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pH-Dependent Chemoselective Synthesis of α-Amino Acids. Reductive Amination of α-Keto Acids with Ammonia Catalyzed by Acid-Stable Iridium Hydride Complexes in Water

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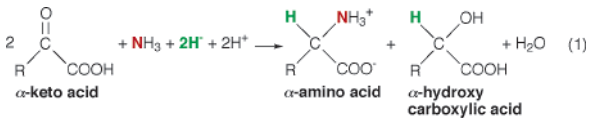
Increasing environmental awareness makes it necessary to develop a sustainable synthesis of α-amino acids without the use of highly toxic agents such as cyanides.[1] In this context, reductive amination of α-keto acids has merited special attention, because it is a close laboratory analogy of a pathway by which amino acids are chemoselectively biosynthesized with aqueous NH_3 that is an essential amine source in natural systems.[2] In the nonenzymatic synthesis of α-amino acids, however, catalytic reductive amination has so far been carried out using amine sources other than NH_3 in organic solvents.[3] Thus, catalytic reductive amination of α-keto acids with aqueous NH_3 has yet to be achieved.[4,5] The difficulty of such reactions mainly arises from the use of water as a reaction media. The aqueous media must be acidic enough for the carbonyl group of α-keto acids to be protonated. However, the presence of proton causes not only the decomposition of a hydride species, which would act as a catalyst, but also formation of the α-hydroxy carboxylic acids as a byproduct by the competitive transfer hydrogenation of α-keto acids (eq 1).



(1)

We report herein the highly chemoselective synthesis of α-amino acids by reductive amination of commercially available α-keto acids, catalyzed by acid-stable mononuclear hydride complexes $[Cp^*Ir^{III}(bpy)H]_n(X)$ {$[\mathbf{1}]_n(X)$, where X = SO_4 (n = 2) or PF_6 (n = 1), Cp* = η^5-C_5Me_5, bpy = 2,2′-bipyridine}[6] with aqueous NH_3 and HCOOY (Y = Na or H) or with $HCOONH_4$ in water.[7] The reductive amination is applicable to the highly chemoselective synthesis of all three major types of α-amino acids with nonpolar (type A),[8] uncharged polar (type B), and charged polar (type C) substituents (R) by controlling pH. This is the first example of highly chemoselective nonenzymatic synthesis of α-amino acids by catalytic reductive amination of α-keto acids with aqueous NH_3 in water. pH-dependent ^{15}N- and ^2H-double-labeling can also be readily accomplished by using $^{15}NH_3$ and DCOONa, which are ideal amine and hydride ion sources, respectively.

The reductive amination was catalyzed by both the isolated hydride complex **1**(PF_6) and the in-situ generated hydride complex $[\mathbf{1}]_2(SO_4)$ from the reaction of an aqua complex $[Cp^*Ir^{III}(bpy)H_2O](SO_4)$ {**2**(SO_4)} with HCOOY (Y = NH_4, Na, or H) in the catalytic cycle. The formation of $[\mathbf{1}]_2(SO_4)$ is pH-dependent as shown in Figure 1 (●). Below pH ca. 3, the protonation of the hydrido ligand of **1** leads to the formation of **2** with the evolution of H_2.[9] Above pH 3.6, HCOOH acts as $HCOO^-$ to bind the iridium center.[10] Above pH ca. 8, the aqua complex **2** is predominantly deprotonated to form a hydroxo complex $[Cp^*Ir^{III}(bpy)(OH)]^+$ that hardly reacts with $HCOO^-$. Thus, the maximum yield of the hydride complex **1** is obtained at pH 5 (● in Figure 1).

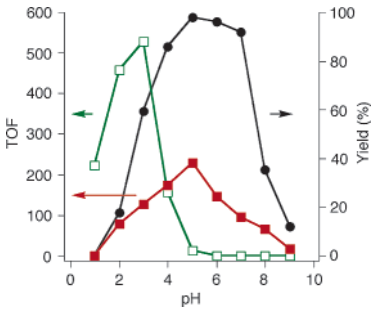


Figure 1. pH-dependence of yield of $[\mathbf{1}]_2(SO_4)$ {●, based on **2**(SO_4)} from the reaction of **2**(SO_4) (5 μmol) and $HCOONH_4$ (0.5 mmol) in water (0.7 mL) at 80 °C for 10 s and TOF for formation of alanine (red ■) and lactic acid (green □) from the reaction of pyruvic acid (0.16 mmol) with **2**(SO_4) (0.8 μmol) and $HCOONH_4$ (3.2 mmol) in H_2O (3 mL) at 80 °C for 15 min.

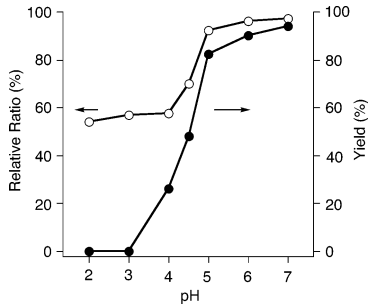


Figure 2. pH-dependence of yield of D-labeled $[\mathbf{1}]_2(SO_4)$ {●, based on **2**(SO_4)} by a reaction of **2**(SO_4) (5 μmol) with DCOONa (25 μmol) in H_2O (0.7 mL) at 80 °C for 1 min and relative ratio of ^{15}N- and ^2H-double-labeled alanine (○) to ^{15}N-labeled ^2H-nonlabeled alanine by a reductive amination of pyruvic acid (0.16 mmol) with 5% $^{15}NH_3/H_2O$ (3.2 mmol), DCOONa (3.2 mmol), and **2**(SO_4) (0.8 μmol) in H_2O (3 mL) at 80 °C for 6 h.

Figure 1 also shows typical pH-dependence of turnover frequencies (TOFs)[11] for the formation of α-amino acid (alanine: red ■) and α-hydroxy carboxylic acid (lactic acid: green □) from the reaction of α-keto acid (pyruvic acid) with $HCOONH_4$ and **2**(SO_4) in H_2O at 80 °C for 15 min. The formation rates of alanine and lactic acid exhibit a maximum value around pH 5 and pH 3, respectively. Thus, we can obtain alanine quite selectively (96%) with a small amount of lactic acid (4%) at pH 5.

The reaction of **2** {= M−OH_2, where M = Cp*Ir(bpy), eq 2} with $DCOO^-$ in H_2O at 80 °C for 1 min in the absence of the reducible α-keto acids gives D-labeled **1** (= M−D, ● in Figure 2) as a main species above pH ca. 5 (e.g., M−D/M−H = 90/10 at pH 6), although the hydride ligand of **1** undergoes H/D exchange in water (eq 3). Thus, ^{15}N- and ^2H-double-labeled α-amino acids

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Table 1. pH-Dependent Synthesis of α-Amino Acids with Nonpolar (Type A, Entries 1−8), Uncharged Polar (Type B, Entries 9 and 10), and Charged Polar (Type C, Entries 11 and 12) Substituents by Reductive Amination of α-Keto Acids with $HCOONH_4$ or with NH_3 and HCOOY (Y = Na or H) in the Presence of **1**(PF_6) or **2**(SO_4) in Water at 80 °C for 6 h[a,b]

		amine and hydride ion	optimum	α-amino acid			α-hydroxy carboxylic acid
entry	complex	donors	pH	symbol	TOF[c]	yield (%)[d]	yield (%)[d]
1	**1**(PF_6)	$HCOONH_4$	5.0	Ala	185	94	6
2	**2**(SO_4)	$HCOONH_4$	5.0	Ala	228	96 (94)[e]	4
3	**2**(SO_4)	NH_3/HCOOH	5.0	Ala	211	96	4
4	**2**(SO_4)	$^{15}NH_3$/DCOONa	5.0	Ala	249	96	4
5	**2**(SO_4)	$HCOONH_4$	5.0	Val	121	97	3
6	**2**(SO_4)	$HCOONH_4$	5.0	Leu	157	93	7
7	**2**(SO_4)	$HCOONH_4$	5.0	Ile	113	95	5
8	**2**(SO_4)	$HCOONH_4$	5.0	Phe	249	92	8
9	**2**(SO_4)	$HCOONH_4$	5.0	Tyr	176	94 (85)[e]	6
10	**2**(SO_4)	$^{15}NH_3$/DCOONa	5.0	Tyr	153	91	7
11	**2**(SO_4)	$HCOONH_4$	6.5	Glu	170	78 (70)[e]	19
12	**2**(SO_4)	$^{15}NH_3$/DCOONa	6.5	Glu	167	81	15

[a] **1**(PF_6) or **2**(SO_4)/α-keto acid/$HCOONH_4$ = 1 (0.8 μmol)/200 (0.16 mmol)/4000 (3.2 mmol). [b] **2**(SO_4)/α-keto acid/5% aqueous NH_3/HCOOY (Y = Na or H) = 1 (0.8 μmol)/200 (0.16 mmol)/4000 (3.2 mmol)/4000 (3.2 mmol). [c] Turnover frequency: {mol of α-amino acids/mol of **2**(SO_4)}/(initial 1 h). [d] For 6 h (based on α-keto acids). [e] Isolated yield for 6 h.

(○ in Figure 2) are obtained exclusively above pH 5 by the catalytic reductive amination of α-keto acids with $^{15}NH_3$, $DCOO^-$, and **2**(SO_4) in H_2O (but not in D_2O) (eq 4).

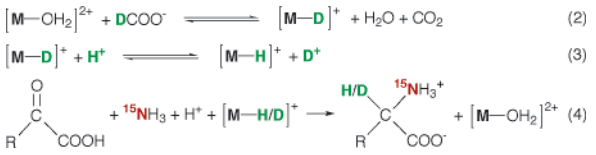
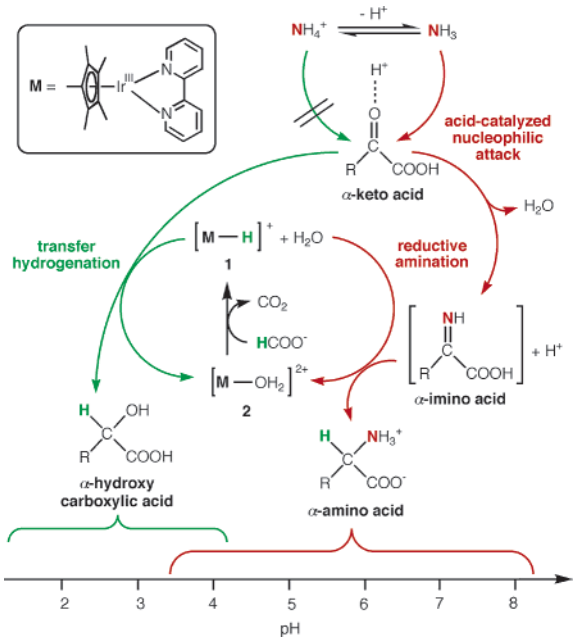


Table 1 shows the results of the reductive amination of α-keto acids with $HCOONH_4$ (entries 1, 2, 5, 6, 7, 8, 9, and 11), 5% NH_3/H_2O and HCOOH (entry 3), or 5% $^{15}NH_3$/D_2O and DCOONa (entries 4, 10, and 12) in the presence of **1**(PF_6) (entry 1) or **2**(SO_4)-(entries 2−12) in water at 80 °C at the optimized pH (5.0−6.5). The product yields determined by ^1H NMR of α-amino acids with type A, B, and C substituents are 92−97%, 91−94%, and 78−81%, respectively. It was confirmed that no reaction occurred in the absence of the catalysts, hydride ion donors, or amine donors (as blank experiments). Moreover, large-scale synthesis of the α-amino acids has been made possible.[12]

The pH-dependent reductive amination of α-keto acids with NH_3 and $HCOO^-$ catalyzed by the iridium complexes is proposed in Scheme 1. The reaction is started by acid-catalyzed nucleophilic attack of NH_3 to the carbonyl carbon of α-keto acids to produce intermediary α-imino acids, followed by subsequent reduction of the C═N bond in the α-imino acids by **1**. Protonation of the carbonyl oxygen of α-keto acids makes carbonyl carbon more susceptible to the nucleophilic addition. Under acidic conditions, NH_3 also undergoes protonation to form NH_4^+ that cannot act as the amine donor, when only transfer hydrogenation of α-keto acids takes place to afford α-hydroxy carboxylic acids. Thus, the highly chemoselective synthesis of α-amino acids with negligible formation

Scheme 1



of α-hydroxy carboxylic acids has been made possible by using acid-stable hydride complexes under the optimized pH conditions in water.

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(7) $HCOONH_4$ acts as an amine source as well as a hydride ion source.
(8) Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry*; John Wiley & Sons: New York, 1999; pp 79−84.
(9) The formation of H_2 was confirmed by GC analysis.
(10) The pK_a value of HCOOH is 3.6 at 25 °C.
(11) Turnover frequencies {TOFs = (mol of α-amino acids/mol of **1**(PF_6) or **2**(SO_4)/(initial 1 h)) were determined by ^1H NMR.
(12) For example, 10 g scale synthesis of tyrosine: 95% isolated yield. Conditions: **2**(SO_4)/α-keto acid/$HCOONH_4$ = 1(277.5 μmol)/200 (55.5 mmol)/4000 (1.11 mol), 80 °C, 24 h.

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