Communications to the Editor

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A TYPICAL E1cB PROCESS IN THE ELIMINATION OF 3-HYDROXY-2-NITRO-2,3-DIHYDROBENZO[b]FURANS TO 2-NITROBENZO[b]FURANS

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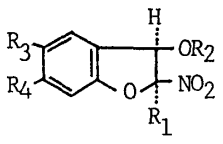
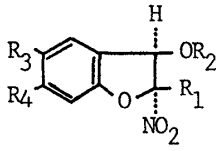
It was clarified that the elimination of the 3-hydroxy-2-nitro-2,3-dihydrobenzo[b]furans proceeded via a typical $(E1cB)_R$ mechanism in the presence of KOH to give the 2-nitrobenzo[b]furans.

KEYWORDS ——— elimination; 3-hydroxy-2-nitro-2,3-dihydrobenzo-[b]furan derivative; 2-nitrobenzo[b]furan derivative; carbanion; conjugate anion; leaving group effect; $(E1cB)_R$ mechanism

In a previous paper,[1] we reported the preparation and stereochemistry of several cis- and trans-3-hydroxy-2-nitro-2,3-dihydrobenzo[b]furan derivatives. The 2,3-dihydrobenzo[b]furans resulted in the elimination of H_2O by treatment with a base to give the 2-nitrobenzo[b]furans[1] which showed considerable antibacterial activities.[2] Recently, much interest has been focussed on the kinetics and mechanisms of elimination in the diastereoisomeric five membered-ring system.[3] This prompted us to investigate the elimination reactions using the 2,3-dihydrobenzo[b]furans.



1: $R_1=R_2=R_3=H$, $R_4=OC_2H_5$
5: $R_1=R_2=R_4=H$, $R_3=Br$
9: $R_1=R_2=D$, $R_3=Br$, $R_4=H$
11: $R_1=H$, $R_2=COCH_3$, $R_3=Br$, $R_4=H$



2: $R_1=R_2=R_3=H$, $R_4=OC_2H_5$
6: $R_1=R_2=R_4=H$, $R_3=Br$
10: $R_1=R_2=D$, $R_3=Br$, $R_4=H$
12: $R_1=H$, $R_2=COCH_3$, $R_3=Br$, $R_4=H$

Although the 2,3-dihydrobenzo[b]furans (1, 2, 5, 6) were stable toward acids (HCl, H_2SO_4, H_3PO_4, and p-TsOH), they were smoothly converted to the corresponding 6-ethoxy-2-nitrobenzo[b]furan[1] (4) or 5-bromo-2-nitrobenzo[b]furan[1] (8) when treated with a small amount of base such as KOH, NaOH and EtONa in EtOH. The elimination process was examined by spectrophotometrically tracing experiments as follows. UV spectra of the ethanolic solutions (1: 8.88×10^{-5}M, KOH: 3.57×10^{-5}M ; 2: 8.88×10^{-5}M, KOH: 3.57×10^{-5}M)[4] were immediately changed into that of the intermediate conjugate anion (3) (carbanion)[5] which showed a strong blue-shifted absorbance [λ_{max}^{EtOH} nm(ε): 266 (ca. 20,000)].[6] Subsequently, the UV spectrum of 3 slowly changed and finally, after about 60 min, it became that of 4 (Fig. 1). Kinetic determinations were simultaneously carried out by monitoring the absorbance (λ_{266}nm-λ_{305}nm)[7] at 28.5°C.

The elimination of the 2,3-dihydrobenzo[b]furans (5 or 6)[4] via the conjugate anion (7) [λ_{max}^{EtOH} nm(ε):269(ca. 20,000)] was similarly checked by UV spectroscopy (Fig.1) and the kinetic determinations were carried out by monitoring the absorbance (λ_{269}nm-λ_{362}nm).[7] The rate constants of the reactions were calculated by the least-squares method. All kinetic data are presented in Table I.

Fig. 1. UV Spectra of the Mixtures of 1 and KOH, and of 5 and KOH

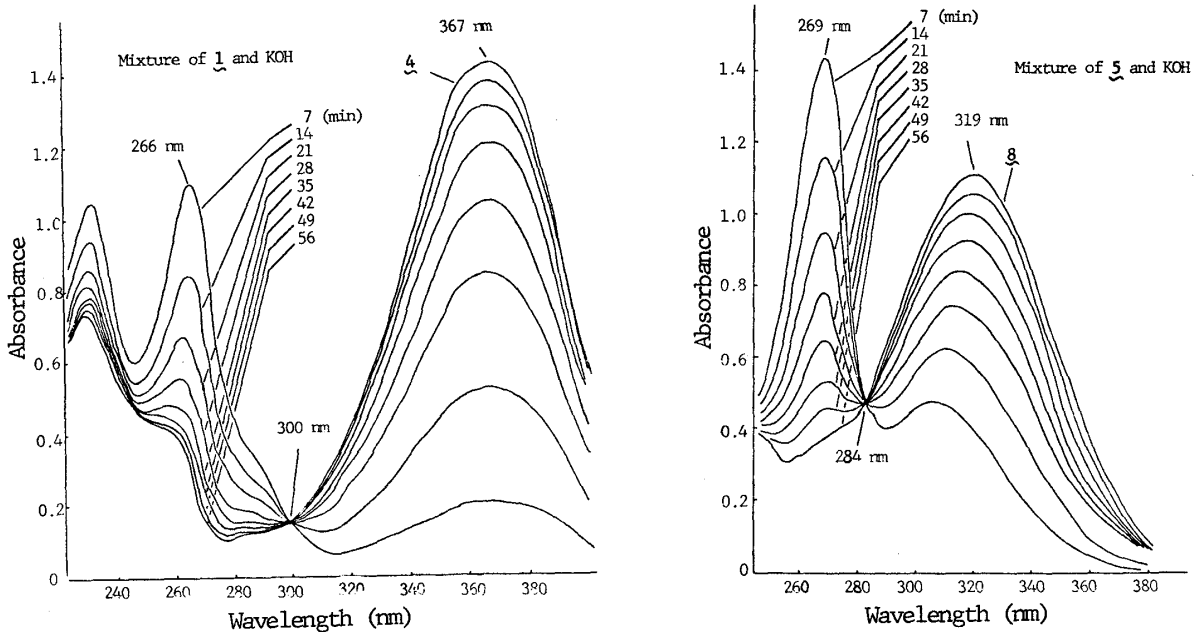


Table I. Kinetic Data for the Elimination Reactions of cis- and trans-3-Hydroxy-2-nitro-2,3-dihydrobenzo[b]furans (1,2,5,6) via Conjugate Anions (3,7) in KOH-Ethanol at 28.5°C

Run	Substrate	Concentration		k_2 [a]	r	Isosbestic point
		Substrate($\times10^{-5}$M)	KOH(M)	($\times10^{-2}$, $M^{-1}m^{-1}$)		(nm)
1	1	8.88	3.57×10^{-4}	4.81	0.9999	300
	2	8.88	3.57×10^{-4}	4.74	0.9997	300
2	1	8.80	3.54×10^{-3}	4.97	0.9996	300
	2	8.80	3.54×10^{-3}	5.01	0.9995	300
3	5	8.15	3.32×10^{-4}	1.96	0.9982	284
	6	8.15	3.32×10^{-4}	1.99	0.9980	284
4	5	8.17	2.33×10^{-3}	2.06	0.9996	284
	6	8.17	2.33×10^{-3}	2.08	0.9995	284
5	5	8.07	6.90×10^{-3}			b)
	6	8.07	6.90×10^{-3}			b)

a) Average of at least two determinations.
b) The first-order plots were not satisfactorily linear and a clear isosbestic point was not found in Run 5.

The formation of conjugate anions (nitronate ions),[8] which were suggested by the UV spectra, was confirmed in the following manner. The trans isomer(6) was treated with a trace of KOD followed within a few minutes by DCl in EtOD in similar conditions as above to give a stereoisomeric mixture consisting of 9 and 10[9:10= 1:3, analyzed by ^{1}H-NMR; deuteration yield 84%; MS m/z:263(M^++2),261(M^+),241,215]. The production of the deuterated stereoisomeric mixture demonstrated that the conjugate anions (3,7) were reversibly formed through the elimination reaction.[9] The conjugate anions may be formed almost quantitatively because clear isosbestic points were observed at 300 (in the case of 1 or 2) and 284 nm (in the case of 5 or 6) in the continuous UV spectra (Fig. 1) of the reaction mixtures.

The results in Table I show that the reaction rate constants were obviously independent of the concentrations of KOH and of the stereoisomerism of the substrates(1,2,5,6), and the kinetic plots of ℓn[3 or 7] against t (min) exhibited excellent linearity ($r > 0.99$). This demonstrates that the elimination reactions were of the first order[10] and the same conjugate anions (3 or 7) were formed from the corresponding cis isomers (1,5) or trans isomers (2,6).

The effect of the leaving group was also examined by using cis- and trans-3-acetoxy-5-bromo-2-nitro-2,3-dihydrobenzo[b]furan (11 and 12): 11[mp 118-120°C. MS m/z :303(M^++2), 301(M^+),255,241,213. ^{1}H-NMR(acetone-d_6) δ:1.96(3H,s,CH_3), 6.42(1H,d,3-H), 6.66(1H,d,2-H), 6.82(1H,d,7-H), 7.26(1H,s,4-H), 7.28(1H,d,6-H). UV λ_{max}^{EtOH}nm:288 (ε=1785)], 12[mp 97-99°C. MS m/z:303(M^++2), 301(M^+),255,241,213. ^{1}H-NMR(acetone-d_6) δ:2.21(3H,s,CH_3), 6.81(1H,s,3-H), 6.93(1H,s,2-H), 7.48(1H,d,6-H), 7.95(1H,d,7-H), 8.01(1H,s,4-H). UV λ_{max}^{EtOH}nm:288(ε=2232)]. Treatment of 11 and 12 with KOH under the same conditions as above gave 8 with elimination of acetic acid, but the reaction rates were too large to be determined by the present method. Considering the effect of the leaving group, the loss of the hydroxy group from the conjugate anions is the rate-determining step[11] ($k_{-1}[BH^+] >> k_2$).

All results described above reveal that the eliminations proceeded via the $(ElcB)_R$ mechanism[9a,12] in which the conjugate anions are formed reversibly and quantitatively as shown in Chart 1.

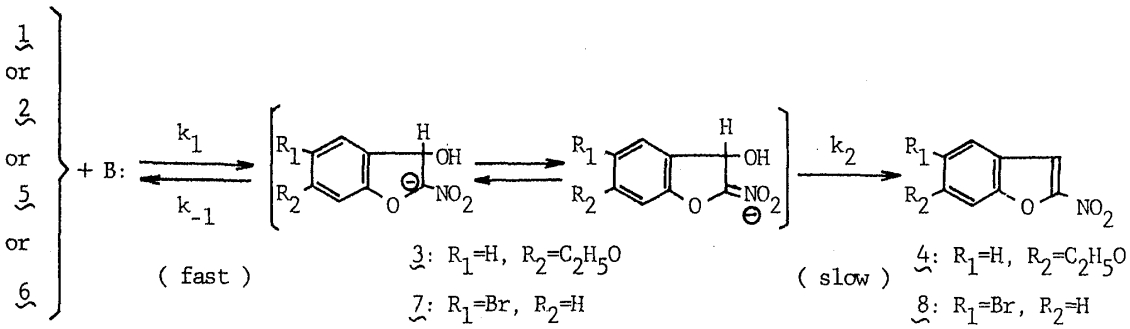


Chart 1

Thus, the elimination reactions of the 3-hydroxy-2-nitro-2,3-dihydrobenzo[b]-furans provide typical instances of the $(ElcB)_R$ mechanism.[9b,13] The 3-hydroxy-2-nitro-2,3-dihydrobenzo[b]furans have several unique structural characteristics as follows.

The 2-proton is acidic; the carbanions are stabilized by conjugation with the 2-nitro group, so they are easily produced; while the leaving property of the 3-hydroxy group of the carbanions (conjugate anions) is relatively poor. This may force the elimination to proceed via the $(ElcB)_R$ process. Further studies of these eliminations under different reaction conditions from the present ones are now in progress.

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