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Using Polarization Effects to Alter Chemical Reactivity: A Simple Host Which Enhances Amine Nucleophilicity

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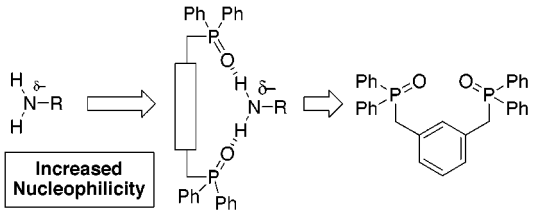
ABSTRACT



The rational design of a bis(phosphine oxide) host which is capable of binding a benzylic amine is presented. The ability of this host to increase the rate of addition of 4-fluorobenzylamine to *N*-phenylmaleimide is rationalized in terms of the enhancement of the nucleophilicity of the benzylic amine.

Enzymes are capable of catalyzing a large range of reactions with complete regio- and stereoselectivity and a variety of mechanisms exist to facilitate catalysis. Many enzymes use[1] strong hydrogen-bond acceptors or donors to polarize substrates toward reaction or to stabilize charge in reaction intermediates or transition states. In many cases, these interactions cause polarization of the substrate thus altering its chemical reactivity. A long-term aim[2] for the organic chemist remains the emulation of some of the specificity and catalytic efficiency of enzymes through the synthesis of artificial receptors designed to function as mimics[3] of enzyme function. A key question in the design of efficient, synthetic catalysts is the role of polarization effects in enzyme catalysis. Recently, we described[4] the formation of an exceptionally short C—H···O hydrogen bond between a terminal alkyne and a water molecule. The formation of this hydrogen bond was facilitated by the presence, in the solid state, of two hydrogen bonds between the protons of the

(1) Bugg, T. *An Introduction to Enzyme and Coenzyme Chemistry*; Blackwell Science: Oxford, 1997. Fersht, A. *Structure and Mechanism in Protein Science*; W. H. Freeman: New York, 1999.

(2) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. Kirby, A. J. *Angew. Chem., Int Ed. Engl.* **1996**, *35*, 707.

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(4) Kariuki, B. M.; Harris, K. D. M.; Philp, D.; Robinson, J. M. A. *J. Am. Chem. Soc.* **1997**, *119*, 12679.

(5) This polarization requires that the effects of the hydrogen bond donation are transmitted effectively throughout the system. This may not be true for certain systems. See: Philp, D.; Robinson, J. M. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1643.

(6) Schrader has described similar bis(phosphonate) and bis(phosphate) hosts which bind several classes of compounds which bear amino groups. See, for example: Schrader, T. *J. Org. Chem.* **1998**, *63*, 264−272. Schrader, T. *J. Am. Chem. Soc.* **1998**, *120*, 11816−11817. Herm, M.; Schrader, T. *Chem. Eur. J.* **2000**, *6*, 47−53.

(7) All calculations were performed using SPARTAN (Version 5.1.3, Wavefunction Inc., Irvine, CA, 1999). Trimethylphosphine oxide was used in place of triphenylphosphine oxide to reduce computation time. An initial guess structure for the 2:1 complex between trimethylphosphine oxide and methylamine was generated from the crystal structure reported in ref 4.

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water molecule and the oxygen atoms of two triphenylphosphine oxide (TPPO) molecules, as shown schematically in Figure 1a. In this aggregate, the water molecule donates two

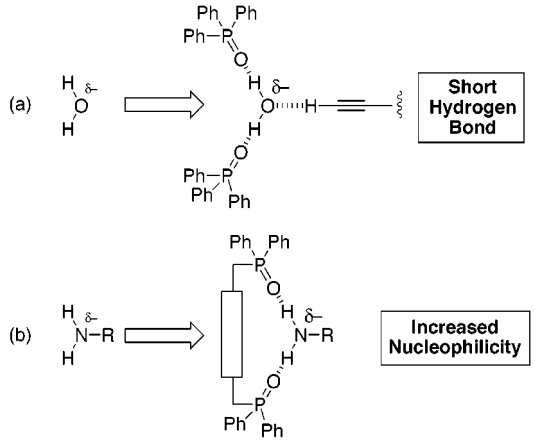
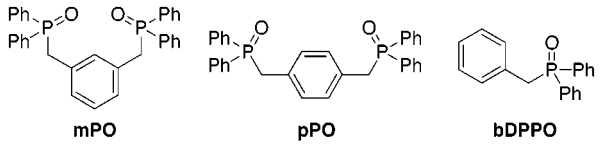


Figure 1. (a) A triphenyl phospine oxide:water aggregate facilitates a short C—H···O hydrogen bond through polarization. (b) A bis(phosphine oxide) receptor enhances amine nucleophilicity through polarization.

hydrogen bonds, one to each of the TPPO acceptors. This double donation increases the partial negative charge on the oxygen atom of the water molecule thus improving[5] its ability to accept a further hydrogen bond from the alkyne. *Ab initio* quantum mechanics calculations suggest that the negative electrostatic potential on the oxygen atom increased by more than 40% as a result of the presence of the two hydrogen bonds to the two TPPO molecules. We reasoned that this polarization effect could also be exploited to enhance the nucleophilicity of a primary amine (Figure 1b) through the synthesis of a bis(phosphine oxide) host.

Data from our previous X-ray diffraction studies suggested that the optimum P···P distance required in a host designed to bind to primary amines was between 5.8 and 7.0 Å. Therefore, we designed[6] the bis(phosphine oxide) hosts **mPO** and **pPO** in which two diphenylphosphine oxide groups are bridged by a xylene-derived spacer. Molecular modeling suggested that the P···P distances are 5.9 Å in the case of **mPO** and 7.0 Å in the case of **pPO**. Additionally, we planned to use benzyldiphenylphosphine oxide **bDPPO** as a comparison compound for the two bis(phosphine oxides).



Ab initio quantum mechanics calculations were used in an attempt to quantify the effect of the formation of two hydrogen bonds to the amine on the electrostatic potential surface around the amine nitrogen atom. Accordingly, we performed calculations[7] on methylamine and a methylamine: trimethylphosphine oxide aggregate at the HF/6-31G(d,p) level of theory. The results (Figure 2) of these calculations

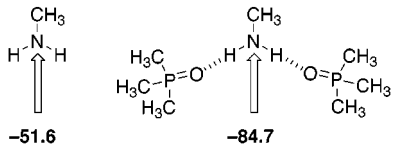


Figure 2. Values of the electrostatic potential at nitrogen in methylamine and in the [$MeNH_2$·$TMPO_2$] aggregate calculated at the HF/6-31G(d,p) level of theory (in kcal mol^{-1}).

suggest that there is a large increase in the magnitude of the most negative value of the electrostatic potential at nitrogen on complexation of methylamine by two trimethylphosphine oxide (TMPO) molecules. We were therefore confident that hosts such as **mPO** should enhance the nucleophilicity of bound amines significantly.

The hosts **mPO** and **pPO** were synthesized[8] in two steps starting from the appropriate xylylene dibromide. Lithiodiphenylphosphide was prepared by reaction of chlorodiphenylphosphine with lithium metal in dry THF. Addition of the appropriate xylylene dibromide to the solution of lithiodiphenylphosphide afforded the corresponding diphenylphosphines which were oxidized directly by treatment with mCPBA in CH_2Cl_2 to afford **mPO** and **pPO** in overall yields of 22% and 17%, respectively. An analogous route, starting from benzyl bromide, was used to synthesize the control compound **bDPPO**.

Unfortunately, the receptor **pPO** was insufficiently soluble in nonpolar solvents, in which hydrogen bonding to primary amines would be expected to be strongest, to permit any systematic studies of its ability to bind primary amines. However, immediate evidence of the ability of **mPO** to bind primary amines came from LSI mass spectrometry. When $CHCl_3$ solutions of 1:1 mixtures of **mPO** and a selection of primary amines were allowed to evaporate and the residues analyzed[9] by LSI mass spectrometry, signals (Table 1) arising from 1:1 complexes between **mPO** and the amines were evident.

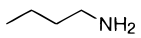
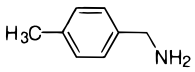
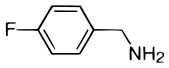
Further evidence for the association of **mPO** with a variety of primary amines was evident in the ^{1}H NMR spectra of 1:1 mixtures of **mPO** and primary amines recorded in $CDCl_3$ solution at room temperature. Strong downfield shifts[10] (∼1.5

(8) Spectroscopic data for **mPO**: mp 58.8−65.7 °C; *m*/*z* (FAB$^+$) 507 ([MH$^+$], 100%), 306 (5), 201 (9); δ_H (300 MHz; $CDCl_3$) 3.53 (d, $^2J_{PH}$ = 13.6, ArCH_2, 4H), 6.85−7.05 (m, Ar*H*, 4H), 7.31−7.72 (m, Ar*H*, 20H); δ_C (75 MHz; $CDCl_3$) 37.8 (d, $^1J_{PC}$ = 66.2 Hz), 128.4 (d, $^3J_{PC}$ = 11.8 Hz), 128.4 (d, $^2J_{PC}$ = 11.8 Hz), 129.6, 131.1 (d, $^3J_{PC}$ = 9.2 Hz), 131.5 (d, $^3J_{PC}$ = 9.6 Hz), 131.8, 131.9 (d, $^1J_{PC}$ = 99.4 Hz), 132.1, 132.2 (d, $^2J_{PC}$ = 22.0 Hz).

(9) Liquid secondary ion mass spectrometry (LSIMS) data were obtained using a VG Zabspec instrument equipped with a Cs^+ ion source and utilizing a *m*-nitrobenzyl alcohol matrix.

(10) The chemical shift of the amine NH_2 resonance is concentration dependent. The values for chemical shift changes quoted in the text are corrected for this concentration dependence.

Table 1. Mass Spectrometric Data for the Complexation of Primary Amines by **mPO**

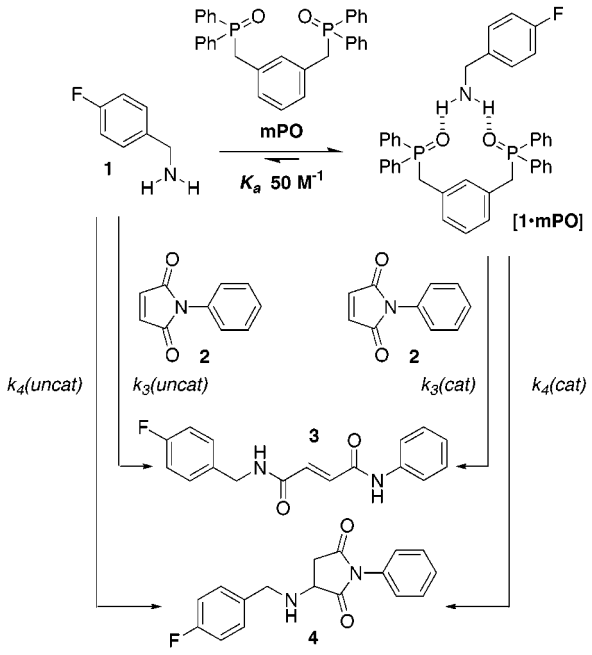
amine	expected $[M+H]^{+a}$	observed $[M+H]^{+}$ (%)[b]
	566	566 (3)
	628	628 (7)
	632	632 (3)

[a] Mass of expected molecular ion for a 1:1 complex between **mPO** and amine shown. [b] Mass of observed molecular ion and intensity relative to base peak in %.

ppm) of the resonances arising from the primary amino group were observed in all cases. Much smaller chemical shift changes were observed in other ^{1}H resonances and in the ^{31}P resonance of **mPO**. All of these data were used to determine an approximate[10] association constant for the complex between **mPO** and 4-fluorobenzylamine of 50 M^{-1}.

To assess the effect of complexation on the nucleophilicity of the amine nitrogen lone pair, we decided to study the reaction between 4-fluorobenzylamine **1** and *N*-phenylmaleimide **2** (Scheme 1). This reaction can give rise to two

Scheme 1



products (Scheme 1): bisamide **3**, which is the result of direct addition to one of the carbonyl groups of **2**, and the aminosuccinimide **4**, which is the result of conjugate addition to the terminus of the α,β unsaturated system present in **2**.

Amine **1** and maleimide **2** were allowed to react in $CDCl_3$ solution at 40 °C from starting concentrations of 50 mM for both **1** and **2**. The progress of the reaction was monitored by 400 MHz ^{1}H NMR spectroscopy and the concentrations of products **3** and **4** were determined from these data. The kinetic data (Figure 3) indicate that the reaction is relatively slow under these conditions and that **3** and **4** are formed in approximately equal amounts. When the reaction was repeated under identical conditions in the presence of 1 equiv of the control phosphine oxide **bDPPO**, no difference in the rates of formation of **3** and **4** was observed. By contrast, when the same reaction was performed under identical conditions in the presence of 1 equiv of the receptor **mPO**, the kinetic data (Figure 3) indicate that the addition of **mPO**

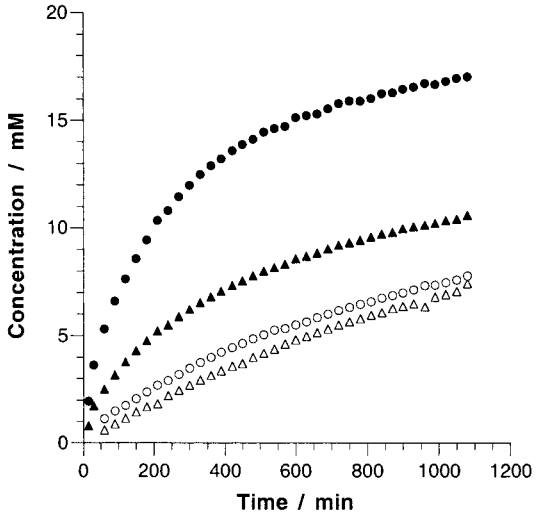


Figure 3. Kinetic data obtained for reactions between **1** and **2** in $CDCl_3$ at 40 °C in the absence of **mPO** (open symbols) and in the presence of 1 equiv of **mPO** (filled symbols). In both cases, the starting concentrations of **1** and **2** were 50 mM. Circles represent the concentration of **3** and triangles represent the concentration of **4**.

dramatically increases the rate of reaction between **1** and **2**. Additionally, the production of bisamide **3**—the product of direct addition to the imide carbonyl—is enhanced significantly over the production of aminosuccinimide **4**—the conjugate addition product. This observation suggests that, in addition to increasing the reaction rate through an enhancement of the partial negative charge at nitrogen, the amine nucleophile has also become harder and now prefers to react with the harder electrophilic center, namely the carbonyl group. The reaction between **1** and **2** was also performed in the presence of 0.2 equiv of the receptor **mPO**. In this case, the kinetic data were almost identical to those obtained when the reaction was performed in the presence of 1 equiv of **mPO**.

(11) Kinetic simulation and fitting was performed with Gepasi (Version 3.21). Mendes, P. *Comput. Appl. Biosci.* **1993**, *9*, 563. Mendes, P. *Trends Biochem. Sci.* **1997**, *22*, 361. Mendes, P.; Kell, D. B. *Bioinformatics* **1998**, *14*, 869.

Table 2. Results of Kinetic Simulation and Fitting of the Kinetic Data for the Reaction between **1** and **2** in the Presence and Absence of **mPO**

rate constant[a]	best fit value, 10^{-5} M^{-1} s^{-1} [b]
k_3(uncat)	5.11 ± 0.08
k_4(uncat)	5.09 ± 0.03
k_3(cat)	33.8 ± 0.7
k_4(cat)	15.2 ± 0.9

[a] The rate constant descriptors refer to Scheme 1. [b] Simulation and fitting were carried out by first obtaining values for k_3(uncat) and k_4(uncat) from the data collected in the absence of **mPO**. These values were then used in the derivation of best fit values for k_3(cat) and k_4(cat) from fitting of the kinetic data obtained in the presence of 1 equivalent of **mPO** to the model shown in Scheme 1. Errors in rate constants are quoted at the 2σ level, on the basis of the standard deviations obtained from the kinetic simulation and fitting procedure.

Kinetic simulation and fitting[11] of the reaction profiles to the model shown in Scheme 1 allowed us to extract values for the rate constants for the addition of **1** to **2** both in the presence and in the absence of **mPO**. These results are summarized in Table 2.

It is clear from the data presented in Table 2 that the production of **3** and **4** are accelerated significantly when 4-fluorobenzylamine is bound to the receptor **mPO**. In particular, the rate constant for the formation of **3** via the catalyzed pathway is between six and seven times higher than that in the uncatalyzed pathway.

In conclusion, we have demonstrated the rational design of a host which is capable of accelerating the nucleophilic addition of an amine to a maleimide through a reagent polarization effect. We are currently engaged in extending this methodology to other reaction classes and in the design of more complex host systems.

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