SHORT PAPER

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Reactivity of ω-hydroxyalkylphosphinic anilides in cyclisation by intramolecular displacement of the aniline moiety†

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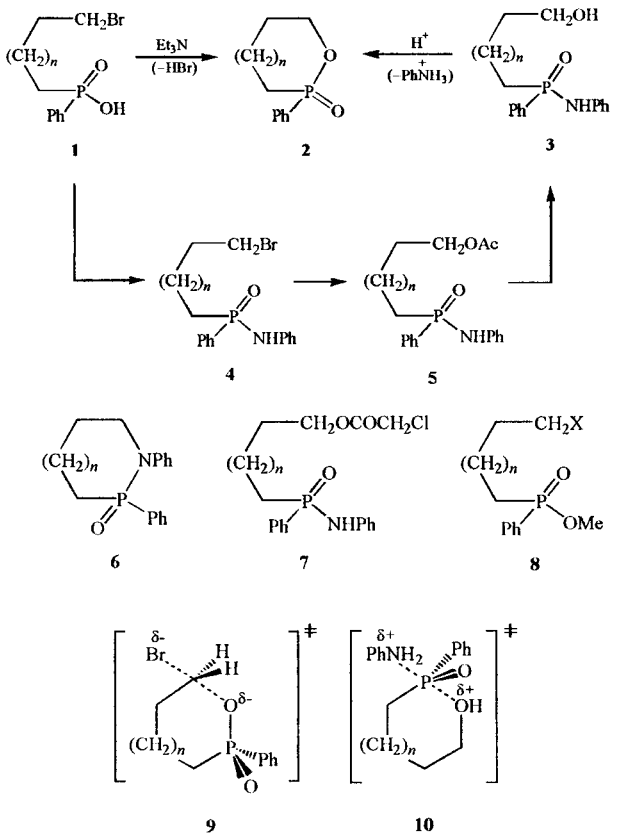
A cyclic phosphinate **2** is formed when $HO(CH_2)_{n+3}P(O)(NHPh)Ph$ (n = 0 or 1) is treated with acid (P–N bond cleavage); five-membered ring formation (n = 0) is 70 times faster than six in $CHCl_3$ and 50 times faster in MeOH.

Cyclisations generally give five-membered rings much more readily than six (k^5/k^6 ~10^2)[1] but the formation of cyclic P=O compounds may be an exception. Ester hydrolysis involving intramolecular nucleophilic catalysis by the phosphonate dianion[2] is only 1.5 times faster when the cyclic anhydride intermediate is five-membered rather than six;[3] also, the rate of formation of the cyclic phosphinate **2** from **1** by nucleophilic substitution (Scheme 1) is only 4.3 times greater when n = 0 than when n = 1.[4] We hoped to clarify this apparent anomaly by looking again at the formation of **2** but with the nucleophile and leaving group transposed. The structure of the product dictates that the nucleophile be an OH group (or O^-) while the need to avoid premature cyclisation restricts the choice of leaving group. We opted for a phosphinic amide, specifically the anilide **3**, because a P–N bond is generally stable in the absence of acid but is cleaved readily by nucleophiles in its presence.

The ω-bromo phosphinic anilides **4** (n = 0, 1) were prepared from the acids **1** and were converted into the ω-acetoxy phosphinic anilides **5** using KOAc in MeCN (catalyst $Me_2NCH_2CH_2NMe_2$).[5] Because of the low solubility of the bromo compounds it was necessary to heat the reactions (75 °C) and in one case (n = 0) the cyclic anilide **6** was a substantial byproduct (~10 %). This presumably results from base-induced cyclisation of **4** or **5**. The acetoxy compounds **5** were rapidly deacetylated by NaOMe in MeOH (transesterification), giving the ω-hydroxy phosphinic anilides **3** (n = 0, 1).

The hydroxy compounds were stable enough to survive recrystallisation but on exposure to acid they formed the cyclic phosphinates **2** (n = 0, 1) (Scheme 1). Using 0.20 mol dm^{-3} $ClCH_2CO_2H$ in $CDCl_3$ the half lives for cyclisation [δ_P 34.7→62.2 (n = 0) or 41.7 (n = 1)] were 14.4 min and 17.8 h at 20.5 °C ($k^5 = 8.05 \times 10^{-4}$ s^{-1}, $k^6 = 1.08 \times 10^{-5}$ s^{-1}). In the slower reaction (n = 1) *ca.* 8 % of the substrate was consumed in formation of a byproduct having almost the same chemical shift (δ_P 34.5); this, we think, is the ester **7** [*m*/*z* (ES) 366, 368 ($M+H^+$); δ_H ($CDCl_3$) 4.04 (s, $OCOCH_2Cl$)] resulting from reaction of the OH group with $ClCH_2CO_2H$. †Using CF_3CO_2H in $CHCl_3$ the reactions were too fast to follow by NMR spectroscopy but by reducing the concentration of the acid (0.02 mol dm^{-3}) and monitoring progress by UV spectroscopy it was possible to measure the rates: $t_{½}$ 6.3 s for **3** (n = 0), 7.5 min for **3** (n = 1) ($k^5 = 1.1 \times 10^{-1}$ s^{-1}, $k^6 = 1.55 \times 10^{-3}$ s^{-1}).

In MeOH the reactions of **3** (n = 0, 1) were much slower than in $CHCl_3$ but again gave the cyclic phosphonates **2** (≥ 97 % by ^{31}P NMR). Rate measurements (UV) revealed half lives of 21.4 s and 19.3 min with 0.20 mol dm^{-3} CF_3CO_2H at 20.5 °C ($k^5 = 3.23 \times 10^{-2}$ s^{-1}, $k^6 = 6.00 \times 10^{-4}$ s^{-1}) and 1.2 s and 56 s using 0.10 mol dm^{-3} HBF_4 ($k^5 = 6.0 \times 10^{-1}$ s^{-1}, $k^6 = 1.25 \times 10^{-2}$ s^{-1}). Now, of course, cyclisation has to compete with intermolecular attack by the solvent and it is an indication of the efficiency of the intramolecular reaction (cyclisation) that very little of the acyclic methyl phosphonate **8** (X = OH) was formed. Even with the less readily cyclised substrate (n = 1) the crude product contained only *ca* 2 % of **8** (X = OH) [δ_P ($CDCl_3$) 46.9, δ_H 3.62, d, J_{PH} 11], implying a 50-fold preference for cyclisation. In accord with this the ω-bromo anilide **4** (n = 1), which cannot cyclise, gives **8** (X = Br) on methanolysis [0.10 mol dm^{-3} HBF_4 in MeOH; $k = 2.28 \times 10^{-4}$ s^{-1}] *ca* 55 times slower than the hydroxy compound **3** (n = 1) cyclises.



Scheme 1

Of particular concern are the relative rates of formation of the five- and six-membered rings. For the acid catalysed cyclisation of **3** (n = 0, 1) the k^5/k^6 ratio is 70 in $CHCl_3$ and 50 in MeOH. Such values are not far removed from the values (~ 10^2) generally seen for cyclisation reactions,[1] but they are much greater than the value of 4.3 (in CH_2Cl_2) found previously for the base-induced cyclisation of the bromo compound

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

1 (n = 0, 1).[4] Since the two types of cyclisation give the same product **2**, however, the anomalously small k^5/k^6 ratio in one case cannot just be a reflection of strain in the product. The probable transition states **9** and **10** for the two types of cyclisation are not the same but they are rather similar, yet only in the case of **10** does $\Delta G‡$ show the normal sensitivity to chain length ($k^5 >> k^6$). We do not know why transition state **9** should be unusually strained (k anomalously small) when n = 0 but partial eclipsing across the C_α–P bond may be a factor.‡

Experimental

^{1}H NMR spectra were recorded at 250 MHz (Me_4Si internal standard; J in Hz) and ^{31}P NMR spectra at 101 or 121 MHz (positive δ_P downfield from 85 % H_3PO_4). Mass spectra were obtained with a Kratos Concept or Micromass Quattro LC spectrometer and UV spectra with a Hewlett Packard 8452A diode array spectrophotometer. Methanol was distilled from the Mg salt; $CHCl_3$ was passed through alumina and dried over 4A molecular sieve.

Bromoalkyl(phenyl)phosphinic anilides **4**: Oxalyl chloride (0.61 g, 4.8 mmol) was added in portions to the acid **1** (n = 0)[4] (0.63 g, 2.4 mmol) in CH_2Cl_2 (5 ml). After 1 h volatile material was removed *in vacuo*. The crude phosphinic chloride was added to a stirred solution of aniline (0.56 g, 6.0 mmol) in CH_2Cl_2 (8 ml). The mixture was warmed (35 °C) for 1 h and was then diluted (CH_2Cl_2, 10 ml) and washed with water (containing a little HCl). Crystallisation from $CHCl_3$–light petroleum gave the anilide **4** (n = 0) (0.78 g, 94 %), mpt 141–143 °C (softens at 130 °C); m/z 339, 337 (M^+, 100 %); δ_P ($CDCl_3$) 27.9; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.8 (5 H), 5.82 (1 H, d, J_{PH} 11, NH), 3.38 (2 H, m, $BrCH_2$) and 2.4–1.95 (4 H) (Found: C, 53.4; H, 5.15; N, 4.0. $C_{15}H_{17}BrNOP$ requires C, 53.3; H, 5.1; N, 4.2 %).

The acid **1** (n = 1)[4] was similarly converted into the anilide **4** (n = 1) (91 %), mpt 148–149 °C (softens > 120 °C); m/z 353, 351 (M^+, 70 %) and 272 (M^+–Br, 100); δ_P ($CDCl_3$) 28.5; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.85 (5 H), 5.69 (1 H, d, J_{PH} 11, NH), 3.29 (2 H, t, J_{HH} 7, $BrCH_2$) and 2.25–1.55 (6 H) (Found: C, 55.2; H, 5.4; N, 3.8; M^+, 351.0387. $C_{16}H_{19}BrNOP$ requires C, 54.6; H, 5.4; N, 4.0; M, 351.0388).

Acetoxyalkyl(phenyl)phosphinic anilides **5**: A suspension of dried KOAc (128 mg, 1.3 mmol) in MeCN (2 ml) was stirred vigorously with $Me_2NCH_2CH_2NMe_2$ (catalyst)[5] (11.6 mg, 0.1 mmol) for 0.4 h. The bromo compound **4** (n = 0) (338 mg, 1.0 mmol) was added and the temperature was raised to 75 °C. After 2 h more catalyst (5 mg) was added and reaction was allowed to continue (1.5 h) until consumption of the starting material was almost complete (TLC). The solvent was evaporated, the residue was partitioned between CH_2Cl_2 and water, and the organic portion was chromatographed on silica. Elution with ether–Pr^{i}OH (12:1) afforded the acetoxy phosphinic anilide **5** (n = 0) (200 mg, 63 %), mpt 104–105 °C, m/z 317 (M^+, 55 %) and 183 (100); ν_{max} (Nujol)/cm^{-1} 3220 (NH) and 1735 (C=O); δ_P ($CDCl_3$) 28.2; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.85 (5 H), 6.04 (1 H, d, J_{PH} 11, NH), 4.02 (2 H, m, $AcOCH_2$), 2.25–1.7 (4 H) and 1.99 (3 H, s, AcO) (Found: M^+, 317.1180. $C_{17}H_{20}NO_3P$ requires M, 317.1181). Later fractions contained the byproduct **6** (n = 0) (*ca* 20 mg), mpt 151–153 °C (from CH_2Cl_2– ether); m/z 257 (M^+, 95 %) and 256 (100); δ_P ($CDCl_3$) 41.0; δ_H ($CDCl_3$) 7.8–7.35 (5 H), 7.2–6.8 (5 H), 3.9–3.7 (2 H) and 2.6–2.0 (4 H) (Found: M^+, 257.0969. $C_{15}H_{16}NOP$ requires M, 257.0970).

The corresponding reaction of **4** (n = 1) was slower; slightly more catalyst was used and the time was increased to 10 h. Less byproduct was formed and chromatography was unnecessary. Crystallisation from CH_2Cl_2–ether gave the acetoxy compound **5** (n = 1) (78 %), mpt 121–122 °C; m/z 331 (M^+, 90 %) and 272 (M^+–AcO, 100); ν_{max} (Nujol)/cm^{-1} 3210 (NH) and 1730 (C=O); δ_P ($CDCl_3$) 28.5; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.8 (5 H), 6.04 (1 H, d, J_{PH} 11, NH), 3.98 (2 H, m, $AcOCH_2$), 2.2–1.5 (6 H) and 1.99 (3 H, s, AcO) (Found: C, 65.1; H, 6.65; N, 4.1. $C_{18}H_{22}NO_3P$ requires C, 65.2; H, 6.7; N, 4.2 %).

Hydroxyalkyl(phenyl)phosphinic anilides **3**: The acetoxy compound **5** (n = 0 or 1) was dissolved in MeOH containing NaOMe (2 equiv., 0.25 mol dm^{-3}). After *ca* 7 min reaction was quenched with NH_4Cl (3 equiv.). The solvent was evaporated (no heat) and the residue was washed with water and cold CH_2Cl_2. Crystallisation from aqueous MeOH then MeOH–ether afforded the hydroxy phosphinic anilide **3** (n = 0) (54 %), mpt 139–141 °C; m/z (FAB) 276 ($M+H^+$, 100 %), 183 ($M+H^+$–$PhNH_2$, 50) and 154 (65); δ_P ($CDCl_3$) 30.1; δ_H ($CDCl_3$) 7.9–7.45 (5 H), 7.2–6.85 (5 H), 6.05 (1 H, d, J_{PH} 9, NH), 3.73 (2 H, m, $HOCH_2$; br but sharpened by exchange of OH group with D_2O), 3.52 (1 H, br s, OH) and 2.3–1.75 (4 H) (Found: C, 65.3; H, 6.6; N, 4.8; $M+H^+$, 276.1153. $C_{15}H_{18}NO_2P$ requires C, 65.4; H, 6.6; N, 5.1 %; M+H, 276.1153) or **3** (n = 1) (90 %), mp 135–136 °C; m/z (FAB) 290 ($M+H^+$, 70 %), 197 ($M+H^+$–$PhNH_2$, 25) and 154 (100); δ_P ($CDCl_3$) 29.5; δ_H ($CDCl_3$) 7.95–7.4 (5 H), 7.2–6.8 (5 H), 5.90 (1 H, d, J_{PH} 9, NH), 3.64 (2 H, br t, J_{HH} 6, $HOCH_2$), 2.70 (1H, br s, OH) and 2.25–1.55 (6 H) (Found: C, 66.9; H, 7.0; N, 4.85; $M+H^+$, 290.1310. $C_{16}H_{20}NO_2P$ requires C, 66.4; H, 7.0; N, 5.1 %; M+H, 290.1310).

Cyclisation reactions: (a) A solution of the substrate **3** (n = 0 or 1) (3 mg) in $CDCl_3$ (0.5 ml) containing $ClCH_2CO_2H$ (0.20 mol dm^{-3}) was maintained at 20.5 ± 1 °C; the ^{31}P NMR spectrum was recorded at intervals (*ca* 8 min or 4 h) to > 90 % completion [δ_P 34.7 →62.2 (n = 0) or 41.7 (n = 1)] and the fraction of unchanged substrate was deduced from the integral. In one case (n = 1) a substantial byproduct (δ_P 34.5, 8 %) was evident. First order plots were reasonably linear and from them the values of k (± 10 %) were deduced. On completion the solution was washed with very dilute aqueous HCl and $NaHCO_3$ and the identity of the cyclic product **2** (n = 0 or 1) was confirmed spectroscopically: m/z (ES) 183 (n = 0) or 197 (n = 1) ($M+H^+$), δ_P ($CDCl_3$) 57.8 (n = 0) or 37.9 (n = 1), δ_H ($CDCl_3$) as previously described for products obtained from **1** (n = 0, 1).[4] In one case (n = 1) the spectra included signals attributable to the byproduct, probably the ester **7** (n = 1), δ_P ($CDCl_3$) 28.5; m/z (ES) 366, 368 ($M+H^+$), δ_H ($CDCl_3$) 4.04 (s, $OCOCH_2Cl$).

(b) The substrate **3** (n = 0 or 1) (~ 1 mg) was added to a solution (2–2.5 ml) of CF_3CO_2H or HBF_4.Et_2O (≥10 equiv.) of the required concentration in $CHCl_3$ or MeOH at 20.5 ± 0.5 °C. The UV spectrum (270–310 nm) was recorded at intervals (0.6 s–5 min) to ≥ 85 % completion. The decline in absorbance at 284 nm was noted. A plot of log ($A–A_\infty$) *vs* time was linear and from it the value of k (± 10 %) was deduced.

(c) The reactions in (b) above were repeated using larger amounts of substrate. When reaction was complete the solutions were concentrated; in every case a single product (≥ 97 %) was dominant (^{31}P NMR). The crude product in CH_2Cl_2 was washed with water and very dilute $NaHCO_3$ solution and the structure **2** (n = 0 or 1) was confirmed as in (a) above.

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Footnotes

† In deducing the value of k^6 (and the corresponding $t_{½}$) for cyclisation (n = 1) allowance was made for the consumption of 8 % of the substrate in the non-cyclisation side reaction.

‡ The bonds at adjacent tetrahedral centres in cyclopentane are partially eclipsed (torison angle < 60°). In the five membered cyclic transition state **9** (n = 0) the tetrahedral centres include the P atom (P, C_α, C_β) whereas in **10** (n = 0) they do not (C_α, C_β, C_γ).