Platinum(II) Catalysed Selective Remote Oxidation of Unactivated C–H Bonds in Aliphatic Carboxylic Acids

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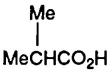
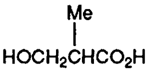
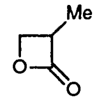
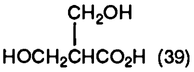
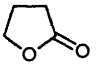
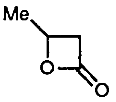
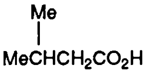
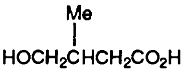
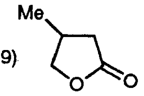
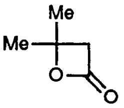
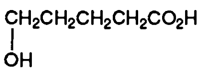
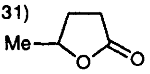
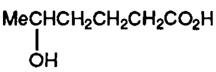
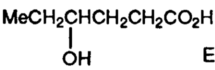
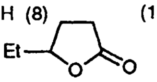
Platinum(II) ion, in the presence of platinum(IV), is found to catalyse the hydroxylation of unactivated C–H bonds of aliphatic carboxylic acids in water with the following order of reactivity: α-C–H << β-C–H < γ-C–H $\geqslant$ δ-C–H $\approx$ ε-C–H.

The catalytic functionalization of aliphatic C–H bonds is one of the most important chemical problems.[1] 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 of the successful reports involve the rigid steroid framework.[2] Additionally, the C–H activation of coordinated ligands by metals in the so-called orthometallation or cyclometallation reactions is known.[3] In the latter systems, apart from stringent geometric requirements, the resultant chelating ligand invariably remains coordinated to the metal and catalytic functionalization through this approach has not been reported. The ultimate challenge in the area of remote functionalization is, of course, to achieve selectivity in the case of highly flexible linear and branched aliphatic chains and to adding a cooxidant that is capable of reoxidizing Pt^0 to Pt^{II}, it was possible to make the system catalytic in Pt^{II}. Finally, with aliphatic chains with appropriate lengths, the 'chelate effect' allowed the formation of the thermodynamically unstable β-lactones.

Our results are summarized in Table 1.† Except for the formation of the chloride as the minor product in two cases, only hydroxylation was observed. There was no significant overoxidation to the aldehyde, ketone or carboxylic acid. The active oxidant was Pt^{II}. For example, under the same conditions, by using 0.23 mmol K_2PtCl_4 and no K_2PtCl_6, the products formed from butyric acid were: γ-hydroxybutyric acid (31%) and γ-butyrolactone (15%). However, as Table 1 shows, the addition of K_2PtCl_6 made the system catalytic and a

Table 1

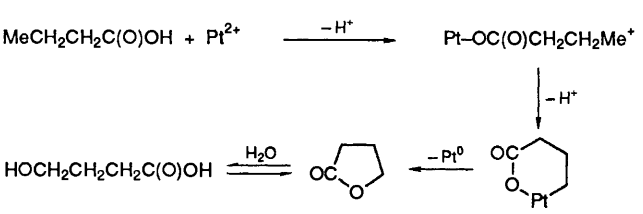
Substrate	Products (% yield)^{a,b}
$\mathrm{MeCO_2H}$	$\mathrm{HOCH_2CO_2H}$ (41) $\mathrm{ClCH_2CO_2H}$ (9)
$\mathrm{MeCH_2CO_2H}$	$\mathrm{HOCH_2CH_2CO_2H}$ (133) $\mathrm{ClCH_2CH_2CO_2H}$ (97)
 $\mathrm{Me\overset{Me}{C}HCO_2H}$	 $\mathrm{HOCH_2\overset{Me}{C}HCO_2H}$ (88)  (29)  $\mathrm{HOCH_2\overset{CH_2OH}{C}HCO_2H}$ (39)
$\mathrm{MeCH_2CH_2CO_2H}$	$\mathrm{HOCH_2CH_2CH_2CO_2H}$ (49)  (97)  (12)
 $\mathrm{Me\overset{Me}{C}HCH_2CO_2H}$	 $\mathrm{HOCH_2\overset{Me}{C}HCH_2CO_2H}$ (39)  (140)  (19)
$\mathrm{MeCH_2CH_2CH_2CO_2H}$	 $\mathrm{\underset{OH}{C}H_2CH_2CH_2CH_2CO_2H}$ (31)  (67)
$\mathrm{MeCH_2CH_2CH_2CH_2CO_2H}$	$\mathrm{HOCH_2CH_2CH_2CH_2CH_2CO_2H}$ (17)  $\mathrm{Me\underset{OH}{C}HCH_2CH_2CH_2CO_2H}$ (11)  $\mathrm{MeCH_2\underset{OH}{C}HCH_2CH_2CO_2H}$ (8)  (13%)

[a] *Conditions*: substrate (0.69 mmol), K_2PtCl_4 (0.115 mmol), K_2PtCl_6 (0.23 mmol), D_2O (3 ml), O_2 atmosphere, 80–90 °C, 144 h. [b] Yields relative to Pt^{II}.

total yield in excess of 100% relative to Pt^{II} was obtained. The function of K_2PtCl_6 was to reoxidize Pt^0, formed at the end of the oxidation step, back to Pt^{II}.[4] Thus, the precipitation of metallic Pt during oxidation was greatly delayed when K_2PtCl_6 was added to the system. Note also that no product formation occurred when either K_2PtCl_6 or metallic Pt was employed in the absence of K_2PtCl_4.

Table 1 indicates the following order of preference for the oxidation of C–H bonds: α-C–H << β-C–H < γ-C–H ⩾ δ-C–H ≈ ε-C–H. For example, no α-C–H oxidation occurred in the presence of β-C–H bonds. The ratio of γ-C–H to β-C–H oxidation was as high as 8. Hence, it was possible to hydroxylate a γ-C–H bond in the presence of α- and β-C–H bonds with relatively high selectivity. There was also a slight (up to 2 : 1) preference for γ-C–H *versus* δ-C–H oxidation.

A rational explanation for the observed order of reactivity is the 'chelate effect' (Scheme 1). Because of the prior coordination of the carboxylate group, a metallacycle was formed following the C-H activation step.[5] Presumably, the activation



Scheme 1

of γ-C–H (and, to a slightly lesser extent, δ-C–H and ε-C–H) bonds was favoured due to the formation of strain-free six- and higher-membered rings. The observation of β-lactones provided strong support for the above mechanism. While aqueous solutions of γ-hydroxycarboxylic acids contain equilibrium mixtures of the acids and their respective lactones, β-hydroxyacids show no tendency to form lactones because of the high strain associated with the four-membered ring.[6] Clearly, the β-lactones observed in our system were kinetic (rather than thermodynamic) products formed by reductive elimination from five-membered metallacycles. The rate of oxidation of α-C–H bonds (such as the methyl group in acetic acid) was found to be particularly slow and was not observed if β-C–H bonds were also present. Presumably the α-C–H bonds were attacked directly without prior coordination of the carboxylate group since it is unlikely that a highly strained metallacyclopropane was involved. Finally, the chlorides may be formed through the cleavage of Pt-alkyl bonds by Cl^- ions present in solution.[7]

In conclusion, we have demonstrated the facile catalytic hydroxylation of unactivated C–H bonds of aliphatic acids with moderate to high regioselectivity. We are currently exploring the possibility of using other (hopefully, more economical) cooxidants that are capable of reoxidizing Pt^0 to Pt^{II}. Additionally, attempts at increasing the regioselectivity of the oxidation by changing the ligand environment around Pt^{II} are under way.

This research was funded by a grant from the National Science Foundation (CHE-8906587). We also thank Johnson Matthey, Inc. for a generous loan of platinum salts.

Received, 4th June 1991; Com. 1/02673I

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