Transmission of Substituent Effects in Heterocyclic Systems. The Solvolysis of Some Substituted 1-(3-Benzofuryl)ethanol Derivatives[1]

DONALD S. NOYCE* AND RICHARD W. NICHOLS[2]

Department of Chemistry, University of California, Berkeley, California 94720

Received July 21, 1972

Two pairs of substituted 1-(3-benzofuryl)ethyl *p*-nitrobenzoates have been prepared and their rates of solvolysis have been measured. Substituents in either the 5-position or the 6-position exert nearly identical influences on the solvolysis rates. These results are in accord with a model using CNDO/2 calculations for predicting relative rates of solvolysis of heteroarylmethyl derivatives.

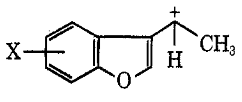
Recent studies from these laboratories have reported the behavior of substituted 1-(2-furyl)ethyl *p*-nitrobenzoates[3,4] and of analogous 3-furyl systems[5] in solvolytic reactions. Similar results have been reported for a set of thiophene derivatives.[6]

The results reported therein show that the use of Brown's[7] $\sigma_p{}^+$ and $\sigma_m{}^+$ substituent constants provides only a limited basis for correlation of the observed reactivities in the furan and thiphene series. We achieved much better success with a modification of the Dewar-Grisdale equation,[8] used to calculate effective substituent constants and expected relative reactivity. In eq 1, Δq_{ij}, is obtained from CNDO/2 calculations on

$$(\sigma_{ij}{}^+)_X = F_X{}^+/r_{ij} + \Delta q_{ij}M_X{}^+ \qquad (1)$$

both the methylarene and the arylmethylene cation; it is the difference in regional charge,[9] at the position to which the substituent X is attached, generated upon conversion to the cationic intermediate. $F_X{}^+$ and $M_X{}^+$ are uniquely determined constants for each substituent, obtained from $\sigma_p{}^+$ and $\sigma_m{}^+$ in conjunction with $1/r_{ij}$ and Δq_{ij} values appropriate for the toluene-benzyl cation pair. Equation 1 is also useful as a predictive tool.

In the present study we wish to examine the results obtained with a modest group of substituted benzofurans generating cation **1** with substituents in the benzene ring, and a side chain as the point of solvolytic reactivity attached at the 3 position. In this structural situation it is to be noted that ordinary valence bond resonance representation does not permit any direct conjugation between the side chain and the substituent X. On this basis the effects of substituents might be expected to be relatively modest, an expectation which is borne out by the facts. One might also expect that the effect of substituents might show a preponderance of inductive influences, an expectation that is not borne out by the facts.



1

As applied to benzofurans, eq 1 generates eq 2 for 6-substituted 3-benzofuryl systems and eq 3 for 5-substituted 3-benzofuryl systems.

$$(\sigma_{6,3}{}^+)_X = F_X{}^+/3.045 + 0.0666M_X{}^+ \qquad (2)$$

$$(\sigma_{5,3}{}^+)_X = F_X{}^+/2.782 + 0.069M_X{}^+ \qquad (3)$$

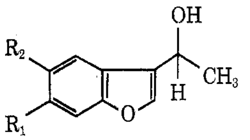
Inserting the values for the $F_X{}^+$ and $M_X{}^+$ constants for appropriate substituents leads to the predicted substituent constants given in Table I. The close similarity of the constant for a particular substituent at either the 5 position or the 6 position is to be noted.

TABLE I

PREDICTED SUBSTITUENT CONSTANTS FOR USE IN SOLVOLYSIS REACTIONS FOR BENZOFURYL DERIVATIVES

	Substituent constants, $\sigma_{ij}{}^+$		
System	CH_3O	CH_3	Cl
6-X-3-Benzufuryl	−0.187	−0.102	0.168
5-X-3-Benzofuryl	−0.177	−0.104	0.191

The *p*-nitrobenzoates of 1-(3-benzofuryl)ethanol (**2**), 1-(6-chloro-3-benzofuryl)ethanol (**3**), 1-(5-chloro-3-benzofuryl)ethanol (**4**), 1-(5-methoxy-3-benzofuryl)ethanol (**5**), and 1-(6-methoxy-3-benzofuryl)ethanol (**6**) were prepared and solvolyzed. The relevant rate data are given in Table II.



2, $R_1 = R_2 = H$
3, $R_1 = Cl$; $R_2 = H$
4, $R_1 = H$; $R_2 = Cl$
5, $R_1 = H$; $R_2 = OCH_3$
6, $R_1 = OCH_3$; $R_2 = H$

Both chloro compounds, **3** and **4**, solvolyze about five times more slowly than the parent system (**2**). They solvolyze at very nearly identical rates, indicating a remarkably similar balance of electronic effects at the two positions, 5 and 6. Similarly both methoxy compounds **5** and **6** have very closely similar rates; more importantly, however, **5** and **6** solvolyze faster than **2**, indicating that appreciable electronic deficiency is transmitted to both the 5 and 6 position in the carbonium ion intermediate (**1**). This indicates the importance of the $M_X{}^+$ term in eq 2 and 3.

Using the substituent constants given in Table II, ρ was calculated to be −3.8 rather than −5.8 observed for the substituted 2-benzofuryl systems.[10] This no

---

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) National Institutes of Health Predoctoral Fellow, 1968–1970 (GM 41,892).

(3) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(4) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2620 (1972).

(5) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2623 (1972).

(6) D. S. Noyce, R. W. Nichols, and C. A. Lipinski, *ibid.*, **37**, 2615 (1972).

(7) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(8) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3548 (1962).

(9) Regional charge: The sum of the charges on a carbon atom and any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

(10) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306 (1972).

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED 1-(3-BENZOFURYL)ETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compd	Temp, °C	k, sec^{-1}
2-OPNB (H)	75.00	$2.07 \pm 0.07 \times 10^{-5}$
		$2.10 \pm 0.05 \times 10^{-5}$
		$2.05 \pm 0.02 \times 10^{-5}$
	100.00	$2.30 \pm 0.05 \times 10^{-4}$
		$2.37 \pm 0.05 \times 10^{-4}$
3-OPNB (6-Cl)	75.00	$3.55 \pm 0.17 \times 10^{-6}$
		$3.47 \pm 0.08 \times 10^{-6}$
4-OPNB (5-Cl)	75.00	$3.62 \pm 0.17 \times 10^{-6}$
		$3.68 \pm 0.07 \times 10^{-6}$
5-OPNB (5-OCH$_3$)	75.00	$4.00 \pm 0.03 \times 10^{-5}$
		$3.95 \pm 0.02 \times 10^{-5}$
6-OPNB (6-OCH$_3$)	75.00	$4.38 \pm 0.05 \times 10^{-5}$
		$4.40 \pm 0.08 \times 10^{-5}$

doubt arises from the interaction of the side chain (position 3) with the peri hydrogen at carbon 4. This influence is difficult to place on a firm quantitative basis, though there are a number of indications that such an effect is operative.

Comparison of α-naphthyl and β-naphthyl systems shows a regular decrease in the relative reactivity of the α-naphthyl moiety as the steric demands of the side chain are increased (Table III), indicative of decreased effectiveness of the resonance interaction.

TABLE III

COMPARATIVE REACTIVITY OF α-NAPHTHYL AND β-NAPHTHYL SYSTEMS IN SOLVOLYSIS

System	Solvent	k_α/k_β[a]	Ref
ArCH$_2$Cl	HCOOH	15.7	*b*
ArCH$_2$OTos	AcOH	7.40	*c*
ArCH(CH$_3$)Cl	80% Acetone	2.56	*d*
ArCH(C$_6$H$_5$)Cl	90% Acetone	1.36	*e*
ArC(CH$_3$)$_2$Cl	90% Acetone	1.02	*d*
ArC(C$_6$H$_5$)$_2$Cl	Et$_2$O–EtOH	0.71	*f*

[a] $k_{\alpha\text{-naphthyl}}/k_{\beta\text{-naphthyl}}$. [b] M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2789 (1956). [c] A. Streitwieser, Jr., H. A. Hammond, R. H. Jagow, R. M. Williams, R. G. Jesaitis, C. J. Chang, and R. Wolf, *J. Amer. Chem. Soc.*, **92**, 5141 (1970). [d] Y. Okamoto and H. C. Brown, *ibid.*, **79**, 1903 (1957). [e] L. Verbit and E. Berliner, *ibid.*, **86**, 3307 (1964). [f] A. C. Nixon and G. E. K. Branch, *ibid.*, **58**, 492 (1936).

In another study Brown and Inukai[11] have shown that an ortho methyl group depresses the response of cumyl chlorides to substituents in the para position. 4-Phenyl-2-methylcumyl chloride is only five times more reactive than 2-methylcumyl chloride, whereas *p*-phenylcumyl chloride is six times more reactive than cumyl chloride. 4-Methoxy-2-methylcumyl chloride is only 1100 times more reactive than *o*-methylcumyl chloride, whereas *p*-methoxycumyl chloride is 3360 times more reactive than cumyl chloride. The value of ρ calculated from the limited data on ortho methyl cumyl chlorides is -4.0 at 0° rather than the standard ρ of -4.54 (at 25°) or -4.9 (at 0°).

In summary, solvolyses of substituted 3-benzofurylmethyl systems have been satisfactorily correlated in a straightforward fashion which is useful for further prediction of reactivities.

Experimental Section[12]

1-(3-Benzofuryl)ethanol (2).—3-Bromobenzofuran was prepared from benzofuran by the method of Stoermer and Kahlert.[13] Conversion to 3-lithiobenzofuran by halogen metal interchange was followed by addition of acetaldehyde. The reaction mixture was worked up in the usual fashion and chromatographed on silica gel. Elution with hexane gave some benzofuran. With 3:1 hexane–ether, 1-(3-benzofuryl)ethanol was eluted: nmr (CCl$_4$) δ 1.43 (d, 3, J = 7 Hz, CH$_3$), 3.38 (b, 1, OH), 4.83 (q, 1, CHOH), 7.28 (s, 1, HC$_2$), and 6.97–7.57 (m, 4, H aromatic).

1-(3-Benzofuryl)ethyl *p*-Nitrobenzoate.—The alcohol **2** was converted in the usual fashion to the *p*-nitrobenzoate: mp 109–110° (from hexane); nmr (CCl$_4$) δ 1.85 (d, 3, J = 6.5 Hz, CH$_3$); 6.73 (q, 1, J = 6.5 Hz, –CHOPNB), 7.01–7.67 (m, 5, benzofuryl protons), and 8.17 (s, 4, OPNB).

Anal. Calcd for C$_{17}$H$_{13}$NO$_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.31; H, 4.10; N, 4.64.

3-Bromo-6-chlorobenzofuran.—4-Chlorosalicylaldehyde[10] was converted to 6-chlorobenzofuran-2-carboxylic acid following the procedure of Andrisano and Duro[14] in 79% yield, mp 244–246° (lit.[14] mp 224–225°). The acid was decarboxylated with copper powder in boiling quinoline to give 6-chlorobenzofuran.

To 6-chlorobenzofuran (5 g) in carbon tetrachloride (10 ml) bromine (5.6 g) in carbon disulfide (10 ml) was added in small portions, while the temperature of the reaction flask was maintained at -5 to $-20°$. The reaction mixture was kept at $-20°$ overnight. The solvent and remaining bromine were removed under reduced pressure, leaving a white solid which was recrystallized from chloroform (20 ml) at $-20°$. This gave 5.33 g of product, and a second crop of 3.14 g was collected from the concentrated mother liquor, total yield 8.47 g (83%) of 6-chloro-2,3-dibromo-2,3-dihydrobenzofuran: mp 63–65°; nmr (CCl$_4$) δ 5.63 (s, 1, HC$_3$), 6.83 (s, 1, HC$_2$), 7.23 [AB q, ν_4 7.36 and ν_5 7.10, 2, J_{4-5} = 8.6 Hz, HC$_4$ and HC$_5$ (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 1.7 Hz)], and 7.03 (m, 1, HC$_7$).

6-Chloro-2,3-dibromo-2,3-dihydrobenzofuran (7.15 g) was added all at once to a solution of potassium hydroxide (2.5 g) in absolute ethanol (35 ml) at 0°. The reaction was stirred for 4 hr at 0° and neutralized with glacial acetic acid, and most of the ethanol was removed under reduced pressure. After the addition of water to the residue, ether extraction, drying (MgSO$_4$), and evaporation of the ether under reduced pressure, 5.20 g (98%) of 3-bromo-6-chlorobenzofuran was obtained: mp 36–37°; nmr (CCl$_4$) δ 7.28 [AB q, ν_4 7.32 and ν_5 7.24, 2, J_{4-5} = 8.6 Hz, HC$_4$ and HC$_5$ (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 1.4 Hz)], 7.41 (m, 1, HC$_7$), and 7.52 (s, 1, HC$_2$).

Anal. Calcd for C$_8$H$_4$BrClO: C, 41.51; H, 1.74; Br, 34.52; Cl, 15.32. Found: C, 41.52; H, 1.75; Br, 34.48; Cl, 15.32.

1-(6-Chloro-3-benzofuryl)ethanol (3).—A solution of 15.2% *n*-butyllithium in hexane (13.0 ml, 0.0212 mol, Foote Mineral Co.) was added from a Dry Ice jacketed addition funnel to a solution of 6-chloro-3-bromobenzofuran (4.0 g, 0.0173 mol) in dry ether (50 ml) maintained at Dry Ice–acetone temperature. The flame-dried apparatus was kept under a nitrogen atmosphere. The addition was completed in 20 min, and the reaction was stirred for 20 min longer. Then acetaldehyde (2.9 ml, 0.052 mol) was rapidly injected into the reaction mixture. The reaction mixture was worked up in the usual fashion. The nmr spectrum of the isolated material indicated that a mixture of products had been formed. Chromatography on silica gel, using hexane–ether eluents, gave 6-chlorobenzofuran (0.73 g, 28%), identified by and pure by the standards of nmr, and 0.23 g (9%) of 2-hydroxy-4-chlorophenylacetylene: nmr (CCl$_4$) δ 3.37 (s, 1, –C≡CH), 5.73 (b, 1, OH), 6.93 (d, 1, J_{3-5} = 2.0 Hz, HC$_3$), and 7.01 ppm [AB q, ν_5 6.80 and ν_6 7.22, 2, J_{5-6} = 8.0 Hz, HC$_5$ and HC$_6$ (superimposed on the upfield half of the AB quartet is a meta splitting, J_{3-5} = 2.0 Hz)]. The resonance for the acetylenic proton at δ 3.37 is identical with the published[15]

---

[11] H. C. Brown and T. Inukai, *J. Amer. Chem. Soc.*, **83**, 4825 (1961).

[12] Melting points and boiling points are uncorrected. Analyses are by the Chemical Analytical Services Laboratory, College of Chemisty, University of California, Berkeley, Calif.

[13] R. Stoermer and B. Kahlert, *Ber.*, **35**, 1633 (1902).

[14] R. Andrisano and F. Duro, *Gazz. Chim. Ital.*, **85**, 381 (1955).

[15] C. C. Cook and J. S. Danyluk, *Tetrahedron*, **19**, 177 (1963).

value.[16] With 4:1 hexane–ether, 0.31 g (9%) of 1-(6-chloro-3-benzofuryl)ethanol was collected: nmr (CCl_4) δ 1.52 (d, 3, J = 6.6 Hz, CH_3), 3.15 (b, 1, OH), 4.86 (q, 1, J = 6.6 Hz, CHOH), 7.25 [AB q, ν_4 7.08 and ν_5 7.42, 2, J_{4-5} = 8.0 Hz, HC_4 and HC_5 (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 2 Hz)], and 7.34 ppm (b, 2, HC_2 and HC_7).

Minimizing the time lapse between addition of *n*-butyllithium and acetaldehyde gave a substantially improved yield (>50%) of 1-(6-chloro-3-benzofuryl)ethanol (**3**), still contaminated with some 6-chlorobenzofuran.

1-(6-Chloro-3-benzofuryl)ethyl *p*-Nitrobenzoate.—The alcohol **3** was converted to the *p*-nitrobenzoate in the usual way, and recrystallized from absolute ethanol: mp 108.5–109.5°; nmr (CCl_4) δ 1.82 (d, 3, J = 6 Hz, CH_3), 6.37 (q, 1, J = 6 Hz, -CHOPNB), 7.37 [AB q, ν_4 7.55 and ν_5 7.19, 2, $J_{4,5}$ = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 7.47 (m, 1, HC_7), 7.67 (s, 1, HC_2), and 8.15 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 58.86; H, 3.36; Cl, 10.23; N, 4.08.

3-Bromo-5-Chlorobenzofuran.—5-Chlorosalicylaldehyde[10] was converted to diethyl 5-chloro-3-hydroxy-2,3-dihydrobenzofuran-2,2-dicarboxylate, mp 93–94°, by the procedure of Andrisano and Duro.[14] Saponification and concurrent decarboxylative dehydration afforded 5-chlorobenzofuran-2-carboxylic acid, mp 264–265° (lit.[14] mp 266–267°). Decarboxylation with copper powder in quinoline afforded 5-chlorobenzofuran.

To a cooled solution of 5-chlorobenzofuran (5.5 g) in carbon disulfide, bromine (6.0 g) in carbon tetrachloride was added as rapidly as decolorization occurred. After 4 hr of additional stirring at −10°, the solvent and remaining bromine were removed under reduced pressure, leaving a white solid which was recrystallized from chloroform at 0° to give 9.6 g (85%) of 5-chloro-2,3-dibromo-2,3-dihydrobenzofuran as heavy, white crystals: nmr (CCl_4) δ 5.60 (s, 1, HC_3), 6.80 (s, 1, HC_2), 7.09 [AB q, ν_6 7.25 and ν_7 6.93, 2, $J_{6,7}$ = 8.0 Hz, HC_6 and HC_7 (the downfield half of the AB quartet is meta split, J_{4-6} = 2.0 Hz)], and 7.43 (d, 1, J_{4-6} = 2 Hz, HC_4).

5-Chloro-2,3-dibromo-2,3-dihydrobenzofuran (7.84 g) was added to a solution of potassium hydroxide (2.9 g) in 95% ethanol (20 ml) at 0°. The reaction was stirred for 5 hr at 0°, and neutralized with acetic acid; water was added, and the mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give 5.70 g (98%) of 3-bromo-5-chlorobenzofuran as a white powder: mp 75–76.5°; nmr (CCl_4) δ 7.30 (m, 2, HC_6 and HC_7), 7.47 (m, 1, HC_4), and 7.60 (s, 1, HC_2).

Anal. Calcd for C_8H_4BrClO: C, 41.51; H, 1.74; Br, 34.52; Cl, 15.32. Found: C, 41.36; H, 1.85; Ar, 34.38; Cl, 15.28.

1-(5-Chloro-3-benzofuryl)ethanol (4).—A solution of *n*-butyllithium in hexane (8.0 ml, 0.0127 mol, Foote Mineral Co.) was added from a Dry Ice jacketed addition funnel to a solution of 5-chloro-3-bromobenzofuran (2.5 g) in dry ether (60 ml), the flame-dried reaction flask being cooled by a Dry Ice–acetone bath and kept under positive nitrogen pressure. The addition was completed in 3 min and the reaction mixture was stirred 7 min longer, at which time acetaldehyde (2.5 ml, 0.038 mol) was rapidly injected, causing the cloudy, light green reaction mixture to clarify. The reaction mixture was worked up in the usual fashion. Low-temperature crystallization from ether–petroleum ether (bp 30–60°) afforded 1.25 g (59%) of 1-(5-chloro-3-benzofuryl)ethanol (**4**) as fine, white needles: mp 84–85°; nmr (CCl_4) δ 1.54 (d, 3, J = 6 Hz, CH_3), 2.50 (s, 1, OH), 4.96 (q, 1, J = 6 Hz, CHOH), 7.27 [AB q, ν_6 7.21 and ν_7 7.33, 2, J_{6-7} = 9 Hz, H-C_6 and H-C_7 (the upfield half of the AB quartet is meta split, J_{4-6} = 2 Hz)], 7.47 (s, 1, HC_2), and 7.60 ppm (m, 1, HC_4).

Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.89; H, 4.45; Cl, 18.18.

1-(5-Chloro-3-benzofuryl)ethyl *p*-nitrobenzoate was prepared in the usual fashion: mp 118–119°; nmr (CCl_4) δ 1.84 (d, 3, J = 7 Hz, CH_3), 6.37 (q, 1, J = 7 Hz, $CHCH_3$), 7.33 (AB q, ν_6 7.25 and ν_7 7.41, 2, J_{6-7} = 8.5 Hz, HC_6 and HC_7), 7.62 (m, 1, HC_4), 7.68 (s, 1, HC_2), and 8.19 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 59.29; H, 3.71; Cl, 10.14; N, 4.20.

4-Bromo-5-methoxybenzofuran.—5-Methoxybenzofuran was prepared by the method of Andrisano, Duro, and Pappalardo.[17,18] A solution of bromine (6.15 g) in carbon disulfide (10 g) was added to 5-methoxybenzofuran (5.65 g, 0.038 mol) in carbon disulfide (10 g) as fast as it could be decolorized, the addition taking 30 min. Throughout the addition, the reaction flask was maintained at −20 to −25°. After an additional 30 min the solvent was removed under reduced pressure. Crystallization from hexane gave 5.5 g (64%) of 4-bromo-5-methoxybenzofuran, mp 81–88°. A small quantity was recrystallized from hexane to give a pure sample: mp 88.0–89.5°; 100-MHz nmr (CCl_4) δ 3.87 (s, 3, OCH_3), 6.72 (dd, J_{2-3} = 2.2 and J_{3-7} = 1 Hz, HC_3), 7.06 [AB q, ν_6 6.84 and ν_7 7.28, J_{6-7} = 8.7 Hz (the downfield half of the AB quartet is split by a long-range coupling, J_{3-7} = 1 Hz)], and 7.57 (d, J_{2-3} = 2.2 Hz, HC_2).

Anal. Calcd for $C_9H_7BrO_2$: C, 47.60; H, 3.11; Br, 35.20. Found: C, 47.79; H, 3.34; Br, 35.38.

2,3,4-Tribromo-5-methoxy-2,3-dihydrobenzofuran.—Bromide (3.8 g) in carbon disulfide (10 ml) was added to a solution of 4-bromo-5-methoxybenzofuran (5.32 g) in carbon disulfide and carbon tetrachloride (10 ml), and the mixture was allowed to stand for 5 days. The solvents were removed under reduced pressure, and the residue was crystallized at low temperature from hexane–ether; 7.1 g (78%) of 2,3,4-tribromo-5-methoxy-2,3-dihydrobenzofuran was obtained as yellow crystals: mp 81–83°; nmr (CCl_4) δ 3.82 (s, 3, OCH_3), 5.56 (s, 1, HC_3), and 6.79 ppm [s, 3, HC_2, HC_6, and HC_7 (HC_6 and HC_7 actually form an AB quartet, but do so near the limit of equivalence of the two protons involved; very small resonances are symmetrically disposed about the central 6.79 peak at a distance of 8 Hz. The appearance of HC_2 at 6.29 is coincidental, but normal for dibromodihydrobenzofurans)].

Anal. Calcd for $C_9H_7Br_3O_2$: Br, 61.97. Found: Br, 60.40. This analysis establishes the presence of three bromine atoms in the molecule. The compound was used without further purification.

3,4-Dibromo-5-methoxybenzofuran.—2,3,4-Tribromo-5-methoxy-2,3-dihydrobenzofuran (5.8 g) was added to a cold (0°) solution of potassium hydroxide (1.1 g) in nitrogen-flushed ethanol (40 ml). After 5 hr of stirring at 0° (with precipitation of potassium bromide) the reaction mixture was left standing at −15° overnight. Water was added, and the mixture was extracted with ether. The ether was removed from the washed (water) and dried ($MgSO_4$) extract to give 4.45 g (97%) of 3,4-dibromo-5-methoxybenzofuran, mp 80–85°. A sample recrystallized from petroleum ether–ether gave needles: mp 84–85°; 100-MHz nmr (CCl_4) δ 3.87 (s, 3, OCH_3), 7.09 (AB q, ν_6 6.88 and ν_7 7.30, 2, J_{6-7} = 9 Hz, HC_6 and HC_7), and 7.59 (s, HC_2).

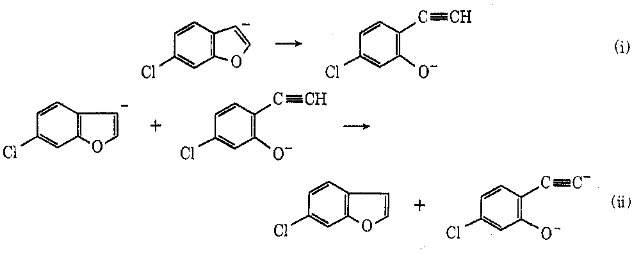
Anal. Calcd for $C_9H_6Br_2O_2$: Br, 52.25. Found: Br, 51.96.

1-(4-Bromo-5-methoxy-3-benzofuryl)ethanol.—A preliminary experiment with a small sample of 3,4-dibromo-5-methoxybenzofuran showed that halogen–metal interchange occurred most facilely at the 3 position, as evidenced by the recovery of 4-bromo-5-methoxybenzofuran upon addition of water.

Thus, to 3.72 g of 3,4-dibromo-5-methoxybenzofuran in 125 ml of dry ether at −78° was added 1 equiv of *n*-butyllithium in

---

[16] These side products may have arisen from the successive side reactions i and ii.



The intramolecular cleavage reaction i is reminiscent of the isolation of *o*-hydroxyphenylacetylene [H. Gilman and D. S. Melstrom, *J. Amer. Chem. Soc.*, **70**, 1655 (1948)] from the products of the reaction of *n*-butyllithium with 3-bromobenzofuran in ether, followed by carbonation. In an analogous experiment in this work, benzofuran was a minor side product, but acetylenic product was not noted. The apparent acceleration of the intramolecular cleavage by a 6-chloro substituent is consistent with the greater acidity of *m*-chlorophenol relative to that of phenol.

[17] R. Andrisano, F. Duro, and G. Pappalardo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **14**, 96 (1956); *Chem. Zentr.*, 667 (1958).

[18] We wish to express our appreciation to the Upjohn Co. for the gift of a generous quantity of 5-methoxysalicylaldehyde.

hexane (Foote Mineral Co.). The addition was completed in 7 min, and the reaction was stirred 7 min longer. Then acetaldehyde (2.5 ml, 0.044 mol) was rapidly injected, causing the white precipitate to dissolve. After 5 min the contents of the reaction flask were mixed with salted water (100 ml) and extracted with three 75-ml portions of ether. The extract was dried ($MgSO_4$) and concentrated; chromatography on silica gel using hexane as eluent gave small amounts of starting material and of 4-bromo-5-methoxybenzofuran. Elution with 85:15 hexane–ether gave an isolated yield of 1.61 g (49%) of 1-(4-bromo-5-methoxy-3-benzofuryl)ethanol as colorless needles: mp 87–88° (from petroleum ether–ether); nmr (CCl_4) δ 1.60 (d, 3, J = 7 Hz, $CHCH_3$), 2.07 (b, 1, OH), 3.92 (s, 3, OCH_3), 5.51 (q, 1, J = 7 Hz, $CHCH_3$), 7.10 (AB q, ν_6 6.93 and ν_7 7.27, 2, J_{6-7} = 9 Hz, HC_6 and HC_7), and 7.63 (s, 1, HC_2).

Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09; Br, 29.47. Found: C, 48.81; H, 4.22; Br, 29.28.

1-(5-Methoxy-3-benzofuryl)ethanol (5).—A solution of 15.2% *n*-butyllithium in hexane (10.1 ml) was added from a Dry Ice jacketed addition funnel to a solution of 1-(4-bromo-5-methoxy-3-benzofuryl)ethanol (1.44 g) in dry ether (100 ml). The dried reaction flask was maintained under a nitrogen atmosphere. During the 5-min addition period the reaction was stirred in a Dry Ice–acetone bath. After 2 hr of stirring at −78° the reaction mixture was quenched with water (10 ml) and methanol (1 ml). After the usual work-up the nmr indicated complete conversion to 1-(5-methoxy-3-benzofuryl)ethanol (**5**): nmr (CCl_4) δ 1.48 (d, 3, J = 7 Hz, $CHCH_3$), 3.17 (b, 1, OH), 3.75 (s, 3, OCH_3), 5.88 (q, 1, J = 7 Hz, $CHCH_3$), 7.00 [AB q, ν_6 6.76 and ν_7 7.24, 2, J_{6-7} = 9 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is meta split, J_{4-6} = 2 Hz)], 7.00 (d, 1, J_{4-6} = 2 Hz, HC_4), and 7.33 (s, 1, HC_2).

The alcohol was converted to the *p*-nitrobenzoate without further purification.

1-(5-Methoxy-3-benzofuryl)ethyl *p*-Nitrobenzoate.—Impure 1-(5-methoxy-3-benzofuryl)ethanol [1.14 g (total possible 1-(5-methoxy-3-benzofuryl)ethanol is 1.02 g, 0.0053 mol)] prepared from 1-(5-methoxy-4-bromo-3-benzofuryl)ethanol (1.44 g, 0.0053 mol) was dissolved in dry pyridine (7 ml), and *p*-nitrobenzoyl chloride (1.15 g) was added. After stirring overnight, most of the pyridine was removed under reduced pressure and the residual solid material was triturated with boiling hexane. From the cooled, filtered hexane solution 1.30 g (78%) of 1-(5-methoxy-3-benzofuryl)ethyl *p*-nitrobenzoate crystallized: mp 126–127°; nmr (CCl_4) δ 1.82 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.74 (s, 3, OCH_3), 6.37 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.05 [AB q, ν_6 6.81 and ν_7 7.29, 2, J_{6-7} = 9 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is meta split, J_{4-5} = 3 Hz)], 7.01 (d, 1, J_{4-5} = 3 Hz, HC_4), 7.59 (s, 1, HC_2), and 8.15 (s, 4, $-C_6H_4-$).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.11. Found: C, 63.35; H, 4.43; N, 4.36.

Ethyl 6-Methoxy-2-carboxybenzofuran-3-carboxylate.—The procedure of Koelsch and Whitney[19] was used. Ethyl *m*-methoxyphenoxyacetate[20] was condensed with diethyl oxalate using commercial sodium ethoxide in ether. The resulting diethyl α-keto-α'-*m*-methoxyphenoxysuccinate (100 g) was cyclized directly using a mixture of acetic acid (200 ml), sulfuric acid (200 ml), and acetic anhydride (10 ml). After the solution had stood overnight, it was heated on the steam bath for 20 min. The reaction mixture was poured over crushed ice, and the resulting precipitate was removed by filtration and was then recrystallized from ethanol. In this fashion there was obtained 33.3 g (39%) of impure ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, contaminated with the 4 isomer. Fractional crystallization from ethanol (three stages) gave pure ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate as brittle, pale yellow needles: mp 164–165°; yield 24%; 100-MHz nmr (CF_3COOH) δ 1.64 (t, 3, J = 7 Hz, OCH_2CH_3), 3.98 (s, 3, OCH_3), 4.74 (q, 2, OCH_2CH_3), 7.20 (dd, 1, J_{4-5} = 9 Hz and J_{5-7} = 2.4 Hz, HC_4).

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.11; H, 4.64.

From the mother liquors, **ethyl 4-methoxy-2-carboxybenzofuran-3-carboxylate** was isolated as long, fine, wooly, colorless needles: mp 153.5–154.5°; yield 1.5 g (2%); 100-MHz nmr (CF_3COOH) δ 1.57 (t, 3, J = 7 Hz, OCH_2CH_3), 4.01 (s, 3, OCH_3), 4.68, (q, 2, OCH_2CH_3), 7.10–7.26 (m, 2, ArH), and 8.20–8.34 (m, 1, ArH).

Anal. Calcd for $C_{13}H_{12}O_{16}$: C, 59.09; H, 4.58. Found: C, 59.22; H, 4.49.

6-Methoxybenzofuran-3-carboxylic Acid.—A mixture of ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, copper powder, and quinoline was heated to 225–230°. After 20 min, evolution of carbon dioxide had virtually ceased. Work-up in the usual fashion gave 12.3 g (76%) of crude **ethyl 6-methoxybenzofuran-3-carboxylate**. A small sample was crystallized from ethanol for purposes of characterization: mp 55–56°; nmr (CCl_4) δ 1.39 (t, 3, J = 7 Hz, OCH_2CH_3), 7.34 [AB q, ν_4 7.81 and ν_5 6.87, 2, J_{4-5} = 9.5 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 6.93 (m, 1, HC_7) and 8.03 (s, 1, HC_2).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.70; H, 5.54.

The remainder of the ester was saponified by potassium hydroxide in aqueous ethanol. Work-up in the usual fashion gave **6-methoxybenzofuran-3-carboxylic acid** (99%) as a white powder: mp 179–180° (from chloroform–methanol); nmr ($CDCl_3$) δ 3.85 (s, 3, OCH_3), 6.98–7.22 (m, 2, HC_5 and HC_7), 7.88 (d, 1, J = 8 Hz, HC_4), and 8.28 (s, 1, HC_2).

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.19. Found: C, 62.38; H, 4.08.

6-Methoxy-3-acetylbenzofuran.—To a cooled solution of 6-methoxybenzofuran-3-carboxylic acid (4.0 g) in dry ether (400 ml), methyllithium in ether (50 ml, 0.075 mol, Foote Mineral Co.) was added over a period of 30 min. After 3 hr more methyllithium solution (25 ml) was added, and the reaction mixture was stirred overnight at room temperature. Methanol (30 ml) was rapidly injected[21] into the cooled, rapidly stirring reaction mixture, and the solution was neutralized with acetic acid. The reaction mixture was washed with two 200-ml portions of water, a 125-ml portion of saturated sodium bicarbonate, and with water again. The ether solution was dried ($MgSO_4$) and the ether was removed to give 3.09 g of crude 6-methoxy-3-acetylbenzofuran as a pale brown solid. The nmr spectrum indicated only a very small gem-dimethyl resonance from the corresponding tertiary alcohol. Recrystallization from petroleum ether gave 2.64 g (67%) of product, mp 68–73°.

A sample was recrystallized from petroleum ether–ether and then sublimed (0.1 mm, bath temperature 65°) for purposes of characterization: mp 72.5–73.0°; nmr (CCl_4) δ 2.39 (s, 3, $COCH_3$), 3.76 (s, 3, OCH_3), 6.72–6.95 (m, 2, HC_5, HC_7), 7.94 (d, 1, J_{4-5} = 9 Hz, HC_4), and 7.97 (s, 1, HC_2).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.41; H, 5.51.

1-(6-Methoxy-3-benzofuryl)ethanol (6).—6-Methoxy-3-acetylbenzofuran (1.2 g) in methanol (35 ml) was reduced with sodium borohydride. The reaction mixture was worked up in the usual fashion to give 1.20 g (99%) of 1-(6-methoxy-3-benzofuryl)ethanol (**6**) as an oil: nmr (CCl_4) δ 1.43 (t, 3, J = 7 Hz, $CHCH_3$), 3.20 (b, 1, OH), 3.71 (s, 3, OCH_3), 4.82 (q, 1, J = 7 Hz, $CHCH_3$), 6.65 (dd, 1, J_{4-5} = 8.5 and J_{5-7} = 2 Hz, HC_5), 6.80 (d, 1, J_{5-7} = 2 Hz, HC_7), 7.21 (s, 1, HC_2), and 7.32 (d, 1, J_{4-5} = 8.5 Hz, HC_4).

1-(6-Methoxy-3-benzofuryl)ethyl *p*-nitrobenzoate was prepared directly from crude **6** in the usual fashion. Purification was achieved by crystallization from hexane–ether: mp 106.5–108.0°; nmr (CCl_4–$CDCl_3$) δ 1.82 (t, 3, J = 6.5 Hz, $CHCH_3$), 3.80 (s, 3, OCH_3), 6.40 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.83 (dd, 1, J_{4-5} = 8.5 and J_{5-7} = 2 Hz, HC_5), 6.98 (d, 1, J_{5-7} = 2 Hz, HC_7), 7.50 (d, 1, J_{4-5} = 8.5 Hz, HC_4), 7.57 (s, 1, HC_2), and 8.17 (s, 4, $-C_6H_4-$).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.26; H, 4.25; N, 4.21.

Kinetic Procedures.—Kinetic methods have been described previously.[10]

Registry No.—**2**, 36739-86-3; **2**-OPNB, 36739-87-4; **3**, 36739-88-5; **3**-OPNB, 36739-89-6; **4**, 36739-90-9; **4**-OPNB, 36739-91-0; **5**, 19303-55-0; **5**-OPNB, 36739-93-2; **6**, 36739-94-3; **6**-OPNB, 36739-95-4; 6-chloro-

---

[19] C. F. Koelsch and A. G. Whitney, *J. Amer. Chem. Soc.*, **63**, 1762 (1941).

[20] J. Myska, V. Ettel, and M. Bowar, *Collect. Czech. Chem. Commun.*, **26**, 904 (1961).

[21] Following the suggestion of Dr. M. J. Jorgenson; *cf. Org. React.*, **18**, 321 (1970).

2,3-dibromo-2,3-dihydrobenzofuran, 36739-96-5; 3-bromo-6-chlorobenzofuran, 36739-97-6; 2-hydroxy-4-chlorophenylacetylene, 36739-98-7; 5-chloro-2,3-dibromo-2,3-dihydrobenzofuran, 36826-29-6; 3-bromo-5-chlorobenzofuran, 36739-99-8; 4-bromo-5-methoxybenzofuran, 36826-30-9; 2,3,4-tribromo-5-methoxy-2,3-dihydrobenzofuran, 36740-00-8; 3,4-dibromo-5-methoxybenzofuran, 36826-31-0; 1,(4-bromo-5-methoxy-3-benzofuryl)ethanol, 36740-01-9; ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, 28238-33-7; ethyl 4-methoxy-2-carboxybenzofuran-3-carboxylate, 36748-73-9; ethyl 6-methoxybenzofuran-3-carboxylate, 36748-74-0; 6-methoxybenzofuran-3-carboxylic acid, 29822-97-7; 6-methoxy-3-acetylbenzofuran, 36748-76-2.

Confirmation of Concurrent General Acid, General Base Catalysis in the Lactonization of 2-(Hydroxymethyl)benzoic Acid

NOBORU TOMOTO, WILLIAM J. BOYLE, JR., AND J. F. BUNNETT*

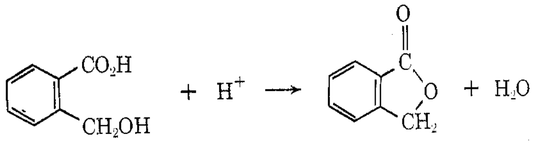
University of California, Santa Cruz, California 95060

Received July 28, 1972

An earlier report that lactonization of 2-(hydroxymethyl)benzoic acid in water is general acid and general base catalyzed (by formic acid and formate ion, respectively) is confirmed, and for the first time substantiating experimental details are presented.

Although *intra*molecular general base catalysis of the reactions of carboxylic acids and esters is fairly common,[1] *inter*molecular general acid catalysis has been observed in only a few cases.[1]

In 1969, Milstien and Cohen[2a] reported in a preliminary communication that the lactonizations of 2-(hydroxymethyl)benzoic acid (**1**) and some phenolic acids in water are subject to concurrent general acid and general base catalysis by formate, acetate, and several other buffers. A subsequent full paper[2b] reported details of their study in respect to the phenolic acids, but details concerning lactonization of **1** have not appeared. Inasmuch as catalysis of the lactonization of **1** was of special interest to us, we undertook a reexamination of the rates of lactonization of **1** in formic acid–formate ion buffers at 60°. Our results confirm the report[2a] that the reaction is catalyzed by both the acidic and basic constituents of the buffer.



1

Results and Discussion

The rates of lactonization of **1** in formic acid buffers were studied under pseudo-first-order conditions identical with those used by Milstien and Cohen,[2a] that is, 60.0° and an ionic strength, μ, of 0.30. Although previous studies[3,4] were available on the hydrogen ion catalyzed lactonization at 60° under slightly different conditions, we also determined this rate constant at 60.0° and μ 0.30 using two different hydrochloric acid concentrations. Also, the apparent ionization constants (K_a's) of **1** and of formic acid were measured under the reaction conditions.

A composite rate law[1] was found for the lactonization in formic acid buffers, as set forth in eq 1, where

$$k_\psi = \alpha(k_0 + k_{H^+}[H^+] + k_{HA}[HA] + k_{A^-}[A^-]) \qquad (1)$$

k_ψ is the pseudo-first-order rate coefficient, α is the fraction of substrate undissociated at a particular pH, k_0 and k_{H^+} are the water and hydrogen ion catalyzed components of the rate, and k_{HA} and k_{A^-} are the rate constants for catalysis by the buffer acid and its conjugate base, respectively.

Since the buffer components are present in large excess over the substrate, α can be calculated for each buffer without knowledge of the actual pH, provided that the relative pK_a's of the buffer acid and the substrate are known under the reaction conditions. The determination of these ionization constants is described in the Experimental Section; the observed values are pK_a = 3.66, formic acid, and pK_a = 3.79, **1**. These values compare with pK_a = 3.77 at 30° and μ 0.3 for formic acid, reported by Milstien and Cohen,[2b] and pK_a = 3.84 at room temperature and μ <0.01, reported[4] for **1**. From these experimental pK_a's, α was evaluated for each buffer and used to calculate the corrected pseudo-first-order rate coefficients, $k_\psi' = k_\psi/\alpha$.

In order to simplify determination of the several rate constants, two sets of buffer experiments were performed. The first set consisted of eight kinetic runs at a constant buffer ratio of [HA]/[A⁻] = 1 but with variation of the total buffer concentration. Under these conditions eq 1 simplifies to eq 2, where

$$k_\psi' = k_0 + k_{H^+}K_{HA} + (k_{HA} + k_{A^-})[HA] \qquad (2)$$

K_{HA} is the ionization constant of formic acid. A plot of k_ψ' *vs.* [HA] for these runs (Table I, runs 1–8) is shown in Figure 1; the slope is ($k_{HA} + k_{A^-}$) and the intercept ($k_0 + k_{H^+}K_{HA}$).

In the second set of experiments the concentration of formate ion was held constant at 0.30 *M* while five different formic acid concentrations were employed (runs 8, 12–15). For these conditions eq 3 applies.

$$k_\psi' = k_0 + k_{A^-}[A^-] + (k_{H^+}K_{HA}/[A^-] + k_{HA})[HA] \qquad (3)$$

The anticipated linear plot of k_ψ' *vs.* [HA] was obtained; it is not shown. Since the intercept is $k_0 + 0.30\ k_{A^-}$,

---

[1] S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

[2] (a) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **91**, 4585 (1969); (b) *ibid.*, **92**, 4377 (1970).

[3] J. Tirouflet, *Bull. Soc. Chim. Fr.*, 799 (1954).

[4] J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, **87**, 2214 (1965).