

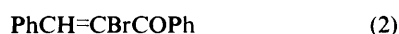
E1cB Elimination from 2-Halogeno-3-methoxy-1,3-diphenylpropan-2-ones

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Kinetic and stereochemical evidence has been obtained from the dehydromethoxylation of 2-halogeno-3-methoxy-1,3-diphenylpropan-2-ones with isopropoxide in isopropyl alcohol that is consistent with an E1cB reversible mechanism. The influence of the halogen both on the deprotonation rate and upon the methoxy-group expulsion has been evaluated.

The reaction of 2-bromo-3-methoxy-1,3-diphenylpropan-2-one (1) with sodium isopropoxide in isopropyl alcohol brings about elimination of methanol and formation of the olefin (2).¹ Ketones having acidic α -hydrogen atoms and poor leaving groups such as methoxide in the β -position have been shown to be structurally suitable for base-induced alkene-producing eliminations, through reversible carbanion formation followed by rate-determining loss of the leaving group.^{2,3}



We now present kinetic and stereochemical evidence which strongly supports the assignment of the (E1cB)_R mechanism to isopropoxide-promoted dehydromethoxylation of (1). This assignment is also in accord with the expectation that insertion of a bromine adjacent to the carbonyl group will favour a pre-equilibrium type of E1cB reaction, for the halogen will confer lability on the α -hydrogen and can stabilise the resulting carbanion.

A first argument favouring an E1cB mechanism comes from the observation that during the elimination reaction of either the *R,R*- or the *R,S*-isomer,⁴ equilibration took place to give an *R,R/R,S*-mixture in the proportions 63:37, respectively. Further, the same *Z/E* ratio of (2) is obtained regardless of whether one starts with the *R,R*- or the *R,S*-isomer.

Besides the stereochemical data, the following features of the dehydromethoxylation of (1) were observed: (i) the diastereoisomers isomerise much more rapidly than they undergo elimination, (ii) the rate of dehydromethoxylation was approximately the same as the rate for the elimination of the α -deuterio-compound, indicating the absence of a primary kinetic isotope effect,^{5,6} and (iii) the *R,R*-diastereoisomer and the equilibrium *R,R/R,S*-mixture have identical rates for elimination.

The present observations are most simply accommodated by the Scheme, where $k_{-1}[\text{Pr}^i\text{OH}]$ and $k_{-2}[\text{Pr}^i\text{OH}] \gg k_3$.

Steady-state analysis of the Scheme gives equation (i).

$$\text{rate} = \frac{k_3 (k_1[\text{R,R}] + k_2[\text{R,S}]) [\text{Pr}^i\text{O}^-]}{(k_{-1} + k_{-2}) [\text{Pr}^i\text{OH}] + k_3} \quad (i)$$

Assuming that $(k_{-1} + k_{-2})[\text{Pr}^i\text{OH}] \gg k_3$, and that $[\text{R,S}]/[\text{R,R}] = k_1k_{-2}/k_{-1}k_2$ equation (i) may be simplified to equation (ii).

$$\text{rate} = \frac{k_1k_3[\text{R,R}][\text{Pr}^i\text{O}^-]}{k_{-1}[\text{Pr}^i\text{OH}]} \quad (ii) \quad \left(k_{\text{obs}} = \frac{k_1k_3}{k_{-1}[\text{Pr}^i\text{OH}]} \right)$$

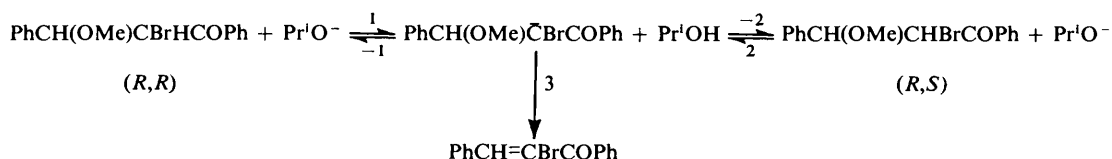
The experimental results showed satisfactory agreement with second-order kinetics [equation (ii)].

When the reaction was conducted in isopropoxide solutions within the concentration range 0.0006–0.0008 mol l⁻¹, no reaction other than equilibration to a mixture of the *R,R*- and *R,S*-isomers occurred. Since the α -bromo-ketone studied here is a very weak acid in the present base-solvent system, its ionisation rate must be much smaller than the rate of its reprotonation $(k_{-1} + k_{-2})[\text{Pr}^i\text{OH}] \gg k_1$. Thus the rate of carbanion formation can be obtained from the rate of equilibration.

In order to provide qualitative insight into this reaction we examined the ability of the α -halogen to withdraw or release electrons according to the reaction step, and the influence of the 4-phenyl substituent both on the ionisation rate and upon leaving group expulsion. The observed rate constants (k_{obs}) include the corresponding deprotonation and reprotonation coefficients together with the methoxy-group departure coefficient (k_3).

Division of these composite rate constants by the calculated k_1 value leads to $k_3/k_{-1}[\text{Pr}^i\text{OH}]$. Because the rate of reprotonation of the carbanion is expected to be large in comparison with the rate of expulsion of a poor leaving group such as OMe, then the differential effect of halogens on $k_{-1}[\text{Pr}^i\text{OH}]$ is likely to be small by comparison with that on elimination (k_3). We believe, therefore, that changes in the value of k_{obs}/k_1 derive largely from changes in the value of k_3 and that the response of this ratio to replacement of bromine by chlorine can be taken as a rough estimate of the sensitivity of the double bond formation to the effect of the α -halogen. Similarly, the direction and magnitude of the 4-MeO-benzyl substituent effect upon k_{obs}/k_1 provide qualitative information on the charge developed at the β -carbon atom during leaving group departure.

Values listed in the Table indicate that ionisation of the substrate is accelerated by the increasing inductive effect of the halogen and inhibited by electron release from the β -



Scheme.

Table. Kinetic data for dehydromethoxylation of 4-RC₆H₄CH(OMe)CHXCOPh with PrⁱO⁻ in PrⁱOH at 25 °C

X	R	$k_1^{a,b}$	$k_{obs}^{a,c}$	k_{obs}/k_1	$\frac{(k_{obs}/k_1)_{Cl}}{(k_{obs}/k_1)_{Br}}$	$\frac{(k_{obs}/k_1)_{OMe}}{(k_{obs}/k_1)_H}$
Br	H	2.65	0.168	0.063	3.35	1.25
	OMe	2.43	0.193	0.079		
Cl	H	5.93	1.20	0.211	5.03	1.88
	OMe	4.02	1.60	0.398		

^a 1 mol⁻¹ s⁻¹. ^b [Subst] = 0.01 mol l⁻¹, [PrⁱO⁻] = 7.8 × 10⁻⁴ mol l⁻¹. ^c [Subst] = 0.01 mol l⁻¹, [PrⁱO⁻] = 0.02 mol l⁻¹.

phenyl group. The simplest interpretation of the remaining data is that the observed rate variations reflect some degree of stabilisation of the incipient olefin due to interaction with the adjacent halogen in the transition state of the elimination step. The α -halogen has a destabilising inductive effect and an electron-donating resonance effect. However, the values of $(k_{obs}/k_1)_{Cl}/(k_{obs}/k_1)_{Br}$ suggest that the effect of the mesomeric electron release outweighs that of a less effective inductive electron withdrawal and that a greater olefinic character is involved in the transition state for the leaving-group expulsion from the α -chloro-carbanion. Values of $(k_{obs}/k_1)_{OMe}/(k_{obs}/k_1)_H$ show a larger enhancement in the rate of release of the OMe group from the α -chloro-carbanion by the 4-MeO-benzyl substituent as compared with that of the α -bromo-carbanion. This can be ascribed to a larger degree of positive charge at the β -carbon atom during the leaving group expulsion from the former and is in accord with the magnitude of the effect of the 4-MeO-substituent upon $(k_{obs}/k_1)_{Cl}/(k_{obs}/k_1)_{Br}$.

Coupled with these observations, the results suggest that the extent of C(β)-OMe bond cleavage in the transition state of the elimination path increases with the higher conjugative interaction of the halogen and with increasing electron donation from the β -phenyl ring.

Experimental

Materials.—The 2-halogeno-3-methoxy-1,3-diphenylpropanones were prepared as reported previously.¹ The α -deuterio-compounds were similarly obtained as described.⁴ Sodium isopropoxide was prepared in solution by heating clean sodium in redistilled isopropyl alcohol under nitrogen, and stored in CO₂-free conditions. For reactions described as run under nitrogen a mercury bubbler was arranged so that the system could alternately be evacuated and filled with the inert gas and left under a positive pressure.

Kinetic Procedure.—Rates were measured at 25 ± 0.05 °C, the reactions being followed to 70% completion. Solutions of suitable concentrations of the reactants in isopropyl alcohol were thermostatted under nitrogen. The reaction was started by transferring 25 ml of isopropoxide solution into the flask containing the solution of the substrate (25 ml, 0.0005 mol) with maximum precautions to exclude atmospheric carbon dioxide. Five samples of the reaction mixture were withdrawn at intervals, quenched in cold water acidified with dilute hydrochloric acid, and extracted with chloroform. The extract was washed with water and evaporated under reduced pressure, and the residue dissolved in CCl₄ was analysed by ¹H n.m.r. The spectra were recorded with a Varian EM-360

60 MHz instrument. The corresponding chemical shift values have been previously reported.^{1,7} Proportions of the eliminated material were determined by integration of the methoxy- and the aromatic-proton signals. Thus the total area in the aromatic region, less that corresponding to the starting material as estimated from the areas under the methoxy-signals, gave the area corresponding to the olefinic and the aromatic protons of the elimination product. The isomeric composition of the olefins was estimated as described.¹ Each spectrum was integrated five times and average integration values were used. The rate constants (k_{obs}) were calculated from the equation $\ln[b(a-x)/a(b-x)]/(a-b) = kt$ where a and b are the initial concentrations of base and substrate respectively and x is the fraction of elimination product. Triplicate runs carried out by this method gave a reproducibility of ±1.5%, confirming the reliability of the analytical technique.

For the equilibration rate determinations pure *R,R*-isomers were used. The proportions of equilibrated material were estimated by comparison of the areas under the methoxy-group resonances. The rates were found to be pseudo-first-order in substrate according to the equation $\ln[a/(a-x)] = kt$, where a is the initial concentration of the *R,R*-isomer and x the fraction of the *R,R*-isomer converted into equilibrium mixture at time t . Since for the equilibrium $(R,R) = (R,S)/K_{eq}$, x is given by the expression $x = (R,S) + (R,S)/K_{eq}$, where (R,S) is the amount of the *R,S*-isomer at time t . Second-order rate coefficients were obtained by division of these constants by isopropoxide concentration.

Acknowledgements

Support of this work and a fellowship (to R. O. G.) from the C.I.C. (Argentina) are gratefully acknowledged.

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Received 18th February 1983; Paper 3/257