An NAD(P)H Model Reaction: Reduction of α-Keto Esters by the Hantzsch Ester Accelerated by Zinc Complex in the Reformatsky Mixture

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The Hantzsch ester (**I**), which is capable of transferring its 4-hydrogen directly to carbonyl function, has been used[1] as an NAD(P)H model compound with *N*-alkylnicotinamide structure.

Recently, Hughes indicated[2] that in the non-enzymatic carbonyl reduction, a mono-ionized metal species (MX^+) played an important role in the region where catalysis occurred. However, no example has so far been found that a mono-ionized zinc species accelerated the non-enzymatic carbonyl reduction.

We wish to report a hydrogen transfer reaction under mild conditions from **I** to α-keto esters accelerated by a mono-ionized zinc species ($ZnBr^+$) formed in the Reformatsky reaction.

The mono-ionized zinc species was prepared[3] by refluxing methyl bromoacetate (94 mg, 0.61 mmole), acetophenone (72 mg, 0.6 mmole) and zinc (38 mg, 0.58 mg-atom) in dry benzene for 1.5 hr. To the Reformatsky mixture in benzene thus formed (10 ml), the Hantzsch ester (**I**, mp 188.5～189°C, lit.[4] mp 189～190°C; 130 mg, 0.51 mmole) and methyl benzoylformate (run 1; **II**, 63 mg, 0.38 mmole) or methyl pyruvate (run 12; **III**, 41 mg, 0.41 mmole) were added at room temperature, and the mixture was allowed to stand in the dark at room temperature for 4.5 hr.

In case (runs 1～11) where **II** was used as substrate, the reduction product, methyl mandelate, was isolated (run 1; 34 mg, 53% yield) by means of silica gel column chromatography and characterized by PMR [δ ($CDCl_3$) 7.50 (5H, phenyl); 5.26 (1H, methine); 3.88 (3H, ester methyl); 3.58 (1H, hydroxyl)] after the usual work-up. 3,5-Diethoxycarbonyl-2,6-dimethylpyridine (**IV**) was recovered and purified by recrystallization (mp 72.5°C; lit. mp 73.5～74.5°C,[4] mp 72～72.5°C[5]).

With **III** used as substrate (runs 12～14), the yield (run 12; 4.6 mg, 11%) of the reduction product, methyl lactate, was determined by vpc (10%-PEGS 3 m column, 100°C, internal reference; *N*,*N*-dimethylformamide) after quenching the reaction with methanol.

In these reactions, the prolonged reaction period did not improve the yields of methyl mandelate (56%; run 2) and methyl lactate (12%; run 13), but under the same conditions, the addition of *p-tert*-butylcatechol (**V**, 13 mg, 0.08 mmole) considerably elevated the yields of methyl mandelate (79%; run 6[6]) and methyl lactate (34%; run 14) after 5 hr's reaction period. The addition of equimolar **V** (66 mg, 0.4 mmole) reduced the yield of methyl mandelate (37%; run 8) after 6 hr's reduction period.

Methyl benzoylformate (**II**, 0.4 mmole) was treated with Hantzsch ester-4,4-d_2 (mp 189～190°C; lit.[5] mp 191.2～192.4°C; 120 mg, 0.47 mmole) in the absence (run 5) or presence (run 7) of **V** (0.3 mmole), and after the usual work-up, the deuterated methyl mandelate was isolated (24%; run 5) after 4.5 hr in the absence of **V**, and (35%, run 7) after 12 hr in the presence of **V**. Both samples of mandelate were quantitatively deuterated at the α-position as revealed by PMR-analysis, no peak having been detected at all at δ 5.26.

In addition, no reaction was observed when **II** in dry benzene was treated in the dark at room temperature for 24 hr, (i) with 1.5 mole equivalent of the Reformatsky mixture (run 3) or **I** (run 4) alone; (ii) with 1.5 mole equivalent of **I** and 0.3 mole equivalent **V** (run 9); (iii) with 1.5 mole equivalent of zinc, acetophenone, methyl bromoacetate and **I**. When **II** was treated in dry benzene with 1.5 mole equivalent of **I** and $ZnBr_2$, prepared by heating

TABLE I. THE REDUCTION OF CARBONYL COMPOUNDS AT ROOM TEMPERATURE IN THE DARK

Run	Substrate[a] (0.4 mmole)	Reformatsky[b] mixture (mmole)	Hydrogen donor (mmole)	Additive (mmole)	Reaction period (hr)	% yield[c] of reduction product
1	II	0.6	I (0.51)		4.5	53
2	II	0.6	I (0.51)		24	56
3	II	0.6	none		24	0
4	II	—	I (0.6)		24	0
5	II	0.6	(I)-4,4-d_2 (0.47)		4.5	24[d]
6	II	0.6	I (0.51)	V (0.08)	5	79
7	II	0.6	(I)-4,4-d_2 (0.47)	V (0.3)	12	35[d,e]
8	II	0.6	I (0.51)	V (0.4)	6	37
9	II	—	I (0.51)	V (0.12)	24	0
10	II	—	I (0.51)	$ZnBr_2$[f] (0.6)	5	21
11	II	—	I (0.51)	Zn, PhCOMe $BrCH_2CO_2Me$ (0.6)	24	0
12	III	0.6	I (0.51)		4.5	11
13	III	0.6	I (0.51)		24	12
14	III	0.6	I (0.51)	V (0.08)	5	34

[a] 0.4 mmole in 10 ml of dry benzene.
[b] The Reformatsky mixture was prepared from equimolar amounts of zinc, methyl bromoacetate and acetophenone.
[c] Determined by means of vpc after addition of methanol to the reaction mixture.
[d] α-Position of methyl mandelate was quantitatively deuterated as revealed by PMR.
[e] Hantzsch ester-4,4-d_2 was added to the mixture of *p-tert*-butylcatechol, Reformatsky mixture and methyl benzoylformate, during 5 hr with stirring.
[f] Prepared by heating commercial product at 120°C for 15 hr *in vacuo*.

commercial product at 120°C for 15 hr *in vacuo*, in place of the Reformatsky mixture, the yield of methyl mandelate (run 10) after 5 hr at room temperature was lowered by 32% as compared with that with the Reformatsky mixture. The experimental results were summarized in the Table.

It is apparent from these findings that the mono-ionized zinc species formed in the Reformatsky reaction plays an important role in the direct hydrogen transfer from the 4-position of **I** to carbonyl group of the substrate, and that no hydrogen is transferred from donors other than **I**.

The ease with which carbonyl functions are reduced by NAD(P)H model compounds in the presence of the mono-ionized zinc species suggests that some ionic metal complex may probably be involved in the biological catalytic activity of some metal-dependent[7] dehydrogenases as well.

It is difficult to rationalize the origin of the activity of zinc ion and **V** in the present system. The mechanistic details of the present model reaction and the scope of this type are currently in progress with special emphasis on asymmetric reduction of substrates.

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