Kinetic Study of the Base-Induced Anti and Syn Eliminations from 2,3-Dihalogeno-2,3-dihydrobenzofurans in Different Base–Solvent Systems

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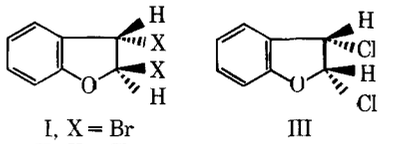
Syn eliminations from *trans*-2,3-dibromo-, *trans*-2,3-dichloro-, *trans*-2,3-dibromo-3-deuterio-, and *trans*-2,3-dibromo-5-chloro-2,3-dihydrobenzofuran and anti eliminations from *cis*-2,3-dichloro-2,3-dihydrobenzofuran have been investigated in different base–solvent systems. Anti elimination is favored over the syn by a factor of ~33 000 in EtONa–EtOH, ~10 000 in *t*-BuOK–*t*-BuOH, and >10 000 in *t*-BuOK–*t*-BuOH, in the presence of 18-crown-6 ether. The rate of both the anti and syn pathway increases with increasing the medium basicity, the syn path being also favored, however to much less extent, by base association. From the values of the deuterium kinetic isotope effect and substituent effect it can be concluded that the transition state structure for the syn elimination from *trans*-2,3-dibromo-2,3-dihydrobenzofuran is significantly affected by base association, but not by medium basicity.

trans-2,3-Dihalogeno-2,3-dihydrobenzofurans are very suitable substrates for the study of elimination processes owing to their tendency to be converted by bases into the aromatic benzofuran system. Recently we have investigated the reactions of *trans*-2,3-dibromo-2,3-dihydrobenzofuran (I) with bromide and chloride ions in dipolar aprotic solvents.[1] With bromide ions I is dehalogenated to benzofuran, whereas with chloride ions it gives mainly *trans*-2,3-dichloro-2,3-dihydrobenzofuran (II)[2] together with ca. 10% of 3-bromobenzofuran presumably formed in a syn dehydrobromination process. Syn dehydrohalogenation, however, is the only reaction observed when I or II reacts with an alkoxide in the corresponding alcohol.

Owing to the increasing importance of syn elimination reactions, it seemed interesting to carry out a detailed kinetic investigation, including the determination of deuterium kinetic isotope effect and substituent effect of the reactions of I and II in different alkali alkoxide–alcohol systems. For comparison purposes some anti eliminations from *cis*-2,3-dichloro-2,3-dihydrobenzofuran (III) have also been studied.[3]

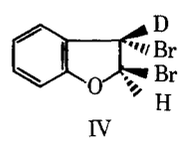
Results and Discussion

The eliminations from I–III, *trans*-2,3-dibromo-3-deuterio-2,3-dihydrobenzofuran (IV), and *trans*-2,3-dibromo-5-chloro-2,3-dihydrobenzofuran (V) have been studied in EtOK–EtOH, *n*-BuOK–*n*-BuOH, *t*-BuOK–*t*-BuOH, *n*-BuOK–18C6–*n*-BuOH (18C6 is 18-crown-6 ether), and *t*-BuOK–18C6–*t*-BuOH. Some experiments for the reactions of I–III in EtONa–EtOH have been also carried out. In each

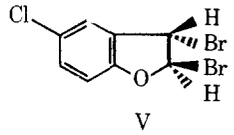


I, X = Br
II, X = Cl

III



IV



V

base–solvent system all of the substrates give the corresponding 3-halogenobenzofuran derivative in a quantitative yield. The product is formed in a bimolecular process since in no case have blank experiments given evidence for the incursion of a unimolecular elimination.

Kinetic experiments have been carried out by following spectrophotometrically the disappearance of the substrate at 300 nm. The concentration of the substrate has been in the range 10^{-4}–10^{-3} M and that of the base between 5×10^{-3} and 0.9 M, depending on the reactivity of the substrate and the base–solvent system. The base has always been in strong excess (at least tenfold) with respect to the substrate and regular first-order kinetics have been observed. The second-order rate constants (k_2), calculated as usual from those of first order, are reported in Table I.

Data displayed in Table I clearly indicate that III exhibits an extremely larger reactivity than II (ca. 33.000-fold in EtONa–EtOH and ca. 10.000-fold in *t*-BuOK–*t*-BuOH). Thus, in the system under consideration anti elimination is very much favored over syn elimination. While this high stereospecificity strongly suggests that the anti process from III is a concerted reaction, the possibility of an E1cb mechanism for the syn eliminations from II (and, of course, also from I) should be considered.

Among the different E1cb mechanisms,[4] that involving an irreversibly formed carbanion is made unlikely by the substantial leaving group effect which can be evinced from the greater reactivity of I with respect to II (33- and 14-fold in EtONa–EtOH and *t*-BuOK–*t*-BuOH, respectively). This difference should be essentially due to the different nature of the leaving group since chlorine and bromine, attached at the β carbon, are expected to have very similar effects on the rate of the elimination reaction.[5] The reversible formation of a carbanion can also be ruled out on the basis of the values of the deuterium kinetic isotope effect for the reactions of I, reported in Table II.[4] Thus, it would remain the choice between a concerted and an E1cb mechanism involving a tightly solvated carbanion.[4–8] We feel that the former is much more probable since our substrates have good leaving groups and a concerted mechanism is commonly accepted also for the syn and anti eliminations from 9,10-dichloroacenaphene,[9] a system very similar to ours with respect to the stability of an intermediate carbanion.[10]

The change of the reaction medium from EtONa–EtOH to *t*-BuOK–*t*-BuOH causes a very significant increase in the rate of both syn and anti elimination (about 350- and 100-fold, respectively), indicating that both pathways are favored by the increase in the basicity of the base–solvent system. The larger increase exhibited by the syn reaction is probably to be related to the favorable influence exerted on this process by base association which is much more important in *t*-BuOK–*t*-BuOH than in EtONa–EtOH. Accordingly, an associated

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Table I. Kinetic Data for the Elimination Reactions of I–V in Different Base–Solvent Systems at 30 °C

substrate	registry no.	base–solvent	[B], M	[18C6], M	k_2,[a] M^{-1} s^{-1}
I	58863-52-8	EtONa–EtOH	0.154		3.05×10^{-2}
			0.330		3.22×10^{-2}
			0.706		4.03×10^{-2}
		EtOK–EtOH	0.170		4.44×10^{-2}
		n-BuOK–*n*-BuOH	0.092		4.69×10^{-2}
			0.034	0.071	1.88×10^{-1}
		t-BuOK–*t*-BuOH	0.0051		5.00
			0.102		8.85
			0.0049	0.0097	770
			0.025	0.053	2231
II	63361-57-9	EtONa–EtOH	0.125		9.10×10^{-4}
			0.342		9.34×10^{-4}
			0.670		1.08×10^{-3}
			0.890		1.19×10^{-3}
		t-BuOK–*t*-BuOH	0.005		3.49×10^{-1}
			0.009		3.30×10^{-1}
			0.05		6.30×10^{-1}
			0.004	0.0083	15.6
III	63361-58-0	EtONa–EtOH	0.11		33.9
		t-BuOK–*t*-BuOH	0.008		3380
			0.0041	0.0091	>200.000
IV	68051-08-1	EtOK–EtOH	0.17		1.49×10^{-2}
		n-BuOK–*n*-BuOH	0.092		1.43×10^{-2}
			0.034	0.071	6.66×10^{-2}
		t-BuOK–*t*-BuOH	0.0051		2.48
			0.102		5.01
			0.0049	0.0102	258
			0.0126	0.026	419
			0.025	0.053	723
V	68051-09-2	EtOK–EtOH	0.17		5.30×10^{-1}
		n-BuOK–*n*-BuOH	0.092		5.10×10^{-1}
			0.034	0.071	2.98
		t-BuOK–*t*-BuOH	0.0051		37.1
			0.102		62.7
			0.0049	0.0102	11840

[a] Average of at least two determinations. The average error is ±2%.

Table II. Deuterium Isotope Effect and Substituent Effect in the Elimination Reactions of *trans*-2,3-Dibromo-2,3-dihydrobenzofuran at 30 °C

base–solvent	k_H/k_D[a]	k_{Cl}/k_H[b]
EtOK–EtOH	3.0	12.0
n-BuOK–*n*-BuOH	3.3	11.0
n-BuOK–18C6–*n*-BuOH	2.8	15.8
t-BuOK–*t*-BuOH	1.8[c]	7.1[c]
	2.0[d]	7.4[d]
t-BuOK–18C6–*t*-BuOH	3.0[d]	15.4[d]
	3.1[e]	

[a] Average error ±3%. [b] Average error ±4%. [c] [*t*-BuOK], 0.1 M. [d] [*t*-BuOK], 5×10^{-3} M. [e] [*t*-BuOK], 2.5×10^{-2} M.

base has the possibility of simultaneously coordinating the proton and the leaving group in the transition state of a syn elimination.[11] Thus, in *t*-BuOK–*t*-BuOH the preference for the anti path is less than in EtONa–EtOH.

When a crown ether is added to *t*-BuOK–*t*-BuOH we have a strong increase in the medium basicity and a significant decrease in the extent of base association. A further large rise in the rate of both syn and anti elimination is observed, thus indicating that in the case of the syn process the unfavorable effect of the decrease in base association is largely outweighed by the increase in the medium basicity. This shows that medium basicity is a much more important factor than base association in determining the rate of a syn elimination. In going from *t*-BuOK–*t*-BuOH to *t*-BuOK–18C6–*t*-BuOH the rate enhancement is greater for the anti than for the syn process, as expected on the basis of the foregoing discussion; however, an exact figure cannot be given in this case owing to the too high reaction rate of III in the latter base–solvent system.

It can also be noted that the anti:syn elimination rate ratios found in our system are, as far as we know, the largest ever observed in reactions of five-membered rings. For instance, in the dehydrochlorination with NaOH–C_2H_5OH of the isomeric 9,10-dichloroacenaphthenes, anti elimination is approximately 750 times faster than syn elimination[9] and lower values are found in other systems.[12] Probably *cis*-2,3-dichloro-2,3-dihydrobenzofuran has a higher degree of rotational flexibility than *cis*-9,10-dichloroacenaphthene allowing anti coplanarity of the proton and leaving group. Moreover, anti elimination should be favored over the syn by less steric hindrance to the approach of the base and steric relief of both eclipsing strain and dipolar repulsion of the two cis chlorine atoms.[12]

Another interesting observation is that the k_2 values for the reactions of I and II in EtONa–EtOH and *t*-BuOK–*t*-BuOH slightly increase with increasing base concentration. The phenomenon could simply be due to an increase in the medium basicity that is more rapid than the increase in the base concentration or to an increase in the elimination rate faster than that in the medium basicity. However, it is noteworthy that when anti eliminations from 2-arylethyl derivatives are considered, k_2 has been found to *decrease* in EtONa–EtOH[13,14] and to remain practically *unchanged* in *t*-BuOK–*t*-BuOH,[15,16] as the base concentration increases. The dependence of k_2 on EtONa concentration in anti eliminations

has been related to the fact that the proportion of contact EtO^-Na^+ ion pairs increases with respect to that of free ions, EtO^-, as the base concentration becomes higher.[13] Since the former are expected to be less reactive than the latter the decrease in the k_2 values is rationalized. If this interpretation is correct the opposite trend observed for the syn eliminations in EtONa–EtOH could indicate that, in this case, contact ion pairs are more reactive than free ions owing to the already mentioned possibility of forming a cyclic transition state.[17] Similarly, the trend in the k_2 values of the syn elimination in *t*-BuOK–*t*-BuOH could be explained by suggesting a greater reactivity of ionic aggregates with respect to contact ion pairs in this base–solvent system. Interestingly, the intervention of more reactive multiple ions has already been suggested for the reaction of 1-halo-2,2-diphenylethylenes in *t*-BuOK–*t*-BuOH.[18] Whatever the explanation, since k_2 is independent of *t*-BuOK concentration in anti eliminations the present kinetic result confirms a previous observation that in *t*-BuOK–*t*-BuOH an increase in base concentration favors the syn pathway with respect to the anti one.[19]

A rise in the k_2 values (in this case very significant) with increasing base concentration is also exhibited by the reaction of I in *t*-BuOK–18C6–*t*-BuOH. This phenomenon, however, does not appear to be peculiar of a syn elimination process, since it has been already observed in the anti eliminations from 2-arylethyl bromides[15] and 1-chloro-1-phenyl-2-arylethanes.[20]

By comparing elimination rates of V and I, and of I and IV (Table I), the rate effect of the 5-chlorine substituent (k_{Cl}/k_H) and the deuterium kinetic isotope effect (k_H/k_D), respectively, for the reaction of I in different base–solvent systems have been evaluated (Table II). In each case, kinetic data at the same base concentration have been used. Since, unlike k_2, both k_H/k_D and k_{Cl}/k_H appear to be independent of the base concentration we feel that they can be safely discussed in terms of transition state structure.

In EtOK–EtOH the value of k_H/k_D is significantly lower than the maximum value expected for a transition state where the proton is about half transferred to the base and therefore can be indicative of an E1-like or an E1cb-like transition state. The latter possibility seems the more probable since the significant accelerating effect (k_{Cl}/k_H = 12) of the 5-chlorine substituent, which acts from a meta position, suggests a transition state with a substantial carbanion character, as expected for a β-phenyl and β-bromine activated system.

No significant variation in k_H/k_D and k_{Cl}/k_H is observed when the base–solvent system is changed from EtOK–EtOH to *n*-BuOK–*n*-BuOH. The reaction rate also remains practically unchanged. There is no doubt, therefore, that the structure of the transition state is very similar for the eliminations in these two base–solvent systems. The addition of 18C6 to *n*-BuOK–*n*-BuOH causes a little accelerating effect on the elimination rate (ca. four-fold), indicating that *n*-BuOK is not associated to a very large extent in *n*-BuOH. No substantial modification of the transition state structure is observed either, even though the small changes in k_H/k_D and k_{Cl}/k_H could suggest a very slight shift toward the carbanionic side.

In *t*-BuOK–*t*-BuOH both k_H/k_D and k_{Cl}/k_H are significantly smaller than in EtOK–EtOH.[21] The decreased value of k_{Cl}/k_H clearly indicates a less carbanion character for the transition state of the reaction in *t*-BuOK–*t*-BuOH. More uncertain is the interpretation of the decrease in k_H/k_D owing to the double-valued nature of the primary deuterium kinetic isotope effect. A possible rationalization is that the change from EtOK–EtOH to *t*-BuOK–*t*-BuOH leads to a decrease in the extent of proton transfer in the transition state which may therefore move from a situation where the proton is more than half transferred to the base to a situation in which it is less than half transferred.[23]

A less carbanionic transition state for the syn elimination in *t*-BuOK–*t*-BuOH with respect to the corresponding reaction in EtOK–EtOH is plausible in light of the already mentioned possibility that the strongly associated *t*-BuOK in *t*-BuOH simultaneously interacts with the proton and leaving group. In this situation the breaking of the leaving group should be easier, thus requiring less buildup of negative charge on the β carbon in the transition state. The major role played by base association in determining the observed variation in the transition state structure is clearly shown by the finding that in *t*-BuOK–*t*-BuOH containing 18C6 the transition state structure undergoes a shift toward the carbanion side, similar to that of the reactions in EtOK–EtOH, *n*-BuOK–*n*-BuOH, and *n*-BuOK–18C6–*n*-BuOH, as indicated by k_H/k_D and k_{Cl}/k_H values. Since *t*-BuOK–18C6–*t*-BuOH has a much larger basicity than the other base–solvent systems, this result clearly indicates that changes in the medium basicity have no significant effect on the transition state structure of the syn eliminations from I.

Finally, it is interesting to compare our results with those obtained in the syn eliminations from *trans*-2-arylcyclopentyl tosylates.[24] In the latter reaction too, a change from *t*-BuOK–*t*-BuOH to *t*-BuOK–18C6–*t*-BuOH leads to a more carbanionic, less concerted transition state. However, the k_H/k_D value is unaffected, whereas a substantial increase is observed with our substrate. Thus, it seems that the extent of proton transfer in the transition state is influenced by base association in the reaction of I but not in that of the cyclopentyl tosylate. Another major difference between the two substrates concerns the effect of changing medium basicity. As already observed the change from *t*-BuOK–18C6–*t*-BuOH to *n*-BuOK–18C6–*n*-BuOH does not modify the structure of the transition state for the reaction of I. In contrast, a very large effect (marked diminution in both k_H/k_D and ρ) has been observed in the reactions of 2-arylcyclopentyl tosylates.

The different response of the transition state structure to changes in the solvent–base system exhibited by the syn eliminations from *trans*-2-arylcyclopentyl tosylate and I is not completely unexpected since recent theoretical study has suggested that in an E2 process the sensitivity of the transition state to structural modifications of reactants depends on the character of the transition state itself and on its position in the More O'Ferrall's potential energy diagram.[25] Interestingly, also in anti eliminations, changes in medium basicity do not significantly affect the transition state structure of the reactions of 2-arylethyl bromides[15,16] but substantially modify that of the reactions of 1-chloro-1-phenyl-2-arylethanes.[20]

Experimental Section

Materials. Benzofuran was a commercial sample (Fluka: bp 173–175 °C) distilled at atmospheric pressure.

3-Deuteriobenzofuran. Attempts to obtain this compound with 3-benzofuryllithium[26] and D_2O were unsuccessful. Thus, it was prepared by distilling at atmospheric pressure 3-hydroxy-3-deuterio-2,3-dihydrobenzofuran obtained by reduction of 3(2*H*)-benzofuranone[27] with $LiAlD_4$ in Et_2O: bp 173 °C; NMR (CCl_4) δ 7.00–7.50 (4 H, m, Ar–H), 7.40 (1 H, s, 2-H); mass spectrum (70 eV) *m/e* 119, M^+, isotopic purity ≥99%.

5-Chlorobenzofuran was prepared as described in the literature:[28] bp 215 °C; NMR (CCl_4) δ 6.56 (1 H, dd, J_{2-3} = 2.2 and J_{3-7} = 0.8 Hz, 3-H), 7.00–7.45 (3 H, m, Ar–H), 7.48 (1 H, d, J_{2-3} = 2.2 Hz, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 152, M^+ (100), 154 (32).

***trans*-2,3-Dibromo-2,3-dihydrobenzofuran (I),[29] *trans*-2,3-dibromo-3-deuterio-2,3-dihydrobenzofuran (IV), and *trans*-2,3-dibromo-5-chloro-2,3-dihydrobenzofuran (V)[30]** were prepared by bromine addition in CS_2 at −10 °C on the corresponding benzofuran. The NMR spectrum (CCl_4) of IV exhibited peaks at δ 6.78 (1 H, s, 2-H) and 6.85–7.55 (4 H, m, Ar–H). The UV spectra of these compounds exhibited very broad maxima at 294 nm (I and IV) and 306 nm (V).

***trans*-2,3-Dichloro-2,3-dihydrobenzofuran (II) and *cis*-2,3-**

dichloro-2,3-dihydrobenzofuran (III) were prepared as previously described.[31] Both of these compounds exhibited a broad UV maximum at 284 nm.

3-Bromobenzofuran,[32] 3-chlorobenzofuran,[33] and 3-bromo-5-chlorobenzofuran[30] were obtained by dehydrohalogenation of I, II, and V, respectively, with alcoholic potassium hydroxide. The UV spectra exhibited very sharp absorption maxima at 275 and 282 nm (3-bromo- and 3-chlorobenzofuran) and at 285 and 292 nm (3-bromo-5-chlorobenzofuran).

18-Crown-6 ether (18C6), a commercial material (Fluka), was purified by crystallizing from *n*-hexane, mp 38.5–39.5 °C.

Base–Solvent Solutions. *tert*-Butyl alcohol and *n*-butyl alcohol (ERBA-RPE) were distilled after treatment with potassium metal. Ethanol (ERBA-RPE) was purified[34] and carefully fractionated with a Todd column. Solutions of alkoxide were obtained by reaction, under nitrogen, of freshly cut potassium or sodium with the alcohol.

Kinetic Studies. Kinetic experiments were carried out by following spectrophotometrically the disappearance of the substrates at 300 nm. At this wavelength no appreciable absorbance is exhibited by the reaction products. In EtONa–EtOH, EtOK–EtOH, *n*-BuOK–*n*-BuOH, and *n*-BuOK–18C6–*n*-BuOH the reactions were brought about in a stoppered two-limb silica cell. In one limb was placed the substrate solution (1 mL) and in the other the base solution (1 mL). The cell was placed in the thermostated compartment of a Beckmann DB-GT spectrophotometer. After 20 min, the solutions of the kinetic run were mixed throughly and the cell was rapidly placed again in the cell compartment of the spectrophotometer. The reference cell contained a solution of alkali alkoxide at the same concentration used in the kinetic run to compensate for the absorption exhibited by the alkoxyde itself at 300 nm especially in the presence of the crown ether. The same procedure was used for the kinetic experiments of II in *t*-BuOK–*t*-BuOH. The eliminations of I, III, IV, and V in *t*-BuOK–*t*-BuOH and *t*-BuOK–18C6–*t*-BuOH were followed on a Durrum-Gibson D110 stopped flow spectrophotometer. The final product was, in each case, the expected 3-halogenobenzofuran, as shown by GPC analysis (2 m × 2 mm column packed with 10% bentone:didecyl phthalate (1:1) at 110–130 °C).

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Registry No.—3-Deuteriobenzofuran, 68051-10-5; 5-chlorobenzofuran, 23145-05-3; 3-bromobenzofuran, 59214-70-9; 3-chlorobenzofuran, 63361-59-1; 3-bromo-5-chloro-benzofuran, 36739-99-8; 3-hydroxy-3-deuterio-2,3-dihydrobenzofuran, 68051-11-6; 3(2*H*)-benzofuranone, 7169-34-8; benzofuran, 271-89-6.

References and Notes

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