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Metal coordination and stacking effects in supramolecular catalysis. Effects of structural variations of copper complexes for the hydrolysis of phosphate esters

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Abstract—Until now barely explored stacking effects with rate constant enhancements by up to two orders of magnitudes and total accelerations of about 10^7 are found by introduction of aromatic substituents at the *N* atoms of ethylenediamine of Cu(II) complexes. Ligands containing more than two nitrogen atoms show as an often overlooked factor a strong dependence of the efficiency towards metal coordination. © 2002 Elsevier Science Ltd. All rights reserved.

The rational design of catalysts for the hydrolysis of phosphate esters is of significance in view of the wide occurrence of related biocides. In addition, it can help to develop new chemical nucleases such as artificial restriction enzymes, and to better understand enzymatic mechanisms.[1] Stacking between aromatic entities has evolved to be a non-covalent interaction of prime importance in synthetic[2] and biological[3] complexes, but to the best of our knowledge has until now, not been explored systematically as a possible contributor in supramolecular catalysts. We wish to report here on rate enhancements by two orders of magnitude due to stacking and on related effects by lipophilic interactions with alkyl groups, with total rate constant enhancements of at least 10^7 compared to metal-free solutions. Solvent effects can be used to characterize the underlying mechanisms. In addition, we observe striking differences due to a variable metal coordination, with rate constant differences spanning several orders of magnitude.

Copper(II) complexes of ethylenediamine (en) have been shown[4] to enhance the hydrolysis of bis(*p*-nitrophenyl)phosphate (**BNPP**, see Fig. 1) by a factor which is difficult to measure due to solubility problems with the Cu(II) salt alone; introduction of e.g. positively charged aminomethyl phenyl groups at the nitrogen atoms of en leads to additional rate enhancements by up to 120.[5] Complexes with macrocyclic ligands can lead to very significant rate effects, but are also hampered by dimerization.[6] If we now increase the size of the aromatic side group R in the naphthalene derivative (ligand **6**, Scheme 1) we reach a factor of $k_{rel} = k_{obs}/k_0 = 400$ compared to $k_{rel} = 1.00$ with ligand **1** (R = H), and $k_{rel} = 18$ with ligand **2** (R = benzyl) (details see Table 1; it should be noted that with the ligand **3** for solubility reasons 7.5% DMSO had to be added, which diminishes the rates, see below). A similar, although smaller, increase is found if alkyl instead of aryl side groups are introduced (ligands **7** and **8**). The corresponding lipophilic interactions are weaker with isopropyl- and *tert*-butyl substituents (**8** and **9**) which may be due to the fact that only part of the methyl groups can produce contacts with the phenyl parts of the substrate. Surprisingly small catalytic effects are seen with the

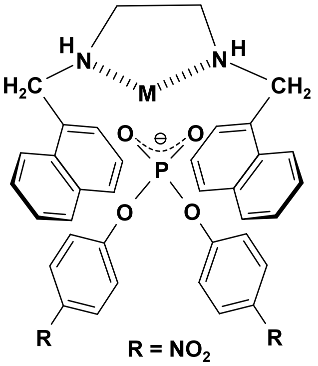

Figure 1. Schematic structure of the ternary complex between **BNPP**, a metal(II) cation **M** and ligand **3**.

Keywords: phosphate ester hydrolysis; catalysis; metal-coordination effects; stacking effects.

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Table 1. Hydrolysis of **BNPP** with Cu^{2+} complexes

Ligand	k_{obs} [10^{-6} s^{-1}]	k_{rel} (k_{obs}/k_o)
1	0.75 (k_o)	1.0
2	13.8	18.3
3[a]	75.2	100
4	10.6	14.0
5	0.21	0.3
6[b]	300	400
7	4.6	6.1
8	8.7	11.4
9	5.7	7.5
10[c]	3.3	4.0
11	0.82	1.1
12	0.14	0.2
13	4.7	6.3
14	0.28	0.4
15	1.8	2.4
16	4.9	6.5
17	<0.1[d]	

Reagents and conditions: pH 7.0; 0.01 M EPPS buffer; 75°C; [BNPP]=4.0×10^{-5} M; [metal complex]=2.0×10^{-4} M (ligand:metal=1:1); observed reaction usually about 1000 min; error in $k_{obs}\pm2\%$ (from duplication).

[a] EPPS buffer with 7.5% DMSO.

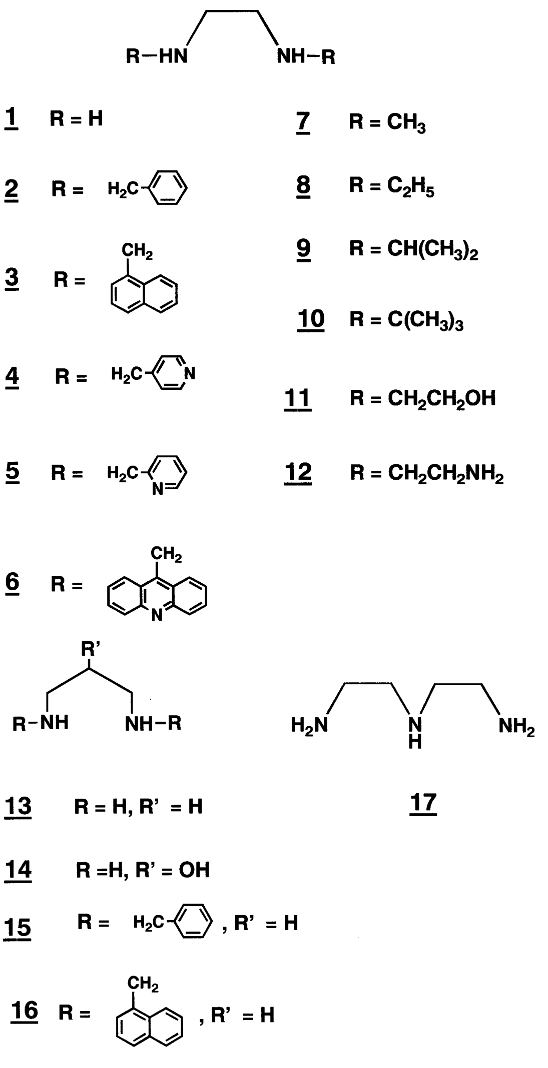
[b] Calculated from reactions up to about 20% conversion due to solubility problems.

[c] EPPS+2.5% DMSO.

[d] The k_{obs} is too small for measurement.

propylene derivatives **13** to **14**, which must be due to different complex structures.[7]

That the metal-complex structure has a strong influence on the catalytic activity of copper complexes is already obvious from results with ligands such as **5**; here, in contrast to ligand **4**, the pyridyl nitrogen atoms provide binding sites for complete saturation of the Cu coordination sphere**.** This aspect was analyzed furthermore with ligand **17** copper complexes; although there could be one free coordination site for the substrate, for intermediates or for the products we find an extremely low catalytic activity. The same is observed with corresponding tetra- and penta-amines (not shown here). It is obvious that only with substituted ethylenediamines the-kinetic and/or thermodynamic-stability of tetra-coordinated Cu complexes is not so large as to inhibit catalytic activity of the copper complexes. (It should be noted that fully saturated CuL_2 can also be formed if one uses 1:1 ratios of ligand and Cu salts, with formation of free Cu(II) which is known to be catalytically close to inactive). In consequence, one needs a distortion of the Cu coordination enforced by a suitable configuration of nitrogen atoms in a ligand, if one wants to use polyamine–copper complexes for catalysis.[8] Rate enhancements with zinc(II) complexes with ligands were so small that they were not analyzed further. It should be noted that reaction with metal-free ligands are slower by many orders of magnitudes; in consequence, the catalyst ligands are not used up by covalent reactions with the substrates.



Scheme 1.

Mono (*p*-nitrophenyl)-phosphate (**NPP**) is a more hydrophilic substrate than **BNPP**, which offers the most simple explanation why here the observed stacking effects on the hydrolysis are significantly smaller (Table 2). The opposite can be expected for the rate of the electroneutral tris (*p*-nitrophenyl)–phosphate (**TNPP**),[9] which was also investigated. Sufficient solubility could only be reached with **TNPP** by adding DMSO (Table 3), which severely lowers the efficiency of the catalyst (see below). If we compare, however, the rate effects on **BNPP** and **TNPP** in the same solvent (25% DMSO, Tables 3 and 4) it becomes apparent that indeed the stacking effects are more pronounced with the more lipophilic substrate **TNPP**.

Table 2. Hydrolysis of **NPP** with Cu^{2+} complexes

Ligand	k_{obs} [10^{-5} s^{-1}]	k_{rel} (k_{obs}/k_o)
1	0.90 (k_o)	1.0
2	1.28	1.4
3[a]	5.33	5.9
4	2.0	2.2
5	0.74	0.81

Reagents and conditions: see Table 1.

[a] EPPS buffer with 7.5% DMSO.

Table 3. Hydrolysis of **TNPP** with Cu^{2+} complexes

Ligand	k_{obs} [10^{-5} s^{-1}]	k_{rel} (k_{obs}/k_o)
1	0.95 (k_o)	1.0
2	3.12	3.3
3	5.94	6.3
4	2.26	2.4
5	1.39	1.4

Reagents and conditions: see Table 1, but here 40.0°C; EPPS buffer with 25% DMSO.

Table 4. Solvent effects on hydrolysis of **BNPP** with **3**-Cu^{2+} complexes

Solvent	Sp	E^N_T	k_{obs} (10^{-5} s)	log k_{obs}
Ethylene glycol	0.376	0.790	3.28	−4.48
Diethylene glycol	0.244*	0.713	1.49	−4.82
DMSO	0.227	0.444	0.97	−5.01
Acetonitrile	0.217	0.460	0.57	−5.24
Methanol	0.120	0.762	1.43	−4.84
Ethanol	0.144	0.654	1.22	−4.91
DMF	0.138	0.404	0.80	−5.09
NMP	0.122		0.75	−5.13
Propane-1-ol	0.108	0.617	1.12	−4.95
Propane-2-ol	0.099	0.546	1.23	−4.91
Dioxane	0.079		0.38	−5.42
Trifluoro methanol			0.91	−5.04

Reagents and conditions: pH 7.0; 0.01 M EPPS buffer with 25% organic solvent; 75°C; [**BNPP**] = 4.0×10^{-5} M; [metal-complex] = 2.0×10^{-4} M (ligand:metal = 1:1); error k_{obs} ±3%.

The influence of the solvent had to be measured with binary water mixtures containing not more than 25% of the organic phase, as with higher contents the reactions became too slow. Although the high water content of 75% attenuates the expected rate variations significantly, the observed rate constants (Table 4) differ by a factor of almost ten, with the most hydrophilic ethyleneglycol solution at one end, and the least polar 1,4-dioxane mixture at the other end. Correlations with known solvent hydrophobicity or polarity parameters like Sp[10] or E_T[11] were both very poor, but the results demonstrate the importance of water as a reaction medium for biologically important catalytic processes. In line with stacking as a major contribution, the solvent effect increases with increasing size of the aromatic side group at the catalyst ligand (Table 5).

Table 5. Hydrolysis of **BNPP** with several Cu^{2+} complexes in EPPS buffer containing 25% DMSO

Ligand	k_{obs} [10^{-6} s^{-1}]	k_{rel} (k_{obs}/k_o)
(**1**[a]	0.75 (k_o)	1.0)
2	6.81	9
3	9.72	12.8
8	6.22	8.2

Reagents and conditions: see Table 1.

[a] Measurement in pure water.

Conclusions. The introduction of cofactors in catalytic metal complexes can in analogy to metal enzymes lead to significantly improved performance.[12] The present results show that large rate enhancements can materialize by the use of stacking effects; attempts to further increase the underlying aromatic surfaces with anthrylderivatives yielded insoluble complexes even in mixtures rich in DMSO. Lack of solubility prevented also saturation kinetics which would allow to analyze which steps of the catalytic cycle are stabilized by stacking. Introduction of e.g. positively charged nitrogen centers could in the future remedy the solubility problem and lead to additional electrostatic stabilization. Transition metal-based catalysts like those presented here gain their activity only by suitable ligands, but their design is limited by the need to provide free coordination sites for the metal. Further studies are planned to establish the nature of the underlying catalytic complexes.[13]

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13. Synthetic details and analytical data of the ligands, as far they are not commercially available, will be reported elsewhere. The complexes were obtained by mixing ligand (as hydrochloride) and copper(II)sulfate with conditions as given at Table 1. Kinetic measurements were performed as described before (Ref. 10) and evaluated by non-linear least-square fitting to a first order equation, without deviation over usual several half-life times.