Elimination from Diastereoisomeric Methyl 2-Acetoxy-1-bromo- and 1,2-dibromo-2-phenylethylphosphonates

Estela M. G. de Casal, Bruno M. Vuano and Mercedes C. Cabaleiro*
Instituto de Qimica Organica, Universidad Nacional del Sur, Bahia Blanca, Argentina

The examination of the kinetics and stereochemistry of dehydroacetoxylation of *erythro*- and *threo*-PhCHOAcCHBrPO$_3$Me$_2$ promoted by triethylamine in various solvents, and comparison with those for *erythro*- and *threo*-PhCHOAcCHBrCO$_2$Me, leads to the conclusion that the acetoxybromophosphonates undergo elimination through a carbanion process of the irreversible type. The similarity of the elimination behaviour of the *threo*-PhCHBrCHBrPO$_3$Me$_2$ and that of *threo*-PhCHBrCHBrCO$_2$Me is interpreted as indicating that the concerted pathway is also operative for the former compound. In the case of *erythro*-PhCHBrCHBrPO$_3$Me$_2$ the kinetics suggest that elimination of the latter occurs *via* a concerted mechanism.

In recent papers we reported on the triethylamine-induced dehydrobromination of methyl 1,2-dibromo-2-phenylpropanoates.[1,2] The kinetic and stereochemical evidence were consistent with a concerted elimination pathway for the *threo*-substrate and with an E1cB mechanism which involves rate-controlling proton abstraction for the *erythro*-isomer. On the other hand, the results of an examination of the dehydroacetoxylation of methyl *erythro*- and *threo*-2-acetoxy-1-bromo-2-phenylpropanoate under the same conditions led to the conclusion that for both isomers the elimination proceeded *via* an E1cB pathway of the irreversible type. As a part of a study of the chemistry of the styrylphosphonic system and its derivatives,[3] we have now examined the triethylamine-promoted elimination of *erythro*- and *threo*-1,2-dibromo- (**1**; X = Br) and methyl *erythro*- and *threo*-2-acetoxy-1-bromo-2-phenylethylphosphonates (**1**; X = OAc) in methanol, and in a range of solvents of different relative permittivities, comparing the results with those corresponding to the phenylpropanoate derivatives.

Results

The ^{1}H NMR spectra of the products showed that the reactions with **1**; X = Br led exclusively to methyl (*Z*)- and (*E*)-α-bromostyrylphosphonate (**2**), but for the acetoxybromides (**1**; X = OAc) in methanol elimination was accompanied by 2-bromo-1-phenylethanol formation.

The rates of elimination were measured by following the appearance of **2** from aliquots of reaction mixtures using UV spectroscopy. Pseudo-first-order coefficients were determined by using a fifty-fold excess of triethylamine. The second-order rate values, calculated as usual, are collected in Table 1.

Discussion

Inspection of Table 1 reveals that there is a close analogy in the stereochemical outcome and a qualitative parallel in the sensitivity of the rate of the reactions with the *threo*-dibromophenylethylphosphonate and the *threo*-dibromophenylpropanoate to the influence of the nature of the solvent. This observation, considered in conjunction with the marked response of the reaction rates of both substrates to the effect of replacing Br by OAc[1,4] seems to demand that the elimination of the *threo*-dibromophosphonate proceeds by the same pathway as does the *threo*-dibromopropanoate, *i.e.*, the E2 mechanism. On the basis of the concerted process, the *ca.* three-fold increase in the reactivity of the latter compound over that of the *threo*-dibromophosphonate (Table 1) is probably a reflection of a better ability of the 2p orbital of the carbonyl compared with the 3d orbital of the phosphoryl phosphorus to overlap with the developing π-bond. The results also indicate that the rates and solvent effect for the dehydroacetoxylation of the *erythro*- and *threo*-acetoxybromophosphonates are approximately equal. The same close similarity was observed for the elimination of the *erythro*- and *threo*-acetoxybromopropanoates for which the irreversible carbanion process was proposed.[1,2] We believe that these facts are manifestations of the same mechanistic behaviour for all the acetoxybromides, *i.e.*, the E1cB irreversible pathway. This conclusion seems to be reinforced by the observation that elimination from the acetoxybromophosphonates, as well as the acetoxybromopropanoates, follows a stereoconvergent course leading predominantly to the more stable alkene (*Z*). The common correlation of ionisation and elimination rate constants[5] also favours a mechanism in which rate-determining proton transfer is operative. An estimate of the kinetic acidity of the acetoxybromophosphonates by measuring the triethylamine-induced diastereoisomerisation rate for PhCHOMeCHBrPO$_3$Me$_2$ in methanol indicated a k^{OAc}/k^{OMe} ratio of *ca.* 63. The ρ^* magnitude as roughly evaluated by the Taft correlation of the relative rates of elimination and diastereoisomerisation ($\rho^* > 5$) seems to be rather large for a Cα-carbanion formation in a phosphonate,[6] according to the observed comparatively low electron withdrawing power of the phosphoryl group. This apparently increased sensitivity of ionisation to a change in the β-substituent from OMe to OAc was also observed for the reactions of the acetoxybromopropanoates (Table 1) and was interpreted as involving some direct interaction between the acetoxy group and the α-proton which facilitates the deprotonation.[1,2,5] However, this assumption does not seem to be consistent with the observations reported here. It is noteworthy that whereas there is a qualitative trend to higher elimination rates of the dibromides with increasing solvent polarity (benzene < acetone < methanol < dimethylformamide < acetonitrile)[7] which seems to be the result of stabilisation of the transition states by electrostatic solvation,[8] the rates of dehydroacetoxylation of the acetoxybromides show a different susceptibility to the change from methanol to acetonitrile ($k_{MeOH} > k_{MeCN}$). One is led to speculate that the most

Table 1 Kinetics and isomeric product distribution (PhCH=CBrR) for the elimination (X = Br, OAc) and diastereoisomerisation (X = OMe) of *erythro*- and *threo*-PhCHXCBrHR with triethylamine at 30 ± 0.05 °C

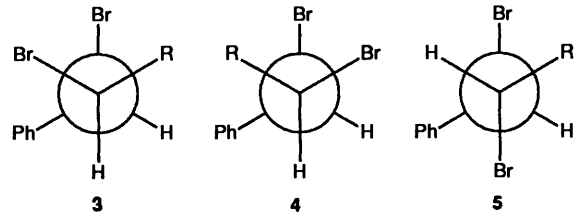
			erythro		*threo*	
R	X	Solvent	k_2[a]	*Z*:*E*	k_2[a]	*Z*:*E*
PO_3Me_2	Br[b]	Methanol	0.52	13:87	7.21	100:00
		Acetonitrile	1.10	09:91	36.50	100:00
		Dimethylformamide	1.02	09:91	35.20	99:01
		Acetone	0.33	26:74	12.65	100:00
		Benzene	0.061 ± 0.006	33:67	0.72	100:00
	OAc[c]	Methanol[d]	0.001 26 ± 0.0008	95:05[e]	0.001 26 ± 0.0008	95:05
		Acetonitrile	0.0005 ± 0.0003		0.0005 ± 0.0003	
		Benzene	<0.0001		<0.0001	
	OMe[c]	Methanol[d]	0.0002 ± 0.0002		0.0002 ± 0.0002	
CO_2Me	Br[b]	Methanol[d,f]	0.058	54:46	23.1	98:02
		Acetonitrile[g]	0.595	29:71	440.0	100:00
		Benzene[g]	0.0097 ± 0.0003		3.1	100:00
	OAc[b]	Methanol[d,f]	0.055	98:02	0.058	98:02
		Acetonitrile[g]	0.018		0.011	
	OMe[b]	Methanol[d]	0.0031 ± 0.0006		0.0028 ± 0.0006	

[a] In $dm^3\ mol^{-1}\ min^{-1}$. [b] [Sust] 0.001 mol dm^{-3}, [TEA] 0.050 mol dm^{-3}. [c] [Sust] 0.01 mol dm^{-3}, [TEA] 0.5 mol dm^{-3}. [d] TEA containing 25% TEA hydrochloride. [e] Together with 5–10% of $PhCHOHCBrH_2$. [f] Ref. 1. [g] R. O. Garay, personal communication.

probable mode of action of the protic solvent is the formation of a hydrogen bond with the carbonyl oxygen of the acetoxy group. The effect of the hydrogen-bonding should be to enhance the electrophilic character of the oxygen linked to the β-carbon atom, and hence to increase the ease with which it affects the lability of the α-proton. This conclusion appears to be related to the subsequent observation that a change of solvent from CCl_4 to CD_3OD causes the ^1H NMR signal due to the β-proton of the acetoxybromophosphonates to move downfield by 0.14–0.16 ppm. Presumably a similar hydrogen-bonding interaction of methanol with the carbonyl or the phosphoryl oxygen of the methoxycarbonyl or the methoxyphosphoryl groups respectively should cause only a rather modest acidifying effect on the α-hydrogen atom, since the increased electronegativity of the carbon or the phosphorus resulting from the oxygen protonation might be satisfied by electron pair release from the methoxy groups.

In contrast to the *erythro*- and *threo*-acetoxybromides and the *threo*-dibromides, the evidence from the rates of elimination with the *erythro*-dibromophosphonate indicates a higher reactivity than that of the *erythro*-dibromopropanoate (Table 1). This result, together with the fact that dehydrobromination of the *erythro*-dibromophosphonate in methanol is much faster than the elimination from the *erythro*-acetoxybromophosphonate cannot be due to the $(E1cB)_I$ mechanism operating for the former and is more easily accommodated by the E2 process.

An interesting feature of the present results is that the similarity between the elimination pathway of the *threo*-dibromopropanoate and the *threo*-dibromophosphonate, and between those of the acetoxybromopropanoates and the acetoxybromophosphonates does not extend to the *erythro*-dibromides. From an examination of the evidence presented here it appears that an important factor in deciding the mechanistic course of the elimination of a leaving group such as bromine from these systems, is the configurational nature of the substrate. The fact that dehydrobromination of the *threo*-dibromides occurs *via* the concerted process could be anticipated according to the stereochemistry of the reaction and the *anti*-geometry preference observed for concerted eliminations from β-halogeno-activated compounds.[9] Inspection of the models corresponding to the *threo*-isomer and predictions based on the assumption that Ph and R have the larger steric requirements support the predominance of the form **3**, a situation that will favour the E2 *anti*-elimination.



3 (*Threo*) **4** **5** (*Erythro*)

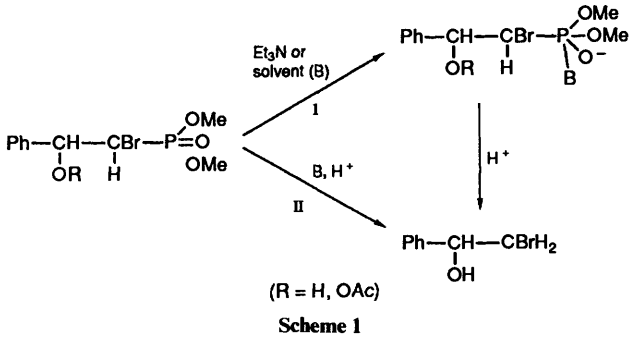
R = CO_2Me, PO_3Me_2

For the case of the *erythro*-dibromides the *anti*-stereochemical requirement for the concerted process demands predominant elimination from **4**, an energetically unfavourable form. However, for the *erythro*-dibromophosphonate the driving force for the concerted preference seems enough to overcome the unfavourable geometry accompanying *anti*-elimination. As regards the elimination from the *erythro*-dibromophosphonate in different solvents, the increased proportion of the less stable alkene (*E*) may be a reflection of a better stabilisation of a E2 transition state related to the more dipolar conformer **4** by the higher relative permittivity of the solvent. On the other hand, the *Z* alkene could arise from an irreversible E1cB mechanism. However, the carbanion elimination would be expected to be less favoured by a decrease in solvent polarity. Thus, we believe that the increase in the *Z* proportion as one progresses toward less polar solvents might be explained as the result of a solvent-induced increased population of the less dipolar conformer **5** which eliminates a *syn*-E2 transition state.

The different mechanistic behaviour of the two *erythro*-dibromides could be accounted for on the basis of simultaneous operation of two opposite factors that determine which type of pathway utilises the dehydrobromination: (i) One causes dissipation of the negative charge of the incipient carbanion into the adjacent acidifying group (CO_2Me or PO_3Me_2) inhibiting π-bond formation. (ii) The other is governed by the β-substituent leaving group ability which leads to a tendency of the Cα-H breaking bond to be involved in some degree of carbon–carbon double bond formation, precluding a possible delocalisation of the incipient negative charge. Thus, it is conceivable that the prevailing mechanism is dictated by the result of a balance between the capability of the activating

group to delocalise the partial negative charge, and the ability of the leaving group to promote carbon–carbon double bond formation. We could suggest that the diminished negative charge stabilisation capacity of the PO_3Me_2 compared with the CO_2Me group is due to a lower electronegative character of the phosphoryl group possibly deriving from the + M effect exerted by the methoxy groups directly linked to the phosphorus atom. On this basis, one difference between $-CHBr-CO_2Me$ and $-CHBr-PO_3Me_2$, as far as α-carbanion formation is concerned, could be that whereas in the former system the carbanion is stabilised by both electron-withdrawing ability and delocalisation of the electron pair into the carbonyl, stabilisation of the carbanion by the α-phosphoryl arises mainly from 2p–3d overlap between the α-carbon and the phosphorus atom respectively, with little incursion of electron-withdrawing inductive influence. However, this interpretation does not explain the fact that the observed relative electron-attracting ability of PO_3Me_2 and CO_2Me seems to be at variance with the reported σ-values.[10] It is tempting to assume that this could be attributed to a through-space 3p–3d interaction between the α-bromine and the phosphorus atom which reduces the electronegativity of the latter. This suggestion is only tentative and further work is clearly necessary to uncover the factors which cause the discrepancy.

A further point of interest is the fact that whereas the elimination of methyl *erythro*-3-acetoxy-2-bromo-3-phenylpropanoate in methanol in a concentration fifty-fold smaller than that of the triethylamine is accompanied by a small proportion of epoxide formation,[1] the reaction of the 3-acetoxy-2-bromo-2-phenylethylphosphonates under identical conditions affords the corresponding alkene along with a product of cleavage of the carbon–phosphorus bond and hydrolysis of the acetoxy group leading to 2-bromo-1-phenylethanol. The fragmentation process might be rationalised as the result of nucleophilic attack of the reagent or the solvent upon the phosphoryl group with formation of a five-co-ordinate addition intermediate.[11] Departure of the electrofugal phosphorus fragment would leave a carbanion which stabilises by protonation (Scheme 1; I).



Scheme 1

Alternatively, this reaction could probably be described as following a S_N2-like pathway[11] involving nucleophilic attack on the phosphoryl group during the phosphorus–carbon bond cleavage step (Scheme 1; II). However, in the absence of more detailed evidence it is not justifiable to draw more definite conclusions. Since neither $PhCHOAcCBrH_2$ nor $PhCHOHCBrHPO_3Me_2$ could be detected experimentally, we feel that fragmentation and acetate hydrolysis are competitive pathways that occur simultaneously or one immediately after the other.

Experimental

Methyl *erythro*- and *threo*-1,2-dibromo-2-phenylphosphonates were prepared as described.[3] The 2-acetoxy-1-bromo-2-phenylethylphosphonates were obtained as a mixture of the *erythro*- and *threo*-isomers in the ratio 7:4 according to the reported procedure.[3] Attempted separation of the diastereoisomers by consecutive recrystallisations or repeated column chromatography did not lead to any detectable change in the isomeric composition. Fortunately, however, evaluation of their relative rate constants $(k_{erythro}/k_{threo})_{OAcBr}$ by ^1H NMR spectroscopy indicated that the isomeric rate coefficients were equal within the limits of the estimated experimental error (±2.7%). Thus, the mixture of the isomers was used as such. Methyl *erythro*- and *threo*-1-bromo-2-methoxy-2-phenylethylphosphonates were obtained by bromination of methyl (*E*)-styrylphosphonate (0.1 mol) with *N*-bromoacetamide (0.2 mol) in methanol (50 cm^3) in the dark at 5 °C. Work-up of the product gave a mixture which was taken up in carbon tetrachloride (20 cm^3). The resulting crystals were filtered off and were shown (^1H NMR) to contain the *threo*- and *erythro*-isomers (88:12) (Found: C, 40.7; H, 5.2; Br, 24.35. $C_{11}H_{16}BrO_4P$ requires C, 40.90; H, 4.99; Br, 24.74%). Crystallisation of the mixture from methanol afforded the pure *threo*-compound, m.p. 115–116 °C. δ(CCl_4) 7.15 (5 H, s, ArH), 4.58 (1 H, dd, J_{H_2,H_3} 6.0, J_{P,H_2} 5.6), 3.79 (3 H, d, $J_{P,OMe}$ 10.8), 3.50 (3 H, d, $J_{P,OMe}$ 10.8), 3.23 (3 H, s, C–OCH_3). The carbon tetrachloride filtrate was concentrated to one half of its original volume, left to stand overnight at −5 °C, and refiltered to remove the precipitate which formed. The above process was repeated twice using an additional 10 cm^3 of carbon tetrachloride. The liquid was evaporated off and the ^1H NMR spectrum of the residual oil indicated the presence of pure *erythro*-1-bromo-2-methoxy-2-phenylethylphosphonate. δ(CCl_4) 7.15 (5 H, s, ArH), 4.32 (1 H, dd, J_{H_2,H_3} 6.2, J_{P,H_2} 8.0), 3.68 (3 H, d, $J_{P,OMe}$ 5.6), 3.52 (3 H, d, $J_{P,OMe}$ 5.6), 3.18 (3 H, s, C–OCH_3). The 2-H signals of these compounds were superimposed on those of the methoxyphosphoryl resonances. The configurations were determined on the basis of stability arguments.

Kinetic Procedure.—Rates were measured at 30 ± 0.05 °C. Reactions with the 2,3-dibromophosphonates were initiated by adding the substrate dissolved in the appropriate solvent (50 cm^3; 0.002 mol dm^{-3}) to a solution containing triethylamine (50 cm^3; 0.1 mol dm^{-3}) in the same solvent, except for the reactions in methanol which were carried out at a buffer concentration ([triethylamine] = 0.08 mol dm^{-3}; [triethylamine hydrochloride] = 0.02 mol dm^{-3}) which showed that the amine was the only reactive basic species in the reactions. Samples (5 cm^3) were withdrawn by a calibrated automatic pipette at suitable time intervals and diluted with 45 volumes of aqueous 0.1 mol dm^{-3} hydrochloric acid. In the case of the acetoxybromophosphonates the reactions were carried out using reactant concentrations 10-fold greater than those corresponding to the dibromides, and the aliquots quenched by dilution with 0.1 mol dm^{-3} aqueous hydrochloric acid by a factor of 100. The absorbance of the resulting solutions was determined at 286 nm. All kinetic runs were conducted at least in triplicate and were estimated to be accurate to within ±2.5% unless noted otherwise in Table 1.

For the relative rate coefficients of the eliminations of the acetoxybromophosphonates the reactions were carried out similarly except that larger volumes of solutions were used in order to obtain appropriate amounts of residue for the ^1H NMR analysis. The rate ratio was determined by the relative integration of the $COCH_3$ peak areas using the equation

$$k_{erythro}/k_{threo} = \frac{\log(\text{fraction of unchanged } erythro)}{\log(\text{fraction of unchanged } threo)}$$

The average value was estimated to be 1 with an exprimental error of ±2.7%.

The rate coefficients for the reactions with the acetoxybromo-

phosphonates in methanol are a composite of elimination and a small amount of 2-bromo-1-phenylethanol formation. However, since the latter was shown to be transparent at the wavelength stated above no correction was required. The proportion of this compound in the product mixture was calculated using the intensity of its 2-H resonances [12] relative to the methoxy signals of the alkene.

The diastereoisomerisation reactions were carried out similarly to those with the acetoxybromophosphonates in methanol and followed by ^{1}H NMR integration of the areas under the C–OMe signals. The rate coefficients were calculated from the pseudo-first-order equation

$$\ln \frac{[\text{isomer}]}{[\text{isomer}] - x} = k_{\text{isomer}}\, t$$

where [isomer] is the initial concentration of *erythro* or *threo*, and x the fraction of the isomer converted into equilibrium mixture at time t.

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