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Stereoretentive C–H Bond Activation in the Aqueous Phase Catalytic Hydrogenation of Amino Acids to Amino Alcohols

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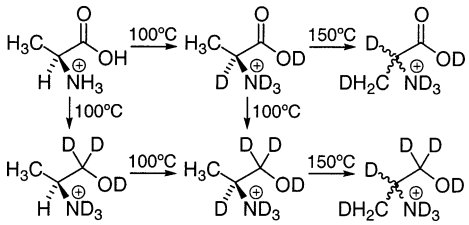
ABSTRACT



At 100 °C and 1000 psi of hydrogen, aqueous L-alanine undergoes facile hydrogenation to L-alaninol over a 5% Ru/C catalyst. In the presence of added acid to protonate the carboxylate moiety, the reaction is faster and more selective than analogous reductions of simple alkanoic acids. Stereochemistry at the α-carbon is retained despite complete exchange of hydrogen at this site, as shown by deuterium incorporation. Similar stereoretentive C–H bond activation at C2 is seen in L-alaninol itself, and when acid is omitted, in L-alanine. These processes reveal a class of mild, highly stereoretentive C–H bond activations occurring in water over a heterogeneous catalyst.

Lactic acid (2-hydroxypropanoic acid) is easily and selectively hydrogenated to propylene glycol (1,2-propanediol) in aqueous solution over Ru/C catalyst.[1] Such direct hydrogenation of simple *n*-alkanoic acids is normally difficult. Surprised by lactic acid's mild reaction, we analyzed its kinetics.[2] The resulting optimized conditions (130−170 °C; 1000−2000 psi of H_2) modestly improved on values (typically 150 °C, 7000 psi) obtained by Carnahan et al. for ruthenium-catalyzed hydrogenation of the closely related glycolic acid (hydroxyacetic acid).[3]

Prompted by the lactic acid results, we extended our studies to amino acid substrates, again finding mild, selective hydrogenation to the corresponding amino alcohols. Amino alcohols are important building blocks in agricultural,[4] pharmaceutical, and peptide chemistry,[5] and are also utilized as chiral auxiliaries.[6] In their extensive review of amino alcohol synthesis methods, Ager et al.[7] provide many examples of amino acid reduction, typically in batch reactions with expensive and/or hazardous hydride reagents. Direct aqueous phase catalytic hydrogenation of free acids offers an alternative that is atom economical and amenable to continuous processing, and that obviates the need for intermediate esterification, use of organic solvents, and

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Table 1. Summary of Alanine Reactions[a]

substrate	*T* (°C)	*t* (h)	pressure (psi)	[phosphoric acid] (M)	alanine conversion	L-alaninol yield	ee (%)
alanine	90	6	1000	0.29	60	60	99.7
alanine	100	6	1000	0	13	8	92.7
alanine	100	6	1000	0.08	46	37	97.2
alanine	100	6	1000	0.15	69	62	98.7
alanine	100	6	1000	0.29	93	91	99.2
alanine	100	6	1000	0.58	70	68	99.4
alanine	125	2	250	0.29	60	52	96
alanine	125	6	250	0.29	>99	76	89
alanine	125	2	500	0.29	88	74	96
alanine	125	6	500	0.29	>99	78	83
alanine	125	6	1000	0.29	>99	89	90.7
alanine	125	2	1800	0.29	96	96	98
alanine	125	6	1800	0.29	>99	99	92
alanine	150	0.75	1000	0.29	>99	78	89
alanine	150	6	1000	0.29	>99	38	42
alaninol	125	6	1000	0.29			89
alaninol	150	6	1000	0.29			40

[a] Reactions performed in a stirred batch reactor; all feeds are 0.22 M; conversion, yield, and ee values were determined from HPLC data.

byproduct waste streams. Two recent patents by Antons et al., filed after this work began, describe similar reductions of lactic and amino acids in good yields and with stereoretention, but give no mechanistic details.[8]

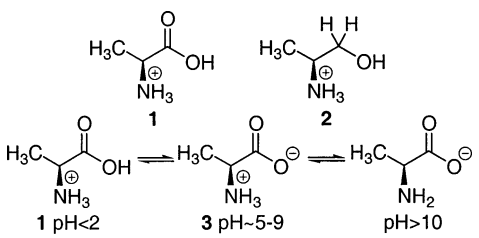
We have probed the mechanism and stereochemistry of hydrogenation of the simplest chiral amino acid, L-alanine ((*S*)-2-aminopropanoic acid), to L-alaninol (*S*-(+)-2-amino-1-propanol) via isotopic labeling together with analyses of product chirality and reaction rates. Table 1 summarizes a series of hydrogenations, run in a stirred batch reactor at 90−150 °C. With 0.22 M alanine in water at 100 °C, conversion ended after 1 h with low yield (8%) and poor selectivity (<60%) to L-alaninol. In contrast, conversion of lactic acid to 1,2-propanediol was complete with selectivity >90% under similar conditions.

Alanine conversion increased markedly when an excess of phosphoric acid (0.29 M H_3PO_4) was added to form protonated alanine **1** ($pK_a = 2.34$). To be thermochemically feasible, hydrogenation requires the carboxylic acid functionality to be undissociated. Reduction of carboxylate anion to alkoxide would be more endothermic by an energy difference corresponding to the ΔpK_a between the starting acid and the product alcohol, ca. 15−17 kcal/mol at ambient temperatures. This effect was clearly seen in our work with lactic acid and its salts. Neutral aqueous alanine exists as zwitterion **3** (Scheme 1) so the poor yield and selectivity in its hydrogenation without added acid are unsurprising. As expected, substoichiometric quantities of acid allowed only partial alanine conversion, which stopped when the pH rose due to basic product formation.

With sufficient acid, protonated L-alaninol **2** was formed with selectivity exceeding 95% and enantiomeric excess (ee) over 99%. Thus, the stereochemistry of the starting amino acid is completely retained through the reduction process. Figure 1 displays alanine and alaninol concentration profiles for reaction at 150 °C. Alanine conversion is complete at 45 min; at this point the yield of L-alaninol peaks, and then decreases slowly via racemization to D-alaninol along with C−C hydrogenolysis to form ethylamine. At no point during the reaction is D-alanine detected. With L-alaninol used as the feed, the extent of racemization observed at 150 °C at 4 h was the same as that shown in Figure 1. Hydrogenation of the carboxylic functionality and loss of optical purity are thus clearly different processes. In fact, at 100 °C alanine hydrogenation is roughly 1/8th as fast as at 150 °C, but product racemization is essentially stopped.

Above 1000 psi rate is independent of hydrogen concentration,[9] though an experiment at 250 psi reduced the rate by ca. $^1/_2$. This finding suggests that catalyst binding sites for H_2 are saturated above 1000 psi. Analysis of reactant transport using the criteria developed by Weisz and Prater[10] indicates no diffusion limitations for either hydrogen or alanine in this three-phase system. The absence of transport resistances and the observed plateau in rate as a function of H_2 pressure signify that at sufficient pressures neither H_2 nor substrate concentrations limit the reaction rate, as seen earlier for lactic acid hydrogenation.[2]

Scheme 1. Alanine·H^+, Alaninol·H^+, and Amino Acid Form vs pH



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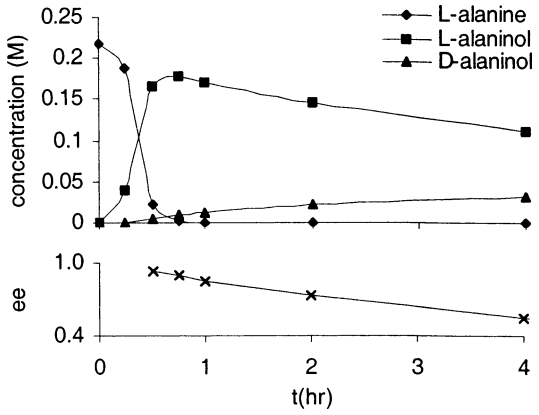
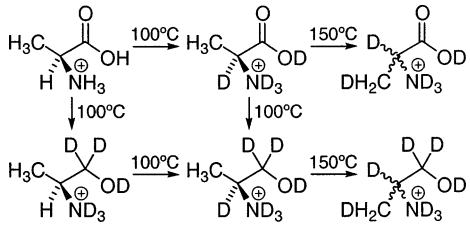


Figure 1. Secondary racemization of L-alaninol. Reaction performed with 100 mL of a 0.22 M L-alanine solution, under H_2 pressure of 1000 psi at 150 °C with 1 g of 5% Ru/C powder catalyst. Phosphoric acid in solution was 0.29 M.

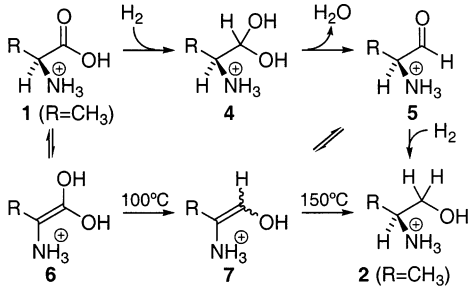
At the outset of this study we sought to probe the hydrogenation's stereochemistry via H/D exchange. Loss of C2−H was expected to lead to racemization, so that D incorporation could stand in for loss of stereochemical purity. Subsequent experiments in which the enantiomeric excesses (ee's) were explicitly measured by HPLC yielded a surprise: *at 100 °C, D incorporation at C2 occurs without loss of optical purity for both alanine and alaninol.* At 150 °C, both compounds undergo complete H/D exchange at C2 in less than 1 h; D also appears at the C3 positions with concomitant racemization of alaninol. Scheme 2 and Table 2 summari ze deuterium (D) incorporation results from alanine hydrogenation in D_2/D_2O. In product alaninol, D incorporation at C1 is complete as expected. Partial D

Scheme 2. Deuterium Incorporation in D_2/D_2O over Ru/C



labeling is also seen at the C2 positions of alaninol product (90% complete at 6 h) and alanine feed (100% complete at 3 h).

Scheme 3. Generalized Amino Acid Hydrogenation Sequence Showing Aldehyde **5** and Potential Enols **6** and **7**



Scheme 3 shows a proposed general pathway for carboxylic acid hydrogenation, without any explicit representation of the catalyst's role. Addition of H_2 across the carbonyl group yields the 1,1-diol **4**, which loses H_2O to form the aldehyde **5**. A second equivalent of H_2 is then added to **5** to

Table 2. Summary of Deuterium Incorporation Experiments[a]

substrate	*T* (°C)	*t* (h)	[acid] (M)	alanine conv.	L-alaninol yield	alaninol ee (%)	% D incorporation at each position: alanine C2	alanine C3	alaninol C1	alaninol C2	alaninol C3
alanine	100	1	0.27	18	18	>99.9	62	6	100	39	1
alanine	100	6	0.27	84	78	99.7	100	2	100	89	0
alanine	100	1	0	8	4	>99.9	92	0	100	*	0
alanine	100	6	0	20	14	95.5	96	0	100	100	0
alanine	150	1	0.26	98	84	95.3			100	100	25
alanine	150	6	0.26	99.5	74	84.1			100	100	61
alanine	150	1	0	34	14	79.3	80	31	100	100	23
alanine	150	6	0	65	21	58.7	100	58	100	100	52
alaninol	100	1	0.28			99.9			75	42	14
alaninol	100	6	0.28			99.7			100	87	15
alaninol	100	2	0			>99.9			100	100	0
alaninol	100	6	0			99.8			100	100	0
alaninol	150	1	0.29			95.7			100	100	30
alaninol	150	6	0.29			80.7			100	100	65
alaninol	150	1	0			91.5			100	100	7
alaninol	150	6	0			60.5			100	100	32

[a] Reactions performed in a stirred batch reactor; alanine feeds 0.26 M; alaninol feeds 0.22 M, in D_2O under 1000 psi D_2; D-incorporation measured by ^1H NMR; an asterisk (*) indicates the peak was obscured by impurity.

form the product alcohol. Both the dehydration and the aldehyde reduction steps would be expected to be fast compared to the first hydrogenation.

We have been unable to detect **5**, but it might be postulated to explain H/D exchange at C2 via equilibration with the related enol **7**. In principle, enol **6** could also enable C2 H/D exchange, but this catalyst-independent process is not seen at the experimentally relevant conditions. However, two findings clearly show that H/D exchange at C2 occurs separately from hydrogenation. First, there is little or no loss of chirality despite the H/D exchange at C2; thus, a free enol, sp^2 hybridized at C2, cannot play a role in this reaction. Second, if hydrogenation is blocked by omission of acid, stereoretentive H/D exchange at C2 still proceeds readily. The results for D incorporation at C2 suggest that the catalyst directly removes H from the amine-bearing carbon to yield a surface-bound intermediate that retains the original C2 configurational information. At 100 °C, this species uniformly undergoes deuteration on the face from which the H loss occurred, thus retaining optical purity, and somehow surviving the elevated temperatures and the aggressive aqueous acid environment.[11] Higher temperatures presumably then disrupt the surface binding, so that D incorporation can take place on the opposite face. The only functional group needed is the amine; besides alanine and alaninol, (*S*)-2-aminobutane undergoes H/D exchange at C2 without loss of chirality.

The discovery of *stereoretentive* C−H bond activation at amine-bearing sp^3 C sites was the most unexpected finding in this work. Related catalytic H/D exchange processes have long been known, but they were typically run in organic solvents and we have found little discussion of their stereochemistry.[12] Such reactions are thought to form imine intermediates, enabling alkyl group transfers via transamination pathways.[13] Indeed, alkyl group exchange via catalytic activation of amines has been explored as a process to convert primary to secondary and tertiary amines.[14] Only in recent years has the potential for functionalization via C−C bond formation at such sites begun to be exploited, enabling addition of alkyl or acyl groups at the α C−H bond sites to amines.[15] In these reactions, however, the amines require attached 2-pyridyl groups, which serve as directing ligands for the transition metals effecting the C−H bond activation.[16]

The chemical behavior that has emerged from our own studies of amino acid hydrogenation mirrors the above C−H bond reactivity, as evidenced by isotopic exchange, and with the added bonuses of complete retention of stereochemistry, simple aqueous-phase heterogeneous catalysis, and relatively mild, "green" conditions. We are actively pursuing the intriguing possibility of stereocontrolled replacement of H with other functionalities under aqueous heterogeneous catalytic conditions.

As for the hydrogenation, why are protonated amino and lactic acid so much more reactive than their simple alkanoic acid counterparts? The obvious explanation is that the NH_3^+ and OH electron-withdrawing groups enhance the neighboring carbonyl group's preference for sp^3 hybridization, as is seen in the hydration equilibria of substituted ketones and aldehydes.[17] Two items support this notion: the fact that alanine's charged ammonium group is more activating than the hydroxyl in lactic acid, and the finding by Antons et al.[9] that 2-chloropropanoic acid is also reactive toward hydrogenation. Alternatively, intramolecular hydrogen bonding might favor hydrogenation.

We are actively exploring the behavior of related systems, such as the alkylated NR_2 and OR analogues of alanine and lactic acids. Exploratory hydrogenations of glycine, serine, and phenylalanine have already revealed brisk rates and high selectivities like those found for alanine. A more detailed account and mechanistic analysis of this ongoing work is in preparation.

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Supporting Information Available: Information regarding experimental and analytical techniques. This material is available free of charge via the Internet at http://pubs.acs.org.

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