Formation of a Stabilised Phospholane Salt†

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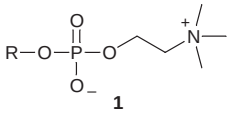
N,N′-Substituted amines (as illustrated using TMEDA) will react with a short chain 2-alkoxy-2-oxo-1,3,2-dioxaphospholane, to form a stabilised phospholane salt and not the corresponding phosphobetaine as anticipated.

There has been a quest for novel zwitterionic compounds for use as surfactants, anti-hazing agents, anti-static agents, as dye-promoters and to make surfaces generally more hydrophilic. Much work has been performed on the synthesis of phosphorylcholine (PC)-based systems **1** and their structural analogues because of their ability to reduce protein adsorption and control cellular adhesion.[1] Both small molecule and polymer systems in which the conventional sequence of the PC head group is 'reversed' have been produced, the resulting phosphobetaine comprising an in-chain quaternary ammonium coupled to an alkyl phosphate (**6** in Scheme 1). This was achieved in two steps, first by the reaction of 2-chloro-2-oxo-1,3,2-dioxaphospholane[2] **2** with an appropriate alcohol **3** to form a 2-alkoxy-2-oxo-1,3,2-dioxaphospholane **4**. This is in turn ring-opened by attack of an appropriate nucleophile, conventionally an appropriate *N,N′*-substituted amine **5**, at one of the phospholane methylene groups, usually in acetonitrile at *ca.* 70 °C for 40 h. This approach has been used to make polymerisable monomers[3] or indeed linear polymers in which the phosphobetaine linkage is formed in-chain.[4] Early patents claimed the use of a variety of R groups including simple alkyls of the formula C_mH_{2m+1}, polymerisable chains and substituted ring structures, and even certain drugs.[5] Despite the broad claims, exemplification is usually by longer chain or aromatic species, although it may be useful to synthesize these derivatives in which the alkyl chain is much shorter, such that the compound has closer structural analogy to PC.



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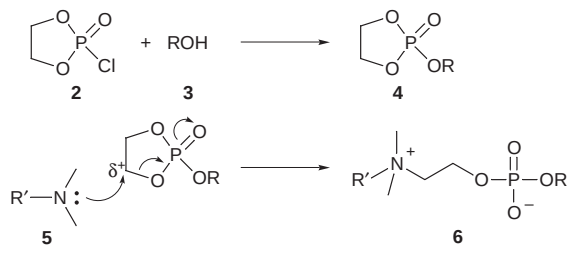
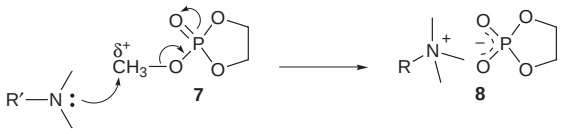
We have demonstrated that ring opening of the phospholane is not always the preferred reaction, depending upon the nature of the R group. Indeed, if 2-methoxy-2-oxo-1,3,2-dioxaphospholane **7** is used the methyl group has a similar electron deficiency to the phospholane methylene groups, is less sterically hindered and therefore more susceptible to nucleophilic attack. Reaction in this case proceeds according to Scheme 2 in which a trimethyl quaternary ammonium cation is generated and ionically paired to a phospholane anion **8** to produce a stable salt species. This reaction has been performed with **7** using a number of *N,N′*-dimethyl-substituted amines and it has been shown that salt formation is the predominant process in each case. Tetramethylethylenediamine (TMEDA) is often used as a base to remove hydrogen chloride generated during step 1 of the preparation of compounds of type **4** as shown in Scheme 1. Here we demonstrate that TMEDA itself will indeed react with **7**.



Scheme 1



Scheme 2

Use of a number of NMR techniques was necessary in order to determine unequivocally that the phospholane salt structure **9** was formed. Previous work had relied mainly on IR which we have shown to be inconclusive for distinguishing between the salt and phosphobetaine compounds.[5] The ^{1}H NMR spectrum of the starting material **7** shows a doublet at δ 3.86 ($J = 11.7$ Hz) due to the methoxy group (split by the phosphorus). The end product also shows a characteristic doublet, now at δ 4.1 ($J = 10.3$ Hz), which could easily be misassigned as the terminal methoxy group of the phosphobetaine. Proton correlation spectroscopy confirms that there are, however, no peaks corresponding to the ethylene bridge that would have formed between the quaternary ammonium and phosphate groups of the phosphobetaine, the only coupling interaction observed being that of the ethylene bridge between the amine groups (**b** and **c** in Fig. 1a). Further evidence for the structure of **9** is given by ^{13}C DEPT135 (Fig. 1b) which clearly shows three methylene and two methyl environments (CH_2 + ve, CH_3 − ve). Clearly now, the doublet at δ 4.1 in the ^{1}H NMR spectrum must be due to the phospholane methylene groups, which lose their fine structure as they become equivalent in the salt. Additionally, examination of the integrals shows that the signal due to the quaternary methyl protons at δ 3.0 is equivalent to 9 protons. ^{31}P NMR adds additional confidence to the structure determination, as a single peak at δ 17.8 is indicative of an intact phospholane ring, this shifting to $\approx\delta$ 1.0 when the ring is opened generating a PO_4^- environment. Mass spectrometry provided further support for the structure, positive electrospray producing a major peak at m/z 131 corresponding to the cationic amine and negative electrospray giving rise to a peak at m/z 123 for the anionic species.

Spectra were run in both D_2O or CD_3OD and it was surprising that the intact phospholane ring (which would ordinarily be ring-opened by these solvents) could be

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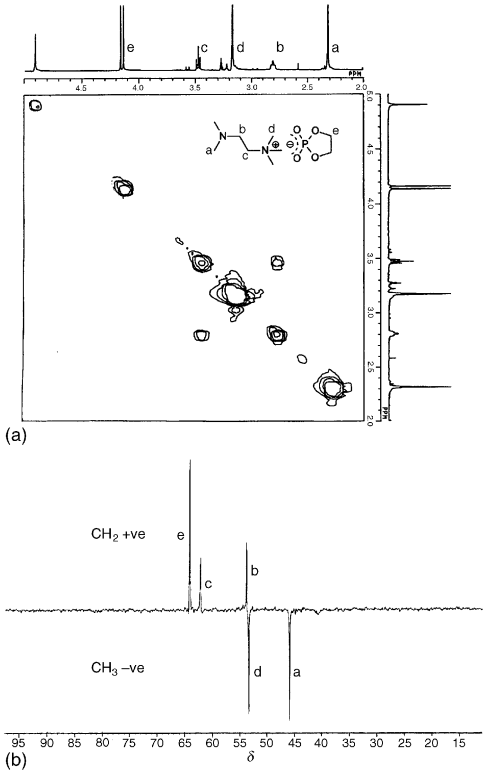
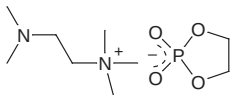


Fig 1 ^{1}H COSY (*a*) and ^{13}C DEPT135 (*b*) of product **9**

identified. It must therefore follow that salt formation stabilised the phospholane, deactivating the ring toward attack from weak nucleophiles. The salt could be dissolved in DCl/D_2O, shaken briefly and ^{31}P NMR spectroscopy used to show that the phospholane ring was opened under acidic conditions (a shift from δ 18.7 to 0.9).



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Analogues of compound **4** in which the alkyl chain length was increased were reacted in favour of the formation of the phosphobetaine over that of the salt. When R = Me, 95% of the isolated product was the phospholane salt; when R = Bu only 10% of the salt was formed, the predominant product being the phosphobetaine. With chain lengths typical of those described in the literature (typically $> C_8$),[5] the major product is phosphobetaine with only trace amounts of the salt detected. The positive electronic inductive effect and increased steric hindrance caused by the alkyl chain combine to make nucleophilic attack at the alkoxy position less attractive and hence ring opening at the phospholane methylene groups more favourable, although extended reaction times at reflux are necessary to obtain reasonable yields of the product.

Experimental

Preparation of 2-*Methoxy*-2-*oxo*-1,3,2-*dioxaphospholane* **7**.—2-Chloro-2-oxo-1,3,2-dioxaphospholane (Fluka) was purified by distillation under reduced pressure prior to use. Fractions collected between 88–89 °C at 0.1 mmHg were shown to be > 92% pure by quantitative ^{31}P NMR. To a stirring solution of 5.08 g of methanol (0.156 mol, 1 equivalent) and 13.0 g of TMEDA (0.109 mol, 0.7 equivalent) in anhydrous THF (100 ml) at −20 °C and under N_2, were added 26.8 g (0.188 mol, 1.2 equivalents) of 2-chloro-2-oxo-1,3,2-dioxaphospholane in THF (50 ml). The temperature was maintained at −20 °C until complete addition, after which it was raised to between 0 and 5 °C with stirring for 2 h. The TMEDA·HCl was removed by filtration and the filtrate concentrated under vacuum to yield a white oil (92%). NMR was performed on a JEOL GSX400 spectrometer. δ_H (399.65 MHz, $CDCl_3$) 3.86 (3 H, d, $J = 11.7$ Hz, MeO), 4.44 (4 H, m, $(CH_2)_2$). δ_C (100.40 MHz, $CDCl_3$) 54.95 and 55.01 (CH_2O), 65.96 (MeO). δ_P (161.70 MHz, $CDCl_3$) 18.9.

Preparation of the Phospholane Salt **9**—5.08 g of compound **7** (0.0368 mol, 1 equivalent) and 5.0 g of TMEDA (0.043 mol, 1.17 equivalents) were stirred at reflux in anhydrous acetonitrile for 48 h. The solvent was removed under vacuum to yield a yellow solid, which was treated with dry THF, filtered off, washed again with THF under N_2 and dried to afford a pale yellow solid (70% yield). **9** with reference to Fig. 1a: δ_H (399.65 MHz, D_2O) 2.17 (6 H, s, **a**), 2.76 (2 H, t, $J = 8.06$, **b**), 3.00 (9 H, s, **d**), 3.39 (2 H, t, $J = 8.06$, **c**) and 4.10 (4 H, d, $J = 10.3$ Hz, **e**). DEPT135, CH_2 + ve, CH_3 − ve with reference to Fig. 1b: δ_H (100.40 MHz, d_6-DMSO) 45.4 (**a**), 52.9 (**d**), 53.2 (**b**), 61.8 (**c**) and 63.9 (**e**). δ_P (161.70 MHz, $CDCl_3$) virtually single peak at 17.8, very small peak at 1.0. FAB MS was performed on a Kratos Concept 1s using Xenon as the fast atom. This showed a major peak at *m/z* 131 (the cationic amine component) but had problems detecting lower masses. Electrospray was run on a Micromass Platform with samples dissolved in methanol and clearly yielded major peaks at *m/z* 131 (+ve) and 123 (−ve) consistent with the assigned structure.

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1 For example, see A. A. Durrani, J. A. Hayward and D. Chapman, *Biomaterials,* 1986, **7**, 121; K. Ishihara and Y. Iwasaki, *J. Biomater. Appl.,* 1998, **13**, 111 and refs therein.
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