The nature of biomimetically relevant rate enhancement of hydrolysis in a coordination sphere of square-planar metal complexes suggested by an X-ray structural study of $a,b\text{-}h,g\text{-}[\text{Pt}\{o\text{-}C_6H_4C(Me)=NOC(=O)Me\}(\mu\text{-}Cl)]_2$

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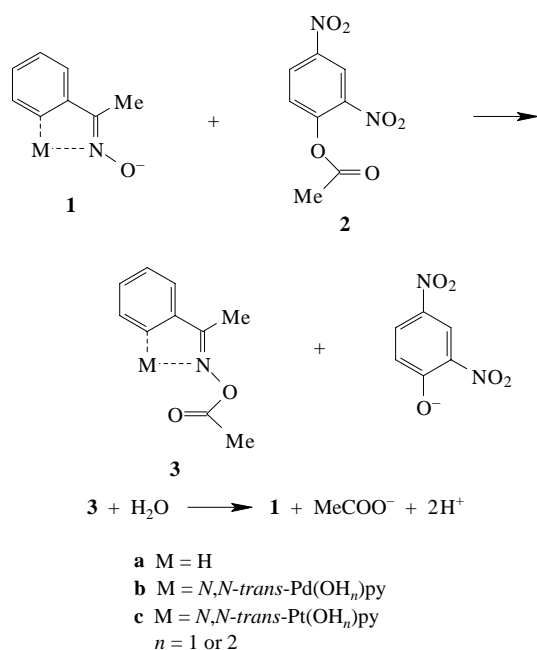*E-mail: ryabov@enzyme.chem.msu.su*

X-Ray structural data for $a,b\text{-}h,g\text{-}[\text{Pt}\{o\text{-}C_6H_4C(Me)=NOC(=O)Me\}(\mu\text{-}Cl)]_2$ and *ab initio* quantum chemical calculations were used to show that the biomimetic hydrolysis of esters and amides within the coordination sphere of a square-planar complex, in general, and the deacylation of cyclometallated aryl oxime esters, in particular, is due to the stereochemical control which arises from the close proximity of the coordinated OH or H_2O ligand and the carbonyl carbon (O⋯C separation 3.47 Å) in the reactive complex $[\text{Pt}\{o\text{-}C_6H_4C(Me)=NOC(=O)Me\}py(OH)]$ generated in aqueous solution.

It is generally accepted by now[1] that the catalytic role of metal centres in hydrolytic metalloenzymes may involve either (*a*) Lewis acid activation of substrate, facilitating solution attack by hydroxide, (*b*) lowering of the pK_a of a bound hydroxide which attacks substrate, or (*c*) the combination of the two former effects (Scheme 1).
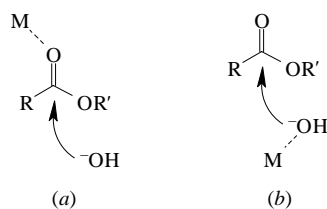

Scheme 1

Among a diversity of metal species designed to carry out biomimetic hydrolysis of amide and ester bonds,[2] square-planar complexes are unique since the coordinative environment is not encountered in biological systems, on one hand, but these metal species offer remarkable rate accelerations and selectivity, on the other. In particular, linked to the methionine sulfur residues of peptides and proteins aqua complexes of palladium(II) and platinum(II) are efficient in the hydrolysis of the adjacent non-activated amide bonds at 40 °C and pH 1–2.[3]

$$3 + H_2O \longrightarrow 1 + MeCOO^- + 2H^+$$

a M = H
b M = *N,N-trans*-Pd(OH$_n$)py
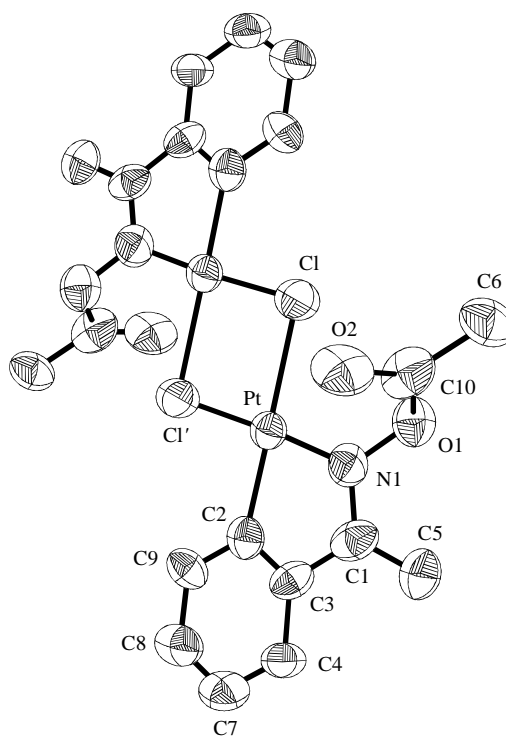**c** M = *N,N-trans*-Pt(OH$_n$)py
   n = 1 or 2

Scheme 2

Metallacycles derived from *N,N*-dimethylbenzylamine and acetophenone oxime targeted to the sulfur atom of *N-t*-BOC-L-methionine *p*-nitrophenyl ester increase the rate of dissociation of *p*-nitrophenolate at pH 8.[4] Recently prepared and thoroughly characterized orthometallated species *N,N-trans*-[M(*o*-C$_6$H$_4$CMe=NOH)Clpy], where M = Pd[5] and Pt,[6] showed catalytic activity in water in hydrolysis of 2,4-dinitrophenyl-acetate.[7] These complexes undergo rapid aquation in aqueous solution to afford reactive compounds **1b,c**. A striking feature of this catalytic system is that the orthometallated acetophenone oxime **1b** or **1c**, in contrast to the free ligand **1a**, appeared to be a true catalyst, *i.e.* the reaction does not end up with formation of acetyl acetophenone oxime esters **3**,[6] but the latter reacts rapidly with water to regenerate the catalytically active species **1** (Scheme 2). The goal of the present investigation was to determine the nature of the catalytic effect in the case of **3b,c** within the framework of the general role of metal ions in biological systems outlined in Scheme 1. The main question here is: why are intermediates **3b,c** so reactive? In previous publications,[5,7] the effect was accounted for by the lowering of pK_a of the key ionogenic groups, *viz.* both the oxime hydroxyl and water, on coordination with the metal centre. This rationalization does not, however, mirror the geometry of the species involved. Square-planar complexes have a superior mechanism for tuning the reactivity through the axial 'coordination' of either ester or amide carbonyl oxygen with palladium(II) or platinum(II) axial sites. The tuning could be accomplished in two ways, *i.e.* electronically, by increasing the effective positive charge at the carbonyl carbon which would accelerate either external or internal nucleophilic attack, or spatially, as suggested by the manipulation with the molecular models which revealed a close contact between the carbonyl carbon and the coordinated hydroxo or aqua ligand in complexes **3b,c**. In order to find direct evidence for the axial M⋯O=C interaction and to analyse its role in the biomimetic processes, we carried out an X-ray structural investigation of platinum compound **4**, which has the same key ester oxime moiety as in **3**, and estimated the effective positive charge at the carbonyl carbon for different conformations of **3b** using *ab initio* quantum chemistry calculations. Since the axial orientation was found in the crystal, but the charge appeared to be insensitive to the geometry of conformers, the rate acceleration was attributed to the spatial correspondence between the hydroxo ligand and the carbonyl carbon.

Crystals of **4** (0.078 g) for an X-ray structural study were prepared by refluxing 0.1 g of [Pt(*o*-C$_6$H$_4$CMe=NOH)-Cl(C$_6$H$_5$CMe=NOH)][8] in 5 ml acetic anhydride followed by the slow cooling of the solution. The ^{1}H NMR spectrum of the compound formed showed two methyl resonances at δ 2.40 (J_{PtH} 6 Hz) and 2.52 ascribed to N=CCH_3 and C(=O)CH_3, respectively, indicative of the acylation. Figure 1 shows the overall view of complex **4**.[†] The complex appeared to be a

4   **5**   **6**
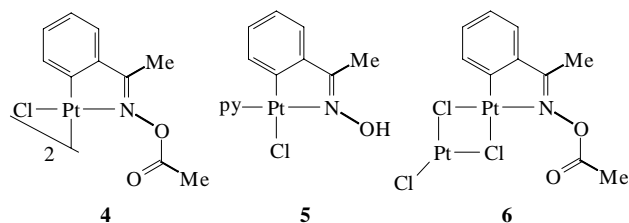
chloro-bridged dimer. A plausible reason is that the acylation by acetic anhydride of both oximes of the parent monomer would afford a sterically demanding material. A key feature of **4** is the anticipated, axially oriented carbonyl oxygen located almost above the platinum plane. The observed Pt–O contact equals 3.65 Å and may be compared with the distance of the closest approach (3.48 Å) or approximate sum of platinum and oxygen van-der-waals radii of *ca.* 3.3 Å estimated according to Bondi.[10] The bond lengths and bond angles of the cycloplatinated fragment are similar to those of compound **5** recently investigated by us.[6] In particular, the Pt–C bond distances are 2.00 and 1.98 Å, the Pt–N (oxime) bond distances equal 1.96 and 2.00 Å, the N–Pt–C bond angle in the platinacycle equals 78.7 and 80.3° in complexes **4** and **5**, respectively. The Pt–Cl distances in **4** are 2.312 and 2.440 Å, and the latter, which is trans to the Pt–C bond, is similar to that of 2.408 Å in complex **5**.

In order to deduce to what extent the axial orientation affects an effective positive charge at C10, *ab initio* quantum chemistry calculations were carried out for a number of conformations of model complex **6** which represents half of the entire complex **4**. Chloride is thus used instead of the cycloplatinated ligand in the modeling, but this is, however,

Figure 1 Crystal structure of complex **4**. Thermal ellipsoids are drawn at the 50% probability level.

non-essential since the local electronic properties of a remote part of the molecule are analysed. The electronic density for distinct conformations of the complex, however, not referring to particular stationary points on the potential energy surface, has been modeled using the conventional self-consistent-field (SCF) method by employing the pseudo-potential approach of the Stevens-Basch-Kraus type and the corresponding valence basis sets available as the library options in the GAMESS program system.[11] Partial charges at atoms were evaluated in accordance with the natural population analysis[11b] which gives reasonable charge distributions in molecules and molecular complexes.[11c] For example, the approach proved to be efficient in analysis of the Grignard cluster reagents.[12]

The charges were computed for three conformers **6a–c** shown in Figure 2. Conformer **6a** matches the geometry of the crystal and possesses the lowest total energy computed at the SCF level of theory. The distance between O2 and Pt equals 3.65 Å. Conformer **6c** refers to the largest Pt–O2 separation (5.19 Å), whereas the closest Pt–O2 approach (3.48 Å) occurs in structure **6b**. Curiously, the partial charges at acetyl carbonyl carbon do not change within the series and equal +0.97, +0.96, and +1.05 for **6a–c**, respectively. Moreover, the same charge of +0.97 is computed for the *O*-acetyl hydroxyl amine $H_3COCONH_2$. The modeling suggests that the movement of the carbonyl oxygen toward and off the metal plane does not increase the electrophilicity at the ester carbonyl carbon and, hence, platinum(II) does not act as a Lewis acid.[1] Consequently, the electronic effect is not the source of the rate acceleration. It should also be pointed out that the modeling rules out the nucleophilic attack at the oxime nitrogen as a mechanistic alternative. The charges are much more negative equal –0.29, –0.28, and –0.24 for **6a–c**, respectively.

The remaining possibility is a geometric control. Provided the axial orientation persists in water, when complexes **3b,c** are plausible reactive species, the carbonyl carbon appears to be close to the oxygen of the coordinated hydroxo or aqua ligand as seen from the space-filling model of **3c**, Figure 3. The C···O separation is lower than 3.47 Å. For this estimate, the Pt–O bond distance of 2.19 Å was taken elsewhere[13] as

6a

6b

6c
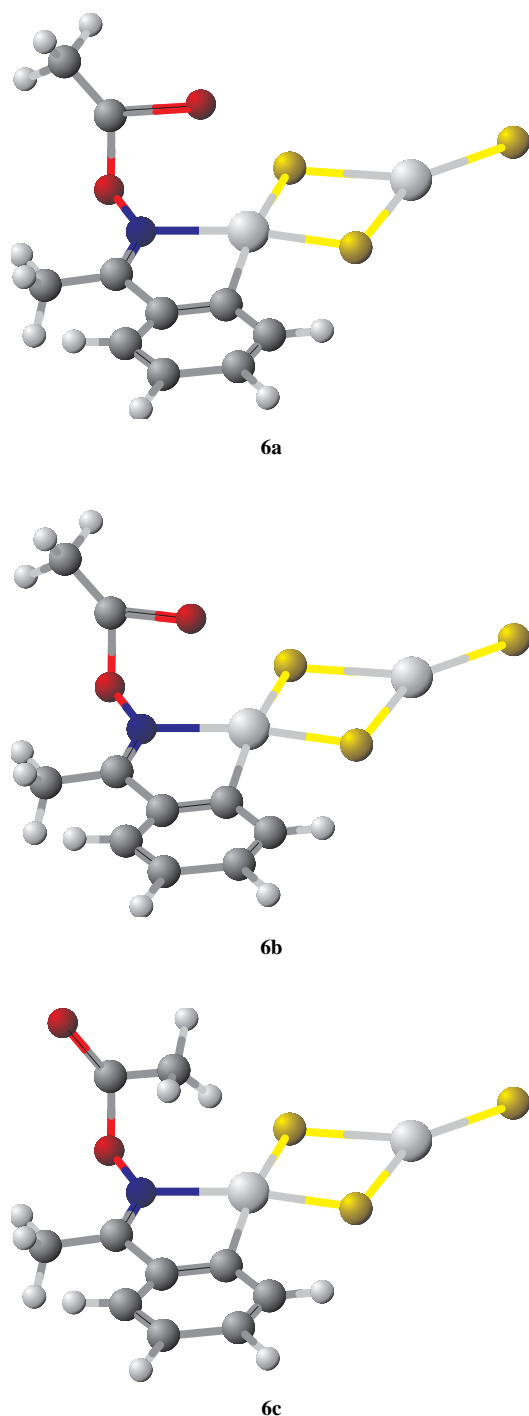
Figure 2 Possible conformations of complex **6** showing different Pt···O2 separations. For details, see text.

reported for the structurally related pincer cation $[Pt\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}(OH_2)]^+$. The C···O separation will be even lower in the case of the hydroxo ligand coordinated to platinum(II), since the Pt–O bond distance must be shorter for the hydroxo compared to aqua ligand. Although the OH ligand rotates freely around the Pt–O bond, the oxygen lone pair may be directed strictly at the carbonyl carbon suggesting efficient intramolecular, stereochemically controlled nucleophilic attack at C10 to afford the tetrahedral intermediate.[14] It should be pointed out that in the absence of axial carbonyl oxygen orientation, the carbonyl carbon may be pretty far away from the coordinated nucleophile due to ready rotation around the N–O bond. However, the most favorable geometry may also be
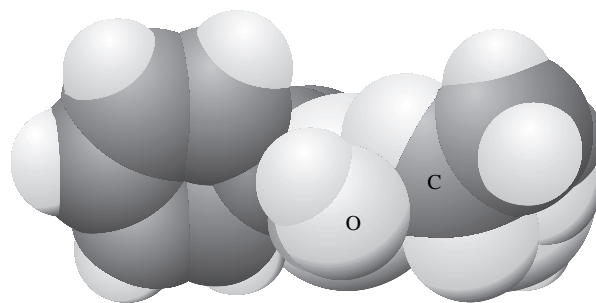
Figure 3 Space-filling model of reactive complex **3c** with the carbonyl above the metal plane revealing close contact between oxygen of coordinated hydroxide and carbonyl carbon.

adopted as a result of the agostic contact as shown by the example of **6c**.

In conclusion, the location of carbonyl oxygen above the metal plane in square-planar complexes does not increase the effective positive charge at the carbonyl carbon. However, this conformation may favour the intramolecular nucleophilic attack by the coordinated hydroxide or aqua ligand at the carbonyl group. This effect is believed to be at least partly responsible for high rates of biomimetically relevant processes in coordination spheres of square-planar transition metal complexes.

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