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Phosphono-Transfer Catalysis Mediated by an Amphoteric Receptor

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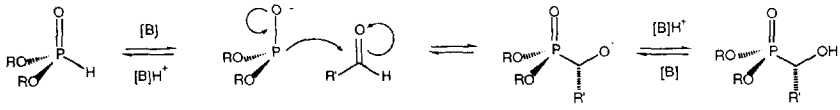
Abstract: *We report here the design of an amphoteric molecule which binds the substrates of and acts as a catalyst for the hydrophosphonylation of aldehydes.*

The base-catalysed hydrophosphonylation of aldehydes (the Pudovik reaction) is one of the most versatile routes to physiologically desirable α-functionalised phosphonate esters (Scheme 1),[1] yet efficient catalytic enantioselective variants which operate under aerobic conditions have still to be developed.[2] As part of a programme of research which seeks to blend approaches from metallo-organic, organic and biological chemistries in the design of novel reagents for stereoselective phospho-transfer processes,[3] one of our main objectives is to develop a catalytic enantioselective variant of the Pudovik reaction.



Scheme 1

One strategy that we are pursuing is based on the recognition that high stereoselectivities in the Pudovik reaction may be acheived by promoting a more intimate level of contact between substrate and catalyst. As an important step towards acheiving this goal we report here that the Pudovik reaction is catalysed by novel, amphoteric molecules which combine both acidic and basic interaction sites.

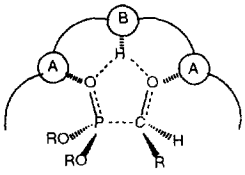
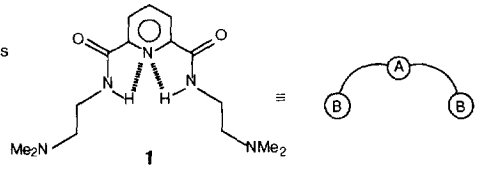


Figure 1 Proposed layout of components for an amphoteric catalyst of the Pudovik reaction in relation to a model transition state.
A = acidic site; B = basic site

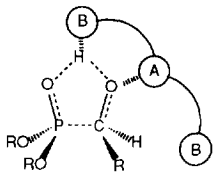


1

One line of enquiry that we are pursuing is based on the proposal that high activities and stereoselectivities in the Pudovik reaction may be acheived by designing a catalyst system which is capable of binding and activating both substrates simultaneously, a scenario common to many enzymes.[4] Here we report an important step towards achieving these objectives, catalysis of aldehyde hydrophosphonylation by a novel amphoteric compound which contains acidic and basic binding functionalities reminiscent of phospho-diester binding and activating enzymes.[5]

Some of the features of a catalyst system capable of stablising a reasonable model for the rate-determining transition state of Scheme 1[6] are illustrated in Figure 1. The combination of acidic and basic binding sites should lead to rate enhancement over simple basic catalysts.

We have synthesised a first generation amphoteric receptor system **1** by reaction of N,N-dimethylethylene diamine with 2,6-pyridinedicarboxylchloride in CH_2Cl_2 solvent.[7] Receptor **1** is an example of a [—B—A—B—] class compound which combines both pre-orientated two-point hydrogen bonding sites in the 2,6-pyridinedicarboxamide function[8] with flexible, endogenous dimethylamino bases. The carboxamide hydrogens were identified as a broadened triplet resonance (coupling to the adjacent methylene hydrogens) at 8.20 ppm, $\Delta_{1/2}$ 17 Hz (0.1 M in $CDCl_3$, 25°C) in the ^1H NMR spectrum which diminished in intensity upon treatment with D_2O due to chemical exchange.



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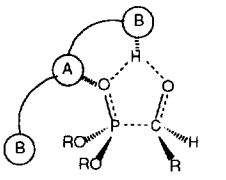

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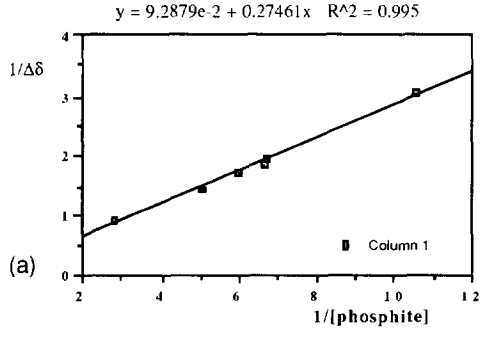
We envisaged that since receptor **1** possesses a functionality profile which is complementary to that shown in Figure 1 it should be possible to stablise a hydrophosphonylation transition state through two scenarios illustrated schematically in **2** and **3** above, both of which could lead to active catalysis. Consequently, it is necessary to probe (i) the strength of interaction between receptor **1** and both substrates of the Pudovik reaction and (ii) the ability of **1** to catalyse the Pudovik reaction.

An interaction between the phosphoryl oxygen atom of $(MeO)_2P(O)H$ and the carboxamide hydrogens of **1** is suggested from ^1H NMR titration experiments. Thus, the carboxamide hydrogen chemical shift of **1** (8.01 ppm, 1 x 10^{-2} M, C_6D_6) is displaced to higher frequency upon treatment with the phosphite (9.09 ppm upon addition of 35.3 equivalents of phosphite) thus providing evidence for intermolecular interaction presumably involving the phosphoryl (P=O) moeity. Subsequent construction of the 1:1 binding isotherm affords an association constant $K_{11}(P)$ of 0.34 $mol^{-1}dm^3$ (Figure 2a) supportive of relatively weak binding.[9]



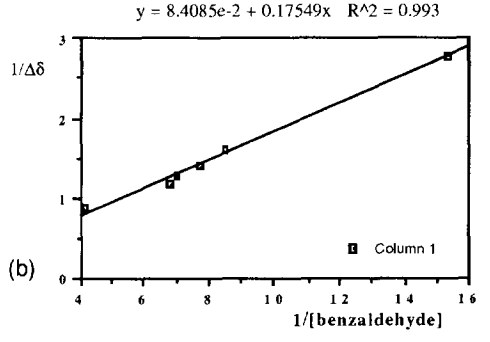


Figure 2 Double-reciprocal plots of the 1:1 binding isotherms[9] for the interaction of receptor **1** with (a) $(MeO)_2P(O)H$ and (b) PhCHO (L) in C_6D_6 solvent at 25°C. Data analysed according to $1/\Delta = 1/\{\Delta_{11}.K_{11}.[L]\} + 1/\Delta_{11}$ where $\Delta = \delta_1(obs) - \delta_1(pure)$; $\Delta_{11} = \delta(complex) - \delta_1(pure)$, both Δ values are in ppm. [1] = 1 x 10^{-2} M. Since $[L]_0 >> [1]$ we approximate $[L] = [L]_0$. (a) K_{11} (P) 0.34 $mol^{-1}dm^3$; (b) K_{11} (A) 0.48 $mol^{-1}dm^3$.

Binding interactions between **1** and PhCHO are revealed by similar high frequency shifts of the carboxamide hydrogen resonance of **1** upon treatment with the aldehyde. The 1:1 binding isotherm (Figure 2b)

affords an association constant $K_{11}(A)$ of 0.48 $mol^{-1}dm^3$. Consequently, binding of the aldehyde is some 40% stronger than the binding of phosphite under the same conditions.

As anticipated, compound **1** is an effective catalyst for the Pudovik reaction.[2] Thus, the hydrophosphonylation of PhCHO with $(MeO)_2P(O)H$ in toluene solvent at 25°C proceeds cleanly to afford $(MeO)_2P(O)CH(OH)Ph$ (δ_P 24.8 ppm) in the presence of 0.05 mole equivalents of **1**. Under these conditions *ca.* 41% of **1** will be bound by phosphite and *ca.* 49% by aldehyde.[10] Unfortunately, the binding constants are not sufficiently large enough to acheive catalyst saturation at suitable concentration levels; higher concentrations lead to precipitation of the product. Analysis of the rate data in terms of second order kinetics (Figure 3) affords a rate constant k_2 (**1**) of 5.9 x 10^{-2} $mol^{-1}dm^3h^{-1}$.[11] This is essentially the same as when the reaction is catalysed by NEt_3 at the same level of catalyst loading (5.9 x 10^{-2} $mol^{-1}dm^3h^{-1}$) which reveals **1** to be as effective a catalyst as NEt_3. However, inherent differences in basicity between NEt_3 and $NMe_2CH_2CH_2NHC(O)$- should result in the former being a significantly better catalyst. Some indication of the effects of basicity can be obtained by recognising that NEt_3 is more basic than NMe_3 by a factor of *ca.* 11.[12] Consequently, that this is not the case is presumably a reflection of greater binding ability of **1** over NEt_3. The presence of the amino groups in receptor **1** is crucial for catalytic activity since a modified receptor, in which both dimethylamino groups are replaced by methyl groups does not catalyse the Pudovik reaction at all under the conditions employed for both **1** and NEt_3. Consequently, under these conditions substrate binding *via* pyridinedicarboxamide hydrogen bonding is not sufficient to induce the hydrophosphonylation reaction in the absence of a basic activating function.

Deviations from simple second order kinetics become apparent after *ca.* 25 h (15 turnovers, 75% reaction) in the reaction catalysed by **1** but are not observed in the NEt_3 catalysed reaction for at least 56 h (*ca.* 17 turnovers, 87% reaction). This deviation leads to a significant slowing of phosphonylation activity after 75% reaction and we presume that this may be due to the binding of $(MeO)_2P(O)CH(OH)Ph$ by **1** thus leading to product inhibition of catalytic activity. We are currently examining the binding of $(MeO)_2P(O)CHPh(OH)$ with **1** in detail and will describe this behaviour in a full report. However, binding between the two is indicated by a shift of the carboxamide hydrogen resonance of **1** from 8.01 to 8.17 ppm (1 x 10^{-2} M, C_6D_6, 25°C) upon addition of one mole equivalent of the phosphonate ester.

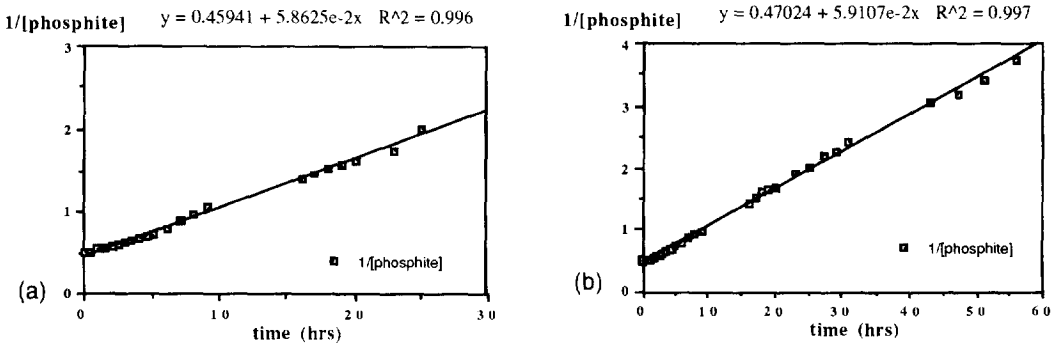


Figure 3 Kinetic runs were performed in toluene solvent at 20°C in 10 mm NMR tubes fitted with 5 mm inserts containing reference and lock solvents. Initial concentrations $[]_0$ used were: $[1]_0 = [NEt_3]_0 = 0.1$ M, $[(MeO)_2P(O)H]_0 = [PhCHO]_0 = 2.0$ M. The composition of the reaction mixture was monitored by $^{31}P\{^1H\}$ NMR and second order rate constants k_2 were obtained by data analysis according to the equation. $1/[P] = k_2.t + 1/[P]_0$ where $P = (MeO)_2P(O)H$.[10] (a) k_2 (1) = 5.9 x10^{-2} $mol^{-1}dm^3h^{-1}$; (b) k_2 (NEt_3) = 5.9 x10^{-2} $mol^{-1}dm^3h^{-1}$. for both reactions, *ca.* 15 turnovers in 25 h. This reaction does not proceed to any measurable degree at room temperature in the absence of a catalyst.

When the hydrophosphonylation of PhCHO is run under aerobic conditions at the same concentration

levels, clean second order kinetics are observed for at least 14 turnovers (*ca.* 25 h). Under these conditions, k_2 = 4.7 x 10^{-2} $mol^{-1}dm^3h^{-1}$ which is only slightly slower than when reaction is run under a dry, inert atmosphere. We presume that the *ca.* 20% rate difference is a reflection of competition between the phosphonylation reaction substrates and trace water for binding sites within the receptor **1**.

Currently, we are focusing on trying to delineate the factors involved in controlling hydrophosphonylation activity by catalysts such as **1**, in particular, the effects of competitive binding between substrates and products and the influence of catalyst loading on activity. We anticipate that both factors will be important in determining the levels of enantioselectivity attainable with chiral derivatives of receptor **1**, the synthesis of which we are also currently investigating.

Acknowledgements

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7. A dichloromethane solution of 2,6-pyridinedicarboxylchloride (3.21 g, 15.7 mmol in 32cm^3) was added dropwise to a stirred solution of N,N-dimethylethylenediamine (2.76 g, 31.3 mmol) and triethylamine (32.9 cm^3, 236 mmol) in dichloromethane (165 cm^3). The resulting clear orange solution was stirred for 1 h after which time a slight precipitate had developed. The dichloromethane solution was removed under reduced pressure to afford a deep red viscous liquid. This liquid was extracted into toluene (3 x 15 cm^3), filtered and all the volatile materials removed under reduced pressure to afford a red liquid. This liquid was dissolved in the minimum amount of dichloromethane and passed down three columns of Florisil (25 g each), each time eluting with *ca.* 150 cm^3 of dichloromethane. All the aliquots were combined and the volatiles removed under reduced pressure to afford **1** as a yellow, waxy solid. Recrystallisation from toluene afforded **1** as colourless crystals (1.32 g, 27 %). Selected data for **1** (assignments facilitated by ^1H-^1H and ^1H-^{13}C COSY experiments). δ_H (0.1 M $CDCl_3$, 25°C) 8.20 (br t, 2H, -C(O)N*H*-), 8.18 (d, 2H, $^3J_{HH}$ 7.7, C_5H_3N-H_m), 7.86 (t, 1H, $^3J_{HH}$ 7.7, C_5H_3N-H_p), 3.44 (dt, 4H, $^3J_{HH}$ 5.8, HNCH_2), 2.41 (t, 4H, $^3J_{HH}$ 6.0, CH_2NMe_2), 2.16 (s, 12H, NMe_2). δ_C (0.1M $CDCl_3$) 163.54 (s, -C(O)NH), 148.83 (s, C_5H_3N-C_o), 138.70 (s, C_5H_3N-C_p), 124.67 (s, C_5H_3N-C_m), 58.20 (s, CH_2NMe_2), 45.32 (s, NMe_2), 37.04 (s, $HNCH_2$). (Found: M^+, 307.200 303. Calc. for $C_{15}H_{25}N_5O_2$: M, 307.200 825).

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10. The fraction of bound catalyst R_S can be calculated from the equation; $R_S = K_{11}.[S]_o/\{1 + K_{11}[S]_o\}$ where S is the substrate of interest, $[S]_o$ its initial concentration and K_{11} its binding constant to the catalyst. This assumes that [S] >> [catalyst].

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