Pergamon

0277-5387(94)00329-7

Polyhedron Vol. 14, No. 1, pp. 197–202, 1995

0277–5387/95 $9.50+0.00

PLATINUM(II) MEDIATED OXIDATION OF REMOTE C—H BONDS IN FUNCTIONALIZED ORGANIC MOLECULES*

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Abstract—The oxidation of remote C—H bonds of aliphatic alcohols, carboxylic acids, sulfonic acids and phosphonic acids by the Pt^{II} ion in water was examined. The reactions were very specific with respect to the degree of oxidation: only hydroxylation (or its equivalent) was observed and further oxidation to the corresponding aldehyde or carboxylic acid functionality did not occur. The order of reactivity was α-C—H $\ll$ β-C—H $<$ γ-C—H $<$ δ-C—H for alcohols and α-C—H $\ll$ β-C—H $<$ γ-C—H $\geqslant$ δ-C—H for the acids. The reactions are thought to proceed by the initial coordination of the functional group followed by the formation of an intermediate platinacycle upon C—H activation. The observed regioselectivity arises from the tendency to form the metallacycle with the least ring strain. It was possible to make the oxidations catalytic in Pt^{II} by the addition of a reoxidant, such as K_2PtCl_6.

The catalytic functionalization of aliphatic C—H bonds is one of the most important problems in chemistry. In particular, the selective oxidation of *remote* C—H bonds of organic substrates continues to be an intellectual and practical challenge despite past efforts by organic and organometallic chemists. Most successes involve the rigid steroid framework.[1] Additionally, the C—H activation of coordinated ligands by metals in the so-called orthometallation or cyclometallation reactions has been reported.[2] In the latter systems, apart from stringent geometric requirements, the resultant chelating ligand usually remains coordinated to the metal and catalytic oxidations through this approach have not been reported. The ultimate challenge in the area of remote functionalizations is, of course, to achieve selectivity in the case of highly flexible linear and branched aliphatic chains and to do so catalytically.

We had earlier reported the selective oxidation (primarily, hydroxylation) of remote C—H bonds in aliphatic carboxylic acids by the Pt^{II} ion in aqueous medium under mild conditions through the use of the "chelate effect" (vide infra).[3] The following order of reactivity was observed: α-C—H $\ll$ β-C—H $<$ γ-C—H $\geqslant$ δ-C—H $\approx$ ε-C—H. Furthermore, by adding a cooxidant that is capable of reoxidizing Pt^0 to Pt^{II}, it was possible to make the system catalytic in Pt^{II}. The reactivity order α-C—H $\ll$ β-C—H $<$ γ-C—H was also observed for the oxidation of alcohols by the Pt^{II} ion.[4,5] Herein, we (a) report that a similar selectivity pattern is also observed for the remote oxidations of other functionalized organics by the Pt^{II} ion, (b) show that the observed reactivity pattern is inconsistent with a radical mechanism involving H-atom abstractions, and (c) provide some experimental evidence for the "chelate effect".

EXPERIMENTAL

General procedure

K_2PtCl_4 (0.038 mmol) and 0.076 mmol of K_2PtCl_6 (0.115 mmol total) were weighed into an NMR tube, 1.0 cm^3 D_2O and 0.23 mmol of sub-

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*Dedicated to Professor John E. Bercaw, friend and mentor, on the occasion of his 50th birthday.

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strate were then added. The tube was partially evacuated, sealed and heated for 3 days in a 110–120°C oil bath.

Reactions with $K_2S_2O_8$

K_2PtCl_4 (0.038 mmol) and 0.076 mmol K_2PtCl_6 (0.115 mmol total) were weighed into an NMR tube, 1.0 cm^3 D_2O, 0.23 mmol of substrate and 0.345 mmol $K_2S_2O_8$ (3 × excess) were added, and the tube was sealed and reacted as above.

Reactions with Cl_2

Metallic Pt (0.115 mmol), 0.23 mmol substrate and 1 cm^3 D_2O were put in a septum-capped NMR tube. The tube was then charged with Cl_2 and heated in an 80°C water bath for 1 day. The two substrates used were propanol and propionic acid.

Competition reactions

Propionic acid (0.23 mmol), 0.23 mmol of the substrate being tested, 0.038 mmol K_2PtCl_4, 0.076 mmol K_2PtCl_6, 1 cm^3 D_2O, and an external capillary standard were placed in an NMR tube. An NMR spectrum was taken to find the exact amount of substrate present, and the tube was sealed. Percentage yield and the decrease in substrate concentration were measured after 3 days at 115°C.

Oxidative addition of ω-iodocarboxylic acids

K_2PtCl_4 (0.115 mmol) and 0.23 mmol of an ω-iodocarboxylic acid were dissolved together in D_2O in an NMR tube. NMR spectra were taken after 2–4 h at room temperature.

RESULTS AND DISCUSSION

Table 1 summarizes our results on the remote oxidation of C—H bonds in aliphatic alcohols, carboxylic acids, sulfonic acids and phosphonic acids by the Pt^{II}/Pt^{IV} combination. The active oxidant was the Pt^{II} ion and the same set of products were obtained when it was used alone. The function of the added Pt^{IV} species was to reoxidize Pt^0 that is formed at the end of the oxidation step, back to Pt^{II}.[3-5] Thus, the precipitation of metallic Pt during oxidation was delayed many hours and the product yield increased substantially when K_2PtCl_6 was added to the system. No product formation occurred when either K_2PtCl_6 or metallic Pt was employed in the absence of K_2PtCl_4. It is clear from Table 1 that the order of selectivity was α-C—H $\ll$ β-C—H $<$ γ-C—H $<$ δ-C—H for alcohols and α-C—H $\ll$ β-C—H $<$ γ-C—H $\geqslant$ δ-C—H for the acids. It should be noted that in acids there is an extra atom between the potentially ligating atom and the C—H bond being attacked. Several points are noteworthy. First, as has been observed in other instances,[3-5] the Pt^{II} ion did not discriminate between primary, secondary and tertiary C—H bonds; the *distance* between the existing functionality and C—H bond being attacked was all that was important. In a separate experiment, the same system showed a 1 : 3 preference in the hydroxylation of the primary versus the secondary C—H bond of propane (on a per hydrogen basis). The above trend is inconsistent with a H-atom abstraction step given that the homolytic C—H bond energies decrease in the order: primary C—H > secondary C—H > tertiary C—H. In addition, an α-C—H bond in alcohols is especially weak due to the stabilization of the radical derived therefrom by donation of electron density from the neighboring oxygen atom. The second trend of note is that only hydroxylation or its equivalent oxidation level was observed; there was no over-oxidation to the aldehyde or the carboxylic acid functionality. Thus, a precise control with respect to the oxidation level was achieved. Finally, when an α- or a β-C—H bond was attacked, a significant amount of chloro product was observed in addition to the hydroxylated derivative.

Regioselective remote chlorinations of terminally functionalized organics by N-chlorodialkylamines have been reported to proceed by a radical chain pathway.[6] In these cases, the chlorination occurs predominantly at the ω-1 position. Although our observed selectivity pattern is very different, we examined the possible role of radical species in our system.[7] It is known that the peroxydisulfate ion, $S_2O_8^{2-}$, undergoes O—O bond homolysis upon mild thermolysis and, furthermore, the resultant radical, $SO_4^{\cdot -}$, can functionalize alkyl groups through a H-atom abstraction pathway (see eq. 1).[8] When the butyric acid oxidation by the Pt^{II}/Pt^{IV} combination was rerun in the presence of $K_2S_2O_8$, there was a marked change in product selectivity. $CH_3CH(OH)CH_2CO_2H$ was now the predominant product with attack on a β-C—H *vs* a γ-C—H bond occurring in an approximately 2 : 1 ratio (cf. Table 1). A similar inversion in regioselectivity was also observed when $K_2S_2O_8$ alone was used as the oxidant. When the substrate was propionic acid, the principal product was $CH_3CH(OH)CO_2H$. We also examined the reactions of *n*-propanol and propionic acid with Cl_2 in the presence of metallic Pt. At 80°C, in water, *n*-propanol was converted solely to propionic acid, and the latter was converted to a

Table 1. Remote oxidation of substrates by Pt^{II}/Pt^{IV} combination[a]

Substrate	Products	Yield[b]
Acetic acid	Glycolic acid	128%
	Chloroacetic acid	40%
Propionic acid	β-Hydroxypropionic acid	210%
	β-Chloropropionic acid	0%[c]
1-Butyric acid	γ-Hydroxybutyric acid	25%
	γ-Butyrolactone	41%
	β-Hydroxybutyric acid	7%
1-Pentanoic acid	δ-Hydroxypentanoic acid[d]	92%
1-Propanol	1,3-Propanediol	84%
2-Butanol	1,3-Butanediol	114%
1-Butanol	1,3-Butanediol	19%
	1,4-Butanediol	38%
	Tetrahydrofuran	32%
Ethanephosphonic acid	β-Hydroxyethanephosphonic acid	246%[e]
1-Propanephosphonic acid	γ-Hydroxypropanephosphonic acid	101%[e]
Ethanesulphonic acid[f]	β-Hydroxyethanesulphonic acid	387%
	β-Chloroethanesulphonic acid	164%
1-Propanesulphonic acid[f]	γ-Hydroxypropanesulphonic acid	198%
1-Butanesulphonic acid[f]	γ-Hydroxybutanesulphonic acid	96%
	δ-Hydroxybutanesulphonic acid	36%

[a] Reaction conditions: substrate (0.23 mmol), K_2PtCl_4 (0.038 mmol), K_2PtCl_6 (0.076 mmol), D_2O (1 cm^3), 110–120°C, 3 days.

[b] Yield with respect to Pt^{II} present initially.

[c] First day: 49% β-hydroxypropionic acid, 42% β-chloropropionic acid; third day: no chloro product remained.

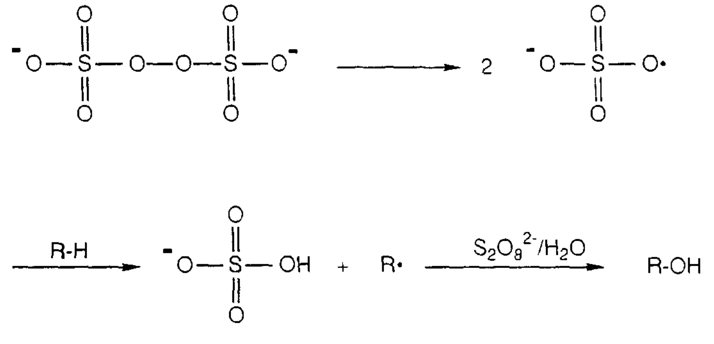
[d] Because of overlapping NMR resonances, γ-hydroxypentanoic acid could not identified with certainty.

[e] Because of overlapping NMR resonances, these yields are less precise than others.

[f] The sodium salt was employed.

2:1 mixture of $CH_3CH(OH)CO_2H$ and $HOCH_2CH_2CO_2H$ (cf. Table 1).

It is clear from the above observations that the remote oxidations by the Pt^{II}/Pt^{IV} combination *do not* follow the regioselectivity pattern exhibited by typical radical oxidants. In particular, radicals invariably prefer to attack a weaker secondary C—H bond rather than a primary C—H bond of a methyl group.



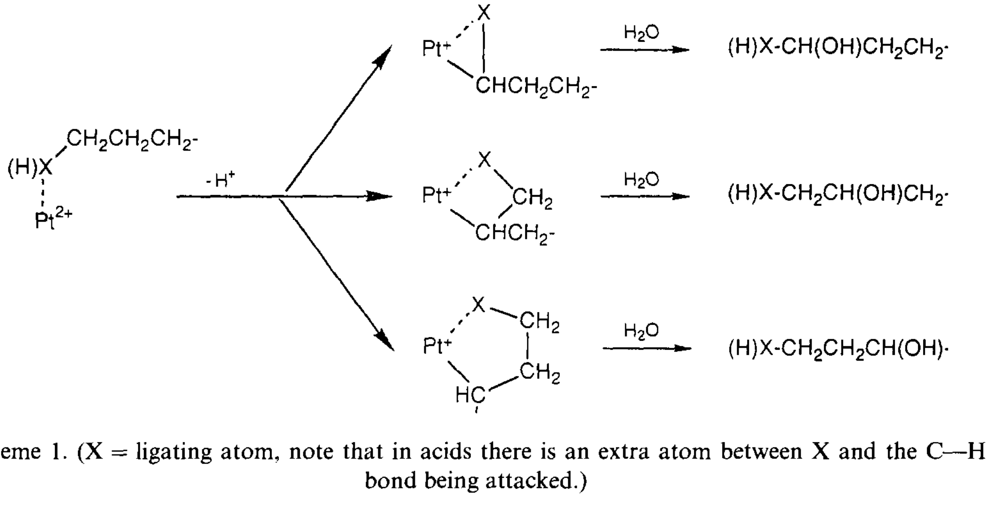
(1)

The simplest explanation for the regioselectivity shown in Table 1 is the "chelate effect" (see Scheme 1). The functional group on the organic substrate would be expected to coordinate to the electrophilic Pt^{II} center. As a result, an intermediate metallacycle will be formed following an electrophilic C—H activation step.[4,5,9] The observed order of reactivity then is a function of the ring-strain present with a five-membered ring being favored over a four-membered analog, which in turn is favored over a highly strained three-membered metallacycle. Note that the selective functionalization of remote C—H bonds by the Fe^+ ion through a similar chelate effect has been observed in the gas phase.[10] Additionally, the formation of platinacycles by remote C—H activation of alkyl ligands bound to Pt^{II} has also been reported.[11]

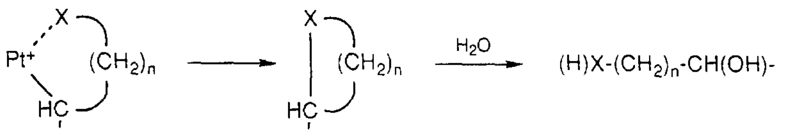
Scheme 1 invokes the hydrolysis of the Pt—C bond by an external water molecule in the product forming step. This step finds support in the observed hydrolysis of discrete Pt^{IV}-alkyls to form alcohols.[4b,12,13] Stereochemical studies by Bercaw and Labinger indicates that this step proceeds by an S_N2 mechanism involving attack by an external nucleophile (H_2O or Cl^-).[12] There is, however, an alternative product forming pathway that involves, first, a reductive elimination to form a cyclic organic molecule, which is subsequently hydrolyzed to the usually observed acyclic hydroxylated product (see eq. 2).[14] Naturally, the reductive elimination pathway will be disfavored where the resultant cyclic species has significant ring strain, e.g. when an α- or a β-C—H bond is involved. In these cases, attack by an external nucleophile (H_2O or Cl^-) is more likely. However, there is some evidence for the latter mechanism in more favorable instances. For example, the γ-lactone arising from butyric acid and tetrahydrofuran derived from 1-butanol must be *kinetic* products formed by reductive elimination from the corresponding metallacycles since the hydrolysis of these cyclic organics to the open-chain form is thermodynamically favored and, indeed, the conversion of γ-butyrolactone to γ-hydroxybutyric acid does occur at longer reaction times (we had previously shown that tetrahydrofuran was converted to γ-butyrolactone under the reaction conditions through a pathway catalyzed by precipitated metallic Pt).[4b]

We have examined the viability of the type of platinacycles shown as intermediates in Scheme 1. $PtCl_4^{2-}$ is known to react with alkyl iodides to form the Pt^{IV} species, $[Cl_5Pt\text{-}R]^{2-}$.[4b,12,13] Following Zamashchikov *et al.*,[13b] when $PtCl_4^{2-}$ was allowed to react with iodoacetic acid in water at ambient temperature, two new Pt-containing species, **1a** and **1b**, were formed (eq. 3). Compound **1b** was the dominant species (**1a** : **1b** as low as 0.1) and was assigned the cyclic structure shown based on the observation of ^{195}Pt—C coupling for the carboxylate group which was absent in **1a**. The coordination of the carboxylate end would be disfavored either in the presence of an excess of a second ligand or when the carboxylate group is protonated. Indeed, the **1a** : **1b** ratio was much higher when the reaction was carried out in the presence of either excess Cl^- ions or at a lower pH. The acyclic and cyclic species (**2a** and **2b**, respectively) were also formed when 2-iodopropionic acid was allowed to react with $PtCl_4^{2-}$[^{1}HNMR (D_2O) (ppm): **2a**, 3.95 (t, $J_{H\text{-}H} = 14.8$ Hz; $J_{Pt\text{-}H} = 88$ Hz), 2.22 (t, $J_{H\text{-}H} = 14.8$ Hz); **2b**, 3.91 (t, $J_{H\text{-}H} = 14.7$ Hz; $J_{Pt\text{-}H} = 81$ Hz), 2.30 (t, $J_{H\text{-}H} = 14.7$ Hz)]. As in the previous instance, **2a** : **2b** ratio was higher when the reaction was carried out in the presence of either excess Cl^- ions or at a lower pH. We are currently attempting to obtain crystals of the above platinacycles in order to confirm their structures by X-ray crystallography.

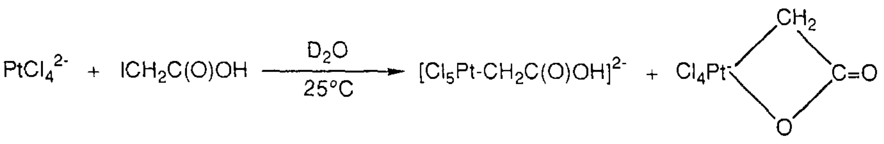
Upon warming, the species **1** and **2** decompose to yield a mixture of ω-hydroxy and ω-chloro acids. However, this information is not very informative



Scheme 1. (X = ligating atom, note that in acids there is an extra atom between X and the C—H bond being attacked.)



(2)



	1a	1b
^{1}HNMR (D$_2$O):	4.21 ppm ($J_{Pt\text{-}H}$ = 94 Hz)	4.28 ppm ($J_{Pt\text{-}H}$ = 98 Hz)
^{13}C{^{1}H}NMR (D$_2$O):	21.5 ppm ($J_{Pt\text{-}C}$ = 478 Hz)	11.1 ppm ($J_{Pt\text{-}C}$ = 526 Hz)
	175.6 ppm	183.2 ppm ($J_{Pt\text{-}C}$ = 37 Hz)

(3)

since the ω-iodo acids undergo ready hydrolysis even in the absence of metal ions. Thus, while the above observations do not prove the intermediacy of platinacycles in the remote hydroxylations, they do demonstrate that these can form under the reaction conditions.

Finally, we attempted to assess of the relative effectiveness of different anchoring functionalities. To this end a series of competition reactions were carried out where the relative rates of functionalization of C—H bonds proximal to a range of functionalities were measured. The rates relative to propionic acid are shown in Table 2. Very curiously, these results differ markedly from relative rates obtained when the substrates were reacted alone in a non-competitive situation (Table 3). For example, the ω-hydroxylations/chlorinations of ethanesulfonic acid and propanol proceeded, respectively, faster and slower than that of pro-

Table 2. Rate of remote functionalization of a given substrate relative to propionic acid in competition reactions[a]

Substrate	Relative Rate	
	Run #1[b]	Run #2[b]
1-Propanol	1.31	1.28
Propionic acid	1.00	1.00
1-Butyric acid	0.81	0.85
Ethanesulphonic acid[c]	0.70	0.72
Ethanephosphonic acid	0.62	0.66
Acetic acid	0.49	0.51

[a] Obtained from the ratio of propionic acid : substrate remaining after 3 days; initial propionic acid : substrate ratio = 1.

[b] Two independent sets of reactions.

[c] Sodium salt used.

Table 3. Rate of remote functionalization of a given substrate relative to propionic acid in non-competition reactions[a]

Substrate	Relative rate
Ethanesulphonic acid[b]	2.62
Ethanephosphonic acid	1.17
Propionic acid	1.00
Acetic acid	0.80
1-Propanol	0.40
1-Butyric acid	0.31

[a] Ratio of product(s) derived from substrate to β-hydroxypropionic acid derived from propionic acid obtained from data in Table 1.

[b] Sodium salt used.

pionic acid. However, *when propionic acid was also present in the reaction mixture*, the relative rates became *reversed*. The simplest explanation for observations of this kind is that while substrate A is more reactive than substrate B, the latter binds more strongly and is therefore preferentially functionalized when both A and B are present in the reaction mixture. Experiments are currently underway to test this hypothesis.

In conclusion, the Pt^{II} mediated remote oxidation of functionalized organics exhibits several interesting features. First, the reactions are very specific with respect to the degree of oxidation: only hydroxylation (or its equivalent) was observed and further oxidation to the corresponding aldehyde or carboxylic acid functionality did not occur. As shown in Scheme 1, this is a result of the strained organometallic intermediate that is involved in the activation of a C—H bond α to the hydroxyl group. Second, the remote oxidation of highly flexible linear alkyl chains with unprecedented regioselectivity is possible. Finally, as is clear from Table 1, it is possible to make the oxidations catalytic in Pt^{II} by the addition of a reoxidant, such as K_2PtCl_6.

Acknowledgments—This research was funded by the National Science Foundation (CHE-9209264). We also thank Johnson Matthey, Inc., for a generous loan of platinum salts.

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14. A referee has suggested an alternative pathway to the cyclic products that involves an intramolecular attack on the Pt—C bond by the now decoordinated functionality. It is not possible to distinguish between the two mechanisms using the data in hand.