CH_3, 6-CH_3, 5-CH_3O, and 5-Cl) has been studied kinetically in acetic acid and by product analysis under various conditions. Product analysis revealed that bromine adds to BF in *trans* fashion, electrophilic bromine attacking at the 2-position. Analysis of substituent effects on the rate of bromination showed that the electronic effects are transmitted through both the bond 8—3 and the bonds 9–1–2 by a comparable magnitude. The transition state of the reaction was concluded to closely resemble a cyclic bromonium ion intermediate.

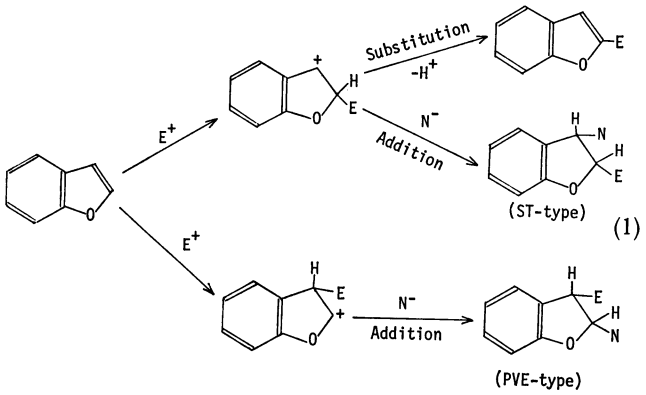
Benzofuran (BF) is a class of heterocyclic compounds which shows a dual character in its reactivity. One type of reactions is the electrophilic substitution as an aromatic compound, resulting in the substitution of the 2-hydrogen. The other is the electrophilic addition to the 2–3 bond as an olefin.[2]

As an olefin, BF can be taken as an analog of either styrene (ST) or phenyl vinyl ether (PVE).



BF ST PVE

BF is often considered as a vinyl ether analog[2] implicitly assuming the 3-attack of an electrophile in addition reaction. However, substitution occurs at the 2-position and, moreover, it was found that the ground-state electronic structure of BF is rather close to ST.[1] Thus, it seems more likely that BF would behave as an ST analog in the addition reaction, an electrophile attacking at the 2-position.

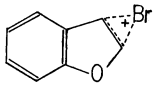


The above confusion arises from the unknown orientation of the addition reaction of BF. The halogenation[3] and the cationic polymerization[4] are the only known electrophilic addition reactions of BF.[2] Product analysis of neither of the two reactions provides any information with regard to the orientation of addition owing to the structural identity of the electrophilic and nucleophilic fragments of the reactions.

The present and the following papers are concerned first with this orientation problem in these reactions. The other purpose of the present investigations is to obtain useful information on the nature of the transition state of the reaction by analyzing the cross-ring transmission of substituent effects.

It is generally accepted that the electrophilic addition of bromine to alkenes proceeds through an intermediate cyclic bromonium ion.[5] However, intermediacy of the cyclic bromonium ion has recently been questioned for some conjugated olefins from the stereochemical studies.[5] Several investigations of the bromination of aryl-substituted olefins have been undertaken, resulting in the above conclusion.[6–9]

The effects of 5- and 6-substituents on the reactivity of BF would be transmitted through both the C–C (8–3) and C–O–C (9–1–2) bonds. This cross-ring transmission of substituent effects can be compared with the effects of *m*- and *p*-substituents of ST and *p*- and *m*-substituents of PVE. Thus, a possible symmetric character of the activated complex like I can be judged by this comparison.

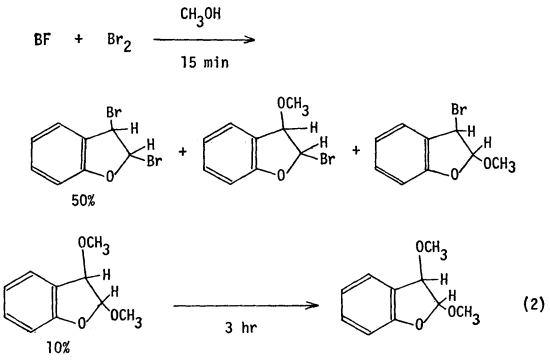


I

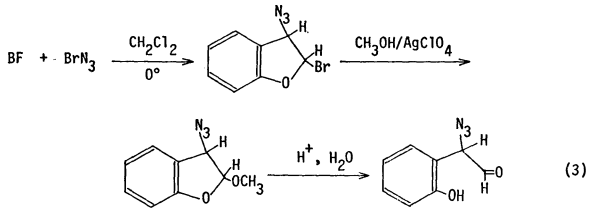
Results and Discussion

Product Analysis. Bromination of BF in carbon disulfide gave quantitatively 2,3-dibromo-2,3-dihydrobenzofuran. In attempts to obtain unsymmetric adducts, the reaction was carried out in nucleophilic solvents. Bromination in acetic acid resulted in essentially the dibromide along with a small amount of acetate. On the other hand, the reaction in methanol initially gave a mixture of several adducts which changed quantitatively into a single product, 2,3-dimethoxy-2,3-dihydrobenzofuran, in 3 hr. The dimethoxide is considered to be a substitution product of the initially formed adducts. The products of the reaction time of 15 min contained about 50% of dibromide, 10% of dimethoxide, and probably two kinds of bromomethoxide by the NMR analysis of the mixture. Thus, it was difficult to know the unambiguous orientation of addition from these products.

Under these circumstances, we have undertaken the addition of an unsymmetric reagent, bromine azide. To the methylene chloride solution of BrN_3 prepared by the method of Hassner *et al.*[9] was added BF. The



3 hr reaction yielded quantitatively 2-Bromo-3-azido-2,3-dihydrobenzofuran. The structure of the bromoazide was determined by the transformation shown in Eq. (3).



This result clearly shows that the electrophilic bromine adds at the 2-position. That is, the orientation is of the ST-type.

The stereochemistry of the products deserves some comment here. Both the adducts, the dibromide and the bromoazide, are isomerically pure by NMR spectrum and the spin-spin coupling between 2-H and 3-H is very small; ~0 and 1.2 Hz, respectively. Brust *et al.*[10] showed that J_{23} is smaller for the *trans* isomer than for the *cis* isomer of 2,3-dimethyl-2,3-dihydrobenzofuran derivatives; $J_{23}(trans)$ ~4 Hz and $J_{23}(cis)$ ~7 Hz. The Karplus equation[11] predicts $J_{23}(trans)=2.3\pm0.7$ Hz and $J_{23}(cis)=6.7\pm0.6$ Hz for the dihedral angles of $120\pm5°$ and $25\pm5°$, respectively.[10] Thus, the small coupling constants of the adducts strongly suggest their *trans* structure.

In conclusion, the addition of bromine to BF takes place in the *trans* fashion by the orientation of the ST-type.

Kinetic Measurements. Kinetic investigations of BF and its derivatives (5-CH_3, 6-CH_3, 5-CH_3O, and 5-Cl) were carried out spectrophotometrically in acetic acid at 25.0 °C. A simple second-order rate analysis by Eq. (4) did not give satisfactory results.

$$\text{rate} = k_2[\text{BF}][\text{Br}_2] \tag{4}$$

The rate equation for styrene bromination under similar conditions[6] was represented by

$$\text{rate} = k_2[\text{S}][\text{Br}_2] + k_3[\text{S}][\text{Br}_2]^2 \tag{5}$$

where [S] denotes olefin concentration. The rate analysis of the present reaction has been carried out according to Eq. (5) by a least-squares curve fitting by the aid of a computer. As is shown in Fig. 1, the values k_2 and k_3 thus obtained gave an excellent linear correlation of Eq. (6), which is derived by integration of Eq. (5).

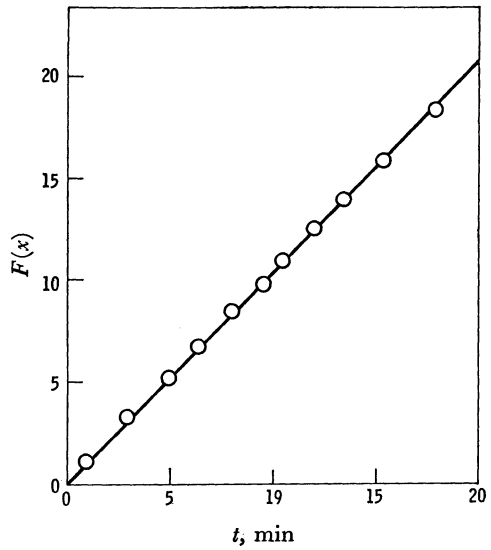


Fig. 1. Typical plots of simultaneous second- and third-order bromination rate according to Eq. (6) (5-methylbenzofuran).

$$t = \frac{\ln[(a-x)/a]}{k_3(a-b)(k_2/k_3+b-a)} + \frac{\ln[(b-x)/b]}{k_2(b-a)} + \frac{\ln[(k_2/k_3+b-x)/(k_2/k_3+b)]}{k_2(a-b-k_2/k_3)} \equiv F(x) \tag{6}$$

where a=initial concentration of BF, b=initial concentration of Br_2, and x=bromine reacted at time t.

Table 1. Rate constants for bromination of substituted benzofurans in acetic acid at 25.0 °C

Substituent	10^2k_2, $M^{-1}s^{-1}$	k_3, $M^{-2}s^{-1}$
H	0.64	3.6
5-CH_3	2.96	35.9
6-CH_3	8.28	616
5-CH_3O	3.48	261
5-Cl	0.053	0.17

The rate constants, k_2 and k_3, for BF and its derivatives are summarized in Table 1. The constants k_2 and k_3 are roughly parallel to each other but analysis of substituent effects will be conducted only on the k_2 values because of lower precision of k_3 determination.

The cross-ring substituent effects can be analyzed by the Jaffé equation.[1,12]

$$\log k = \rho_1\sigma_1 + \rho_2\sigma_2 + \log k_0 \tag{7}$$

where suffixes 1 and 2 correspond to the values concerning the transmitting routes 8–3 (ST-type) and 9–1–2 (PVE-type), respectively. The least-squares treatment of k_2 according to Eq. (7) gave the values with standard deviations: $\rho_1=-2.21\pm0.41$, $\rho_2=-2.23\pm0.53$, and $\log k_0=-2.01\pm0.08$. For the present analysis, the σ^+ values were used for σ_1. Linearity of the calculated and the observed values of $\log k_2$ is illustrated in Fig. 2.

Equality of ρ_1 and ρ_2 ($\rho_2/\rho_1=1.01$) is rather un-

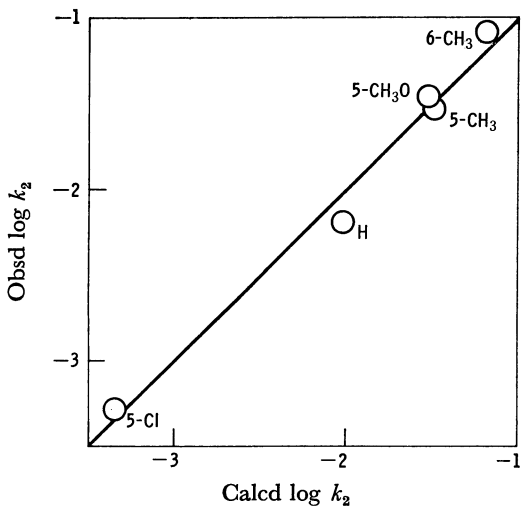
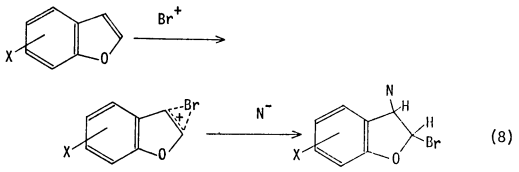


Fig. 2. Linearity of the observed and the calculated log k_2 values (Eq. (7)).

expected because we concluded that both the ground-state electronic structure[1] and the orientation of addition of BF are of the ST-type but not of the PVE-type. The present observation is explainable only by assuming the symmetric transition state closely resembling the intermediate I; the transmission of electronic effects through the route 9–1–2 (PVE-type) cna become effective.



The value of $\rho_2/\rho_1=1.01$ is very close to the relative ρ values of PVE and ST observed for the silver-ion π-complex formation ($\rho_{PVE}/\rho_{ST}=1.03$).[13]

The kinetic observations also show that the electronic effects on the ionic reactivity operate predominantly at the transition state and the ground-state electronic structure seems to have virtually no effect. The ρ_1 value of −2.21 is a reasonable magnitude which is close to the ρ value (−2.24)[6] for the bromination of styrenes bearing an electron-attracting substituent.[15] The latter reaction is assumed to involve a cyclic bromonium ion intermediate.[6]

In conclusion, the assumption of a symmetric cyclic bromonium ion mediating in the bromination of BF is confirmative. The stereochemistry of addition, exclusively *trans*, conforms to this assumption.

Experimental

Materials. The preparation of benzofuran (BF) derivatives was described previously.[1] Acetic acid was refluxed overnight over triacetyl borate and distilled. Bromine and sodium azide were of the best grade commercially available.

Bromination in CS_2. The solutions of BF and Br_2 in CS_2 were prepared separately (*ca.* 1 M) and mixed together at room temperature. Color of Br_2 faded in 1 hr. The reaction mixture was washed with aqueous sodium thiosulfate (0.01 N) and then water. Drying with anhydrous sodium sulfate and evaporation of the solvent left white solid. Recrystallization from petroleum ether gave 2,3-dibromo-2,3-dihydrobenzofuran melting at 86 °C (lit,[16] 86—87 °C). NMR (CCl_4); δ 5.67 (s, 1, 3-H), 6.81 (s, 1, 2-H), and 7—7.5 (m, 4, aromatic H).

Bromination in Acetic Acid. Reaction of equimolar BF and Br_2 (1 M) was carried out in the same way as above. The ethereal extract was dried (Na_2SO_4) and concentrated *in vacuo* leaving an oily product. NMR spectrum of the product was essentially the same as that of the dibromide obtained in CS_2 with indication of the formation of a small amount of acetate (~10%); NMR (CCl_4), δ 2.0 (s, $OCOC\underline{H}_3$).

Bromination in Methanol. The solutions of 1 M Br_2 in methanol and 1 M BF in methanol were mixed together at room temperature. The color of Br_2 faded essentially in 15 min. The reaction mixture was withdrawn by a syringe at appropriate time intervals, added to 0.01 N sodium thiosulfate, and shaken with ether. The ethereal layer was washed with water, dried over sodium sulfate, and evaporated to dryness leaving an oily product, which was applied to NMR analysis. The final product after 3 hr reaction was 2,3-dimethoxy-2,3-dihydrobenzofuran, which was isolated by distillation in 60% yield, boiling at 130—132 °C (5 mm). NMR (CCl_4); δ 3.31 (s, 3, 3-CH_3O), 3.48 (s, 3, 2-CH_3O), 4.53 (broad s, 1, 3-H), 5.26 (d, J=1.4 Hz, 1, 2-H), and 6.6—7.3 (m, 4, aromatic H).

Reaction with Bromine Azide. A solution of BrN_3 in CH_2Cl_2 was prepared according to the method of Hassner *et al.*[9] To this solution, an equimolar amount of BF was added under stirring at 0 °C and left to stand for 3 hr. The solvent was evaporated under reduced pressure to yield an oil. This crude oil was applied to spectral analyses. NMR spectrum showed that the product is essentially pure bromoazide. NMR (CCl_4); δ 5.03 (broad s, 1, 3-H), 6.03 (d, J=1.2 Hz, 1, 2-H), and 6.9—7.5 (m, 4, aromatic H).

The reaction of the bromoazide with methanol in the presence of $AgClO_4$ gave quantitatively a methoxyazide (an oil), which is a mixture of two isomers (1/2) by NMR spectrum. NMR (CCl_4); δ 3.28 (s, 1, CH_3O), 4.46 (broad s, 0.3, 3-H), 5.66 (d, J=1.2 Hz, 0.3 2-H), 3.47 (s, 2, CH_3O), 4.71 (d, J=5.8 Hz, 0.7) 5.17 (d, J=5.8 Hz, 0.7), and 6.7—7.3 (m, 4, aromatic H). IR (thin film); 2130 cm^{-1} (N_3).

The methoxyazide obtained above (1 g) was hydrolyzed at room temperature in acidic 50% aqueous dioxane (0.2 M HCl). After 5 hr of reaction, the reaction mixture was extracted with ether. The ethereal layer was then shaken with 0.1 M NaOH. The aqueous layer was acidified with 0.1 M HCl and extracted with ether again. The ether extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to leave an oil (0.2 g). IR (thin film); 3300 (broad, OH), 2110 (N_3), and 1675 cm^{-1} (C=O). The product was not pure but further attempts of purification was given up because of its high lability. It is considered from its IR spectrum and acidic character to be mainly *o*-hydroxyphenylazidoacetaldehyde.

Kinetic Measurements. The rate of bromine addition was followed spectrophotometrically at the bromine maximum of 395 nm (ε=200) with use of a Cary Model 15 spectrophotometer. Bromine concentration of a stock solution (10^{-2}—10^{-3} M in acetic acid) was determined by titration with standard thiosulfate. Ten ml of a bromine solution and 10 ml of a benzofuran solution in acetic acid were respectively thermally equilibrated at 25.0 °C, mixed together and placed in a stoppered quartz cuvette inserted in a water-

jacketed cell holder. The decrease of bromine absorption was followed.

Footnotes

1) Part I: T. Okuyama and T. Fueno, This Bulletin, the preceding paper.

2) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, Inc., New York, N. Y., (1968), Chapt. 5.

3) R. Stroermer, *Ann.*, **312**, 237 (1900).

4) G. Kraemer and A. Spilker, *Ber.*, **23**, 78 (1890).

5) For reviews, see a) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, (1966), Chapt. 7; b) R. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968).

6) K. Yates and W. V. Wright, *Can. J. Chem.*, **45**, 167 (1967).

7) R. C. Fahey and H.-J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).

8) J. H. Rolston and K. Yates, *ibid.*, **91**, 1469, 1477, 1483 (1969).

9) A. Hassner, F. P. Boerwinkle, and A. B. Levy, *ibid.*, **92**, 4879 (1970).

10) D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *J. Org. Chem.*, **31**, 2192 (1966).

11) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

12) H. H. Jaffé, *ibid.*, **76**, 4261 (1954). Noyce and Nichols (*J. Org. Chem.*, **37**, 4306, 4311 (1972)) have recently treated the solvolysis rates of 2- and 3-benzofuryl derivatives in terms of the σ_{ij} parameters. However, such treatments are not adequate to the reactions such as those concerned here, during which the aromatic skeleton is partly broken by the addition.

13) T. Fueno, T. Okuyama, T. Deguchi, and J. Furukawa, *J. Amer. Chem. Soc.*, **87**, 170 (1965); O. Kajimoto, Doctorate thesis, Osaka University, 1971. See further Ref. 14 for the comparisons of ρ's like this.

14) T. Fueno, T. Okuyama, I. Matsumura, and J. Furukawa, *J. Polym. Sci. A-1*, **7**, 1447 (1969).

15) Rolston and Yates[8] have reported $\rho^+ \simeq -4.5$ for the bromination of reactive styrene derivatives. The reaction of these styrene derivatives is considered to involve highly unsymmetric (α-carbonium ion-like) transition state.

16) B. B. Corson, H. E. Tiefenthal, J. E. Nickels, and W. J. Heintzelman, *J. Amer. Chem. Soc.*, **77**, 5428 (1955).