1000 *J. Am. Chem. Soc.* **2001,** *123,* 1000−1001

Catalytic Shilov Chemistry: Platinum Chloride-Catalyzed Oxidation of Terminal Methyl Groups by Dioxygen

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Received June 1, 2000

The selective catalytic oxidation of remote primary C−H bonds of organic substrates remains an intellectual and practical challenge.[1] One example of metal-mediated functionalization (hydroxylation) of remote primary C−H bonds involves the combination of $PtCl_4^{2-}/PtCl_6^{2-}$ (the Shilov system).[1a,b,2] Despite its many attractive features, however, the Shilov system suffers from one crippling drawback: dioxygen has not hitherto been used efficiently as the reoxidant.[3] We have discovered that, with a proper cocatalyst at elevated temperature, Shilov chemistry can be made catalytic with dioxygen as the ultimate oxidant. A number of aliphatic acids were tested, and turnover numbers of up to 15/h with respect to platinum were observed. This study constitutes the first example of the direct use of dioxygen in the catalytic oxidation of unactivated primary C−H bonds under mild conditions that does not involve the use of a coreductant (e.g., sacrificial metals, $2H^+ + 2e^-$, dihydrogen, or carbon monoxide[4−6]).

Our results on the catalytic oxidation of ethanesulfonate is summarized in Table 1.[7] The predominant reaction involves the hydroxylation of the remote methyl group. In the absence of added dioxygen, the use of either K_2PtCl_4 alone or in conjunction with 1 equiv of $CuCl_2$ results in one "turnover" to $HOCH_2CH_2SO_3^-$, along with the precipitation of metallic platinum. In the presence of dioxygen and an excess of chloride ions, reoxidation of platinum does occur resulting in multiple turnovers with respect to the metal (however, when too much chloride is present, the reoxidation of platinum occurs but the substrate oxidation is inhibited, presumably because of reduced accessibility of the metal center to the substrate). Higher turnover rates are observed in the presence of ***both*** chloride and copper ions. A low solution pH is necessary for catalysis, and while sulfuric acid was normally added, an equivalent amount of trifluoroacetic acid is also equally effective. The dioxygen pressure has a modest effect on the reaction rate; for example, the rate approximately doubled when the partial pressure of dioxygen was raised from 300 to 1300 psi. At either 300 or 1300 psi pressure of dioxygen, doubling the $PtCl_6^{2-}$ concentration led to a 2-fold increase in rate, suggesting that the reaction is first-order with respect to platinum.

Table 2. Catalytic Hydroxylation of Substrates[a]

Na_2PtCl_6 (mmol)	substrate	ω-hydroxy (mmol)	$(\omega-1)$-hydroxy (mmol)	turnover/ Pt
0.028	CH_3SO_3Na	0.23	N/A	8
0.010	$C_2H_5SO_3Na$	0.53	0	53
0.005	$C_3H_7SO_3Na$	0.15	0.03	28
0.005	$C_2H_5PO_3H$	0.17	0	35
0.010	C_2H_5COOH	0.16	0	16

[a] Reaction conditions: substrate, 2.0 mmol; $CuCl_2$, 0.1 mmol; H_2O, 2 mL; H_2SO_4, 0.08 mL; O_2, 1300 psi; 150 °C, 4 h.

Table 2 summarizes our results on the catalytic remote hydroxylation of the methyl group of a number of organic acids.[7] While ethanesulfonate gave the fastest rate, catalytic turnovers were also observed with other substrates. Methanesulfonate was the most sluggish substrate, presumably because the electron-withdrawing sulfonate group makes the adjacent C−H bonds less susceptible to an electrophilic attack. In every case, the predominant product was formed by the functionalization of the strongest C−H bond in the substrate; a reactivity pattern that is clearly inconsistent with a mechanism involving organic radicals.

The reason for the lower reactivity of propanesulfonate compared to ethanesulfonate is unclear. It is clear, however, that the possible coordination of the sulfonate group is not a significant factor in the reactivity.[1a,8] Thus, as shown in Table 3, in direct competition experiments the amount of product formed from ethane was equal to or greater (see footnote *e*, Table 3) than that formed from ethanesulfonate when normalized with respect to the number of primary C−H bonds present. Table 3 also illustrates that the relative reactivity of ethane versus ethanesulfonate does not change on moving from the $PtCl_4^{2-}/PtCl_6^{2-}$ system to the catalytic $PtCl_4^{2-}/CuCl_2$ system, suggesting that the copper ion is not involved in the C−H activation step (also see below).

A key question that needs to be addressed is whether the nature of the C−H activation process is different in the present system compared to that in the original Shilov system, particularly since a second metal (Cu(II)) is present in the catalytic system. For reasons given below, we believe that the C−H activation mechanism remains, for the most part, the same upon moving to the catalytic system.

Table 1. Catalytic Oxidation of $C_2H_5SO_3Na$[a]

catalyst (mmol)	$HOCH_2CH_2SO_3^-$ (mmol)	$(HO)_2CHCH_2SO_3^-$ (mmol)	$HO_2CCH_2SO_3^-$ (mmol)	$HOCH_2CO_2H$ (mmol)	CH_3CO_2H (mmol)	turnovers/ Pt
K_2PtCl_4 (0.012)	0.02	0.01	0	0	0	2
K_2PtCl_4 (0.015) NaCl (0.15)	0.12	0.02	0	0.02	0.01	11
K_2PtCl_4 (0.015) NaCl (0.30)	0.03	0.01	0	tr.	tr.	3
K_2PtCl_4 (0.012) $CuCl_2$ (0.074)	0.50	0.12	tr.	0.01	0.01	43
Na_2PtCl_6 (0.009)	0.04	0.02	0	0	0	7
Na_2PtCl_6 (0.009) $CuCl_2$ (0.074)	0.24	0.08	0.06	0.08	0.01	52
Pt metal (0.014) $CuCl_2$ (0.074)	0.02	0.05	0.02	0.01	0.02	9
Pt metal (0.014) $CuSO_4$ (0.074)	0	0	0	0	0	0
$CuCl_2$ (0.074)	0	0	0	0	0	0

[a] Reaction conditions: $C_2H_5SO_3Na$, 2.0 mmol; H_2O, 2.0 mL; H_2SO_4, 0.1 mL; O_2, 300 psi; N_2, 1200 psi; 160 °C; 4 h.

10.1021/ja001926+ CCC: $20.00

Table 3. Relative Reactivity of $C_2H_5SO_3Na$ and C_2H_6[a]

catalyst (mmol)	$C_2H_5SO_3^-$ (mmol)[d]	product (mmol)	$C_2H_5SO_3^-$ consumed/Pt	C_2H_6 (mmol)[e]	products (mmol)	C_2H_6 consumed/Pt
$PtCl_4^{2-}$ (0.024) $CuCl_2$ (0.036)[b]	0.124	$HOC_2H_4SO_3^-$ (0.062)	2.6	0.062	C_2H_5OH (0.021) HOC_2H_4OH (0.028) CH_3CO_2H (0.012)	2.5
$PtCl_4^{2-}$ (0.024) $PtCl_6^{2-}$ (0.036)[c]	0.124	$HOC_2H_4SO_3^-$ (0.027)	0.6	0.062	C_2H_5OH (0.011) HOC_2H_4OH (0.011) CH_3CO_2H (0.005)	0.6

[a] Reaction conditions: H_2O, 2 mL; C_2H_6, 550 psi; O_2, 200 psi; 160 °C, 4 h. [b] 0.03 mL of H_2SO_4 was added. [c] 0.03 mL of HCl was added. [d] Initial amount. [e] Calculated for 100 °C from data in International Critical Tables; the number should be lower for 160 °C. Amount present in solution does not change with time because of the presence of ethane in the headspace.

Table 4. Catalytic H/D Exchange in Unreacted Substrate in the Absence of Dioxygen[a]

catalyst (mmol)	substrate (mmol)	ω-C(H/D)$_3$ (%D)	(ω−1)-C(H/D)$_2$ (%D)	(ω−2)-C(H/D)$_2$ (%D)	(ω−3)-C(H/D)$_2$ (%D)
K_2PtCl_4 (0.060) $CuCl_2$ (0)	$C_2H_5SO_3Na$ (2.0)	64	tr.	N/A	N/A
K_2PtCl_4 (0.077) $CuCl_2$ (0.074)	$C_2H_5SO_3Na$ (2.0)	88	0	N/A	N/A
K_2PtCl_6 (0.045) $CuCl_2$ (0)	$C_2H_5SO_3Na$ (2.0)	63	tr.	N/A	N/A
Pt metal, (0.010) $CuCl_2$ (0)	$C_2H_5SO_3Na$ (2.0)	0	0	N/A	N/A
Pt metal, (0.010) $CuCl_2$ (0.074)	$C_2H_5SO_3Na$ (2.0)	0	0	N/A	N/A
K_2PtCl_4 (0.060) $CuCl_2$ (0)	$C_3H_7SO_3Na$ (2.0)	28	7	0	N/A
K_2PtCl_4 (0.060) $CuCl_2$ (0.074)	$C_3H_7SO_3Na$ (2.0)	26	11	0	N/A
K_2PtCl_4 (0.060) $CuCl_2$ (0)	$C_4H_9SO_3Na$ (2.0)	21	7	0	0
K_2PtCl_4 (0.060) $CuCl_2$ (0.074)	$C_4H_9SO_3Na$ (2.0)	29	9	0	0

[a] Reaction conditions: D_2O, 2 mL; H_2SO_4, 0.1 mL; N_2, 1300 psi; 130−150 °C, 24 h.

Table 5. Catalytic H/D Exchange in Unreacted Substrate in the Presence of Dioxygen[a]

catalyst (mmol)	substrate (mmol)	ω-C(H/D)$_3$ (%D)	(ω−1)-C(H/D)$_2$ (%D)	(ω−2)-C(H/D)$_2$ (%D)	(ω−3)-C(H/D)$_2$ (%D)
K_2PtCl_4 (0.048) $CuCl_2$ (0)	$C_2H_5SO_3Na$ (1.0)	75	0	N/A	N/A
K_2PtCl_4 (0.028) $CuCl_2$ (0)	$C_3H_7SO_3Na$ (2.0)	42	16	0	N/A
K_2PtCl_4 (0.048) $CuCl_2$ (0)	$C_4H_9SO_3Na$ (2.0)	93	68	15	0
K_2PtCl_4 (0.048) $CuCl_2$ (0.031)	$C_4H_9SO_3Na$ (2.0)	89	75	20	0

[a] Reaction conditions: D_2O, 2 mL; H_2SO_4, 0.1 mL; O_2, 300 psi; N_2, 1200 psi; 130−150 °C, 24 h.

First, as in the original Shilov system, the predominant site of hydroxylation in the substrate is the primary C−H bond. Second, by using D_2O as the solvent, we examined the extent of H/D exchange (thereby revealing the preference for C−H activation at the different sites) in the unreacted substrate for a series of homologous alkanesulfonates both in the absence (Table 4) and presence (Table 5) of dioxygen. In the absence of dioxygen, the methyl group is the preferred site of attack, and the presence of copper chloride has little effect on the selectivity. As expected, metallic Pt is inactive under these conditions. Not unexpectedly, the extent of H/D exchange is higher in the presence of dioxygen because of the continuous regeneration of the active platinum species. More interestingly, although the preference for attack on the remote methyl group remains, the overall regioselectivity is somewhat lower with more H/D exchange observed at the (ω-1)-CH_2 group, especially with the longer butyl chain. Again, the presence of copper chloride appears to have relatively little effect on the regioselectivity. The observed lowering of the regioselectivity in the presence of dioxygen may be due to a parallel nonselective (radical?) pathway as a minor component of the overall reaction.

Finally, linear Arrhenius plots were obtained for the oxidation of ethanesulfonate, carried over the temperature range 120−160 °C (reaction conditions: **A** $PtCl_4^{2-}$, 0.01 mmol; $CuCl_2$, 0.1 mmol; H_2O, 2 mL; H_2SO_4, 0.08 mL; $C_2H_5SO_3Na$, 2 mmol, O_2, 300 psi; N_2, 1000 psi. **B** $PtCl_6^{2-}$, 0.01 mmol; $CuCl_2$, 0.1 mmol; H_2O, 2 mL; H_2SO_4, 0.08 mL; $C_2H_5SO_3Na$, 2 mmol; O_2, 1300 psi.). These yielded activation energies of 27.4 and 31.6 kcal/mol for reactions **A** and **B**, respectively. For comparison, the reported activation energies for H/D exchange in benzene and acetic acid by the traditional Shilov system are 25.7 and 23.7 kcal/mol, respectively.[2]

In conclusion, we have demonstrated that under appropriate conditions the Shilov chemistry can be made catalytic with dioxygen as the ultimate oxidant. This allows for the first time the fairly selective catalytic hydroxylation of remote methyl groups in organic acids. The procedure is superior to that described recently by us in that (a) a coreductant (carbon monoxide) is not required and (b) side-products derived through C−C cleavage steps are not formed.[6] Additionally, the catalytic Shilov system is the first "dioxygenase" (biological or otherwise) where the oxidation equivalents of ***both*** oxygen atoms of dioxygen are utilized in the hydroxylation of unactivated primary C−H bonds under mild conditions.[4−6]

Acknowledgment. This research was supported by a grant from the National Science Foundation.

JA001926+

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