Products, Kinetics, and Mechanism in the Acetolysis of 2,3-Dichloro-2,3-dihydrobenzofuran. An E1 Elimination with a Rate-Determining Proton Transfer

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The acetolysis of *trans*-2,3-dichloro-2,3-dihydrobenzofuran (I) leads to the formation of 65% 2-chlorobenzofuran (II) and 31% 2(3*H*)-benzofuranone (III), together with smaller amounts of 3-chlorobenzofuran (IV) and *trans*-2,3-diacetoxy-2,3-dihydrobenzofuran (V). In the presence of sodium acetate the yield of V increases at the expense of that of III. Normal salt effects on the solvolysis rate are exhibited by LiCl, LiClO$_4$, and CH$_3$COONa. A deuterium kinetic isotope effect of 1.9 at 102 °C is calculated by comparing the reactivities of I and of *trans*-2,3-dichloro-2-deuterio-2,3-dihydrobenzofuran (I-*d*). These results indicate that the acetolysis of I takes place by a reversibly formed intimate ion pair from which elimination and substitution products are obtained in rate-determining steps. A route for the conversion of the first formed substitution product into III and V is suggested.

Within the aim of obtaining information on the role of addition compounds in the electrophilic substitutions of benzofurans we are currently investigating the course of the decomposition reaction of these adducts under different experimental conditions.[1-4] Recently, the reactions of *trans*-2,3-dibromo-2,3-dihydrobenzofuran with halide ions have been studied;[4] in this paper we wish to report the products, analysis, and kinetics of the solvolysis of *trans*-2,3-dichloro-2,3-dihydrobenzofuran (I) and *trans*-2,3-dichloro-2-deuterio-2,3-dihydrobenzofuran (I-*d*) in acetic acid.

Results

In dry acetic acid at 102 °C the solvolysis of I leads to the formation of four compounds: 2-chlorobenzofuran (II), 2(3*H*)-benzofuranone (III), 3-chlorobenzofuran (IV), and 2,3-diacetoxy-2,3-dihydrobenzofuran (V), II and III being by far the main reaction products.

Compounds III and IV have been identified by comparison with authentic specimens, while structures of compounds II and V have been assigned by spectral analysis and comparison with literature data. Appropriate experiments have shown that III is formed in the reaction medium and not during the workup of the reaction mixture. Details are reported in the Experimental Section.

The yields of the solvolysis products have been determined by GPC and the results are reported in Table I. It is immediately noted that when the solvolysis is carried out in the presence of sodium acetate the yield of V increases significantly at the expense of that of III, whereas the yields of II and IV are unaffected. Starting from I-*d* the yield of II decreases and a corresponding increase in that of the other three compounds is observed. The presence of sodium acetate has the same effect as in the solvolysis reaction of I.

The kinetic study has been carried out by following spectrophotometrically the disappearance of I or I-*d* at 300 nm. In each case excellent first-order plots have been obtained up to 80% of reaction. The results, reported in Table II, indicate that sodium acetate, in spite of its remarkable effect on the products composition, does not influence the solvolysis rate of I apart from a normal salt effect. LiClO$_4$ and LiCl also exhibit normal salt effects.

Comparing the reactivity of I with that of I-*d* a deuterium kinetic isotope effect (k_H/k_D) of 1.9 ± 0.05 has been calculated.

Discussion

The observation that the presence of sodium acetate does not change the relative yield of the elimination products and has only a small rate effect clearly indicates that no bimolecular elimination induced by the solvent takes place[5] and that both II and IV are formed in an E1 process.

Information on the nature of the main E1 process, leading to II, is given by the study of the deuterium kinetic isotope effect. The observed value (1.9 at 102 °C) appears to be too high to be attributed to a secondary isotope effect of a β hydrogen on the formation of a carbonium ion type intermediate. Abnormally high secondary isotope effects have been observed in solvolytic reactions involving neighboring hydrogen participation in the displacement of the leaving group;[6] however, this possibility is precluded with I by the syn relationship between the β hydrogen and chlorine. We therefore conclude that the k_H/k_D value found for the solvolysis of I is strongly indicative of a slow proton loss from a cationoid intermediate.[7]

Concerning the structure of this intermediate, the absence of a mass-law effect by chloride ions rules out a reversibly formed solvated carbonium ion. A solvent-separated ion pair which undergoes external return can also be excluded, as no special salt effect is exhibited by LiClO$_4$. A reasonable conclusion is therefore that II derives from the intimate ion pair VI, as shown in Scheme I, with k^H_{-1} significantly larger than k^H_E.[8] In the intimate ion pair, which can also give substitution

Scheme I
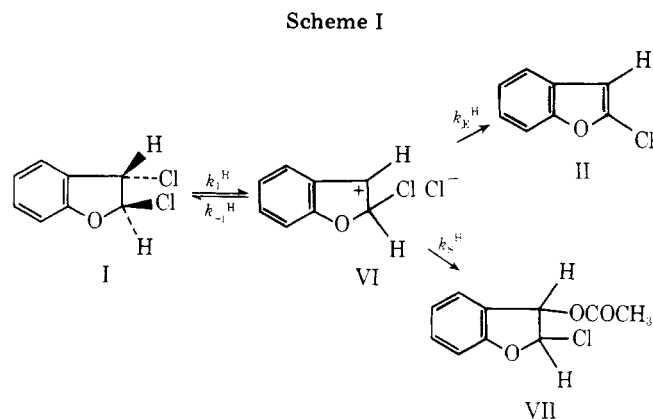
Table I. Product Distribution (mol %)[a] in the Acetolysis of *trans*-2,3-Dichloro-2,3-dihydrobenzofuran (I) and *trans*-2,3-Dichloro-2-deuterio-2,3-dihydrobenzofuran (I-*d*) at 102 °C

substrate[b]	II[f]	III[g]	IV[h]	V[i]
I[d]	64.8	31.0	3.1	1.0
I-*d*[e]	47.9	44.1	4.8	3.4
I[c]	67.9	4.9	3.0	24.6
I-*d*[c]	50.2	6.0	4.5	39.5

[a] Average values of several runs (±5%). [b] Substrate 0.016 M. [c] In the presence of 0.0415 M CH_3COONa. [d] Registry no. 63361-57-9. [e] Registry no. 68024-40-8. [f] Registry no. 63361-60-4. [g] Registry no. 553-86-6. [h] Registry no. 63361-59-1. [i] Registry no. 68024-41-9.

products (see infra), the proton is probably abstracted by the counterion Cl^-, a fairly strong base in acetic acid.

A support to the suggestion that an ion pair such as VI prefers reverting to the starting material rather than proceeding toward the products is furnished by the observation that *cis*-2,3-dichloro-2,3-dihydrobenzofuran isomerizes to the trans isomer I, in acetic acid at 80 °C, without giving solvolysis products. The rate constant for the isomerization is ca. 6 × 10^{-4} s^{-1}. Clearly, the tight ion pair formed from the cis derivative (which should be very similar to VI, though not identical) exhibits a rate of internal return, with isomerization, much larger than that of the other possible processes, proton loss or nucleophilic attack by the solvent.

When the observed k_H/k_D value is corrected for the different yields of II from I and I-*d*, Table I, a value of 2.5 is obtained which is the product between the isotope effect in the equilibrium formation of the ion pair (K^H/K^D) and in the elimination step (k^H_E/k^D_E).[9] Since the K^H/K^D value is expected to be not significantly different from 1.2,[10] a k^H_E/k^D_E value of ca. 2.1 at 102 °C can be estimated. At this temperature the maximum value of a primary deuterium kinetic isotope effect is ca. 4.2; therefore, our result indicates an unsymmetrical transition state, presumably more reactant-like than product-like, for the reaction leading from VI to II. Values of deuterium kinetic isotope effect for proton loss from carbocations larger than that observed in our system have been found in the solvolytic elimination of some phenyldimethylcarbinyl derivatives[13] and in some acid-catalyzed dehydrations.[12,14] In these cases, however, much lower temperatures were used.

Since II accounts only for ca. 65% of the reaction product, it is reasonable to suggest that, as indicated in Scheme I, a substitution product, probably 2-chloro-3-acetoxy-2,3-dihydrobenzofuran (VII), is formed from VI. In the reaction medium, VII is then converted into both III and V. This suggestion is supported by the fact that the relative yields of III and V increase significantly with respect to that of II when the substrate is changed from I to I-*d*, which is easily rationalizable if both these compounds derive from the ion pair VI and take therefore advantage of the slowing down of the proton loss rate when the ion pair is formed from I-*d*. If VII is formed directly from VI it should have a cis structure since the collapse of an intimate ion pair occurs with inversion of configuration.[15] However, VII could also derive from a solvent-separated ion pair formed from VI in a slow step and have therefore the more stable trans structure.[16] If *trans*-VII is formed, the mechanism reported in Scheme II for the conversion of VII into III and V may be suggested. According to this mechanism the acetoxonium ion VIII is rapidly formed by neighboring participation of the acetoxy group. From VIII the formation, irreversible, of the diacetoxy adduct V and that, reversible, of the carbocation IX is possible. Proton loss from IX then gives 2-acetoxybenzofuran (X) which, in turn, may

Table II. Rate Constants for the Acetolysis of *trans*-2,3-Dichloro-2,3-dihydrobenzofuran (I) and *trans*-2,3-Dichloro-2-deuterio-2,3-dihydrobenzofuran (I-*d*) at 102 °C

| substrate[a]	added salt, M	$k_1 \times 10^4$, s^{-1}
I		1.79[b]
	$LiClO_4$,[c] 4.3 × 10^{-4}	2.06
	1.3 × 10^{-3}	2.09
	2.1 × 10^{-3}	2.11
	1.2 × 10^{-2}	2.40
	3.0 × 10^{-2}	3.06
	6.2 × 10^{-2}	4.35
	CH_3COONa,[d] 1.6 × 10^{-3}	1.97
	4.9 × 10^{-3}	2.29
	2.1 × 10^{-2}	2.39
	4.2 × 10^{-2}	2.73
	$LiCl$,[e] 1.5 × 10^{-2}	1.71
	3.3 × 10^{-2}	1.82
	4.9 × 10^{-2}	1.89
I-*d*		0.93[b]

[a] Substrate ca. 1.3 × 10^{-3} M. [b] Average of at least two runs. [c] Registry no. 7791-03-9. [d] Registry no. 127-09-3. [e] Registry no. 7447-41-8.

Scheme II
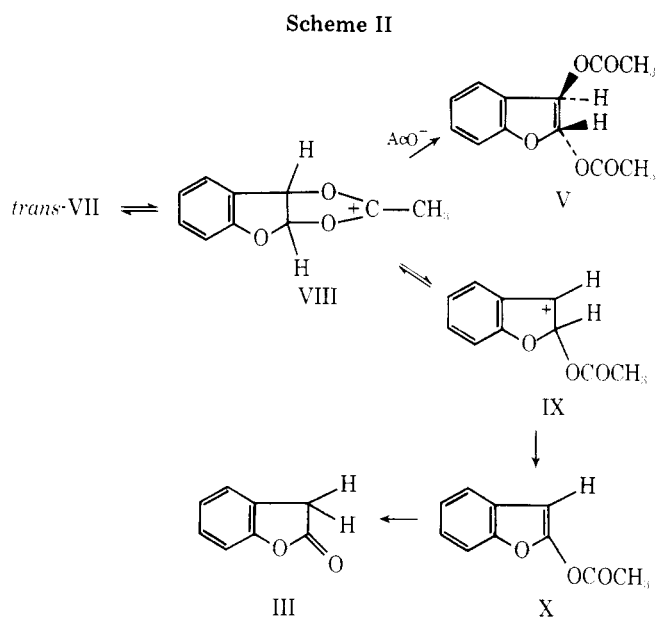
be converted into 2(3*H*)-benzofuranone (III).[17] Since it seems reasonable to expect an increase in the rate of the step leading from VIII to V in the presence of sodium acetate, this mechanism would explain the increase in the yield of V at the expense of that of III observed when the solvolysis is carried out in the presence of this salt. Moreover, the mechanism of Scheme II is also consistent with the finding that the product ratio III/V decreases when the substrate is changed from I to I-*d*, as the pathway leading to III is negatively affected by the isotopic substitution.

If both III and V derive from VII, the ratios of the yields of elimination and substitution products II/(III + V), in the solvolysis of I and I-*d*, can be divided by one another to give the ratio between the kinetic isotope effects in the elimination (k^H_E/k^D_E) and in the substitution (k^H_S/k^D_S) reactions of the ion pair. Since k^H_S/k^D_S should be very close to unity, we again obtain a k^H_E/k^D_E value of ca. 2.1, in perfect agreement with that previously evaluated from the kinetic data on the basis of an assumed value of K^H/K^D.

Finally, the presence of 3-chlorobenzofuran (IV) in the re-

XI
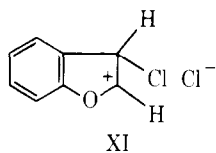
action products indicates that also the ion pair XI, where the carbocation has the positive charge on the 2 position, can be obtained from the ionization of I. If, as it is likely, XI is also formed in a fast preequilibrium, no certain indication can be drawn on the relative stability of VI and XI from the relative yields of II and IV since the rate of proton loss from the two ion pairs might be significantly different. For the same reason, from the orientation observed in the electrophilic aromatic substitutions of benzofuran[18] no firm conclusion can be drawn on the relative stability of the intermediate σ complexes, structurally similar to VI and XI formed by the electrophilic attack at the 2 and 3 positions.

Experimental Section

***trans*-2,3-Dichloro-2,3-dihydrobenzofuran** (I) and ***trans*-2,3-dichloro-2-deuterio-2,3-dihydrobenzofuran** (I-*d*) were prepared from benzofuran and benzofuran-2-*d* respectively as previously described.[3] Benzofuran-2-*d* was in turn prepared, as described in the literature,[19] by D$_2$O quenching of benzofuryllithium[20] in Et$_2$O: bp 62 °C at 15 mm; NMR (CCl$_4$) δ 6.60 (1 H, s, 3-H), 7.00–7.55 (4 H, m, Ar–H); mass spectrum (70 eV) *m/e* 119, M$^+$, isotopic purity ≥98%.

3-Chlorobenzofuran (IV) was prepared by treating I with alcoholic KOH: NMR (CCl$_4$) δ 7.42 (1 H, s, 2-H), 7.00–7.55 (4 H, m, Ar–H); mass spectrum (70 eV) *m/e* (rel intensity) 152, M$^+$ (100), 154 (32); bp 198–199 °C (lit.[21] bp 199–201 °C).

2(3*H*)-Benzofuranone (III) was prepared by lactonization of *o*-hydroxyphenylacetic acid: mp 49–50 °C (lit.[22] mp 49 °C); NMR (CCl$_4$)[23] δ 3.54 (2 H, s, ArCH$_2$), 6.80–7.40 (4 H, m, Ar–H); mass spectrum (70 eV) *m/e* 134, M$^+$; IR (Nujol) 1820 cm^{-1}.

Identification and Quantitative Analysis of the Solvolysis Products. *trans*-2,3-Dichloro-2,3-dihydrobenzofuran (I) (6 g) in AcOH (200 mL) was kept at about 100 °C for 12 h. The reaction mixture was added to petroleum ether and the resulting solution was poured into H$_2$O. The separated organic layer was washed with H$_2$O and dried and the solvent was removed at room temperature. From the fractionated distillation of the residue at atmospheric pressure, two compounds boiling at 200–206 °C and at 239–244 °C were collected. The former, redistilled under reduced pressure, was shown to be 2-chlorobenzofuran (II): NMR (CCl$_4$) δ 6.39 (1 H, s, 3-H), 7.00–7.55 (4 H, m, Ar–H); mass spectrum (70 eV) *m/e* (rel intensity) 152, M$^+$ (100), 154 (32); lit.[21] bp 203–204 °C. The second compound, a colorless solid, mp 49–50 °C (crystallization from petroleum ether), turned out to be 2(3*H*)-benzofuranone (III) after spectral analysis and comparison with an authentic specimen.

GLC analysis showed that two other products were formed, in very small amount, in the solvolysis of I. One of the two resulted in 3-chlorobenzofuran by comparison of retention times with a sample prepared as described above. The other, isolated by preparative GLC, from an acetolysis experiment in the presence of CH$_3$COONa, showed spectral characteristics: NMR (CCl$_4$) δ 2.03 (6 H, s, 2- and 3-COMe), 5.93 (1 H, s, 3-H), 6.50 (1 H, s, 2-H), 6.80–7.50 (4 H, m, Ar–H); IR (film) 1760 cm^{-1}; mass spectrum (15 eV) *m/e* 236, M$^+$ in full agreement with the structure of *trans*-2,3-diacetoxy-2,3-dihydrobenzofuran.

For the quantitative product analysis solvolyses were carried out at 102 °C in sealed Pyrex tubes, using ca. 40 mg of substrate in 10 mL of AcOH (fractionated twice). After an appropriate time (8–24 h, depending on the reactivity of the substrate) an internal standard (*o*-methoxyacetophenone) was added to the reaction mixture which was worked up as described above. The residue was analyzed by GPC on a C. ERBA Model GI gas chromatograph at 160 °C on a 2 m × 2 mm column packed with 10% LAC 728 (compounds II + IV, III, and

V) and at 110 °C on 10% bentone:didecylphthalate (1:1) (compounds II and IV). The overall recovery was always greater than 95%. Appropriate experiments showed that: (a) no decomposition of the monochlorobenzofurans occurs under solvolytic conditions; and (b) no change in the products distribution was observed when the residue for the analysis was directly obtained by removing the solvent acetic acid under reduced pressure.

Isomerization of *cis*-2,3-Dichloro-2,3-dihydrobenzofuran. *cis*-2,3-Dichloro-2,3-dihydrobenzofuran[3] (30 mg) was placed in 0.5 mL of CH$_3$COOD in a NMR tube, and this was heated at 80 °C in the probe of a JNM-C-60HL spectrometer equipped with a variable temperature controller (JES-VT-3). In ca. 3 h the doublets at δ 5.66 (3-H) and 6.63 (2-H) disappeared and were replaced by the singlets at δ 5.48 (3-H) and 6.53 (2-H) attributable to the trans isomer.[3]

Kinetic Procedure. The substrate and, when necessary, the added salt were weighed in a 50-mL volumetric flask and AcOH was added to the mark. Aliquots (4 mL) were placed in a constant-temperature bath using the sealed tube technique. At recorded times the tubes were plunged into ice-cold water and the content analyzed spectrophotometrically at 300 nm on a Beckman DB-GT instrument for the disappearance of the substrate.

References and Notes

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(7) The observed results could also be compatible with a single-step intramolecular syn elimination of HCl. The intervention of the carbonium ion type intermediate in the solvolysis of I is, however, strongly supported by the observation of a relatively fast isomerization in acetic acid of *cis*-2,3-dichloro-2,3-dihydrobenzofuran into I (see infra).
(8) (a) For review on the role of ion pairs on solvolytic reactions see: D. J. Raber, J. M. Harris, and P. v. R. Schleyer in "Ions and Ion Pairs in Organic Reactions", Vol. 2, M. Szwarc, Ed., Wiley, New York, N.Y., 1974, Chapter 3. (b) Proton loss from a solvent-separated ion pair formed in a slow step is incompatible with the observation of a primary kinetic isotope effect.
(9) k^D_E is the rate constant for the proton loss from the intimate ion pair formed, I-*d*.
(10) A value of 1.23 has been estimated for the equilibrium formation of the intimate ion pair in the solvolysis of *cis*-β-*d*-cyclopentyl brosylate in ethanol–water and trifluoroethanol–water mixtures.[11] A value of 1.17 has been assumed in the reversible formation of the 1,2-diphenylethyl cation in aqueous sulfuric acid.[12]
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