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Notes

Facile Reduction of Carboxylic Acids by Zinc Borohydride

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It is well-known that basic borohydrides do not reduce carboxylic acids directly and invariably need addition of other reagents[1] such as $AlCl_3$,[2] I_2,[3] etc. to effect this transformation. However, zinc borohydride, which is considered to be a mild reagent,[4] readily reduces both aliphatic and aromatic acids to the corresponding alcohols in refluxing THF. The reaction requires only stoichiometric quantities of hydride for this conversion.

$$8RCOOH + 3Zn(BH_4)_2 \xrightarrow[80-95\%]{THF,\ 67\ ^\circ C} 8RCH_2OH + 8H_2$$

The following representative acids were chosen for the rate and stoichiometric studies: palmitic acid, pivalic acid, benzoic acid, and 10-undecenoic acid. Addition of zinc borohydride resulted in an instantaneous evolution of hydrogen with all the acids studied, and within few minutes 1 equiv of hydrogen was evolved. Hydride uptake per acid group was determined by analyzing aliquots at regular intervals. The results are presented in Table 1. Curiously, pivalic acid was reduced much faster compared to other aliphatic saturated acids. Also, the reduction of 10-undecenoic acid resulted in the formation of a gel in 15 min. The residual hydride was estimated by the hydrolysis of the whole reaction mixture which indicated $4H^-$ uptake per acid. The hydroboration of the double bond is established by the oxidative workup which yielded 1,11-undecanediol.

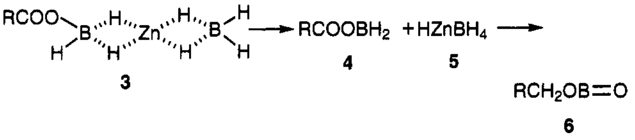
$$\underset{\mathbf{1}}{RCOOH} + \underset{\mathbf{2}}{Zn(BH_4)_2} \rightarrow \underset{\mathbf{3}}{RCOOBH_3(ZnBH_4)} + H_2$$

The enhanced reactivity of the borohydride in the presence of an olefinic group attracted our attention to probe the possibility of any catalysis. Accordingly, we studied the catalytic effect of 10 mol % of cyclohexene on the rate of reduction of acids. A small enhancement in the rate of reaction was observed in the reduction of palmitic acid only. Although the initial reaction of acids with all borohydrides is the formation of the (acyloxy)borohydride, interestingly, only the $Zn(BH_4)_2$ is able to reduce the (acyloxy)boron intermediate to the alcohol. The counterion seems to play a definite role in this reaction. Presumably, the reagent is present as a contact ion pair[5] and assists in the formation of a trivalent boron species **4** which would reduce the acyl group rapidly.

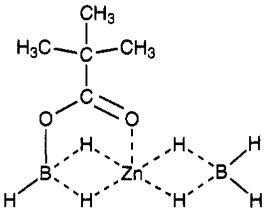
Table 1. Rate and Stoichiometry of Reduction of Carboxylic Acids with $Zn(BH_4)_2$[a]

acid	mmol of H^- consumed/mmol of acid							
	0.25 h	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	5.0 h	6.0 h
benzoic	1.38	1.54	1.67	1.83	1.93	2.31	2.56	2.82
benzoic[b]	1.38	1.54	1.76	1.86	2.02	2.34	2.63	3.10
palmitic	1.06	1.96	2.21	2.53	2.63	2.76	2.83	2.95
palmitic[b]	1.83	1.96	2.53	2.99	3.10			
pivalic	2.15	2.40	2.84	2.92				
pivalic[b]	2.15	2.41	2.82	2.92				
undecenoic[c]	gel							

[a] Ratio of H^- to acid, 8.25:2.5. [b] Catalyzed by 10 mol % of cyclohexene. [c] $[H^-]:[acid] = 11:2.5$.



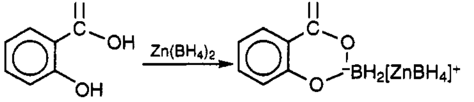
Faster reduction of pivalic acid could be due to the bulky *tert*-butyl group. Thus, the steric crowding in the intermediate **3a** probably assists the formation of the (acyloxy)borane species **4** resulting in the enhanced rate of reduction.



3a

Hydroboration could then be a side reaction, since $Zn(BH_4)_2$ could hydroborate olefins,[5] but the resulting alkyl boron species would not catalyze the reduction since hydride transfer in species **4** could occur intramolecularly.

In a preparative study a number of acids are reduced to the alcohols in excellent yields. Presence of groups such as chloro, nitro, bromo, etc. are tolerated. However, double bonds are readily hydroborated. For example, 10-undecenoic acid produced 1,11-undecanediol after oxidative workup. Cinnamic acid produced a mixture of 1,2- and 1,3-diols in the ratio 3:2 indicating lesser preference for benzylic position. Salicylic acid was not reduced due to the formation of a stable intermediate.



However, acylation of the *o*-hydroxyl group resulted in the complete reduction of the acid group. Thus, acetylsalicylic acid was readily reduced to yield 2-hydroxybenzyl alcohol. Dicarboxylic acids are also reduced to the corresponding diols. The results are presented in Table 2.

In conclusion, the ready conversion of carboxylic acids to alcohols by $Zn(BH_4)_2$ with good selectivity and con-

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[2] Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582.

[3] Bhaskarkanth, J. V.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964.

[4] Ranu, B. C.; Das, A. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1561.

[5] Ranu, B. C. *Synlett* **1993**, 885.

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comitant hydroboration of unsaturated acids to the corresponding diols by $Zn(BH_4)_2$ should be a valuable method for application in synthetic organic chemistry.

Table 2. Reduction of Carboxylic Acids by $Zn(BH_4)_2$

substrate[a]	time (h)	product	yield[e] (%)
benzoic acid	6	benzyl alcohol	90
palmitic acid	6	cetyl alcohol	95
valeric acid	3	amyl alcohol	95
2-chlorobenzoic acid	6	2-chlorobenzyl alcohol	90
4-nitrobenzoic acid	4	4-nitrobenzyl alcohol	90
3-nitrobenzoic acid	4	3-nitrobenzyl alcohol	90
3-bromopropionic acid	6	3-bromopropanol	75
3,4,5-trimethoxybenzoic acid	5	3,4,5-trimethoxybenzyl alcohol	70
pivalic acid	2	neopentyl alcohol	70
phenylacetic acid	3	phenethyl alcohol	95
cinnamic acid[b]	5	3-phenylpropanediol[d]	90
2-hydroxybenzoic acid[b]	4	no reaction	
acetylsalicyclic acid	3	2-hydroxybenzyl alcohol	85
10-undecenoic acid[b]	1	1,11-undecanediol	90
brassylic acid[c]	4	1,13-tridecanediol	70
terephthalic acid[c]	5	1,4-benzenedimethanol	70

[a] $[Acid]:[H^-] = 5:16.5$. [b] $[Acid]:[H^-] = 5:22$. [c] $[Acid]:[H^-] = 5.33$. [d] Mixture ratio of 1,2-diol:1,3-diol = 3:2 from ^{1}H NMR. [e] Isolated crude product.

Experimental Section

Preparation of Zinc Borohydride. A predried 500 mL side arm flask fitted with a reflux condenser and connected to a mercury bubbler was charged with 20.8 g (165 mmol) of freshly fused $ZnCl_2$ and 12.9 g (330 mmol) of $NaBH_4$, followed by 250 mL of dry THF using a double-ended needle. The contents were stirred using a magnetic stirrer for 24 h at room temperature. The active hydride content of the supernatant solution was estimated by quenching aliquots with 2 N H_2SO_4 and estimating the hydrogen evolved using a gas burette. The supernatant solution which was 0.66 M in $Zn(BH_4)_2$ was used as such for further reactions.

Procedure for Rate Study: Reduction of Benzoic Acid Is Representative. To 0.3 g (2.5 mmol) of benzoic acid was added 2.5 mL of dry THF followed by 1.5 mL of $Zn(BH_4)_2$ (0.66 M in THF, 0.99 mmol). The contents were refluxed, and the hydride uptake was recorded by quenching 0.25 mL of the reaction mixture withdrawn at various time intervals and measuring the volume of hydrogen evolved. To ascertain the effect of added catalyst, a similar procedure was followed by adding 25 μL (0.25 mmol) of cyclohexene.

Reduction of Palmitic Acid. To 1.3 g (5 mmol) of palmitic acid placed in a round-bottom flask with a side arm connected to a mercury bubbler was added 3.2 mL of $Zn(BH_4)_2$ (0.66 M, 2.12 mmol in THF) with stirring. The addition was accompanied by vigorous liberation of hydrogen. After the gas evolution was complete (5 min) the reaction mixture was refluxed for 6 h and then cooled to room temperature, and the excess hydride was quenched with 4 mL of dilute H_2SO_4 (2 N). Then the reaction mixture was saturated with anhydrous K_2CO_3 and the organic layer was separated. The residue was extracted with 2 × 5 mL of THF. The combined organic extracts were dried over anhydrous K_2CO_3 and then concentrated under reduced pressure to yield 1.2 g (95%) of cetyl alcohol, mp 52 °C (54–56 °C).[6] The products were characterized by spectral data, physical constants, and comparison with authentic samples.

Reduction of 10-Undecenoic Acid. To 1 mL (5 mmol) of the acid was added 4.2 mL of $Zn(BH_4)_2$ (0.66 M in THF, 2.77 mmol) and refluxed for 1 h. The excess hydride was quenched by adding dilute H_2SO_4 (2 N). The reaction mixture was made basic by adding NaOH followed by oxidation with hydrogen peroxide (30% by volume, 2 mL). The product was extracted as above. Removal of solvent yielded 0.9 g of 1,11-undecanediol (90%), mp 60 °C (61 °C).[7]

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