Solvent effects in the β-(phosphatoxy)alkyl radical migration as revealed by deuterium labelling and ^{1}H NMR spectroscopy

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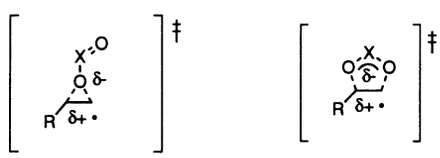
It has been demonstrated through use of a deuterium labelled probe that the β-(phosphatoxy)alkyl radical migration of 1a, previously shown to be non-dissociative in benzene, occurs through a fragmentation recombination mechanism in the polar, protic solvent *tert*-butanol. Most likely the reaction occurs through the intermediacy of a contact ion pair which does not allow crossover with an external nucleophile. Parallel experiments for the β-(acyloxy)alkyl migration, however, provided no evidence for a dissociative mechanism in any of the solvents tested.

Introduction

Recent work from this laboratory has focused on elucidating the mechanism of the β-(phosphatoxy)alkyl and β-(acyloxy)-alkyl rearrangements[1] and, to a lesser extent, the related β-(nitroxy)alkyl rearrangement.[2] The deuterium labelled probes **1a** and **1b**, designed to differentiate between dissociative and non-dissociative mechanisms, revealed both the phosphatoxy and the acyloxy migration to be non-dissociative in benzene at reflux. This conclusion is readily drawn from inspection of the ^{1}H NMR spectrum of the reaction mixture whereby a 1:1 ratio for the olefinic protons in the homoallylic product and an unequal ratio for the olefinic protons in the allylic product indicates a mixture of **2**–**4** and so a non-dissociative migration. Conversely, an uneven ratio for the homoallylic olefinic protons and a 1:1 ratio for the allylic olefinic protons would suggest a product mixture comprised of **2**–**6** and hence a dissociative pathway (Scheme 1).

Stereochemical[1,3] and ^{18}O- and ^{17}O-labelling studies[2,4] brought to light the existence of two, parallel, non-dissociative, pathways involving three-centre-three-electron (**E**) and five-centre-five-electron (**F**) processes with the former typically favoured by the phosphatoxy migration and the latter, with one notable exception, [5] favoured by the acyloxy shift.



E F

The polarized nature of the transition state for the five-centre-five-electron acyloxy migration is derived from the observation that the migration is accelerated in polar solvents and by electron-withdrawing substituents capable of stabilizing a partial negative charge on the acyloxy moiety.[4,6] We have suggested a similar polarization in the transition state for the three-centre-three-electron pathway on the grounds that the phosphatoxy migration is several orders of magnitude faster than the acyloxy migration as demonstrated by simple competition experiments. This hypothesis is supported by a strong linear correlation between log *k* for the migration of a series of *p*-substituted diarylphosphate esters and the Hammett σ-constant for the substituents.[1] In the extreme case the rearrangements can be expected to become dissociative and proceed through an ion-pair mechanism involving an alkene radical cation and a phosphate (or carboxylate) anion with recombination either within the solvent cage, or following diffusion into the bulk of the solvent.[7] Below we report on the results of a study of the phosphatoxy and acyloxy migrations using probes **1a** and **1b** conducted in polar solvents and in the presence of quaternary ammonium salts with a view to identifying any such dissociative pathways.

Results and discussion

Probe **1a** and unlabelled samples of the anticipated migration products **2a** and **3a** were synthesized as described previously,[1] and examined for stability in THF, *tert*-butyl alcohol, acetonitrile and DMF. Probe **1a** was found to undergo decompositition in acetonitrile and DMF, which were consequently excluded from the study, but to be moderately stable in THF and *tert*-butyl alcohol at reflux for prolonged periods. The homoallylic phosphate **2a** (unlabelled) was recovered unchanged from both THF and *tert*-butyl alcohol after 24 h at reflux. The allylic phosphate **3a** (unlabelled) was likewise found to be unchanged in THF at reflux but suffered decomposition in hot *tert*-butyl alcohol. The fate of the cyclohexenyl moiety in this decomposition was not determined, largley due to the volatility of the products, but all of the phosphate moiety was converted to diethyl hydrogen phosphate as determined by ^{31}P NMR spectroscopy (δ, $CDCl_3$: 1.80) with the aid of an authentic sample. In spite of the instability of **3a** in *tert*-butyl alcohol we decided to continue with experiments in both THF and *tert*-butyl alcohol as all the necessary information can be deduced from the relative integrations of the two olefinic hydrogens in **2a**/**5a**.

Probe **1a** was reacted with tributyltin hydride and AIBN in benzene and *tert*-butyl alcohol at 80 °C, and in THF at 65 °C. After removal of tin residues by column chromatography, the mixtures of allylic and homoallylic phosphates were examined by ^{1}H NMR spectroscopy in $CDCl_3$. Partial spectra of the experiments conducted in THF and *tert*-butyl alcohol are given in Fig. 1.

The spectrum obtained for the reaction in THF [Fig. 1(*a*)] is qualitatively the same as that from the reaction in benzene,[1] with a 1:1 ratio of H_γ and H_δ within the limits of experimental error. As noted previously[1] for the reaction in benzene, the olefinic region for the allylic product shows a depletion of H_σ with respect to H_τ. For the reaction in THF [Fig. 1(*a*)] H_σ is clearly also depleted with respect to H_τ but full interpretation is pre-

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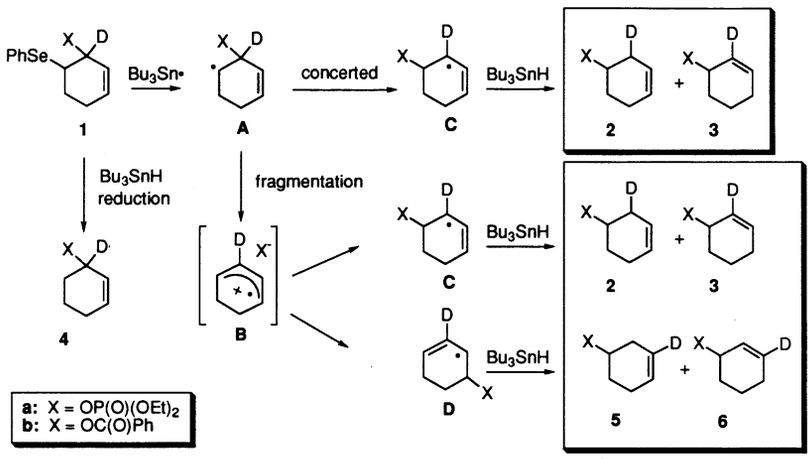

Scheme 1

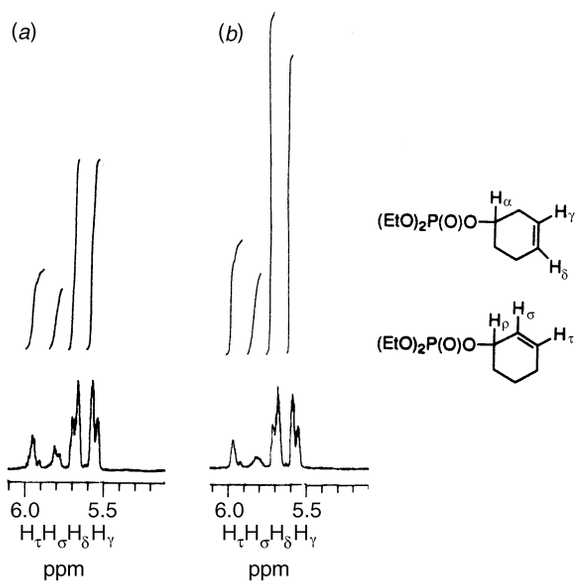

Fig. 1 Partial ^{1}H NMR spectra for the reaction of **1a** with Bu_3SnH in (*a*) THF and (*b*) Bu^{t}OH

vented by the presence of an unidentified byproduct which artificially augments the signal intensity for H_τ. It is clear that in THF, as in benzene[1], the β-(phosphatoxy)alkyl migration of radicals derived by abstraction of PhSe$^\bullet$ from **1a** proceeds in a non-dissociative manner. However, when the reaction was conducted in *tert*-butyl alcohol at 80 °C a different pattern of signal intensities was observed and H_γ was found to be somewhat depleted with respect to its partner H_δ, the ratio being *ca.* 0.87:1 [Fig. 1(*b*)]. The decomposition of **3a** in hot *tert*-butyl alcohol prevents interpretation of its spectrum. The uneven ratio of H_γ and H_δ in [Fig. 1(*b*)] is strongly suggestive of a dissociative mechanism in *tert*-butyl alcohol. Consider the fate of ion pair **B**, formed following fragmentation of radical **A** (Scheme 1). The nature, contact or solvent separated, of the ion pair, and correspondingly its lifetime, will have an effect on the distribution of the radicals **C** and **D** following recombination and so on the distribution of the product between **2** and **5** (and **3** and **6**). If the ion pair is solvent separated, and so relatively long lived, it is reasonable to expect, in the absence of a significant secondary deuterium isotope effect, that recombination will occur with equal probability at either terminus of the cyclohexadiene radical cation leading to a 1:1 ratio of **C** and **D** and so of **2** and **5**. Such a scenario would provide a 1:2 ratio of signal intensities for H_γ and H_δ. This clearly is not the case [Fig. 1(*b*)]. Alternatively, for a contact ion pair the only barrier to recombination is the realignment of the phosphate anion with either terminus of the cyclohexadiene radical cation, possibly coupled with an extremely rapid[8,9] conformational inversion of the latter. Realignment to give radical **C** can be thought of as requiring an approximately 60° rotation of the radical cation or a translation of *ca.* 1.5 Å of the phosphate anion or, more realistically, some combination of the two. However, realignment to give **D** requires a 120° rotation, or a 3 Å translation of the anion, or a combination of both. Such a situation leads to the conclusion that **C** and **D**, and so **2** and **5**, would be formed in unequal amounts with a probable preponderance of **C** and so of **2**. The experimental ratio for H_γ:H_δ of *ca.* 0.87:1 is therefore in reasonable agreement with the contact ion pair mechanism in *tert*-butyl alcohol as solvent. Alternatively, it could be argued that the observed ratio for H_γ:H_δ in *tert*-butyl alcohol arises from the parallel operation of two mechanisms, one concerted (three- or five-centre or both) and one dissociative, leading to an experimental ratio in between the expected extremes of 1:1 and 1:2, respectively.

In a further attempt to distinguish between solvent separated and contact ion pairs we turned to crossover experiments. In a fully homogeneous system, probe **1a** was subjected to reaction with tributyltin hydride and AIBN in *tert*-butyl alcohol under the standard conditions and in the presence of tetrabutylammonium acetate. No incorporation of acetate into the prducts was observed, leading to the firm conclusion that any ion pairs formed in the course of the rearrangement are of the contact type.

Finally, with probe **1a**, we note that the isolated yield of the **2a**/**3a** mixture varies somewhat in the range 37–55%. This, and the ^{31}P NMR spectrum of the crude reaction mixtures which display several peaks additional to those derived from **2a** and **3a**, suggests that one or more of the products and intermediates is undergoing decomposition in the course of the reaction.[10] The above blank experiments indicate **3a** to be unstable in hot *tert*-butyl alcohol but, as poor yields are also observed in benzene and THF, alternative modes of decomposition must also be occurring. One of several possibilities is the fragmentation of radicals **C**/**D** to diethyl phosphatoxyl radicals and cyclohexadiene. Indeed, Giese and Almstead have previously characterized a closely related fragmentation.[11]

Probe **1b** was subjected to rearrangement in benzene, THF, DMSO and *tert*-butyl alcohol.[12] In each case the reactions were clean and inspection of the ^{1}H NMR spectra revealed 1:1 ratios of the homoallylic olefinic hydrogens strongly suggesting that even in *tert*-butyl alcohol as solvent the acyloxy rearrangement proceeds through non-dissociative pathways. In full agreement with this conclusion crossover experiments with **1b** in the presence of tetrabutylammonium acetate did not result in incorporation of acetate. Professor Beckwith has informed us of similar crossover experiments conducted in his laboratory with comparable negative results.[13]

Conclusions

By use of probe **1a** it has been demonstrated that the β-(phosphatoxy)alkyl radical migration proceeds through a non-dissociative mechanism in non-polar solvents but in the polar, protic solvent *tert*-butyl alcohol the reaction occurs *via* the intermediacy of a contact ion pair. The recombination of this ion pair is on the timescale of rotational diffusion of the cyclohexadiene radical cation and so precludes crossover with external acetate as nucleophile. The related probe **1b** was found to rearrange by a non-dissociative pathway in all solvents surveyed. Of course, for different substrates, the crossover point in terms of solvent polarity for going from concerted mechanisms with polar transition states to ion pair mechanisms will differ and be a factor of the stability of the particular radical cation and anion involved.

Experimental

General

Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^{1}H and ^{31}P NMR spectra were run in $CDC1_3$ at 300 and 121 MHz, respectively. ^{1}H NMR chemical shifts are downfield from tetramethylsilane as internal standard. ^{31}P NMR shifts are quoted with respect to external H_3PO_4. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled from sodium benzophenone ketyl under N_2 immediately prior to use. Ether refers to diethyl ether. Microanalyses were conducted by Midwest Microanalytical, Indianapolis. All experiments were repeated at least twice with reproducible results.

General procedure for rearrangement of 1a with Bu_3SnH

To a solution of **1a**[1] (100 mg, 0.25 mmol) in 10 cm^3 of the solvent at 80 °C for benzene and *tert*-butyl alcohol, and at reflux for THF, under N_2, was added a solution of tributyltin hydride (110 mg, 0.37 mmol) and AIBN (15 mg, 0.09 mmol) in the solvent (10 cm^3) over 12.5 h with the aid of a motor driven syringe pump. After addition, heating was continued for a further 3 h. After cooling to room temperature, the solvent was removed under vacuum and the residue subjected to column chromatography on silica gel (eluent: CH_2Cl_2–EtOAc 4:1) to give a mixture of the rearranged and reduced products which was examined by ^{1}H NMR spectroscopy.

In benzene. Reaction of **1a** with tributyltin hydride according to the general procedure, followed by column chromatography, gave 29 mg (49%) of a mixture of allylic and homoallylic phosphates in an approximate ratio of 31:69 as determined by ^{1}H NMR spectroscopy.

In THF. Compound **1a** was reacted with tributyltin hydride according to the general procedure. After the addition, reflux was continued after 14 h. Cooling, evaporation and column chromatography gave 22 mg (37%) of a 30:70 mixture of allylic and homoallylic phosphates by ^{1}H NMR spectroscopy [Fig. 1(*a*)].

In Bu^{t}OH. Reaction of **1a** (100 mg, 0.25 mmol) in 10.0 cm^3 of Bu^{t}OH with tributyltin hydride in 14 cm^3 of Bu^{t}OH and 1 cm^3 of THF under the general procedure followed by column chromatography gave 33 mg (56%) of a 27:73 mixture of allylic and homoallylic phosphates as determined by ^{1}H NMR spectroscopy [Fig. 1(*b*)].

Attempted crossover of 1a with tetrabutylammonium acetate in Bu^{t}OH

To a solution of **1a** (100 mg, 0.25 mmol) and tetrabutylammonium acetate (75 mg, 0.25 mmol) in 10 cm^3 of Bu^{t}OH at reflux under N_2 was added a solution of tributyltin hydride (109 mg, 0.37 mmol) and AIBN (2 mg, 0.012 mmol) in Bu^{t}OH (10 cm^3) and 1 cm^3 of THF over 5 h. A further portion of AIBN (6 mg, 0.04 mmol) in Bu^{t}OH was then added over 10 h. After the addition, heating was continued for another 5 h. After cooling to room temperature, the solvent was removed under vacuum and the residue subjected to column chromatography on silica gel (eluent: hexane–EtOAc 90:10 to 50:50) to give 28 mg (46%) of a mixture consisting mainly of the homoallylic phosphate as determined by ^{1}H NMR spectroscopy.

General procedure for rearrangement of 1b with Bu_3SnH

To a solution of **1b**[1] (50 mg, 0.14 mmol) in 10 cm^3 of the solvent at reflux under N_2 was added a solution of tributyltin hydride (80 mg, 0.27 mmol) and AIBN (2 mg, 0.012 mmol) in the solvent (10 cm^3) over 10 h with the aid of a motor driven syringe pump. After reflux for a further 8 h, the reaction mixture was cooled to room temperature and the solvent removed under vacuum. Column chromatography on silica gel (eluent: hexane–EtOAc 99:1 to 85:15) gave an inseparable mixture of the reduction and rearrangement products which was analysed by ^{1}H NMR spectroscopy.

In benzene. Reaction of **1b** (50 mg, 0.14 mmol) with tributyltin hydride according to the general procedure, followed by column chromatography, gave 28 mg (98%) of an inseparable mixture of the allylic and homoallylic benzoates in an approximate ratio of 4:1 as determined by ^{1}H NMR spectroscopy.

In THF. Reaction of **1b** (100 mg, 0.27 mmol) with tributyltin hydride according to the general procedure, followed by column chromatography gave 48 mg (85%) of an inseparable mixture of the allylic and homoallylic benzoates in an approximate ratio of 22:1 as determined by ^{1}H NMR spectroscopy.

In Bu^{t}OH. Reaction of benzoate (50 mg, 0.14 mmol) in 10.0 cm^3 of Bu^{t}OH with tributyltin hydride in 9.5 cm^3 of Bu^{t}OH and 1 cm^3 of THF under the general procedure followed by column chromatography gave 25 mg (88%) of an inseparable mixture of the allylic and homoallylic benzoates in an approximate ratio of 5:1 as determined by ^{1}H NMR spectroscopy.

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